

**A guide for the procurement
of anti-tuberculosis drugs**

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**International Union Against Tuberculosis
and Lung Disease**

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and Lung Disease**

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List of abbreviations and acronyms

CEP	Certificate of Conformity with the European Pharmacopeia
DMF	Drug Master File
DOT	directly observed treatment
DOTS	directly observed treatment, short-course
E	ethambutol
GDF	Global Drug Facility
GLC	Green Light Committee
GMP	good manufacturing practices
H	isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
NGO	non-governmental organisation
NTP	National Tuberculosis Programme
PIC	Pharmaceutical Inspection Convention
R	rifampicin
ReMeD	Réseau Médicaments et Développement
S	streptomycin
T	thioacetazone
Z	pyrazinamide

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Preface

In March 2000, Ministers of Health and Finance from the 21 countries with the largest tuberculosis burdens worldwide met in Amsterdam and produced a declaration calling for global action to stop the deadly epidemic. They called for collective action by all their national counterparts and international partners to overcome key challenges in controlling TB. Among their priorities were improving financing, procurement and delivery of TB drugs to patients in need.

For decades, the International Union Against Tuberculosis and Lung Disease (IUATLD) has been in the forefront of efforts to assist low and middle-income countries in designing, supplying, monitoring and evaluating TB programmes integrated in primary care services. The IUATLD-devised TB control strategy, now known as DOTS, recognises efficient TB drug supply as a fundamental element of the approach. The IUATLD has also been a leader with WHO and their national constituents in demonstrating that poor drug supply and inappropriate use contribute to the emergence and spread of drug-resistant strains of disease – a major threat to the capacity of this generation and the next to stop TB. The other NGO partners who collaborated in producing this volume have also played pivotal roles in increasing access to TB control and to medicines for some of the world's poorest and most vulnerable populations.

This succinct guide for National TB Control Programmes, national essential drug programmes or central medical stores, and their partners, is a needed and welcome addition to tools to improve effective supply of essential drugs in low- and middle-income countries. The major challenge for most countries today is not whether or not to launch a DOTS programme, but how to urgently scale-up its coverage while improving quality and impact. Safe and efficient drug procurement is a prerequisite for any such expansion. Getting the procurement principles right is especially important for TB control, even relative to many other primary care interventions. Mistakes in quantification of need, standardisation of regimens, quality of products purchased and timely and efficient purchase and delivery, all could have dangerous repercussions for ill tuberculosis patients and for the communities within which they live.

Twice in the last decade, I have been involved in WHO surveys of National TB Programmes to document their resources, skills and results in

supplying TB drugs. While their financing, capacity and procurement efficiency appears to be improving as a whole, many countries still face great challenges and uncertainties as they go through the process of planning and procurement each year. Planning and meeting needs is becoming more challenging with the rapid resurgence of the disease due to the associated HIV/AIDS epidemic and/or economic and social crises. New global efforts to mobilise resources for drug procurement and control programmes, such as the Stop TB partnership, the Global TB Drug Facility and the WHO Green Light Committee for the purchase of drugs for treatment of multi-drug-resistant TB, are all important advances. At the heart of these initiatives, however, must be the ongoing efforts by the high-burden nations themselves to improve their capacity and effectiveness in drug supply for public health. Tools such as this one enable such efforts.

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Introduction

Tuberculosis can only be controlled successfully in the context of a National Tuberculosis Programme (NTP). The programme should be integrated into the general health system of each country. Its main priority is the treatment and cure of tuberculosis patients, in particular those who transmit infectious bacilli.¹

Tuberculosis treatment is based on chemotherapy. This is also one of the most effective methods of preventing the spread of the tubercle bacillus. The conditions necessary for adequate chemotherapy are the following:

- an appropriate *combination* of anti-tuberculosis drugs to prevent the emergence of resistance to these drugs;
- prescription of anti-tuberculosis drugs in the *correct dosages*;
- treatment taken *regularly* by the patient;
- for a *sufficient period* to prevent relapse of the disease after completion of treatment.

One of the essential elements of the tuberculosis control strategy, known as the DOTS strategy (directly observed treatment, short-course), is to make anti-tuberculosis drugs available in all health centres that treat tuberculosis patients. The five essential points of the strategy are as follows:

- government commitment to developing the activities necessary for tuberculosis control;
- detection of cases by smear microscopy in patients who present spontaneously to the health services;
- utilisation of standardised 6-8 month short-course treatment regimens for at least all smear-positive cases; adequate management of those cases detected, including directly observed treatment (DOT) during the intensive phase of treatment for all smear-positive cases, during the continuation phase of rifampicin-containing regimens, and throughout the retreatment regimen;
- regular, uninterrupted supplies of all essential anti-tuberculosis drugs;

- a standardised reporting and recording system that allows both the case-finding and treatment results for each patient and the general performance of the programme to be evaluated regularly.

For the drugs to be available and effective, the Central Unit of the National Tuberculosis Programme (NTP) must purchase them in sufficient quantity and assure their quality. It is this purchasing procedure that is discussed in the present Guide.

A – What are the specific problems associated with the procurement of anti-tuberculosis drugs?

The requirement for tuberculosis patients to take several drugs for several months (generally 6-8 months) in order to reach cure and to prevent them from infecting those around them creates constraints that can only be resolved in an appropriate context.

1. Why should treatment be given free of charge?

In order for all the drugs to be taken, tuberculosis treatment should not depend on the patient's purchasing power. If this were the case, patients would select only those drugs they could afford, and the length of treatment would depend on their financial situation.

The consequences of an inadequate combination of anti-tuberculosis drugs are well-known: it leads to the selection of bacilli that are resistant to these drugs. This must be avoided, particularly as the number of effective anti-tuberculosis drugs available at an affordable price is very limited, and no new drugs have appeared on the market for some time (the last to be developed was rifampicin, in 1969). Any development of resistance immediately compromises the patient's chances of cure and threatens the treatment options of the whole community.

If the anti-tuberculosis drugs are correctly combined, but for too short a period, the main risk for the patient is relapse and a renewed risk of infection of close contacts.

For a patient to have access to the prescribed treatment for a sufficient period, the anti-tuberculosis drugs must be given *free of charge*. This and the specificity of tuberculosis treatment have a direct effect on drug procurement and management techniques.

2. Who knows what needs to be purchased?

It is the responsibility of the Ministry of Health to ensure, in the name of equity, that good quality anti-tuberculosis drugs are provided free of charge

to tuberculosis patients in all those health centres that treat such patients throughout the country.

As part of its prescriptive role, it is the Central Unit of the NTP that decides which drugs should be used for tuberculosis treatment, at which doses and in which combinations. This should be standardised and set out in the manual of the National Tuberculosis Programme.

It is also the responsibility of the programme's Central Unit to collect and compile health statistics on tuberculosis, particularly on case-finding. These data are recorded in the *Quarterly report on tuberculosis case-finding*, which is filled out by all those health centres that diagnose and/or treat tuberculosis and have a *Tuberculosis Register* (see the IUATLD guide "Management of tuberculosis. Guide for low-income countries"¹). The calculation of the drug requirements is based on the number of patients recorded in these reports and on existing drug stocks (see Chapter C). The Central Unit therefore has information on what drugs are needed at a national level.

It is thus the Central Unit of the NTP that determines the quantities of anti-tuberculosis drugs necessary for the country according to the forms and combinations decided upon in the NTP manual, taking into account the reserve stock required. It is also the responsibility of the Central Unit of the NTP to convert these needs into budgetary terms so that the Ministry of Health can find the ways and means to finance these purchases. The intermediary and peripheral levels of the health pyramid are also involved in this process, but it is not their responsibility to make decisions on the forms of the drugs, nor to prioritise budgets for anti-tuberculosis drug supplies.

Nevertheless, in certain large countries, the responsibility for budgeting lies with the provinces or states. It is important for good coordination to be achieved between the federal government and those of the provinces/states in order to place a bulk order.

3. Who should be responsible for purchasing anti-tuberculosis drugs?

Once the NTP's Central Unit has estimated the anti-tuberculosis drug requirements for the whole country, the organisation of their purchase on the international market varies from one country to the next depending on the identified source(s) of funding.

For certain countries it is the programme itself or a department of the Ministry of Health; for others it is an external donor (such as a bilateral or multilateral cooperation or a non-governmental organisation). A third category might be a central medical store – a not-for-profit para-public organisation responsible for buying essential generic drugs that enters into the system of cost-recovery.

Each purchaser has its own operating restrictions, but there are certain rules that must always be followed. These are outlined in the following chapters.

