Annex 7

Guidelines on the conduct of surveys of the quality of medicines

1. Introduction

Good quality medicines are essential for efficient disease management. To ensure that good quality medicines are available to patients in their countries, national medicines regulatory authorities (NMRAs) can apply various regulatory instruments. These are:

- authorization/registration for marketing following the assessment of product documentation, inspection to ascertain manufacturers' compliance with the principles of good manufacturing practices (GMP) and approval of product information;
- post-marketing surveillance activities, including maintenance of products' authorization and/or registration through variations or renewals, regular inspections of manufacturers, wholesalers, distributors and retailers, quality control testing and pharmacovigilance;
- implementation of regulatory actions in the event of any quality problem being found.

Quality surveys may serve as a source of information about the quality of medicines available to patients and are an important part of regulatory systems in all countries, whether they are strong or weak. However, it has to be borne in mind that quality surveys that rely only on laboratory testing cannot offer complete assurance that medicines are safe and effective as formulated. Quality surveys can be organized by NMRAs, international organizations, procurement agents, nongovernmental organizations (NGOs) or academic and research groups.

If properly collected, interpreted and used relevant data are vital for the planning of effective interventions to improve the quality of medicines. Surveys give snapshots of the medicine quality situation; however, the accuracy, reliability and interpretation of the data obtained depend on the survey design, organization of sample collection and available resources. Medicine quality surveys are costly and limitations on resources may restrict the number of samples collected, parameters tested, techniques to be used for analysis or number of staff available to conduct the survey and analysis. Therefore it is important to optimize use of resources by focusing on those medicines and parameters that pose a higher risk to patients and apply risk analysis during planning of the survey. Also cooperation with partners, joint organization of surveys in several countries, and sharing testing capacities, experience and information can enhance the effectiveness of quality surveys.

These guidelines outline the steps to consider when preparing and conducting a survey of medicines quality. They provide recommendations

and examples of various methodological approaches with a discussion of their advantages and disadvantages, and suggestions on preparation of reports on the results obtained from such surveys.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

pharmaceutical outlet. Any point (licensed or unlicensed) of sale or provision of medicines for individual patients or other medicine providers.

sample collected in a quality survey. A product in a given presentation (identified by its name, content of active pharmaceutical ingredient(s) (API(s)), dosage form, strength, batch number, production date (if known), expiration date, collection date and name of manufacturer or labelled registration holder) collected at the specific sample collection site. It means that the same product characterized by the same name, content of APIs, dosage form, strength, batch, and from the same manufacturer collected in two different sites represents two samples. Each sample should consist of the number of dosage units (e.g. tablets, capsules, ampoules, vials or bottles) required by the sampling plan.

sampling plan. A plan that contains detailed identification of sites where samples will be collected, medicines to be sampled, minimum number of dosage units to be collected per sample, number of samples to be collected per medicine and total number of samples to be collected in the area for which the sampling plan is prepared. It also contains detailed instructions for sample collectors.

3. Objectives of the survey and initial planning

In general, quality surveys are organized to assess the quality of medicines provided to patients and generate the data that can help to formulate strategies and plans to ensure provision of good quality medicines. They may be organized to confirm that patients are receiving satisfactory medicines and give reassurance that the regulatory system is functional, or when there is a suspicion that patients are not receiving satisfactory medicines. Detailed objectives must be set at the start of planning since all the activities and requirements of the survey should be derived from its objectives. The objectives of a quality survey should reflect the reasons why the survey is being conducted and should be formulated in a way that enables identification of medicines for the survey, sites of sample collection, surveyed areas, regions or countries, and tests to be conducted. Clearly defined objectives are essential for setting the conditions for sampling and testing, which should be described in detail in the survey protocol.

There is a wide range of possible objectives, a few examples of which are given below:

- to evaluate the quality of selected medicines available in the market, in selected areas, regions or countries, at various levels of the distribution/supply chain with the aim of assessing the exposure of patients to poor-quality medicines and proposing appropriate actions;
- to evaluate the quality of specific medicines used in the treatment programme;
- to compare the quality of domestically produced and imported medicines in order to recommend appropriate regulatory actions and adjust pharmaceutical policy in the country concerned;
- to identify possible causes of inferior quality of specific products to which patients are exposed and to propose possible strategies and implementation plans to address the problems identified by the survey;
- to test the quality of selected medicines in order to support the NMRA in identification of manufacturers that are not in compliance with quality standards and regulatory measures;
- to find out if, within a selected category of medicines, any spurious/ falsely labelled/falsified/counterfeit (SFFC) products have penetrated the market in selected areas, regions or countries, what the possible health impacts may be for patients, and to propose possible strategies and implementation plans to prevent harm to patients.

