PROPOSAL FOR A PROCEDURE ON SAMPLING AND MARKET SURVEILLANCE SURVEY

(JULY 2012)

DRAFT FOR COMMENTS

Please address any comments on this proposal by 5 October 2012 to Dr S. Kopp, Medicines Quality Assurance Programme, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int with a copy to gaspardm@who.int and to bonnyw@who.int.

We will now send out our working documents electronically and they will also be placed on the Medicines web site for comment. If you do not already receive our documents please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

Please send any request for permission to:

Dr Sabine Kopp, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/12.510: PROPOSAL FOR A PROCEDURE ON SAMPLING AND MARKET SURVEILLANCE SURVEY

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey and feedback from national organizations and nongovernmental</td>
<td>June-September 2011</td>
</tr>
<tr>
<td>organizations</td>
<td></td>
</tr>
<tr>
<td>Presentation to forty-sixth meeting of the WHO Expert Committee</td>
<td>9-12 October 2011</td>
</tr>
<tr>
<td>on Specifications for Pharmaceutical Preparations</td>
<td></td>
</tr>
<tr>
<td>Expert Committee recommendation to develop sampling procedure</td>
<td>October 2011</td>
</tr>
<tr>
<td>(WHO Technical Report Series, No. 970)</td>
<td></td>
</tr>
<tr>
<td>Proposal for a procedure on sampling and market surveillance</td>
<td>August 2012</td>
</tr>
<tr>
<td>Working document sent out for comment</td>
<td>September 2012</td>
</tr>
<tr>
<td>Collation of comments</td>
<td>September-October 2012</td>
</tr>
<tr>
<td>Presentation to forty-seventh meeting of the WHO Expert Committee</td>
<td>October 2012</td>
</tr>
<tr>
<td>on Specifications for Pharmaceutical Preparations</td>
<td></td>
</tr>
<tr>
<td>Any further action as necessary</td>
<td>…</td>
</tr>
</tbody>
</table>
Following the recommendation of the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-sixth meeting in October 2011, i.e.

“Sampling procedures for monitoring of market situations
Continue development of sampling procedures based on the numerous examples obtained from many countries as feedback to the secretariat’s communications.”

internal discussions took place to propose a new guidance on sampling and market surveillance survey.

In view of the fact that colleagues from the WHO Prequalification Laboratory Programme have been extensively involved in the establishment of survey protocols for major studies for antimalarials and antituberculosis medicines, it is proposed to use the approach described in Annex 1 as a basis for a general guidance document.

A similar approach has been applied for the antituberculosis study which is attached for reference only (Appendix 1).

It would be appreciated if you would comment as to:

1. Whether you find this approach acceptable.
2. Whether it should be used in a more general manner.
3. Whether it should be used for a specific group of medicines, such as the antimalarials, antituberculosis, etc.;
4. In addition, we would like your feedback as to whether you would suggest the further development of a general guidance to specifically investigate for spurious/falsely-labelled/falsified/counterfeit medical products.
Recommendations on the content of a Survey protocol

Survey of the quality of antimalarial medicines

A Survey protocol may follow chapters as suggested below or may be appropriately modified.

Explanatory notes are in italics.
## CONTENTS

1. Introduction and background ................................................................. 6
2. Glossary of terms and abbreviations ........................................................ 6
3. Objectives ............................................................................................... 6
4. Survey management ................................................................................. 8
5. Methodology ............................................................................................ 9
   5.1 Participating countries ........................................................................ 9
   5.2 Medicines surveyed ........................................................................... 9
   5.3 Selection of sample collection sites ....................................................... 9
   5.4 Sample collection .............................................................................. 12
   5.5 Storage and transport of samples ......................................................... 13
   5.6 Testing laboratory ............................................................................. 13
   5.7 Tests conducted ............................................................................... 14
   5.8 Test methods and specifications ......................................................... 15
   5.9 Receipt and testing of samples by a testing laboratory ......................... 15
6. Data management, reporting and publication ........................................... 16
Annex 1 ........................................................................................................ 17
Annex 2 ........................................................................................................ 19
Annex 3 ........................................................................................................ 21
Annex 4 ........................................................................................................ 23
1. **INTRODUCTION AND BACKGROUND**

Provide information about situation in the territory, where the monitoring is planned. It is a basis for setting objectives of the survey.

2. **GLOSSARY OF TERMS AND ABBREVIATIONS**

- **ACT** Artemisinin-based combination therapy products
- **API** active pharmaceutical ingredient
- **BP** British Pharmacopoeia
- **FDC** Fixed-dose combination
- **INN** International Nonproprietary Name
- **NDRA** national drug regulatory authority
- **Ph.Int.** *The International Pharmacopoeia*
- **QCL** quality control laboratory
- **USP** United States Pharmacopeia
- **WHO** World Health Organization

3. **OBJECTIVES**

It is very important to set detailed objectives in the beginning of planning because all the activities and requirements for the survey are derived from the objectives. Clearly defined objectives are essential for setting up conditions for sampling and testing, which are reflected in the protocol of the survey. Objectives for a quality survey should be formulated in a way, which makes possible to identify the following:

- **products to be surveyed** – it is possible to characterize them, e.g.
  - by active ingredients (e.g. ACTs, sulfadoxine/pyrimethamine, ...), or
  - by manufacturer (specific manufacturer, if he poses some problems, or domestically produced medicines or imported medicines focusing on selected manufacturers, ...), or
  - by specific programme under which they are supplied (The Global Fund grant, national programme, ...), or
  - as widely used (then a pre-survey of medicines on the market may be necessary before the survey can be planned);

- **types of sample collection sites** - which may be specified as, e.g.
  - close to patients – covering manufacturing quality as well as possible influence of distribution and storage conditions on medicines quality, or
  - at points of entry to the market – excluding possible influence of distribution and storage conditions on medicines quality, or
  - at a specific manufacturer, if he poses some problems;

- **countries in which the survey will be performed** should be identified
conduct in more countries in the region according to the same survey protocol can bring broader picture of quality of medicines in the region and enable comparison.

Examples:

- to evaluate pharmaceutical quality of ACT medicines close to patients in selected countries with the aim to assess exposure of patients to substandard medicines and plan appropriate actions;
- to monitor pharmaceutical quality of selected antimalarial medicines supplied under The Global Fund grant as required by the Global Fund Quality assurance policy;
- to compare pharmaceutical quality of domestically produced medicines with imported ones in order to adopt appropriate regulatory actions and adjust pharmaceutical policy in the country;
- to identify possible causes of inferior quality of ACT medicines to which patients are exposed. To propose possible strategies and implementation plans to address the problems identified by the survey:
  - close cooperation with national drug regulatory authorities is normally necessary to address these two questions;
- test quality of ACT medicines in order to support regulatory authority in identification of manufacturers non-compliant with quality standards and in adoption of regulatory measures;
- to evaluate content of the information accompanying collected products on labelling and/or in package leaflets:
  - if products from various suppliers are collected, it may be useful to evaluate if package leaflets are available and evaluate the quality and completeness of essential information in the following parts of package leaflets
    - indications
    - dosage and administration
    - contraindications
    - other important warnings (which may be under various headings, e.g. special warnings and precautions for use, interactions, pregnancy and lactation)
    - undesirable effects (to look at, e.g. the five most important adverse reactions).

Questions to be addressed in the survey should be clearly formulated, e.g.:

- What proportion of samples fails quality testing?
- What proportion of samples at different points of the regulated and informal distribution chain fails quality testing?
- What proportion of samples at different geographical regions fails quality testing?
- What proportions of sampled domestically produced and imported products fail quality testing?
- Which specific quality tests do the samples fail?
- Are any of the deficiencies critical, i.e. could they substantially affect treatment efficiency and/or cause harm to the patient?
What is the registration status of sampled products and what proportions of registered and non-registered products fail quality testing?

What is the WHO Prequalification status of sampled products and what proportions of registered and non-registered products fail quality testing?

4. SURVEY MANAGEMENT

Responsibilities and tasks of persons having key roles in survey organization (e.g. survey coordinator, focal persons in individual countries) should be identified and should include also responsibility for monitoring of conduct of the survey, for processing results, preparation of report. Communication lines and means should be agreed in advance.