The specific case of the procurement unit for generic drugs

As a rule, procurement units for generic drugs supply health centres with essential generic drugs and laboratory agents against payment. The selling price of each product is fixed so that all of the costs generated by their purchase, transport, storage, insurance, handling, etc., are covered. The profit margin on each product depends on the original price, the quantity consumed and the requisite equality in access to essential generic drugs. However, to avoid bankruptcy, the selling price can at no time be lower than the cost price, transport included.

The case of anti-tuberculosis drugs is unusual, as the health centres do not buy them but receive them free of charge according to the norms of distribution established by the national programme. In order to benefit from the experience that these central medical stores have acquired as professional drug purchasers, and so as not to affect their budgets, it is essential that the funds necessary for purchasing the anti-tuberculosis drugs – whatever their provenance – should be transferred before the order is confirmed.

4. What are the difficulties involved in purchasing good quality drugs on the international market at the best price and in the required time frame?

It is important to purchase the necessary quantities of anti-tuberculosis drugs within the required time frame, in the required forms, and at the best prices, at the same time assuring their quality. None of the above is specific to anti-tuberculosis drugs, and these requirements apply systematically to all drug purchasers.

The difficulties that are encountered, however, are linked to the specificity of tuberculosis control:

- the quantity ordered must truly correspond to the needs of the programme (including the constitution of reserve stocks). *For the patient, there is no supply alternative on the private market.* If the programme, directly or indirectly, does not supply the anti-tuberculosis drugs in time, the patient cannot buy them from private pharmacies: the cost is too high for the majority of patients. The consequence is anarchic treatment that is dangerous for the patient and for the community;
- the formulations, combinations and concentrations of the anti-tuberculosis drugs are very precisely defined for each programme and must be rigorously respected when ordering;
- documentation providing proof of the quality of the drugs, particularly studies of bioequivalence, must be requested;
- the budget must be available to make the order in time. As indicated above, the quantities needed are calculated by the NTP, but then the budget for the purchase must be available immediately. This often requires a certain foresight and flexibility with the budget that does not always exist in government departments;
- there are relatively few manufacturers of anti-tuberculosis drugs. The internationally recommended combinations and concentrations have only recently been standardised, and these are not always easily available on the international market.

The importance of sustained inter-personal communication and trust between the heads of the NTP and those responsible for drug purchasing cannot be overemphasised. This means that the purchasers should be extremely attentive, even though the budget is relatively small compared to the funds required for non-specific drugs.

B – How are the drugs selected?

1 – What drugs are used?

There are six anti-tuberculosis drugs included in the WHO list of essential drugs and in the lists of most countries: streptomycin (S), ethambutol (E), rifampicin (R), isoniazid (H), pyrazinamide (Z) and thioacetazone (T).

They are available in single or combined preparations: {RH}, {RHZ}, {RHZE}, {TH}, {EH}.*

The dosages that are usually recommended and available, depending on whether the products are in single or combined form, are given in the following tables.

Table 1. The most frequently recommended dosages for single drugs

Streptomycin (S) : 1 g (injectable)	Isoniazid (H) : 100 mg
Ethambutol (E) : 400 mg	Pyrazinamide (Z) : 400 mg
Rifampicin (R) : 150 mg or 300 mg	

It is always advisable to buy rifampicin in a combined form with one or more other anti-tuberculosis drug.

Table 2. Recommended formulations for rifampicin-containing drug combinations

Two-drug combinations R150/H75 for daily treatment R300/H150 for daily treatment R150/H150 for three times weekly treatment
Three-drug combinations R150/H75/Z400 for daily treatment R150/H150/Z500 for three times weekly treatment
Four-drug combinations R150/H75/Z400/E275 for daily treatment Not recommended for three times weekly treatment
For children R60/H30/Z150 for daily treatment (initial phase) R60/H60 in the continuation phase or for three times weekly treatment

(*) Thioacetazone does not exist in single form; it is always combined with isoniazid.

Table 3. Recommended formulations for other combined drugs

{EH}: ethambutol 400 mg / isoniazid 150 mg
{TH}: thioacetazone 150 mg / isoniazid 300 mg or thioacetazone 50 mg / isoniazid 100 mg

2 – What are the recommended treatment regimens?

One of the fundamental elements of the DOTS strategy is the use of standardised treatment regimens depending on the type of tuberculosis. Standardisation is indispensable if patients are to receive the optimal combination of anti-tuberculosis drugs and length of treatment throughout the country, even in non-specialised health centres. Treatment regimens have been tested in numerous clinical trials; the best of these are recommended by the international experts.

Furthermore, it is important for the drug combinations used to be standardised at the national level so as to facilitate drug ordering and management by health personnel and so that they are correctly coded on the patients' individual treatment cards. There are several treatment regimens and drug combinations possible, and each country selects those best suited to its own situation. Standardisation of the treatment regimens and combinations of drugs is a prerequisite for correctly estimating the country's drug needs, and for ordering drug supplies (see Chapter C).

The treatment regimens for patients notified as new tuberculosis cases (patients who have never been treated or who have been treated for less than one month) always comprise two phases:

- the initial phase, during which at least three drugs are given together for a minimum of 2 months: RHZE or SRHZ or STH or SEH or RHZ.
- the continuation phase, during which two drugs are given for 4-6 months: TH or EH or RH.

The so-called "retreatment" regimens are for patients who have already been treated for one month or more. These regimens combine SRHZE for 2 months, then RHZE for one month, followed by RHE or RHZE daily or three times weekly for 5 months.

The treatment regimens and their mode of administration (daily or three times per week) vary from one country to the next. *It is the responsibil-*

ity of each NTP to decide on the regimens and drug formulations that should be used in the country. The drugs are then purchased based on these specifications.

3 – What technical specifications need to be checked?

As for all drugs, a certain number of rules must be followed in order to guarantee their quality (see Chapter C).

However, for rifampicin-containing combinations, a very specific test is necessary: the bioequivalence of the product must be guaranteed, i.e., it needs to be ascertained that a sufficient amount of the drug is detected in the blood system for a sufficient period.²

The IUATLD and the WHO have published a protocol for testing the bioequivalence of rifampicin.³ *These tests must have been performed by the manufacturer of the drug*, and are a prerequisite for participating in a drug tender.

3.1 Interpreting tests for rifampicin bioequivalence

It is not an easy task to interpret rifampicin bioequivalence tests (conducted in 22 healthy volunteers): this needs to be done by a competent person in the country that is importing the drugs. The following parameters must be evaluated to judge the quality of these tests:

- comparison of the combination with the reference product;
- use of high pressure liquid chromatography (HPLC) to measure the rifampicin concentrations;
- a minimum of six measurements performed at 0, 1, 2, 4, 6 and 8 hours;
- principal parameters measured: maximal serum concentration (C_{\max}) and area under the curve for 0 to 8 hours (AUC_{0-8});
- the test/reference ratio should lie completely within the range 80% to 125%.

To assure the quality of bioequivalence studies, it is recommended that they be performed in laboratories with proven proficiency; an international laboratory network is currently being set up under the auspices of the WHO.

3.2 Monitoring the quality of fixed-dose combinations (FDCs)

The bioequivalence of FDCs is sensitive to changes in the production process. The supplier will consequently be required to submit a declaration that since the last rifampicin bioequivalence test:

- the same raw materials are still being used;
- no changes have been made in the production process;
- dissolution tests have been performed on each consecutive batch – following the first test for which the bioequivalence test was performed – and the results were satisfactory (if required, results of these tests must be provided by the supplier).

Manufacturers or suppliers who wish to participate in the tender should be advised that tests may be carried out on a sample taken from any of the batches supplied under the current contract.

4 – What are the second-line drugs?

These products are not on the WHO list of essential drugs, nor on those of most low-income countries, as they are extremely costly (more than US\$10.000 to treat one person) and of poor efficacy.

They include different aminoglycosides (kanamycin, amikacin, capreomycin), ethionamide (and prothionamide), ofloxacin (and ciprofloxacin), cycloserin, and PAS (para-aminosalicylic acid). The WHO proposes several standardised regimens using different combinations of these drugs.⁴ The length of treatment is 21 months minimum.

It is not recommended to purchase these drugs unless the programme is functioning very well and there is a sufficient budget. In this case, it is advisable to contact the committee composed of partners in tuberculosis control that has been set up within the WHO. The Green Light Committee, as it is known, obtains second-line drugs at a rate well below that of the market. Certain conditions must be fulfilled for an application to be approved (see Appendix 6).

C – What quantities should be ordered, and what delays should be expected?