To ensure that a survey provides the necessary information it is essential, in addition to a primary objective, to set appropriate and relevant questions to be addressed in the survey. Some examples of such questions include:

- What proportion of sampled medicines fails quality testing?
- What proportions of sampled medicines fail quality testing at different levels of the regulated distribution chain and in the informal market?
- What proportions of medicines sampled from different geographical regions fail quality testing?
- What proportions of sampled domestically produced and imported medicines fail quality testing?
- Which specific quality tests do the selected medicines fail?
- Are any of the deficiencies critical, i.e. could they substantially affect treatment efficiency and/or cause harm to patients?
- Are there treatment failures related to a specific disease, which can be associated with low-quality medicines?

- What is the registration status of the sampled products and what proportions of registered and unregistered products fail quality testing?
- What are the supply chains by which poor-quality medicines are distributed and what are the market segments they serve?
- Are there any indicators of poor storage and distribution conditions that influence quality of sampled medicines?
- Are there poor-quality medicines in the selected area, e.g. at the border checkpoint?
- What is the proportion of poor-quality medicines being sold and/ or the proportion of pharmaceutical outlets selling poor-quality medicines in a particular area?
- Does the proportion of poor-quality medicines or the proportion of pharmaceutical outlets selling poor-quality medicines exceed a predetermined level?
- Has there been a change in the quality of a medicine or medicine category, or in an area (in the case of repeated random surveys with consistent design)?

Setting reasonable objectives and an appropriate design for a survey needs initial planning. Some examples of questions that should be considered in the planning phase are given below.

- *What is already known about the quality and risk of inferior quality of the target medicines?*

  The information may be available from the scientific literature, alerts on medicines quality, or a search of published studies (e.g. in PubMed or Google Scholar). When an NMRA is involved in the survey it is important to gather information from inspectors, assessors, laboratory and pharmacovigilance experts and to design the survey in cooperation with such a multidisciplinary team. Discussions with pharmacists and other health-care professionals may also help to prioritize surveys.

- *What is the distribution/supply system of the target medicines?*

  Distribution/supply chains vary between countries and even within a country they may be different for different categories of medicines. In order to design the survey properly it is important to understand how the target medicines are supplied in the surveyed area and how they reach patients. Knowledge of the distribution/supply chain of the target medicines enables risk-based selection of the sampling

sites that best serve the survey objectives. Complex supply chains pose a higher risk of quality deterioration and should be prioritized in market surveillance activities. Information on distribution/supply chains should be available to NMRAs, ministries of health, provincial health departments and health centres or other governmental organizations. In the public domain, some information can be found on the World Health Organization (WHO) Essential Medicines and Health Products Department website (http://www.who.int/medicines/areas/coordination/partnerscoordination/en/). Several international NGOs are mapping pharmaceutical outlets in various areas and publishing the information on their websites, e.g. Population Services International (PSI) (http://www.psi.org/) or, specifically for antimalarials, ACTwatch (http://www.actwatch.info/). If the survey is intended to focus on unlicensed outlets, an initial investigation may be necessary to identify and map the relevant locations.

▪ *What health-seeking behaviour is associated with the target medicines?*

For some surveys it may also be important to understand where different categories of patients tend to buy their medicines and what kind of product they buy. In many countries the medicines market is heavily segmented with different markets for people with different spending power and different ethnicity. For example, the wealthier people may go to pharmacies or private clinics, whereas the poorest go to grocery shops or street peddlers, and people in the middle-income category may go to hospitals. There will also be brands of the same product sold at different prices aimed at different market segments. If such information is needed, an initial pre-survey should be performed.

▪ *What is the overall volume of use of the target medicines?*

The higher the volumes of a particular medicine used the bigger the impact the inferior-quality medicine will have on patients. Therefore medicines with high consumption volumes should be prioritized in market surveillance activities. It may be difficult to obtain data on consumption volumes in some countries but estimates based on distribution volumes or information from various disease control programmes can be used.

▪ *What registered medicines are available in the surveyed area?*

It may be useful for the evaluation of survey results to have available lists of registered medicines in the surveyed countries. These lists

can often be obtained from NMRAs or ministries of health and sometimes may be published on their websites. Additionally, most countries make available unregistered medicines under certain conditions, e.g. specific medicines may be used in public health programmes or donated.

- ▪ *What brands of the target medicines are available in the surveyed area or in the selected outlets?*

  If the objective of the survey is to obtain an overall impression of the quality of medicines available on the market, samples produced by as many manufacturers as possible should be collected and it may be necessary to visit several sampling sites. Often, it is very difficult to know in advance how many brands of a specific medicine (containing the same API in the same dosage form) are sold in a particular market or what their market share is. A pilot study asking for a product list at the selling points may help in collecting the data needed to better plan the survey.

For correct understanding and proper interpretation of the results and conclusions of the survey, its limitations should always be stated and explained.

4. Survey management and time frame

Ideally, the authorities (ministry of health and/or NMRA) of target countries should be involved and should agree with the survey plan before it is implemented. The responsibilities and tasks of the people who have key roles in the survey organization (e.g. principal survey coordinator and the local coordinators in individual areas or countries) should be identified at the beginning and should include those with the responsibility for monitoring the conduct of the survey, performing analysis, processing results and preparing the final report. Lines and means of communication should be agreed in advance.