It is necessary to plan the financial resources expected for the whole survey in the beginning.

The survey period with key milestones and organizations/persons responsible for individual parts should be predefined together with estimated timeframe.

Timeframe and responsible officers for the survey (as an example)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Timeframe</th>
<th>Responsible officers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of countries and medicines to be surveyed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement with countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of testing laboratory/ies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation of testing protocol in agreement with testing laboratory/ies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting held with focal points from countries to explain the survey protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation of detailed national sampling plans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of samples and transport to testing laboratory/ies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing of samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compilation of results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting held with the participating countries to discuss the results and the actions needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Report finalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. METHODOLOGY

5.1 Participating countries

Each involved country (Ministry of Health/National Drug Regulatory Authority) should agree with the participation before the survey commences. Issues like utilization of results and their public availability should be clearly understood by responsible authorities and all the parties involved in the survey.

5.2 Medicines surveyed

Based on the objectives of the survey, medicines to be sampled (active ingredient/s, dosage form, strength) should be listed. It is reasonable to formulate the objectives and organize the survey in a way to focus on medicines:

- For which inferior quality has documented serious implications for the health of patients
- Used in large volumes
- Susceptible to quality deterioration (unstable active ingredients, liquid dosage forms, ...)
- For which quality problems were already experienced.

Not more than 5 different types of products (identified by active ingredient/s and dosage form) should be included in one survey, otherwise the project would be difficult to manage.

5.3 Selection of sample collection sites

Based on the objectives of the survey, the types of sample collection sites should be identified, e.g.:

- If samples should be collected close to patients and manufacturing quality as well as possible influence of distribution and storage conditions on medicines quality should be covered, then:
  - Sampling should be performed in hospitals, clinics, treatment centres, pharmacies, retailers, dispensing facilities, ... (depending on the distribution system for given medicines in the particular country) - both public and private sector should be included - as well as at “informal market” (i.e. outside the approved distribution chain), if exists in the country.
  - For estimation of possible influence of distribution and storage conditions on medicines quality, approx. 10-15% proportion of samples should be collected also at points of entry to the market, i.e. at domestic manufacturers, importers and central medical stores.
- If samples should be collected at points of entry to the market, excluding (from reasons defined in objectives of the survey) possible influence of distribution and storage on medicines quality, then
Sampling should be performed at domestic manufacturers, importers and central medical stores, i.e. the first level of the distribution chain.

*It is advantageous to organize a meeting with participation of focal persons involved in sample collection to explain the project, survey protocol and provide detailed instructions.*

A detailed national sampling plan will be prepared for collection of samples in each participating country in cooperation with the respective NDRA.

**Definition of a sample** – for the purposes of the survey, a sample means an item collected from each presentation at the same collection site. All units of one sample must be of the same batch. That means, that an identical product (the same name, content of APIs, the same dosage form, same strength, same batch and produced by the same manufacturer) collected in two different sites represents two samples.

National sampling plan will identify:

- Names and addresses of the sites, where samples shall be collected
  - The risk analysis should be applied when selecting sample collection sites to assure that sites, where quality deterioration can occur, are involved. It should consider way of product distribution to the site, transport conditions, storage conditions and handling products in the site, experience of the NDRA with the distribution chain and sites.
  - Different geographical areas, preferably those of high malaria prevalence, should be involved. Samples should not be collected in the capital city only, as situation in other areas often differs.
  - To obtain a better picture of quality of medicines available on the market (if required by objectives of the survey), samples produced by as many manufacturers as possible should be collected at sampling sites. In order to collect samples from more manufacturers it may be necessary to visit more sampling sites.
- Identification of medicines to be collected (active ingredients by INNs, dosage form, strength, number of batches from one manufacturer to be collected in each site and number of units to be collected per batch of each medicine)
  - Number of dosage units or multidose packages of selected medicines to be collected should allow for:
    - conducting the agreed tests,
    - possible confirmative testing due to out-of-specification investigations,
    - retention samples.
The following general rules can be used, if not justified otherwise:

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Packaging (typical)</th>
<th>Number of dosage units or multidose packs per batch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets &amp; capsules</strong></td>
<td>Blisters, co-blisters, bottles, securitainers</td>
<td>Approx. 100 units</td>
</tr>
<tr>
<td>(immediate/modified release, chew, dispersible, etc.)</td>
<td></td>
<td>(e.g. 5 packs of 20 units)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 packs of 30 units</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 packs of 40 units</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 packs of 60 units</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 pack of 90 units and above)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In case of co-packaged products approx. 100 units shall be collected from each medicine.</td>
</tr>
<tr>
<td><strong>Multidose</strong> oral solutions/suspensions, powder for oral solution/suspension &amp; injections or powders for injections</td>
<td>Multidose bottles and vials</td>
<td>6 containers of 60 ml / 100 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 containers of 240 ml</td>
</tr>
<tr>
<td><strong>Single dose</strong> powders for oral solution/ suspension &amp; single dose injections or powders for injections</td>
<td>Sachets and single dose bottles, vials &amp; ampoules</td>
<td>Unless otherwise specified, 15 units (20 units if dose is below 50 mg)</td>
</tr>
</tbody>
</table>

- The collection of sufficient number of units per sample is very important for proper testing and successful conduct of the survey. It should be remembered that sampling cannot lead to the shortage of medicines available for patients.

- Maximum number of samples collected per country
  - Testing of approximately 300 samples per survey is manageable (not taking into account financial resources, which may be another limiting factor). Therefore the maximum number of samples to be collected should be set before sample collection starts. If more countries are involved, maximum number of samples should be set for each country.

For the example of a national sampling plan see Annex 1.

The focal person will arrange for training of collectors to be familiar with the project, survey protocol, national sampling plan and instructions for collection of samples.
5.4 Sample collection

Samples should be collected by the NDRAs staff (preferably inspectors or staff trained for sampling of medicines). Cooperation with the WHO country offices staff in the respective country is useful.

The following instructions for sample collection shall be applied:

• The time period, within which samples should be collected in the countries and the deadline for sending the last sample to the testing laboratory, should be clearly indicated and followed.
• The number of units per sample and number of batches to be collected from each collection site for each selected medicine as indicated in the national sampling plan shall be followed. There should not be a mix-up with batches; all units of one sample must be of the same batch. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.
• Only intact unopened original packages shall be collected.
• The medicine samples should not be taken out of the original primary packaging and outer containers (though removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened.
• Samples collected should have at least six months remaining to expiry.
• The medicine labels and package leaflets should not be removed or damaged.
• Sampling will be recorded using the Sample Collection Form individually for each sample (Annex 2). Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.
• In order to avoid confusion, each sample will be identified by a unique Sample Code (coding system shall be defined in the Sample Collection Form template) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
• Manufacturer’s batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.
• The samples should be collected and kept under controlled conditions, as per label requirement. The cold chain should be maintained, where required.

If needed, the appropriate arrangements shall be made with treatment centres to ensure that there is no shortage due to collection of samples (e.g. requesting for replacements of medicines).
5.5 Storage and transport of samples

Storage and transport of the sample should be done according to the requirements set out in paragraph 2.3 of WHO Guidelines for Sampling of Pharmaceutical Products and related materials:\(^1\):

- The samples should be kept in original packaging and under storage conditions specified on the label.
- For transport all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport. Any residual space in the container should be filled with a suitable material. Where required, the cold chain should be retained during storage and transport.
- A covering letter, the copies of Sample Collection Form and, if available, copies of Manufacturer’s batch certificate of analysis should accompany the samples.
- Samples with the accompanying documents should be sent straightforward to the assigned testing laboratory by a courier service. For each shipment it should be clearly indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. Low price just for customs purposes should be indicated to avoid problems with the customs clearance.
- The laboratory should be informed about the shipment and the tracking number as provided by the courier service to be able to follow the shipment and pick it up as soon as possible.
- Copies of Sample Collection Forms and, if available, copies of Manufacturer’s batch certificates of analysis should be sent also to survey coordinator/person preparing the report on the survey.