Unlike most non-specific drugs, the management of anti-tuberculosis drugs is based on theoretical consumption, i.e., it is linked to the number of tuberculosis patients on treatment during a defined time period.

The quantity of anti-tuberculosis drugs that needs to be ordered depends on several factors:

- the number of tuberculosis patients detected and notified in the *Quarterly report on case-finding*;
- the standardised treatment regimens used and set out in the NTP manual, and the fixed-dose combinations used;
- the quantity of drugs currently stocked at the central level;
- the reserve stock required (it is recommended to have a 3-month stock at the intermediate level, a 3-month stock at the peripheral level and a 6-month stock at the central level, i.e., a total reserve stock equal to the drug needs for a full year)
- the drug consumption from the moment the order is made to the moment it arrives (this depends on the transport time);
- the frequency of the ordering;
- the budget.

At the central level, it is advisable to order drugs twice yearly. If there is a reserve stock of 6 months, this means that there should still be sufficient drugs in stock for 6 months' consumption of anti-tuberculosis drugs when the new order arrives.

The orders are made based on the notifications in the *Quarterly report on case-finding* using the *Order form for treatment supplies* (Table 4). The quantity of drugs necessary for the treatment of patients each quarter is calculated in the following way:

- the number of patients to be treated is indicated in the *Quarterly report on case-finding*, which is completed every quarter by each health centre that keeps a *Tuberculosis Register*; the data from the two previous quarters are added together;

- the number of patients is entered in the column headed “Cases”; each patient category corresponds to a defined treatment regimen;
- the theoretical quantity consumed for each drug (standard form) is calculated by multiplying the number of cases by a “factor” (the average number of tablets that a patient must take during the course of treatment) and taking the sum of the three columns: $D = A+B+C$;
- this number (D) is recorded in the lower part of the table, in column E;
- the quantity of drugs to keep in reserve corresponds to the consumption if the programme wishes to have a 6-month reserve at central level ($F = D$);
- the quantity of drugs still in stock at the central unit at the time the drug order form is filled out should be inventoried, and the result of the inventory should be noted in column “G”; the expiry dates of the drugs should be checked to ensure that the drugs are being used correctly;
- it is then necessary to calculate the time it will take from the moment the order is made for the drugs to reach the central store of the programme; this length of time, in months (column H), should never exceed 6 months, i.e., the consumption of 6 months’ worth of drugs; if it is too complicated to estimate the transport time, a period of 6 months can be entered if the budget will allow it;
- the next column (I) calculates drug consumption during time H; this is reached by multiplying the monthly consumption ($D/6$) by the value of H;
- the total quantity to order for the 6-month period (J) is the sum of the running requirements for 6 months (E) added to the reserve stock necessary (F) and the expected consumption while awaiting delivery (I), minus the stock existing on the day of the order (G): $J = E+F+I-G$.

It is the responsibility of the NTP’s Central Unit to fill out this table. The only information needed in order to fill it out is indicated in the shaded areas: number of cases during the last 6 months by treatment regimen, stocks remaining in the central warehouse, number of months between making the order and delivery of the drugs.

When drugs are purchased only once yearly, the same table can be used using the annual declaration of the number of cases instead of the 6-month declaration. For the reserve stocks (column F), half of total consumption should be entered (column D), as it is recommended to keep a 6-month reserve stock. Storage capacity on arrival will necessarily be greater than for 6-monthly orders.

Table 4. Example of a 6-monthly external drug order

6-month period:

Item	Treatment regimen 2 ERHZ/6TH	Number of cases (1) 8 625	Treatment regimen 2 STH/10TH	Number of cases (2) 1 312	Treatment regimen 2SERHZ/1ERHZ/5(ERH) ₃	Number of cases (3) 844	Total cases 10 781
	Factor	Total A No 1 × factor		Total B No 2 × factor	Factor	Total C No 3 × factor	Total D A+B+C
{RH} 150/75	210	1 811 250	0	0	540	455 760	2 267 010
Z 400	210	1 811 250	0	0	320	270 080	2 081 330
S 1 g	0	0	60	78 720	60	50 640	129 360
{ ² } 150/300	180	1 552 500	360	472 320	0	0	2 024 820
H 100	0	0	0	0	100	84 400	84 400
E 400	150	1 293 750	0	0	450	379 800	1 673 550
	Running requirement E = D	Reserve requirement F = D	Currently in stock G	Number of months before arrival of order H	Estimated drug consumption before arrival of order I = D/6 × H	Total to be ordered J = E+F-G+I	
{RH} 150/75	2 267 010	2 267 010	2 125 000	5	1 889 175	4 298 195	
Z 400	2 081 330	2 081 330	2 050 000	5	1 734 442	3 847 102	
S 1 g	129 360	129 360	125 000	5	107 800	241 520	
{TH} 150/300	2 024 820	2 024 820	3 000 000	5	1 687 350	2 736 990	
H 100	84 400	84 400	170 000	5	70 333	69 133	
E 400	1 673 550	1 673 550	1 650 000	5	1 394 625	3 091 725	

The information required in order to be able to fill out the form is shown in the shaded area.

D – What rules need to be respected when purchasing drugs?

The rules set out in this chapter are not specific to anti-tuberculosis drugs, but are valid for all drugs, particularly generics. The only element specific to anti-tuberculosis drugs is the bioequivalence of rifampicin-containing fixed-dose combinations, described in Chapter B3.

Drugs differ from other products in their diversity, the vocabulary used, the problems of stability and shelf life, storage conditions (particularly their sensitivity to temperature and/or humidity), and the criteria of quality required for both the product and the manufacturer. Prices can differ widely, depending on whether certain criteria are more or less well respected. It is therefore necessary to prepare a detailed, precise list of the technical specifications so as to stimulate competition and ensure transparency in the evaluations, which must be neutral and impartial.

Furthermore, the pharmaceuticals market is atypical in that patients do not choose the drugs they take, nor are they capable of judging the suitability of the prescription. Nor can the prescribers and the dispensers verify the quality, efficacy or tolerance of the drugs they give out. It is also difficult to detect products of poor quality, as this requires costly tests that are rarely available.

1 – What type of procedures can be used?

There are all kinds of ways of procuring anti-tuberculosis drugs, from direct negotiation to open international tender. However, for reasons of transparency and to justify that funding is being put to good use, the tender is preferable, because:

- the open competition required in a tender means that the best current prices can be obtained;
- the transparency of the procedures, which are well documented, corresponds to the criteria for public purchasing;
- the separation of the key functions corresponds to the criteria for public purchasing;
- the neutrality and impartiality of the evaluation of the tenders corresponds to the criteria for public purchasing;

- the annual audit, whose results are published, corresponds to the expectations of the purchaser.

When direct negotiation or mutual agreement is reached with a supplier, the choice of supplier can be subjected to unacceptable bias.

Different types of tenders

There are several types of tenders:

- *International open tenders*

The procedure is very formal. It implies that the tenders will come from suppliers informed through the use of national and/or international media. As a result, all of the bids will need to be evaluated in terms of the quality of the products on offer and that of their manufacturer. The process is long, costly, and out of proportion with the goal of purchasing anti-tuberculosis drugs.

- *Restricted tender*

This procedure involves only those suppliers who are *already qualified*. It has the advantage of saving time, but it also implies that all potential suppliers have already been evaluated.

- *Limited national/international shopping*

In this case the purchaser contacts a certain number of suppliers directly (in principle at least three). Although rapid, this method can be biased by the choice of the suppliers contacted.

Why perform a separate tender for anti-tuberculosis drugs ?

- Because the demand comes from a programme that has precise conditions;
- to ensure that drugs are supplied in the required quantity and time frame, thus allowing patients to follow their treatment as recommended;
- because there are very few manufacturers of quality drugs, and a restricted tender is suitable;
- because the drugs are given free of charge and receive specific funding, and a separate tender facilitates their management;
- because the tender is the final point of a process that involves several different public departments, all of whom have a say in the final result.

2 – What certificates and other information are needed to assure the quality of the drugs?

Those who respond to a drug tender are manufacturers, wholesalers, or official representatives of pharmaceutical companies. A certain number of certificates and declarations are requested by the purchaser to assure the quality of the products required. We describe these different elements before discussing how they can be used.

2.1 Terms used

Good Manufacturing Practices (GMP)

Good Manufacturing Practices is a norm developed for the pharmaceutical industry, comparable to the ISO (International Standardisation Organisation) series 9000 in industry. It aims to establish procedures which will reduce the risk of errors that can occur in production and which will guarantee the reproducibility and quality of manufacture. Among other things, it aims to eliminate cross-contamination from one product to another during manufacture. GMP certification (which must always be requested) is the responsibility of the National Drugs Regulatory Authorities of the product's country of origin. There is no standardisation for generic drugs, and their credibility also depends on the level of independence of these authorities. It is indispensable to obtain the GMP certificate of the *site of manufacture*. If there is any doubt, a certificate can be requested from an independent agency, such as a member agency of the Pharmaceutical Inspection Convention (PIC).* As its name indicates, this is an organisation whose objective is to standardise methods of inspection. The GMP certificate should conform to the WHO model.

Pharmacopeia

Conformity with a pharmacopeia is a guarantee of the quality of a product. There are several pharmacopeias. Those that are recognised internationally are the British Pharmacopeia (BP), the American Pharmacopeia (USP), the French Pharmacopeia (PF) and the European Pharmacopeia (EP). The pharmacopeias are regularly revised, and it is important to ensure that the product conforms to the latest edition.

* Pharmaceutical Inspection Convention, Secretariat, Rue de Varembe 9-11, 1211 Geneva, Switzerland. Tel.: (+22) 749 1324. Fax: (+22) 740 1437.

Marketing licence

When the product is used in the country where it is manufactured, it needs a marketing licence. In order to deliver this marketing licence, the controlling authorities request detailed information on the raw materials, the manufacturing process and the quality control measures made throughout production. This requires the manufacturer to constitute a very complete and detailed file.

However, as the generic anti-tuberculosis drugs used in the National Tuberculosis Programmes are used only in developing countries, they do not all have a marketing licence in the country of origin. They do sometimes have an export licence, for which the procedure varies from one country to the next and which does not provide at all the same guarantees of quality as a marketing licence.

WHO Certificate applicable to all pharmaceutical products in circulation in the international market

In order to standardise the approach to drugs manufactured for export only, the WHO has published recommendations and a standardised model certificate applicable to all pharmaceutical products in circulation in international commerce (WHO 1996, 34th report, n°863). This model is presented in Appendix 4. Even if a marketing licence is not available, all manufacturers of pharmaceutical products should be able to provide this document. It engages the responsibility of the National Drugs Regulatory Authority of the producing country towards that of the importing country with regard to the information concerning the product and its manufacturer. Although it does not suffice to guarantee the quality, efficacy and safety of the drug in question, it nevertheless does aid in improving transparency in international exchange and in creating a healthier market.

Certificate of batch analysis, WHO type

The manufacturer must present this certificate for every batch of drug provided. It lists the characteristics of the product and the results of analyses performed during the manufacture of the batch.

Stability studies

The stability studies should be documented (an indication of shelf-life is not sufficient). A summary of the relevant studies should be requested. Note that the degradation of drugs accelerates in conditions of high tem-

perature and humidity, and thus the tender document should indicate the temperature and humidity of the storage conditions that need to be respected. The absence of this information can lead the manufacturer to limit studies to moderate climates that may bear no relation to conditions in the country of destination.

Raw materials

Although generic drugs are of interest due to their low cost, it is still necessary to verify certain conditions of fabrication that have an influence on their cost, particularly the raw materials, which represent 50-70% of the final price. For the manufacturer of generics, who is rarely a manufacturer of raw materials, it is essential to make a profit. This should not, however, detract from their quality; it is therefore useful to check that the supply sources are long term and of good quality. The manufacturer must indicate their sources and keep to them. As a guarantee of the quality of the raw materials, the manufacturer can produce the Drug Master File or a certificate of Conformity with the European Pharmacopeia (CEP).

Licence to operate

A producer of pharmaceutical drugs is distinguished from a chemical production unit in that its capacity to manufacture pharmaceutical drugs must be justified. In particular, the manufacturer must provide proof that the site and equipment used respect the conditions required in the application of the international certification system of the quality of pharmaceutical products. The site is then granted a certificate known as a "Licence to operate for a pharmaceutical manufacturer". The licence is valid for a specific period, and must be renewed. It can also be revoked if any violation is noted on inspection. This document is specific to the pharmaceutical domain. Nevertheless, the criteria for issuing such a licence can vary from one country to the next, which is why another questionnaire specifically about the quality of the drugs should also be filled out.

Rifampicin bioequivalence

This has been widely covered in Chapter B3.

2.2 Registration

The different certificates described above will often have enabled the manufacturer to obtain a *preliminary licence* for the drug in the country of destination.

By licensing the drug, the authorities of the country of destination guarantee that the population has access to drugs of quality. Licensing ensures, among other things, that the site of manufacture respects Good Manufacturing Practices (GMP), and that the product conforms to the reference pharmacopeia. In order to do this the supplier must provide proof of the quality of the supplies, in the form of a file that is submitted to the authorities of the receiving countries along with samples of the products in question. The file is constituted at the request of the authorities. In general, the authorities will grant a licence for the drug after examining the file; in other words, the product can be sold or distributed in the receiving country. The licence is valid for a limited period (usually 3-5 years), and it must be renewed before the expiry date. It should also be emphasised that both the supplier and the product must be licensed.

However, licensing is not in itself sufficient, and it should not serve private interests to the detriment of the community. For example, the time required to license a drug can be an indirect method of closing the door to competition. By the same token the licensing fees can be disproportionately high: the fees are often as high for generics as for new drugs, despite the fact that the file for a generic drug is expected to be less exhaustive than that for a new drug because the clinical and toxicological studies are already available in the literature. Furthermore, as the manufacturers of generics only supply on demand, they cannot risk obtaining a preliminary licence: they prefer to win a tender so as to license only those drugs that have been selected. As a result a vicious circle emerges whereby the country of destination invites only licensed suppliers to tender, whereas the suppliers await the results of the tender before applying for a licence.

It is nevertheless important to ensure that the products that are selected are regularly licensed by the National Regulatory Drugs Authority of the country of destination; as the programme that uses the drugs must be run under the responsibility of the local authorities, the procedures in place must be respected. A model of a file for licensing a generic drug is given in Appendix 3.

3 – Can the supplier be believed?

The supplier can be either the manufacturer or an agent (wholesaler). As in the case of the drugs, it is necessary to be sure of the technical and financial ability of the supplier to fulfil the contract in the optimal conditions.

The following information should therefore be checked carefully:

- average turnover in the last two years (preferably five times greater than the sum of the transaction);
- results of the last three years, if possible with certified documents;
- production capacity (preferably three times greater than the size of the transaction);
- quality assurance: the manufacturers must present the GMP and WHO certificates for the drug; wholesalers must present a letter from their manufacturers allowing them to participate in the tender, *as well as* the GMP and WHO certificates of their manufacturers;
- years since the start of production of the drug (*for certain newly developed combinations, expect the production history to be missing*);
- experience with similar contracts (products, quantities, dates, destinations);
- quality assurance: provide name, qualifications and title of the person responsible;
- raw materials: origin, control protocols;
- presence of an internal control laboratory, with details of equipment.

These points are covered in the questionnaire to be sent to the suppliers (Appendix 1) and the product questionnaire (Appendix 2).

4 – What other elements need to be verified?

Other elements that are specific to the pharmaceutical products should also be taken into account by the purchaser during the preparation of the tender: traceability, distribution, importation procedures and packaging. Furthermore, it is important to keep an eye on the market so as to be informed of any suspected violations by the manufacturers.

Importation procedures

It is important to break the importation procedures down into the different stages and costs involved, so as to limit as much as possible the reduction of the drug's shelf-life. It is the purchaser's responsibility to identify any possible anomaly that may prevent the drugs from reaching their destination.

Here is a list of questions that should be asked:

- Is the drug licensed for free circulation in the context of the programme?
- What is the procedure and time scale for obtaining the import licence?
- Will there be import taxes? When do they need to be paid?*
- What documents are required for importing drugs?
- Are there fees for demurrage (delays incurred by the transporter)?
- What are the costs of storage and who is responsible for paying them?
- Do you need to perform the customs clearance yourself, or do you need to contract a specialist agency? What costs would be involved?

Primary and secondary packaging, labelling and delivery

The type of primary packaging, tropicalised if possible, should be indicated, as should the appearance of the drug: blister, bulk or other, depending on the needs of the NTP.

The labelling should be described, and should include at least the following information:

- INN (international non-proprietary name)
- dosage form
- strength of raw material(s)/active ingredients
- number of units per box/packaging
- batch number, date of manufacture, expiry date
- conditions of drug storage and handling
- name and address of the manufacturer
- name and address of the supplier

The type of packaging required for transport should be defined.

The method and deadlines for delivery should be given.