5.6 Testing laboratory

An appropriate laboratory has to be selected for testing. Preferably a prequalified laboratory should be used (see the list of WHO-prequalified laboratories at [www.who.int/prequal](http://www.who.int/prequal)). Should such a laboratory not be available or should it not have sufficient capacity, then another laboratory, for which evidence of reliability is available, should be chosen.

The appropriate arrangement with the laboratory has to be made in advance to give the laboratory time to be ready for testing (find the appropriate time slots, purchase necessary materials and standards, ...). The request for testing should be in line with WHO guideline: Considerations for requesting analysis of drug samples\(^2\) and no sample will be sent before such an arrangement is made. A contract with the laboratory should be concluded in advance to allow the laboratory to prepare for testing.

---


Detailed address of the laboratory selected for the survey shall be provided to sampling organization. If there are more laboratories involved, clearly specify products which should be sent to each laboratory.

<table>
<thead>
<tr>
<th>Name of the laboratory</th>
<th>Detailed address, incl. name of contact person, phone number and e-mail</th>
<th>Products to be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The laboratory normally starts testing only when all the samples are received. Therefore it is important to set and adhere to the deadline for sending to the testing laboratory.

5.7 Tests conducted

Laboratory testing of all collected samples will be performed according to the testing protocol, which is a part of the survey protocol and has to be agreed with the testing laboratory/ies.

- Tests to be conducted depend again on the objectives of the respective survey. For example of testing protocol see Annex 3.

In principle the following tests should be included in quality surveys of products on the market:

- Appearance
- Identity
- Assay
- Related substances test
- Dissolution or Disintegration and Uniformity of mass for (solid dosage forms, e.g. tablets, capsules)
- pH value for liquid dosage forms (e.g. oral solutions, injections, powders for injection)

Some tests, such as Uniformity of content for single dose dosage forms or sterility and bacterial endotoxins for parenteral products are not normally included in quality surveys of products on the market, unless there is a specific reason to include them. These tests are costly and to assure these parameters there are other more efficient tools in medicines regulation, namely inspections and enforcement of compliance to good manufacturing practices (GMP).
To monitor pharmaceutical quality of medicines, it is recommended to perform testing in QC laboratory as described above and not only screening using some basic tests and simple methods (such as GPHF-Minilab). Screening methods do not provide full picture of quality of medicines and, as shown in QAMSA study, often underestimate non-compliant findings in comparison with laboratory testing. Basic tests and simple screening methods are more suitable for screening of large number of samples in the field, e.g. to search for counterfeits.

5.8 Test methods and specifications

Test methods and specifications are in general selected according to the following rules:

- Preferably Ph.Int. monographs should be used, if available.
- If no monograph exists in the Ph.Int., then BP or USP can be used.
- If there is no pharmacopoeial monograph or the existing monographs do not provide for desired tests, a validated method of the laboratory or manufacturer's method, if available, should be used.

For the example of testing protocol used in QAMSA study for ACTs and Sulfadoxine/Pyrimethamine see Annex 3.

In general, when samples from different manufacturers are collected within a quality survey, all samples containing the same combination of active ingredients are tested according to the same specification to enable comparison of samples from different manufacturers. This specification is then used to decide on compliance or non-compliance of tested samples for the purposes of this survey. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products and these specifications and methods may be approved by regulatory authorities in individual countries. Non-compliance with the specification selected for the survey does not necessarily imply non-compliance with the specifications approved in the country. But it indicates the need to look at the product and conditions of regulatory approval more closely and further actions should be considered by the respective NDRA.

5.9 Receipt and testing of samples by a testing laboratory

When samples received, the testing laboratory will:

- Inspect each sample to ensure that the labelling is in conformance with the information contained in the Sample Collection Form or test request.
- Store the samples according to the respective medicine requirements. If appropriate, ensure compliance with the cold chain.
• Conduct quality testing in line with the testing protocol and in compliance with WHO standards recommended for quality control laboratories³.
• Complete an Analytical Test Report (Annex 4). In the case that non-compliant results are found and confirmed after application of a laboratory out-of-specification procedure, they have to be reported immediately to the contact point⁴.
• Keep records of each sample, accompanying document/s and retention samples for at least six months if the sample complied with the analytical test requirements, or for at least one year or until the expiry date (whichever is longer) if it did not comply.
• An electronic databank (e.g. photos of medicine such as tablets, packaging, package leaflet) is recommended.

6. DATA MANAGEMENT, REPORTING AND PUBLICATION

About any non-compliant result the respective NDRA will be informed as soon as possible and it should be investigated in line with regulatory practice and legislation with the respective manufacturer.

The analytical test reports of the testing laboratory/ies will be provided to all NDRA involved in the project. The outcomes of the project will be discussed by national authorities and WHO in a meeting, and corrective actions, if necessary, will be recommended. To take the relevant measures in countries lies within the responsibility of the NDRA.

Agreed outcomes and report from the survey should be reviewed and published by WHO. It should be remembered that non-compliant result not necessarily indicate sub-standard medicine and deviation from manufacturer's specifications.

⁴ Specify the contact point.
ANNEX 1

Survey of the quality of antimalarial medicines …………

National Sampling Plan

Country: _____________________ Focal Person: ________________________

MEDICINES TO BE COLLECTED:

• INN(s), dosage form, strength

NUMBER OF UNITS TO BE COLLECTED PER SAMPLE:

• Approx. 100 units for tablets/capsules

TOTAL NUMBER OF SAMPLES PER COUNTRY:

NAMES AND ADDRESSES OF THE SITES, WHERE SAMPLE SHALL BE COLLECTED:

<table>
<thead>
<tr>
<th>Facility name</th>
<th>Address</th>
<th>Facility type</th>
</tr>
</thead>
</table>
|               |         | 1. (private/public; level 1/level 2; wholesaler/retailer/treatment centre/…)
| 1.            |         |               |
| 2.            |         |               |
| 3.            |         |               |
| 4.            |         |               |
| 5.            |         |               |

INSTRUCTIONS FOR COLLECTORS
• The amount of the selected products defined above will be sampled from the identified sites. All these samples are inclusive of the samples needed for the out-of specifications investigations and retention samples.

• An item collected from each presentation at the same collection site will be called a sample. All units (tablets, capsules, vials) of one sample must be of the same batch, there should not be a mix-up with batches. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.

• Samples collected shall have at least six months remaining to expiry. Products with shorter period remaining to expiry date are not collected.

• One batch of each product will be collected from each collection site and only unopened original packages shall be collected.

• The medicine samples should not be taken out of the original primary packaging and outer containers (though removal of blisters from large secondary packs is appropriate). Containers such as bottles and vials should not be opened.

• The medicine labels and package leaflets should not be removed or damaged.

• Sampling will be recorded using the Sample Collection Form. Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.

• In order to avoid confusion, each sample will be identified by a unique Sample Code (for coding system see the Sample Collection Form) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).

• Manufacturer’s batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.

• The samples should be collected and kept under controlled conditions, as per label requirement. The cold chain should be maintained, where required.

• Samples should be collected in all the countries involved within the period ………. and the deadline for sending the last sample to the testing laboratory is ……….
ANNEX 2

Survey of the quality of antimalarial medicines  

Sample Collection Form*

**Country:** __________________________

**Sample code:** __________________________

(Country code/product abbreviation/sequence
number/sampling date ddmmyy)**

Name of location/place where sample was taken: ____________________________________________

Address (with telephone, fax number and email address, if applicable):

__________________________________________________________________________________

__________________________________________________________________________________

Organization and names of people who took samples:

1. __________________________________________

2. __________________________________________

**Product name of the sample:** __________________________

**Name of active pharmaceutical ingredient(s) (INN) with strength:**

__________________________________________________________________________________

**Dosage form (tablet, capsule, powder for injection, etc.):** __________________________

**Package size, type and packaging material of the container:** __________________________

__________________________________________________________________________________

**Batch/lot number:** __________________________

**Date of manufacture:** __________________________  **Expiry date:** __________________________

**Regulatory status in the country, registration number, if applicable:**

__________________________________________________________________________________

**Name and address of the manufacturer:** __________________________

__________________________________________________________________________________

**Quantity collected (number of sample units or of multidose containers taken):**

__________________________________________________________________________________

* This Sample Collection Form should always be kept with the sample collected. Proper sampling procedures should be followed.