* Note that the WHO recommends that pharmaceutical products should be exempt from import tax.

Shelf-life and expiry date

For all drugs, the date of manufacture and the expiry date should be clearly and indelibly marked.

At the time of delivery, all drugs should have more than three-quarters of the total duration of their shelf-life remaining.

Distribution

This includes storage, checking and dispatch. It is important to ensure that the drugs can be traced throughout the chain of distribution (even when there is no well-organised system of pharmacovigilance), and that all operations are in accordance with pharmaceutical norms (Good Distribution Practices). It is the purchaser's responsibility to check the chain of distribution and to point out the risks to all those concerned. If this is not taken into account during the preparation of the tender the purchaser will be exposed to the risk of losing drugs, having them stocked in inadequate conditions leading to further loss, or having them distributed in quantities that bear no relation to requirements. The Central Unit of the NTP has an important role to play in this domain.

E – How, in practical terms, is a tender for anti-tuberculosis drugs launched?

As a result of the above, in most cases the restricted tender will be the best solution, mainly because the number of manufacturers of anti-tuberculosis drugs is limited, and some manufacturers (and their products) are already registered in the countries of destination.

It is recommended to perform a specific tender for anti-tuberculosis drugs, i.e., do not include them in a general drugs tender for the country of destination. As anti-tuberculosis drugs are ordered in limited quantities, and there are few suppliers, they need to fulfil certain specific criteria of quality, and they are generally managed by a dedicated tuberculosis programme.

Nevertheless, the procedure for the restricted tender needs to be slightly modified in order to be able to invite suppliers who are not yet registered in the country (but who are qualified to do so), so as to benefit as much as possible from the resulting competition. Organisations specialising in tuberculosis control can provide useful information to update lists of potential suppliers.

In particular, in the framework of the Stop TB Initiative, a “Global Drug Facility” (GDF) was created on 24 March 2001 to provide anti-tuberculosis drugs for certain countries, using suppliers whose products are of proven quality. The conditions for obtaining drugs through this facility are given in Appendix 5.

The questionnaire to be sent to the suppliers (manufacturers or agents) and the product questionnaire are given in Appendices 1 and 2.

The tender procedure and the key points that require attention are given step by step in the table below.

Procedure	Key points
a) Data collection	This requires close collaboration between the programme managers and those who manage the stock. It can be difficult if there are several groups involved.
b) Calculation of drug requirements	To be done in close collaboration with the programme managers, in order to respect the treatment regimens (combinations and dosages).

Procedure	Key points
c) Calculation of quantities	Based on the drug requirements, it must be decided whether the quantity should be bought in a single operation, or whether several orders of defined quantities should be made. This will depend on the financial capacity, and the storage capacity, of the circuit of distribution. In general it is recommended to make two orders annually.
d) Preparation of the tender	It is necessary to have a standard document that has been approved by the National Drugs Regulatory Authority (ministry, donor agency, etc). Decide whom the tender should be sent to.
e) Approval of the tender document	Has someone been given this responsibility? NB: according to current regulations, this person may be held personally financially responsible, with all that this may imply.
f) Dispatch of documents	As the tender document can run to more than 60 pages, and one copy must be sent to each supplier invited, it is important to ensure that the copies can be made in time.
g) The suppliers prepare their tender	4 to 6 weeks is generally necessary.
h) Date and time of closure of the tender	The date and time must be clearly stated in the tender document. Furthermore, the tenders must arrive sealed, and should be registered and stored in a safe place.
i) Opening of the tender	The bids are opened in public. The candidates can attend. Each tender is announced, as are the key elements, which are determined by the purchaser with the participation of those responsible for the project. The winner is necessarily one of the candidates. The meeting results in a report that is signed by all those present.
j) Evaluation and recommendations	The evaluation is conducted by the purchasing service, with the aid of experts from the programme, from the pharmacy, and from the financial services. The roles and responsibilities must therefore be clearly defined. Furthermore, if unlicensed suppliers have been invited to bid, they need to go through the licensing procedures. The time necessary for this process should be included in the calendar of the tender.

Procedure	Key points
k) The Contract Review Committee passes a verdict on the recommendations	The role of the Contract Review Committee is to verify that the procedure has been respected. In no case does it play a technical role. Nevertheless, it may spot anomalies in the technical (or financial) evaluation that indicate that the procedure has not been respected. It must therefore raise the issue. If this leads to a technical problem that requires a special meeting, the decision on the product should be delayed. The members of the Contract Review Committee should not have participated in the tender in any way.
l) Approval of the Contract Review Committee's recommendation	The report of the meeting of the Contract Review Committee and its recommendations are transmitted to the authority responsible for the transaction for endorsement. This authority may seek to assert a different opinion, which could lead to further delays. Nevertheless, this person has no right to impose a decision (transparency is of the utmost importance!).
m) The manufacturers are informed of the result of the tender	A document is sent to the winner(s) of the tender. This can be in the form of a letter accompanied by a contract, or simply the contract itself. The award procedure should be defined before the dispatch of the tender, as the manufacturers need to know how they will be informed of the result in the tender document.
n) The manufacturers acknowledge receipt and return the contract	No order can be made in the absence of the contract – its content should be decided upon before the dispatch of the tender (see reasons above).
o) The orders	The orders are prepared as stated in the tender, and as authorised by the Contract Review Committee.

F – How is the drug tender evaluated?

1 – Summary of the key points of a drug tender

The key points of a tender are summarised below.

General items

- Who benefits from it?
- Who finances it?
- Closing date for the tender?
- Date and venue of the opening of the tender and whether it is public?
- Currency of the tender: indicate the currency; if open, indicate how the exchange rate will be calculated.
- Request information (with proof provided) on the licence to operate, the GMP certification of the manufacturing site, the Site Master File, the inspections of the national regulatory agencies, or other audits performed by international reference agencies, etc. An ad hoc questionnaire can be attached to the tender document, to be filled out by all those candidates who are not yet licensed or whose licence needs to be renewed (this last point must be clearly indicated in the tender document).

Items concerning the products

- Complete description of articles (e.g., coated tablets, in boxes of 50 blisters of 10 tablets, bulk in boxes of 1000 tablets, etc.).
- Quantities (indicate if they are expressed in boxes or individual units).
- Price: Unit FOB, unit CIF, total FOB, total CIF, in the currency indicated in the tender documents
- The following information should also be requested for every tender submitted:
 - address of the manufacturing site
 - for the reference pharmacopeia, indicate that *only the latest edition is acceptable*

- edition of the reference pharmacopeia
- references of the raw materials
- shelf-life
- stability studies
- delivery date
- sample
- bioequivalence study

2 – Tender evaluation chart

The chart below summarises the key points of the product and manufacturer under consideration, as set out in the tender document.

The chart is filled out by the person responsible, i.e., the questions that are strictly pharmaceutical can only be answered by a pharmacist. It enables the drugs to be differentiated, and allows the non-specialist to grasp the main points, at the same time indicating how well the key requirements are met.

FOB* (Free on board): the price of the drugs placed by the vendor on board a ship or plane at the port of embarkation designated in the sales agreement. It is up to the purchaser to find (and pay) the transporter who will deliver the products to their final destination.

CIF* (Cost/Insurance/Freight): the price of the drugs delivered to the agreed port of disembarkation, with the cost of transport insurance included. NB: it is also usually necessary to budget for the costs of transit between the port of disembarkation and the warehouse where the drugs are to be stocked.

Example of interpretation

Suppose that the product in question is rifampicin 150 mg + isoniazid 75 mg, loose in boxes of 1.000 tablets. Opposite “Bioequivalence”, “OK” is entered if the bioequivalence study has been received and if it conforms to the standard required. If not, or if the study is missing from the tender, “no” is entered and the tender is disqualified.

Be careful to check the dates of validity of the documents.

* INCOTERMS 2000, International Chamber of Commerce (ICC), Paris, France.