** Product abbreviations: …….. . Sample code system can be extended to be appropriate for a particular country collection system.
Storage/climatic conditions at sampling site/point (temperature and humidity, indication of conditions during daytime only is acceptable, comments on suitability of premises where products are stored at the particular site for the NDRA information):


Abnormalities, remarks or observations that may be considered relevant, if any:


Date:

Signature of person(s) taking samples

Signature of representative of the establishment where sample(s) was taken (optional)

1. ..............................................................

2. ..............................................................

Note: Samples collected must remain in their original containers, intact and unopened
### ANNEX 3

Survey of the quality of antimalarial medicines ……………

#### TESTING PROTOCOL

<table>
<thead>
<tr>
<th>Product</th>
<th>Tests to be performed and specifications for testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether/ Lumefantrine tablets FDC</td>
<td>International Pharmacopoeia monograph</td>
</tr>
<tr>
<td></td>
<td>• Appearance - general requirements of Ph.Int. for tablets</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass – Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
</tr>
<tr>
<td></td>
<td>• Assay – Ph.Int. - HPLC</td>
</tr>
<tr>
<td></td>
<td>• Artemether related substances – Ph.Int. - TLC</td>
</tr>
<tr>
<td></td>
<td>• Dissolution - laboratory validated method similar to the method used for Lumefantrine and Artemether tablets in USP Non–US Monograph (authorized 1.3.2009);</td>
</tr>
<tr>
<td></td>
<td>Requirements: lumefantrine - not less than 60% (Q) in 45 min,</td>
</tr>
<tr>
<td></td>
<td>artemether - not less than 40% (Q) in 1 hour and not less than 60% (Q) in 3 hours.</td>
</tr>
<tr>
<td>Artesunate / Amodiaquine tablets Co-blistered</td>
<td>Artesunate tablets:</td>
</tr>
<tr>
<td></td>
<td>International Pharmacopoeia monograph</td>
</tr>
<tr>
<td></td>
<td>• Appearance - general requirements of Ph.Int. for tablets</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass – Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
</tr>
<tr>
<td></td>
<td>• Assay – Ph.Int. - HPLC</td>
</tr>
<tr>
<td></td>
<td>• Artesunate related substances – Ph.Int. - HPLC</td>
</tr>
<tr>
<td></td>
<td>• Dissolution - Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>Amodiaquine tablets:</td>
</tr>
<tr>
<td></td>
<td>US Pharmacopeia monograph</td>
</tr>
<tr>
<td></td>
<td>• Appearance - general requirements of Ph.Int. for tablets</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass - PhInt</td>
</tr>
<tr>
<td></td>
<td>• Identity - USP</td>
</tr>
<tr>
<td></td>
<td>• Assay - USP - UV spectrophotometry</td>
</tr>
<tr>
<td></td>
<td>• Dissolution - USP</td>
</tr>
<tr>
<td>Artesunate / Amodiaquine tablets FDC</td>
<td>Laboratory validated methods</td>
</tr>
<tr>
<td></td>
<td>• Appearance - general requirements of Ph.Int. for tablets</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass – Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
</tr>
<tr>
<td></td>
<td>• Assay - HPLC; 90-110%</td>
</tr>
<tr>
<td></td>
<td>• Artesunate-related substances - tested without specifications</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Sulfadoxine/</td>
<td>Dissolution - not less than 75% of each API at 30 minutes</td>
</tr>
<tr>
<td>Pyrimethamine tablets FDC</td>
<td>US Pharmacopeia monograph</td>
</tr>
<tr>
<td></td>
<td>• Appearance - general requirements of Ph.Int. for tablets</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass – Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC</td>
</tr>
<tr>
<td></td>
<td>• Assay - USP - HPLC</td>
</tr>
<tr>
<td></td>
<td>• Dissolution - USP</td>
</tr>
<tr>
<td>Sulfamethoxypyrazine/</td>
<td>Manufacturer validated methods</td>
</tr>
<tr>
<td>Pyrimethamine tablets FDC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Appearance - package leaflet</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass – Ph.Int.</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
</tr>
<tr>
<td></td>
<td>• Assay - HPLC - 90-110 %</td>
</tr>
<tr>
<td></td>
<td>• Dissolution - not less than 80% (Q) in 30 min</td>
</tr>
</tbody>
</table>
ANNEX 4

Content of the Analytical Test Report

Analytical test report♦

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing.

The Analytical Test Report shall in accordance with the Good practices for pharmaceutical quality control laboratories provide the following information:

1. Name and address of the laboratory performing the sample testing,
2. Number/code of the Analytical Test Report,
3. Name and address of the originator of the request for testing,
4. Laboratory registration number of the sample,
5. Sample code from the Sample Collection Form,
6. Date on which the sample was received,
7. Name of the country where the sample was collected,
8. Sample product name, dosage form, active ingredients, strength, package size, type and packaging material of primary container,
9. Description of the sample (both product and container),
10. Batch number of the sample, expiry date and manufacturing date, if available,
11. Name and address of the manufacturer,
12. Reference to the specifications used for testing the sample, including the limits,
13. Reference to the reference standards used for quantitative determinations,
14. Detailed results of all the tests performed (numerical results, if applicable), including any observations made during analysis,
15. Conclusion whether or not the sample was found to be within the limits of the specifications used,
16. Discussion of the results obtained,
17. Date on which the test was completed, and
18. Signature of the head of the laboratory or authorized person.

APPENDIX 1

Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Version: Final (May 2009)

1. Introduction

WHO estimates that nearly half a million multidrug-resistant tuberculosis (MDR-TB) cases emerge each year, as a result of inadequate or poorly administered treatment regimens, insufficient supply or quality of anti-TB medicine, and transmission of drug-resistant strains. Newly independent states of the former Soviet Union (NIS) have some of the highest prevalence rates of MDR-TB, with proportions of MDR-TB among new and previously treated TB cases have been reported as high as 28.3% and 61.6% respectively.

It has been hypothesized that one of the most important factors for the resurgence of TB, and the high rates of MDR-TB, in the NIS, was the socio-economic crisis that followed the disintegration of the Soviet Union in 1991. This crisis resulted in interruptions in medicines supply and overall deterioration of the health sector, which had an impact on the transmission of and susceptibility to TB and MDR-TB. The lack of standardized treatment regimens in many countries is also likely to have contributed to the development of drug resistance.

Limited research has been conducted into the factors contributing to drug resistance in this region, and to the marked regional and national differences in drug resistance rates. In particular, there has been little consideration of the extent to which substandard, spurious, falsely-labelled, falsified and counterfeit anti-TB medicines might circulate in this region. This survey aims to investigate the quality of anti-TB medicines in use in selected NIS.

2. Definitions

Country code for the purposes of this project means a 2-digit code used for the country in an email address.

Delivery centre for the purpose of this project means a point, where a medicine enters the country, central stores and stores, where a medicine is kept during the in country distribution.

5 MDR-TB is defined as resistance to at least rifampicin and isoniazid, the two most powerful anti-TB medicines.


7 Raviglione MC et al. Tuberculosis trends in eastern Europe and the former USSR. Tubercle and Lung Disease, 1994 Dec, 75(6):400-16.


Product abbreviations (for the purposes of coding samples):

- Isoniazid = H
- Rifampicin = R
- Isoniazid + rifampicin = H-R
- Kanamycin = Km
- Ofloxacin = Ofx

**Sample** for the purposes of this project means an item collected from each presentation at the same collection site. That means that a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.

**Treatment centre** for the purpose of this project means the final site, where a medicine is delivered and where it is provided to a patient.

### 3. Objectives

The WHO Stop TB and Essential Medicines and Pharmaceutical Policies Departments, and counterparts in the WHO Regional Office for Europe, are collaborating with NMRAs to study the quality of first and second-line anti-TB medicines circulating in the countries with the highest MDR-TB and XDR-TB rates. The project will commence in countries of Eastern Europe and the NIS as indicated in this study protocol, and will subsequently expand to China and India.

The aim of this project is therefore to evaluate the pharmaceutical quality of widely used anti-TB medicines (first and second-line) obtained at public and private sector procurement and treatment centres in selected countries of Eastern Europe and the NIS. The following questions will be addressed:

- Which anti-TB medicines are mostly used?
- What proportion of anti-TB medicines samples, including fixed-dose combination products, collected at approved procurement and treatment centres fail quality testing?
- Which specific quality tests do the samples fail, if any?
- Are any of the deficiencies critical, i.e. could most likely affect treatment efficacy and/or cause harm to the patient?

The results of this study are expected to assist responsible authorities in the countries surveyed to adopt regulatory actions, if necessary, and to develop appropriate quality assurance strategies for anti-TB medicines. They will also provide information for WHO to adapt its prequalification procedures. Finally, they will be of use in awareness and advocacy programmes on quality issues in anti-TB medicines in general.

### Limitations of the study

This quality survey cannot completely solve the problem of bioavailability, which may be of special relevance in case of rifampicin.

Appropriate bioavailability must be assured by complex regulatory measures, which include compliance of manufacture with GMP standards, appropriate quality specifications for both...
active ingredients and finished product and proof of bioequivalence with proper comparator. These parameters should be assessed during registration and followed up in post-registration period.

From anti-TB medicines included in this survey only rifampicin strictly requires bioequivalence testing \textit{in vivo}, for other appropriate bioavailability may be judged upon based on \textit{in vitro} testing. However, organization of bioequivalence studies for rifampicin containing products cannot be applied as quality control method without proper understanding of GMP compliance and registration conditions and as a control method for the given purpose is considered unethical. Instead of that, comparative dissolution is performed to respond at least partially to the issue of bioavailability.

It is obvious that study findings are relevant only to tested samples and extrapolation to individual batches and products is limited.

4. **Methodology**

4.1 **Participating countries**

The study should involve some six countries, where anti-TB medicines are not produced or are produced in a small scale.

The following nine countries were approached before the selection of countries was made:

- Armenia
- Azerbaijan
- Belarus
- Estonia
- Kazakhstan
- Moldova
- Latvia
- Ukraine
- Uzbekistan

The countries where samples should be collected were selected as follows:

1. A questionnaire (Annex 1) was sent to the NMRA in the 9 above mentioned countries. The questionnaire asked for first and second-line anti-TB medicines, including FDCs, that were in 2008 used in the country in both public and private sectors, the volumes used, the manufacturers of these medicines and also which institutions were involved in importation and distribution of these medicines (to identify sampling locations).

2. Following the compilation of the results of the questionnaire, six relevant countries were selected, focusing on those where the widest choice of medicines selected for this study was in use.

3. A certain amount of medicines is procured through the Global Drug Facility (GDF), including the Green Light Committee. These medicines should also be tested. However, it is important to select countries using other sources than GDF.

4. An official WHO letter was sent to the Ministries of Health of the six selected countries. The letter described the project and asked for the willingness of the Ministry
of Health to collaborate on this project. Without the consent of the Ministry of Health, the country was not included in the project.

Based on the results of the questionnaire and taking into account the above mentioned aspects, the following countries were selected for sampling:

- Armenia
- Azerbaijan
- Belarus
- Kazakhstan
- Uzbekistan
- Ukraine

The Ministries of Health of the above-mentioned six countries also nominated focal persons for this project.

4.2 Anti-tuberculosis medicines surveyed

Based on the information on medicines used in individual countries, the final medicines selection was made. Apart of the availability, volumes and sources of medicines used in individual countries, the susceptibility of medicines to quality deterioration such as low stability was taken into account.

Based on these considerations the following medicines were selected to be surveyed:

- Isoniazid tablets 300mg, 100mg, injection 10% (5ml)
- Rifampicin capsules 300mg, 150mg
- Isoniazid/rifampicin tablets 150mg/300mg, 150/150mg, 75/150mg, 60/60 mg, 30/60mg
- Kanamycin powder for injection 1g
- Ofloxacin tablets/capsules 200 mg, 400mg, solution for injection 0.2% (200ml)

4.3 Study period

The study period should last from summer 2008 to beginning 2010 and as indicated in the below table.

Table 1. Timeframe and responsible officers for the survey of the quality of anti-TB medicines circulating in selected countries of Eastern Europe and the NIS.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Timeframe</th>
<th>Responsible officers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TB medicines quality survey questionnaire sent to the 9 countries</td>
<td>June 2008</td>
<td>EURO Pharmaceutical programme</td>
</tr>
<tr>
<td>Compilation of results of the questionnaire</td>
<td>October 2008</td>
<td>EURO Pharmaceutical programme</td>
</tr>
<tr>
<td>Selection of countries and anti-TB medicines to be surveyed</td>
<td>November 2008</td>
<td>EURO Pharmaceutical programme and HQ TB and EMP/QMS departments</td>
</tr>
<tr>
<td>Letters sent to Ministers of Health of six countries for collaboration in this project</td>
<td>December 2008</td>
<td>EURO Pharmaceutical programme</td>
</tr>
<tr>
<td>Laboratory/ies selected for the performance of the tests</td>
<td>January 2009</td>
<td>HQ EMP/QMS</td>
</tr>
<tr>
<td>Preparations of contracts with NMRA</td>
<td>May 2009</td>
<td>EURO Pharmaceutical programme</td>
</tr>
</tbody>
</table>
### Selection of sample collection sites

Samples should be collected from the following levels of distribution chain:

- **Level 1** - delivery centres (private and/or public); as the aim of the survey is to assess the quality of medicines available to patients, samples should be collected at the manufacturing sites only in case that it is not possible to collect appropriate samples at the other sites
- **Level 2** - wholesalers, regulated retailers including dispensing facilities and treatment centres, in both private and public sectors.

A meeting should be held with participation of focal persons from individual countries and WHO representatives from EURO Pharmaceutical Programme and HQ TB and EMP/QMS departments to explain the project, to provide detailed instructions and to identify names and addresses of sample collection sites in each country involved.

Samples will be collected by the staff of the NMRAs in cooperation with the WHO country offices staff in the respective country and with backup support from the EURO Pharmaceutical programme and HQ EMP/QMS department.

### Sample collection

For the purposes of this project, a sample means an item collected from each presentation at the same collection site. That means that a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.

A detailed national sampling plan will be prepared for each country by the focal person in the NMRA in cooperation with WHO pharmaceutical experts (Annex 2). The focal person in each country will arrange for training of collectors to be familiar with the national sampling plan and instructions.
In general the following information shall be included in the national sampling plan:

- Identification of the country and the person responsible for sampling
- Names and addresses of the sites, where samples shall be collected
- Identification of medicines to be collected (active ingredients by INNs, dosage form, strength, manufacturer, number of batches to be collected in each site and number of units to be collected per batch of each medicine)
- Maximum number of samples collected per country
- Detailed instructions for collecting samples (see below).

Number of dosage units or multidose packages of selected medicines to be collected should allow for:

- conducting the agreed tests
- possible confirmative testing due to out-of-specification investigations, and
- retention samples.

The following general rules are used, if not justified otherwise:

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Packaging (typical)</th>
<th>Number of dosage units or multidose packs per batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets &amp; capsules (immediate/modified release, chew, dispersible, etc.)</td>
<td>Blisters, co-blisters, bottles, securitainers</td>
<td>Approx.100 units (e.g. 5 packs of 20 units 3 packs of 30 units 3 packs of 40 units 2 packs of 60 units 1 pack of 90 units and above) In case of co-packaged FPPs approx.100 units shall be collected from each medicine.</td>
</tr>
<tr>
<td>Multidose oral solutions/suspensions, powder for oral solution/suspension &amp; injections or powders for injections</td>
<td>Multidose bottles and vials</td>
<td>6 containers of 60 ml / 100 ml 3 containers of 240 ml</td>
</tr>
<tr>
<td>Single dose powders for oral solution/ suspension &amp; single dose injections or powders for injections</td>
<td>Sachets and single dose bottles, vials &amp; ampoules</td>
<td>Unless otherwise specified, 15 units (20 units if dose is below 50 mg)</td>
</tr>
</tbody>
</table>
Instructions for sample collection:

- The time period, within which samples should be collected in the countries and the deadline for sending the last sample to the testing laboratory, should be clearly indicated and followed.
- The minimum quantity of sample per batch and number of batches to be collected from each collection site for each selected medicine as indicated in the Sampling Plan shall be followed. Note that there should not be a mix-up with batches, all units of one sample must be of the same batch. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.
- Samples collected should have at least six months remaining to expiry.
- Only unopened original packages shall be collected.
- The medicine samples should not be taken out of the original primary packaging and outer containers (though removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened.
- The medicine labels and package leaflets should not be removed or damaged.
- Sampling will be recorded using the Sample Collection Form (Annex 3). Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.
- In order to avoid confusion, each sample will be identified by a unique Sample Code (for coding system see the Sample Collection Form, Annex 3) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
- Manufacturer’s batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.
- The samples should be collected and kept under controlled conditions, as per label requirement. The cold chain should be maintained, where required.