Tender evaluation chart

Item Code	Description	Quantity	Manufacturer's name XXX				Manufacturer's name YYY			
			Unit FOB price	Total FOB	Unit CIF price	Air Total CIF	Unit FOB price	Total FOB	Unit CIF price	Air Total CIF
5.1.3 E400	Ethambutol 400 mg film-coated tablets	25,000	10.65		12.03		23 024.04	25 556.68		
	Exchange rate		7.00		7.00		0.0033877	0.0033877		
	Total		74.55	1 863 750.00	84.24	2 106 037.50	78.00	86.58	1 950 000.00	2 164 459.49
	Port of embarkation (air)		Bombay				Milan			
	Port of embarkation (sea)									
	<u>Criteria</u>									
	Pharmaceutical Manufacturer Licence		Dec. 2002				Dec. 2003			
	Marketing licence or WHO Certificate of the product		OK				OK			
	Manufacturing site		OK				OK			
	GMP Certificate		OK				OK			
	Reference pharmacopeia		BP				EP			
	Pharmacopeia: edition		2000				2000			
	Origin of raw materials (active ingredients) DMF, CEP		NG*				OK			
	Bioequivalence		NG*				NG*			
	Stability study		OK				OK			
	Shelf-life		48 months				36 months			
	Samples		OK				OK			
	Delivery time		16 weeks				8-10 weeks			

* NG: not given

3 – Results of the drug tender

The International Union Against Tuberculosis and Lung Disease provides support for a number of NTPs, and purchases anti-tuberculosis drugs on behalf of several of them. This is why it regularly invites drug tenders. The minimum and maximum prices of the last tender are given below, rounded out in Euros. Prices are given as an indication for large quantities, based on a preselection of suppliers who have a reputation for selling products of good quality.

Generic name	Unit dose	Form	Presentation	FOB price per unit of presentation (Euros)	
				Minimum	Maximum
Isoniazid (H)	100 mg	Tablet	Bulk (1000)	2.1	3.3
Ethambutol (E)	400 mg	Scored coated tablet	Bulk (1000)	12.2	22.0
Pyrazinamide (Z)	400 mg	Tablet or capsule	Bulk (1000)	14.3	26.2
Rifampicin + isoniazid {RH}	150 / 75 mg	Tablet or capsule	Bulk (1000)	13.4	15.7
Rifampicin + isoniazid + pyrazinamide + ethambutol {RHZE}	150 / 75 / 400 / 275 mg	Tablet or capsule	Bulk (1000)	36.8	55.7
Thioacetazone + isoniazid {TH}	150 / 300 mg	Coated tablet	Bulk (1000)	6.1	7.8
Ethambutol + isoniazid {EH}	400 / 150 mg	Scored tablet	Blister pack of 10 tablets	13.9	36.6
Streptomycin (S)	1 g	Vial (powder for injection)	1 vial	3.3	9.3

Appendix 1

Suppliers of pharmaceutical products Identification and Information Questionnaire

*developed by Médecins Sans Frontières**

INTRODUCTION

This questionnaire has three parts:

Section I: General and commercial information

Section II: Pharmaceutical information - Wholesaler

Section III: Pharmaceutical information - Manufacturer

How to complete the questionnaire:

If you are an official agent for a pharmaceutical company, you should fill in Section I.

If you are a wholesaler, you should fill in Sections I and II.

If you are a manufacturer, you should fill in Sections I and III.

A “Manufacturer” is defined as a product-licence holder or as a company responsible for the marketing of the product.

Companies with both wholesaler and manufacturing activities should fill in all three sections.

Section II and Section III end with an “Agreement” that must be completed by the identified persons.

If you have a **Site Master File**, you may enclose it in full or in part, and refer to it for certain questions.

Any other relevant appendices or lists can also be included with the questionnaire.

All information provided in this questionnaire will be treated in total confidentiality.

* This questionnaire refers to the following WHO documents: “Technical Report 823”, “Technical Report 863”, “Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials”, Volumes 1 and 2, 1992.

SECTION I

General and commercial information

I.1. SUPPLIER IDENTIFICATION

Name:.....

Address:

.....

Legal status:

Trade Register N°:..... VAT number:.....

Year activities started:

I.2. ACTIVITIES AND LICENCE NUMBERS (*tick relevant box*)

Manufacturer Licence number:(enclose a photocopy)

Wholesaler Licence number:.....(enclose a photocopy)

Official agent of pharmaceutical compan(y)ies:

list of companies:.....

.....

.....

for the domestic market for export

Products:

specialties generics

other medical supplies, please specify:

.....

non-medical supplies, please specify:.....

.....

I.3. PERSONNEL

Number of employees:

Key personnel and positions (*if possible, enclose an organisational chart*):

.....

.....

.....

I.4. TURNOVER IN THE LAST 2 YEARS

Year: Turnover:.....

Year: Turnover:.....

I.5. PRINCIPAL CLIENTS

Please mention principal clients on the domestic market and on the export market (specify type of client: NGO, not-for-profit, public health facilities, private business...)

Name	Type	Client since (year)
.....		
.....		
.....		
.....		
.....		
.....		

I.6. COMMERCIAL CONTACT

Name of export manager:.....

Telephone: Fax:

I.7. STOCK

Do you maintain a permanent stock of anti-tuberculosis drugs? Yes No

Explain if necessary:.....

.....
.....
.....

I.8. AFFILIATES

Name of parent company (if applicable):.....

Names of any subsidiary companies (if applicable):

.....
.....

SECTION II

Pharmaceutical information – Wholesaler

(to be completed by wholesalers only)

II.1. CHIEF PHARMACIST

Name of chief pharmacist:

II.2. QUALITY ASSURANCE MANAGER

Name (if other than chief pharmacist):

II.3. SYSTEM OF QUALITY ASSURANCE

Describe the quality assurance system you use to validate your sources (*or enclose separate documentation if necessary*):

.....

.....

.....

.....

.....

.....

.....

.....

II.4. LABELLING

Do the labels of all of the products sold by your company mention the name of the manufacturer (*licence holder or person responsible for product marketing*)? Yes No

II.5. LICENCES AND CERTIFICATES

Are you able to supply a copy of the marketing licence or the certificate of pharmaceutical product (WHO type) for each of the products proposed? Yes No

If not, what document can you supply?

.....

.....

Are you able to systematically supply a copy of the certificate of analysis for each batch? Yes No

If not, explain why not:
.....
.....

II.6. BATCH TRACING AND RECALL PROCEDURE

Do you trace all batches supplied to your customers? Yes No

Are you able to launch a fast recall procedure in case of problems with a batch? Yes No

Explain if necessary:.....
.....
.....

II.7. GOOD DISTRIBUTION PRACTICES

Do you have a Good Distribution Practices (GDP) Certificate? Yes No

If so, please enclose a copy.

II.8. AGREEMENT

We, the undersigned,

Mr/Ms, **General Manager**
and

Mr/Ms, **Chief Pharmacist**
(*tick relevant box*) **Quality Assurance Manager**

hereby certify that the information provided in this questionnaire is correct.

Date:
.

Signature of the Manager

.
Signature of Chief Pharmacist or Quality Assurance Manager

SECTION III

Pharmaceutical information – Manufacturer

(to be completed by manufacturers only)

Products and licences

III.1. FORMS OF PHARMACEUTICAL PRODUCTS MANUFACTURED *(tick relevant boxes)*

- Oral forms: Tablets
 Solutions or syrups
 Capsules
 Dry powder for oral suspension
 Other:
- Parenteral forms: Liquid (ampoules or vials)
 Intravenous transfusion
 Dry powder for injection
 Other:
- Others: Creams and ointments
 Ophthalmic preparations
 Suppositories
 Lotions or emulsions for external use
 Other:

III.2. REGISTRATION OF ANTI-TUBERCULOSIS PRODUCTS

Please attach a list of those of your products that have a marketing licence for your domestic market and a list of products registered for export. Indicate the registration numbers of the products in each list.

Do you have marketing licences in other countries? Yes No

If yes, attach a list of products and countries.

III.3. CERTIFICATES AND DOCUMENTS

Can you provide WHO-type certificates applicable to all pharmaceutical products in circulation in international commerce? Yes No

If yes, attach an example copy of a certificate.

Production

III.5. INTERNAL PRODUCTION / SUB-CONTRACTING

Are all the stages of manufacture (processing, packaging, labelling) performed by your company on site? Yes No

If not, state which operations are performed externally and by which companies:

.....
.....
.....
.....
.....

III.6. HEAD OF DEPARTMENT OF INTERNAL PRODUCTION (*if relevant*)

Name and qualification of the head of the department of internal production:

Name:

Qualification:

III.7. INTERNAL PRODUCTION LINES (*if relevant*)

Give a brief description of the different internal production lines, with their production capacity:

.....
.....
.....
.....
.....

Are the production sites situated in the same place as the main offices? Yes No

If not, indicate the address of the production site:

.....
.....
.....