If needed, the appropriate arrangements shall be made with treatment centres to ensure that there is no shortage due to collection of samples (e.g. requesting for replacements of medicines).

4.6 Storage and dispatch of samples

Storage and transport of the sample should be done according to the requirements set out in paragraph 2.3 of WHO’s Guidelines for Sampling of Pharmaceutical Products and related materials:\n
---

• The samples should be kept in original packaging and under storage conditions specified on the label.

• For transport all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport. Any residual space in the container should be filled with a suitable material. Where required, the cold chain should be retained during storage and transport.

• A covering letter, the copy Sample Collection Form and, if available, copy of Manufacturer’s batch certificates of analysis should accompany the samples.

• Samples with the accompanying documents should be sent straightforward to the assigned testing laboratory by a courier service. For each shipment it should be clearly indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. Low price just for customs purposes should be indicated to avoid problems with the customs clearance.

• The laboratory and WHO contact point\(^\text{11}\) should be informed about the shipment and the tracking number as provided by the courier service.

• Copies of all Sample Collection Forms and, if available, copies of Manufacturer’s batch certificates of analysis should be sent to WHO contact point\(^\text{7}\) after dispatch of samples.

4.7 Testing laboratory

An appropriate laboratory has to be selected for testing. Preferably a prequalified laboratory should be used. Should such a laboratory not be available or should it not have sufficient capacity, then another laboratory should be chosen, where evidence of reliability is available.

The appropriate arrangement with the laboratory has to be made. The request for testing should be in line with WHO’s guideline: Considerations for requesting analysis of drug samples\(^\text{12}\) and no sample will be sent before such an arrangement is made. An agreement for performance of work between WHO and the laboratory should be prepared and agreed upon by both parties.

\(^{11}\) Dr Jitka Sabartova - Phone: +41 22 7913376, Fax: +41 22 7914730, E-mail: sabartovaj@who.int
World Health Organization, HSS/EMP/QSM, Prequalification Programme, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland.

http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page69
For this project the following laboratories have been selected:

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Products to be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGES - PharmMed - Austrian Agency for Health and Food Safety</td>
<td>Zimmermanngasse 3 A-1090 Vienna AUSTRIA</td>
<td>• Isoniazid tablets, injection</td>
</tr>
<tr>
<td>in cooperation with Laboratoire National de Santé, Luxembourg</td>
<td></td>
<td>(AGES will be responsible for the logistics and all the mono-component isoniazid samples will be sent to Austria)</td>
</tr>
</tbody>
</table>
| COUNCIL OF EUROPE European Directorate For The Quality Of Medicines & Healthcare (European Pharmacopoeia) | 7 allée Kastner (entrance on rue de la Carpe Haute) - CS 30026 F-67081 Strasbourg FRANCE | • Kanamycin powder for injection  
• Ofloxacin tablets/capsules, solution for injection |
| SGS Lab Simon S. A.                                                 | Vieux Chemin du Poète 10 B-1301 Wavre BELGIUM                             | Testing for identity, assay, related substances and uniformity of mass:  
• Rifampicin capsules  
• Isoniazid + rifampicin tablets |
| J. W. Goethe University Institute of Pharmaceutical Technology Biocenter | Max-von-Laue-Str.9 60438 Frankfurt am Main GERMANY                      | Comparative dissolution study:  
• Rifampicin capsules  
• Isoniazid + rifampicin tablets |

4.8 Tests conducted

Laboratory testing of all collected samples will be performed according to the testing protocol agreed with the testing laboratories. In principle the following tests will be included:

- Appearance
- Identity
- Assay
- Related substances test
- Dissolution and Uniformity of mass for tablets and capsules
- pH value for injections and powders for injection
- Sterility, Bacterial endotoxins tests for parenteral products

In the light of known problems with bioavailability of rifampicin, contradictory outcomes of studies evaluating correlation between bioavailability and dissolution in vitro, and no clear conclusion on the recommended dissolution methodology in the literature it has been decided to conduct comparative dissolution study of collected products containing rifampicin.
4.9 Test methods and specifications

Tests methods and specifications are in general selected according to the following rules:

- Preferably Ph. Int. monographs should be used, if available.
- If no monograph exists in the Ph. Int., then BP or USP can be used.
- If there is no pharmacopoeial monograph or the existing monographs do not provide for desired tests, a validated method of the laboratory or manufacturer's method, if available, should be used.

Dissolution methodology from various pharmacopoeias and literature was compared and conditions for comparative dissolution study of products containing rifampicin were outlined in cooperation with experts involved in Prequalification Programme and specializing on quality of anti-TB medicines, pharmaceutical technology and waivers of in vivo bioequivalence testing.

For the agreed testing protocol for products selected for this survey see Annex 4.

4.10 Receipt and testing of samples by a testing laboratory

- Inspect each sample to ensure that the labelling is in conformance with the information contained in the Sample Collection Form or test request.
- Store the samples according to the respective medicine requirements. If appropriate, ensure compliance with the cold chain.
- Conduct quality testing in line with this protocol and in compliance with WHO standards recommended for quality control laboratories.\textsuperscript{13}
- Complete an Analytical Test Report (Annex 5). In the case that non-compliant results are found and confirmed after application of a laboratory out-of-specification procedure, report them immediately to WHO contact point.\textsuperscript{7}
- Keep records of each sample, accompanying document/s and retention samples for at least six months if the sample complied with the analytical test requirements, or for at least one year or until the expiry date (whichever is longer) if it did not comply.
- An electronic databank (e.g. photos of medicine such as tablets, packaging, package leaflet) is recommended.

5. Data management, analysis and publication

Any non-compliant result found in the survey will be investigated with the respective manufacturer and NMRA.

A data analyst/statistician will be hired to compile and analyse the laboratory test results.

The analytical test reports of the testing laboratories will be provided to all NMRA involved in the project. The outcomes of the project will be discussed by national authorities and WHO.


in a meeting, and corrective actions, if necessary, will be recommended. To take the relevant measures in countries lies within the responsibility of the NMRA.

Agreed outcomes and report from the project will be published by WHO.
Annex 1 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union
Questionnaire

please fill in ONLY for products, which are actually available in July 2008

<table>
<thead>
<tr>
<th>Name and address of the site</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsible person(s) and contact details (phone, mobile, e-mail)</td>
<td></td>
</tr>
<tr>
<td>Type of the site</td>
<td>Hospital pharmacy</td>
</tr>
<tr>
<td>what organization is best to approach for sampling, i.e. which one has the longest list of TB-products available.</td>
<td></td>
</tr>
<tr>
<td>Please mark with X in the box under the right answer</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Finished Pharmaceutical Product and dosage form</th>
<th>Strength</th>
<th>Quantity (Packs)</th>
<th>Manufacturer name and manufacturing site address</th>
<th>Country of origin</th>
<th>Not used in the country</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single ingredient first-line anti-tuberculosis medicines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol, tablet</td>
<td>400 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, tablet</td>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide, tablet</td>
<td>400 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin, capsule</td>
<td>150 mg; 300 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin, powder for injection (vial)</td>
<td>1g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other single ingredient anti-tuberculosis medicines used for the first-line treatment (please specify in the same format below)**