Quality management

III.8. PERSON(S) RESPONSIBLE

Name and qualification of the person(s) responsible for batch release:

Name:

Qualification:

III.9. QUALITY MANAGER *(if relevant)*

Name and qualifications of Quality Manager:

Name:

Qualification:

III.10. HEAD OF QUALITY CONTROL DEPARTMENT *(if relevant)*

Name and qualifications of the head of the Quality Control Department:

Name:

Qualification:

III.11. QUALITY CONTROL

Do you perform quality control tests on *(please tick the relevant box)*:

Active raw materials

Intermediate products

Excipient(s)

Bulk products

Packaging materials

Finished products

Are all quality control tests performed internally? Yes No

If not, state which tests are conducted externally and by what laboratory/ies:

.....
.....
.....

III.12. RAW MATERIALS

Explain briefly what method you use to approve the sources of raw materials and their requisite specifications

.....
.....
.....

Do you test each container of active raw materials? Yes No

If not, explain how you do your sampling:

.....
.....
.....

Do you test each container of non-active raw materials? Yes No

If not, explain how you do your sampling:

.....
.....
.....

Are you prepared to reveal (confidentially) the sources of the raw materials to your clients? Yes No

Explain if necessary:

.....
.....
.....

III.13. BATCH FILE

Do you keep a file for each batch? Yes No

Including (*please tick relevant boxes*):

- Batch numbers of raw materials
- Quality control results for the raw materials
- Date and duration of each stage of production
- Identification of equipment used during production
- Names of persons in charge at each stage of production
- Results of intermediary controls
- Results of environmental controls
- Remarks on production incidents
- Comments if the master formula is not followed
- Yield and reconciliation
- Batch numbers for packaging materials
- Quality control results of bulk product
- Quality control results of finished product

Explain if necessary:

.....
.....
.....

III.14. BATCH RELEASE

Explain your method of batch release for finished products:

.....
.....
.....
.....

III.15. STABILITY STUDIES AND SHELF-LIFE

Do you perform stability studies systematically on your products?

Yes No

Explain if necessary:

.....
.....
.....

What type of studies do you perform?

Type: Test conditions:

Accelerated studies

Real time studies

Explain if necessary:

.....
.....
.....

How do you determine the shelf-life of your products?

.....
.....
.....

III.16. BIOEQUIVALENCE

Have you conducted bioequivalence studies for some of your products?

Yes No

If so, list the products and the reference products:

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

III.17. SAMPLING

Do you keep samples of each batch that is marketed?

Yes No

How long do you keep the samples for?

Are they kept in the packaging they are marketed in?

Yes No

III.18. BATCH TRACING AND RECALL PROCEDURES

Do you trace all batches supplied to your clients?

Yes No

Are you able to launch a rapid recall procedure if there is a problem with a batch?

Yes No

Explain if necessary:

.....
.....
.....
.....
.....

III.19. AGREEMENT

I the undersigned,

Mr/Ms, **General Manager**,

hereby certify that the information provided in this questionnaire is correct.

Date:

Signature:

I the undersigned,

Mr/Ms **Person responsible**
for the batch release of finished products, hereby certify that the information given in the sections on “Production” and “Quality Control” is correct.

Date:

Signature:

If relevant:

I the undersigned

Mr/Ms **Quality Control Manager**,

hereby certify that the information given in the sections on “Production” and “Quality Control” is correct.

Date:

Signature:

Appendix 2

Product Questionnaire

developed by Médecins Sans Frontières

Introduction

This questionnaire aims to standardise the product information provided in order to facilitate quality assessment of the products.

Instructions

If your company (the potential supplier) is neither the manufacturer of the product nor the market-licence holder for your own national market, this questionnaire should be filled out and signed by the manufacturer of the product as indicated in Question III. The name of your company should be indicated in response to Question II.

The required documents should be attached to this questionnaire.

Certificate of Pharmaceutical Product

The Certificate of Pharmaceutical Product (CPP) according to the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce should be provided with this questionnaire. The model used should be the most recent format recommended by the WHO.* A copy of a recent CPP (less than 12 months) can be provided provisionally, but an original CPP should be provided before a contract can be awarded. If a CPP can not be obtained, please give the reasons and enclose a copy of the marketing licence.

* See WHO Technical Reports Series N° 863, or <http://www.who.int/medecines/team/qsm/certifscheme.html>

I. PRODUCT IDENTIFICATION

Active ingredient(s) (use international non-proprietary name “INN”):

Trade name of the product (if any):

Dosage form:

tablet capsule ampoule flask other:

Strength per dosage unit:

Route of administration:

oral IM IV SC other:.....

Number of units/volume or weight/package:

50 100 1000 1000 ml other:.....

Type of packaging:.....

II. SUPPLIER IDENTIFICATION

Name:.....

Address:.....

Association with the product:

Marketing licence holder Distributor
 Manufacturer Other:.....

III. PRODUCT MANUFACTURER

Name of manufacturer (or manufacturer under contract), if different from the one given in question II:

Address(es) of manufacture site(s) (*if more than one please list all sites*):

**IV. REGULATORY SITUATION (LICENSING STATUS)
IN THE COUNTRY OF MANUFACTURE**

Product registered and currently marketed Licence n°

- Product registered in the country of manufacturer, but not currently marketed
Licence n°
- Product registered for export only Licence n°
- Product not licensed

V. REGULATORY SITUATION (LICENSING STATUS) IN OTHER COUNTRIES

List the other countries in which the product is registered and where it is currently being marketed:

.....

**VI. CERTIFICATE OF PHARMACEUTICAL PRODUCT
ACCORDING TO WHO CERTIFICATION SCHEME**

see WHO Technical Reports Series N° 863, or
<http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/modcert.html>

- The Certificate of Pharmaceutical Product is attached to the questionnaire
(*the model used should refer to the last format recommended by the WHO*)
- The Certificate of Pharmaceutical Product cannot be obtained by
the National Drugs Regulatory Authorities for the following reasons:
.....
.....

VII. ACTIVE PHARMACEUTICAL INGREDIENT(S)

(If more than one active ingredient is used, please replicate this question)

Active ingredient used (in INN, if any):

- has a Certificate of Conformity with the European Pharmacopeia (CEP).
Certificate N°:
- The CEP is in our possession (including appendices, if any)
- The CEP is in the possession of the manufacturer of the final product (including appendices, if any)
- has a Drug Master File (DMF)
licensed in the following country/ies:
- Licence N°

- The full or open part of the DMF is in our possession
- The full or open part of the DMF is in the possession of the finished product manufacturer.

Manufacturer (name + country):.....

.....

GMP certified: Yes (*attach a copy of the GMP certificate, if any*)
 No Unknown

Certified by:

Manufacturer unknown

Quality standard:

BP edition: EP edition:..... USP edition:

International edition:

Other or additional specifications*:

.....

VIII. SPECIFICATIONS OF THE FINISHED PRODUCT

BP edition: USP edition:..... Other*:

Are you willing to provide the necessary information (analytical methods) for the tests to be replicated by another control laboratory? Yes No

Limits in % for the assay in active ingredient(s):

95-105% 90-110% Other:

Specifications in addition to those in the pharmacopoeia (e.g., dissolution, for injection):.....

.....

Attach a copy of the model certificate of analysis for batch release.

IX. STABILITY

Data on stability testing available: Yes No

Type and conditions of satisfactory testing (no significant change):

accelerated testing 40°/ 75% RH/ 6 months other:

Type of packaging:

Identical to that specified in question I?

Yes No

Explain if necessary:

(*) Attach a copy of the specifications of the active ingredients.

- in different packaging:
- real time testing
 Temperature: ambient 25°C 30°C
 other:.....
- Relative humidity: not controlled 45% 60% 70%
 other:.....
- Time: 1 year 2 years 3 years
 other:.....
- Packaging: Type of packaging:
 Identical to that specified in question I?
 Yes No

X. LABELLING AND INSERT INFORMATION

- Shelf-life: 2 years 3 years 4 years 5 years
 other:.....

Storage conditions (e.g.: “Store below 30°C – protect from light”):

.....

- Language of labelling: bilingual English/French English French
 Other:.....

Attach a copy of the label

- Package insert: Yes (*attach a copy*) No

XI. THERAPEUTIC EQUIVALENCE

- demonstrated by *in vivo* bioequivalence study*
 Reference product:
 Number of volunteers: Year performed:
 Country of study:
- demonstrated by another method:
- Reference product:
- not demonstrated N/A

*Attach a copy of the study if it includes rifampicin.

XII. MISCELLANEOUS

Normal batch size:

XIII. AGREEMENT

I, the undersigned,,
.....(*position in the company, e.g.,
General Manager, Authorised Person, * Chief Pharmacist*), acting on behalf
of the company(*name of the
manufacturer or name of the holder of the marketing licence of the coun-
try of origin*), hereby certify that the information contained in this ques-
tionnaire is correct and truthful,

and I certify that the proposed product is identical in all aspects of man-
ufacture and quality to the product marketed in
(*country of origin*), including formulation, method and site of manufacture,
sources of active and excipient raw materials, quality control of the prod-
uct and of the raw materials, packaging, shelf-life and product notice,

and I certify that the product proposed is identical to the product mar-
keted in (*country of origin*), except:
.....

(e.g.: formulation, method and site of manufacture, sources of active raw
materials and excipients, quality control of the product and of the raw mate-
rials, packaging, shelf-life, indications and product notice).

Date:.....

Signature:.....

* See WHO publication: "Technical report 823" or "Quality Assurance of
Pharmaceuticals, compendium of guidelines and related materials" vols 1 & 2, 1992).

Appendix 3

Model list of conditions that need to be fulfilled in order to register a generic drug

	Conditions
1	Letter of submission
2	Marketing licence in the country of origin, or, if absent, WHO Certificate
3	List of countries where the product is registered
4	Copy of the contract between the manufacturer and the wholesaler, distributor or agent
5	Dosage form and batch
6	Technical specifications for raw materials
7	Certificates of analysis of raw materials
8	Certificates of analysis of final products
9	Technical specifications for final products
10	Complete description of the methods used, the site and the quality control of the manufacture and the packaging
11	Details of quality control procedures for the final products with the results of the analysis
12	Detailed report of stability studies justifying the expiry date
13	Samples in sufficient quantity of the drug marketed (or to be marketed) for testing by our services
14	Examples of all labelling and packaging: label, box, product notice, blisterpack/strip
15	For imported products: a) Certificate of free circulation in the country of origin b) Pharmaceutical manufacturer licence delivered by the government of the country of origin
16	For products in a plastic container: 1) Study confirming the conformity of the plastic for this usage: <ul style="list-style-type: none"> • Composition of the plastic used • Chemical tests • Physical tests • Biological tests • Methodology of the tests, results of the tests indicating limit values 2) Samples of empty containers and their lids
17	Bioavailability/bioequivalence studies

Appendix 4
Model of the WHO certificate applicable
to all pharmaceutical products circulating
in the international market
(WHO 1996, 34th report, n° 863)

Specimen Certificate of a Pharmaceutical Product

Certificate of a Pharmaceutical Product¹

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

No. of Certificate:.....
Exporting (certifying) country:.....
Importing (requesting) country:

1. Name and dosage form of product:

.....

1.1 Active ingredients² and amount(s) per unit dose.³

.....
.....
.....

For complete qualitative composition including excipients, see attached.⁴

1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2 Use, whenever possible, international non-proprietary names (INNs) or national non-proprietary names.

3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4 Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-licence holder.

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

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

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

2A.1 Number of product licence⁷ and date of issue:

.....

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

.....
.....
.....

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

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹

.....
.....
.....

5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

6 Sections 2A and 2B are mutually exclusive.

7 Indicate, when applicable, if the licence is provisional or if the product has not yet been approved.

8 Specify whether the person responsible for placing the product on the market:
(a) manufactures the dosage form;
(b) packages and/or labels a dosage form manufactured by an independent company;
or
(c) is involved in none of the above.

9 This information can be provided only with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence must be updated or it will cease to be valid.

2A.4 Is Summary Basis of Approval appended?¹⁰ yes/no (*key in as appropriate*)

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

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

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

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

2B.2.1 For categories b and c the name and address of the manufacturer producing the dosage form are:⁹

.....
.....
.....

2B.3 Why is marketing authorisation lacking?

Not required/not requested/under consideration/refused (*key in as appropriate*)

2B.4 Remarks:¹³

10 This refers to the document, prepared by some national regulatory authorities, that summarises the technical basis on which the product has been licensed.

11 This refers to product information approved by the competent national regulatory authority, such as a Summary of Product Characteristics (SPC).

12 In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission must be provided to the authority by the applicant.

13 Please indicate the reason that the applicant has provided for not requesting registration:

(a) The product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the country of export.

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

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

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

(e) Any other reason, please specify.

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?

yes/no/not applicable¹⁴ (*key in as appropriate*)

If no or not applicable, proceed to question 4.

3.1 Periodicity of routine inspections (years):

3.2 Has the manufacture of this type of dosage form been inspected?

yes/no (*key in as appropriate*)

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization?¹⁵

yes/no/not applicable¹⁶ (*key in as appropriate*)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?¹¹

yes/no (*key in as appropriate*)

If no, explain:.....

.....
Address of certifying authority:

Telephone number: Fax number:.....

Name of authorised person:

Signature:.....

Stamp and date:

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

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

16 This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 7 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

The layout for this Model Certificate is available on diskette in WordPerfect from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

General instructions

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

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

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

Appendix 5

Conditions for purchasing through the Global Drug Facility

The “Global Drug Facility” (GDF) provides aid only for those countries with a GNP of less than US \$1.000 per capita, an incidence rate of tuberculosis (all forms) higher than 100 per 100 000 population and a national plan to develop the DOTS strategy.

To obtain aid from the GDF, the following criteria must be fulfilled:

- a. The country must have an anti-tuberculosis programme in place that is based on the DOTS strategy, in accordance with WHO guidelines.
- b. Mechanisms should be in place to guarantee the high quality of any anti-tuberculosis drugs obtained through channels other than those of the GDF.
- c. There is an agreement on the import licence and the tax exemption for the anti-tuberculosis drugs provided by the GDF.
- d. There is an agreement to accelerate the drug registering procedures.
- e. There is an agreement for an independent review of the performance of the programme.
- f. There is an agreement to transfer the funds that would have been used for purchasing drugs to other activities allowing the DOTS strategy to be expanded.

The form to be filled out can be requested from the following address:

Stop TB Partnership Secretariat (CDS/STB)
20, avenue Appia
1211 Geneva, 27
SWITZERLAND

Appendix 6

Conditions for obtaining second-line drugs with the help of the Green Light Committee

A working group on DOTS-Plus was constituted between different partners, including the WHO, to approve, direct and monitor pilot projects set up to manage multidrug-resistant tuberculosis cases – i.e., resistant to at least rifampicin and isoniazid. These projects must follow the guidelines given in the brochure entitled “Guidelines for establishing Dots-Plus pilot projects for the management of multidrug-resistant tuberculosis (MDR-TB)” (World Health Organization 2000, WHO/CDS/TB/2000.279).

One of the problems posed by multiresistant cases is the very high cost of the second-line drugs that are used to treat them – a drug protocol that comes to more than US \$10,000. The working group has negotiated preferential prices with the manufacturers that are incomparably lower than those on the open market.

In order to gain access to these concessional tariffs, it is necessary to submit an application to the Green Light Committee, which is responsible for reviewing each request and, as its name indicates, grants or refuses its authorisation for the applicant to purchase second-line drugs at the preferential price negotiated.

For the request to be considered, the project must:

- show that the DOTS strategy has been implemented and is functioning correctly
- provide proof of the government’s commitment and the availability of funding
- have developed a coordinated management plan for the project
- have determined a rational treatment strategy
- have developed a well-functioning system of data collection

A form can be filled out following the instructions given in the document “Application to the Green Light Committee, *Instruction manual*”. This document is available from the following website address:

<http://www.who.int/gtb/policyrd/DOTsplus.htm>

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Further reading

- Marketing authorization of pharmaceutical products with special reference to multi-source (generic) products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No. 5 (WHO/DMP/RGS/98.5). Geneva, Switzerland: World Health Organization, 1999.
- WHO technical reports 823 and 863 on Quality Assurance for Pharmaceuticals, vol 1 & 2. Geneva: WHO, 1992.
- Managing drug supply. Quick JD, Rankin JR, Laing RO, O'Connor RW, Hogerzeil HV, Dukes MNG, Garnett A, eds. 2nd ed. West Hartford, Connecticut, USA: Kumarian Press, 1997.

References

- 1 Enarson D A, Rieder H, Arnadottir Th, Trébuq A. Management of tuberculosis. Guide for low income countries. 5th ed. Paris: UICTMR, 2000.
- 2 Assuring bioavailability of fixed-dose combinations of anti-tuberculosis medications. Official IUATLD/WHO joint statement. *Int J Tuberc Lung Dis* 1999; 3 (Suppl 3): S282-S283.
- 3 Quality assurance: protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers. *Int J Tuberc Lung Dis* 1999; 3 (Suppl 3): S284-S285.
- 4 Crofton J, Chaulet P, Maher D, Grosset J, Harris W, Horne N, Iseman M, Watt B. Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210 Geneva: WHO, 1998.