**Fixed dose combination products of first-line anti-tuberculosis medicines**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
</tr>
</thead>
</table>
| Isoniazid + rifampicin, tablet               | 75 mg + 150 mg  
|                                              | 150 mg + 150 mg |
| Ethambutol + isoniazid, tablet               | 400 mg + 150 mg |
| Ethambutol + isoniazid + rifampicin, tablet  | 275 mg + 75 mg  
|                                              | + 150 mg |
| Ethambutol + isoniazid + pyrazinamide + rifampicin, tablet | 275 mg + 75 mg  
|                                              | + 400 mg + 150 mg |

**Other single ingredient anti-tuberculosis medicines used for the first-line treatment (please specify in the same format below)**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
</tr>
</thead>
</table>
**Single ingredient second-line anti-tuberculosis medicines**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin, solution for injections (vial 2 ml, 4 ml)</td>
<td>250 mg/ml</td>
</tr>
<tr>
<td>Amikacin, powder for injection (vial)</td>
<td>1g</td>
</tr>
<tr>
<td>Capreomycin, powder for injection (vial)</td>
<td>1g</td>
</tr>
<tr>
<td>Cycloserine, capsule</td>
<td>250 mg</td>
</tr>
<tr>
<td>Ethionamide, coated tablet</td>
<td>125 mg</td>
</tr>
<tr>
<td>Ethionamide, coated tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>Kanamycin, powder for injection (vial)</td>
<td>1g</td>
</tr>
<tr>
<td>Levofloxacin, tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>Moxifloxacin, tablet</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ofloxacin, tablet</td>
<td>200 mg</td>
</tr>
<tr>
<td>Ofloxacin, tablet</td>
<td>400 mg</td>
</tr>
<tr>
<td>Prothionamide, coated tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>P-aminosalicylic acid, granules</td>
<td>4g</td>
</tr>
<tr>
<td>P-aminosalicylic sodium, granules</td>
<td>100 g</td>
</tr>
<tr>
<td><strong>Other single ingredient anti-tuberculosis medicines used for the second-line treatment (please specify in the same format below)</strong></td>
<td></td>
</tr>
<tr>
<td>Scored solid dosage formulations for children, preferably dispersible</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Ethambutol, tablet</strong></td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Isoniazid, tablet</strong></td>
<td>50 mg</td>
</tr>
<tr>
<td><strong>Isoniazid, tablet</strong></td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Isoniazid + rifampicin, tablet</strong></td>
<td>60 mg + 60 mg</td>
</tr>
<tr>
<td><strong>Isoniazid + rifampicin, tablet</strong></td>
<td>30 mg + 60 mg</td>
</tr>
<tr>
<td><strong>Isoniazid + pyrazinamide + rifampicin, tablet</strong></td>
<td>30 mg + 150 mg + 60 mg</td>
</tr>
<tr>
<td><strong>Pyrazinamide, tablet</strong></td>
<td>150 mg</td>
</tr>
</tbody>
</table>

**Other scored solid dosage formulations for children, preferably dispersible, used for the TB treatment (please specify in the same format below)**
Instructions to fill the questionnaire

1. Before completion of the questionnaire please select the **SITES** which will have products actually available for sampling in July 2008. The site must have the longest list of the medicines and amounts available for sampling.

2. Complete the form only for **PRODUCTS** that would be available at the selected sites for sampling in July 2008.

3. If the site will have more than one product in the line, e.g. Ethambutol, tablet, 400mg, please insert the row below the specified product name and complete it with all requested information.

4. Please complete the form in electronic format (as it is in MS Excel file) and send it by e-mail to Olexandr Polishchuk WHO/EURO at apo@euro.who.int
Annex 2 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

National Sampling Plan

Country: ____________________________________________________
Focal Person: ______________________________________________

MEDICINES TO BE COLLECTED

• Isoniazid tablets 300mg, 100mg, injection 10% (5ml)
• Rifampicin capsules 300mg, 150mg
• Isoniazid / rifampicin tablets 150/300mg, 150/150mg, 75/150mg, 60/60 mg, 30/60mg
• Kanamycin 1g powder for injection
• Ofloxacin tablets/capsules 200mg, 400mg, solution for injection 0.2% (200ml)

NUMBER OF UNITS TO BE COLLECTED PER SAMPLE

• Approx. 100 units for tablets/capsules
  o In case of rifampicin capsules and isoniazid/rifampicin tablets collect for 1 sample per each strength and each manufacturer at least 24 additional units (in intact original primary packaging) for comparative dissolution study, which will be carried out by the different laboratory than the other tests. Collection of smaller pack-sizes should be preferred to be possible to divide sample for dispatch and not interfere with the primary packaging.
• 5 bottles of 200ml
• 15 ampoules of 5ml
• 6 vials for powder for injection

NUMBER OF BATCHES TO BE COLLECTED PER PRODUCT IN EACH SITE

• Maximum 3 batches per product at one collection site; if the same product (same manufacturer, same dosage from, same strength) is collected in more sites, please select different batches, if possible.

TOTAL NUMBER OF SAMPLES PER COUNTRY

60 samples (12 samples per product preferably produced by different manufacturers)
### NAMES AND ADDRESSES OF THE SITES WHERE SAMPLE SHALL BE COLLECTED

<table>
<thead>
<tr>
<th>Facility name</th>
<th>Address</th>
<th>Facility type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4. (private/public; 5. level 1/level 2; 6. wholesaler/retailer/treatment centre/…)</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SELECTION OF PRODUCTS

#### Isoniazid

<table>
<thead>
<tr>
<th>Strength / Dosage form</th>
<th>Pack size</th>
<th>Manufacturer</th>
<th>Sampling site</th>
<th>Batch no</th>
<th>Sample code</th>
<th>No of units per sample</th>
<th>Additional 24 units needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Rifampicin

<table>
<thead>
<tr>
<th>Strength / Dosage form</th>
<th>Pack size</th>
<th>Manufacturer</th>
<th>Sampling site</th>
<th>Batch no</th>
<th>Sample code</th>
<th>No of units per sample</th>
<th>Additional 24 units needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Isoniazid/rifampicin

<table>
<thead>
<tr>
<th>Strength / Dosage form</th>
<th>Pack size</th>
<th>Manufacturer</th>
<th>Sampling site</th>
<th>Batch no</th>
<th>Sample code</th>
<th>No of units per sample</th>
<th>Additional 24 units needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS FOR COLLECTORS

- The amount of the selected products defined above will be sampled from the identified sites. All these samples are inclusive of the samples needed for the out-of specifications investigations and retention samples.

- An item collected from each presentation at the same collection site will be called a sample. **All units (tablets, capsules, vials) of one sample must be of the same batch**, there should not be a mix-up with batches. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.

- Samples collected shall have **at least six months remaining to expiry**. Products with shorter period remaining to expiry date are not collected.

- One batch of each product will be collected from each collection site and **only unopened original packages shall be collected**.

- The medicine **samples should not be taken out of the original primary packaging and outer containers** (though removal of blisters from large secondary packs is appropriate). Containers such as **bottles and vials should not be opened**.

- The medicine labels and package leaflets should not be removed or damaged.

- Sampling will be recorded using the Sample Collection Form (Annex 3). Whenever the required information is not available, it should be indicated in the appropriate space on the Sample Collection Form, where also any abnormalities should be recorded.

- In order to avoid confusion, each sample will be identified by a unique Sample Code (for coding system see the Sample Collection Form, Annex 3) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
• Manufacturer’s batch certificates of analysis will be collected with samples, if available, and kept with the Sample Collection Form.

• The samples should be collected and kept under controlled conditions, as per label requirement. The cold chain should be maintained, where required.

• Samples should be collected in all the countries involved during June 2009 and the deadline for sending the last sample to the testing laboratory is 3 July 2009.
Annex 3 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Sample Collection Form*

<table>
<thead>
<tr>
<th>Country:</th>
<th>Sample code:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Country code/product abbreviation/sequence number/sampling date ddmmyy)**</td>
</tr>
</tbody>
</table>

Name of location/place where sample was taken:

Address (with telephone, fax number and email address, if applicable):

Organization and names of people who took samples:
1. 
2. 

Product name of the sample:

Name of active pharmaceutical ingredient(s) (INN) with strength:

Dosage form (tablet, capsule, powder for injection, etc.):

Package size, type and packaging material of the container:

Batch/lot number:

Date of manufacture: Expiry date:

Regulatory status in the country, registration number, if applicable:

* This Sample Collection Form should always be kept with the sample collected. Proper sampling procedures should be followed.

** Product abbreviations: Isoniazid = H, Rifampicin = R, Isoniazid + rifampicin = H-R, Kanamycin = Km, Ofloxacin = Ofx. Sample code system can be extended to be appropriate for a particular country collection system.
Name and address of the manufacturer: ________________________________

_________________________________________________________________

Quantity collected (number of sample units or of multidose containers taken):

_________________________________________________________________

Initialize first page

Product name: ________________________ Sample code: ________________

Storage/climatic conditions at sampling site/point (temperature and humidity, indication of conditions during daytime only is acceptable, comments on suitability of premises where products are stored at the particular site for the NMRA information):

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

Abnormalities, remarks or observations that may be considered relevant, if any:

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

Date:

Signature of person(s) taking samples

Signature of representative of the establishment where sample(s) was taken (optional)

1. .........................................................................................................................

2. .........................................................................................................................

Note: Samples collected must remain in their original containers, intact and unopened
Annex 4 to Survey protocol

Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union

Testing Protocol

<table>
<thead>
<tr>
<th>Product</th>
<th>Tests to be performed and specifications for testing</th>
<th>Reference substances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Isoniazid tablets</strong></td>
<td><strong>USP</strong></td>
<td><strong>USP</strong></td>
</tr>
<tr>
<td>100mg, 300mg</td>
<td>• Appearance - package leaflet</td>
<td>Isoniazid - 1349706,</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
<td>200mg</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Assay - HPLC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dissolution - UV</td>
<td></td>
</tr>
<tr>
<td><strong>2. Isoniazid injection</strong></td>
<td><strong>USP</strong></td>
<td><strong>USP</strong></td>
</tr>
<tr>
<td>10% (5ml)</td>
<td>• Appearance - package leaflet</td>
<td>Isoniazid - 1349706,</td>
</tr>
<tr>
<td></td>
<td>• Visual inspection - clear and free from</td>
<td>200mg</td>
</tr>
<tr>
<td></td>
<td>visible particulate matter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Volume in container/Extractable volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Assay - HPLC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• pH - 6.0-7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sterility (to be performed for 1 sample per</td>
<td></td>
</tr>
<tr>
<td></td>
<td>batch/manufacturer)</td>
<td></td>
</tr>
<tr>
<td><strong>3. Rifampicin capsules</strong></td>
<td><strong>Ph.Int.</strong></td>
<td><strong>Ph. Int.</strong></td>
</tr>
<tr>
<td>150mg, 300mg</td>
<td>• Appearance - package leaflet</td>
<td>9930409 - Rifampicin,</td>
</tr>
<tr>
<td></td>
<td>• Identity - HPLC as for assay</td>
<td>300mg</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass</td>
<td>9930410 - Rifampicin</td>
</tr>
<tr>
<td></td>
<td>• Assay - HPLC</td>
<td>quinone, 200mg</td>
</tr>
<tr>
<td></td>
<td>• Related substances - HPLC</td>
<td>BP:</td>
</tr>
<tr>
<td></td>
<td>• Comparative dissolution study - 2 sets of</td>
<td>627 - 3-formylrifamycin,</td>
</tr>
<tr>
<td></td>
<td>comparison - 1 using Ph. Int. conditions, the</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>other USP/BP conditions, 7 points up to 60 min</td>
<td></td>
</tr>
<tr>
<td><strong>4. Isoniazid / rifampicin</strong></td>
<td><strong>Ph.Int.</strong></td>
<td><strong>Ph. Int.</strong></td>
</tr>
<tr>
<td>tablets 150/300mg, 150/150mg,</td>
<td>• Appearance - package leaflet</td>
<td>9930331 - Isoniazid,</td>
</tr>
<tr>
<td>75/150mg, 60/60mg, 30/60mg</td>
<td>• Identity - HPLC as for assay</td>
<td>100mg</td>
</tr>
<tr>
<td></td>
<td>• Uniformity of mass</td>
<td>9930409 - Rifampicin,</td>
</tr>
<tr>
<td></td>
<td>• Assay - 2x HPLC</td>
<td>300mg</td>
</tr>
<tr>
<td></td>
<td>• Related substances - for rifampicin only - HPLC</td>
<td>9930410 - Rifampicin</td>
</tr>
<tr>
<td></td>
<td>• Comparative dissolution study - 1 set of</td>
<td>quinone, 200mg</td>
</tr>
<tr>
<td></td>
<td>comparison using laboratory method based on</td>
<td>BP:</td>
</tr>
<tr>
<td></td>
<td>Ph. Int. conditions for Rifampicin</td>
<td>627 - 3-formylrifamycin,</td>
</tr>
<tr>
<td></td>
<td>tablets, 7 points up to 60 min.</td>
<td>25 mg</td>
</tr>
<tr>
<td>Product</td>
<td>Tests to be performed and specifications for testing</td>
<td>Reference substances</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| 5. Kanamycin powder for injection 1g (vial) | **USP monograph for kanamycin injection**  
- **Appearance** - package leaflet  
- **Identity** - HPLC as for assay  
- **Assay** - HPLC with amperometric detection  
- **pH** - 3.5 - 5.0  
- **Sterility** (to be performed for 1 sample per manufacturer) | **USP:**  
Kanamycin Sulfate - 1355006, 200mg  
Amikacin - 1019508 (for system suitability), 300 mg |
| 6. Ofloxacin tablets/capsules 200 mg, 400mg | **USP monograph for ofloxacin tablets**  
- **Appearance** - package leaflet  
- **Identity** - HPLC as for assay  
- **Uniformity of mass**  
- **Assay** - HPLC  
- **Related substances** - HPLC  
- **Dissolution** - UV | **USP:**  
Ofloxacin - 478108, 200mg |
| 7. Ofloxacin solution for infusion 0.2% (200ml) | **USP monograph for tablets**  
- **Appearance** - manufacturers' specification: clear, light yellow liquid  
- **Visual inspection** - clear and free from visible particulate matter  
- **Volume in container/Extractable volume** - not less than the nominal volume  
- **Identity** - HPLC as for assay  
- **Assay** - HPLC with USP limits for tablets 90.0-110.0%  
- **Related substances** - HPLC with USP limits for tablets  
- **pH** - manufacturers' specification  
- **Bacterial endotoxins** (to be performed for 1 sample per batch/manufacturer)  
  The manufacturer uses test for pyrogens.  
  **Limits for BE in products containing ofloxacin found in:**  
  o Brazilian pharmacopoeia (max. 5 E. U. /mg of ofloxacin for ofloxacin injection)  
  and  
  o Chinese pharmacopoeia (less than 0.5 E. U. /ml for ofloxacin and sodium chloride injection and less than 0.75 E. U. /mg for ofloxacin substance)  
- **Sterility** (to be performed or 1 sample per manufacturer and in case a positive BE result is found) | **USP:**  
Ofloxacin - 478108, 200mg |
Annex 5 to Survey protocol

Content of the Analytical Test Report

Analytical test report

*The report of the results, including the final conclusion of the analysis of a sample which has been submitted by a laboratory in another country or in the field not having appropriate facilities to perform certain tests, and issued by the official pharmaceutical control laboratory that performed the test. This is often in the same style as a certificate of analysis.*

The Analytical Test Report shall in accordance with the Good practices for national pharmaceutical control laboratories provide the following information:

19. Name and address of the laboratory performing the sample testing,
20. Number/code of the Analytical Test Report,
21. Name and address of the originator of the request for testing,
22. Sample code from the Sample Collection Form,
23. Date on which the sample was received,
24. Name of the country where the sample was collected,
25. Sample product name, dosage form, active ingredients, strength, package size, type and packaging material of primary container,
26. Description of the sample (both product and container),
27. Batch number of the sample, expiry date and manufacturing date, if available,
28. Name and address of the manufacturer,
29. Reference to the specifications used for testing the sample, including the limits,
30. Reference to the reference standards used for quantitative determinations,
31. Results of all the tests performed (numerical results, if applicable),
32. Conclusion whether or not the sample was found to be within the limits of the specifications used,
33. Date on which the test was performed, and
34. Signature of the head of the laboratory or authorized person.