The primary aim of a medicines quality survey is to reduce harm to patients and enforce medicines quality standards. Surveys are organized for market surveillance or to generate new scientific knowledge. Normally they do not require ethical approval; however, such approval may be needed for an epidemiological survey. As the requirements for ethical clearance vary between countries, the regulations on ethical approval in the target countries should be verified before planning a specific survey.

It is recommended that before sample collection starts, a meeting with local coordinators is organized to explain and discuss the project and the survey protocol, and to provide detailed instructions to ensure survey consistency.

After data analysis and before publication of the report it is useful to hold a meeting with appropriate stakeholders to discuss the results, conclusions and actions needed.

Timing of sample collection is important since seasonal changes in environmental conditions may have an influence on the quality of the medicine collected. It is possible that falsified antimalarials are more common during the malaria season, or that access to outlets in rural areas may be impeded in the rainy season, for example as a result of floods or landslides.

Issues such as the use of the results and their public availability should be clearly understood by the responsible authorities and all parties involved in the survey from the beginning. Relevant regulatory measures in individual countries lie within the responsibility of the NMRA, when applicable in collaboration with the police or other enforcement bodies (with respect to falsified medicines or criminal negligence). Therefore, if an NMRA does not organize the survey directly, it should be provided with the results before their publication to be able to investigate in line with the regulatory practice and legislation with the relevant manufacturer and, if appropriate, adopt necessary regulatory measures.

A publication plan including authorship of any papers to be submitted for peer-reviewed publication and a distribution list of those to whom the report will be disseminated should be agreed at the beginning of the survey. A policy should be adopted concerning public release of data that might be considered confidential. The default position should be to distribute the data as widely and openly as possible.

The survey protocol should include the plan of survey activities and the personnel responsible for the completion of the different steps within the estimated time frames (Table A7.1). It is important to plan the financial resources expected for the whole survey before it commences.

Table A7.1
Example plan of survey activities

Activity	Time frame	Responsible person
Selection of areas/regions/countries and medicines to be surveyed		
Preparation of survey protocol		
Agreement with authority/authorities in surveyed country/countries		

Table A7.1 *continued*

Activity	Time frame	Responsible person
Seeking ethical clearance for an epidemiological survey		
Selection of testing laboratory/laboratories		
Finalization of testing protocol in agreement with testing laboratory/laboratories		
Meeting held with local coordinators from the target areas to discuss the survey protocol		
Preparation of detailed sampling plans		
Preparation and pilot test of data collection instructions and procedures, if needed		
Training and supervision of personnel collecting samples		
Collection of samples and transport to testing laboratory/laboratories in a manner that assures sample chain of custody and maintaining samples in a state of control, to preclude compromising the samples during shipment or transfer to the laboratory		
Database of information on collected samples (including scanned pictures or photographs of the dosage form, label and package leaflet)		
Testing of samples		
Compilation of results		
Data analysis		
Report drafting		
Meeting with appropriate stakeholders to discuss the results and the actions needed		
Report finalization		
Distribution and publication of the results		

5. Methodology

All surveys should be conducted according to a predefined survey protocol. Inadequate instructions on the protocol or noncompliance with the protocol, e.g. insufficient sample size, incorrect sampling and/or testing, may lead to inaccurate results and policy recommendations. Careful consideration of the methodology and ethical issues should guide the survey preparation and the people involved should comply with the instructions and with appropriate ethical standards.

In principle, in addition to the background and explanation of the survey objectives and limitations, the survey protocol should contain information on the following.

5.1 Selection of areas to be sampled

A number of different geographical areas should be sampled unless the objectives expressly justify targeting only one area. Samples should be collected in various locations, as situations in rural and suburban areas often differ. Depending on the survey objectives, the following variables may be considered when selecting areas to be surveyed:

- population density;
- incidence or prevalence of the disease for which the target medicines are indicated;
- level of risk of poor-quality medicines, e.g. the risk may be higher along trade routes across country borders, in areas where poor-quality medicines have been previously found, areas where formal health services are limited, and in areas where the NMRA has few or no resources to monitor the distribution of medicines;
- degree of urbanization;
- income level of the population in the target area;
- areas with complex distribution systems;
- areas with outlets selling predominantly unregistered and/or illegal medicines.

Sampling several countries according to the same survey protocol gives a broader picture of the quality of medicines in the region and enables comparisons between countries to be made.

Selection of the sampled areas should be explained and justified.

5.2 Selection of medicines to be surveyed

The category of medicines to be surveyed may be characterized in various ways, e.g. according to their content of APIs, therapeutic group classification,

formulation, the specific programme under which they are supplied, or the manufacturer or distributor declared on the label. If collection of commonly used products is required, a pre-survey investigation of treatment-seeking behaviour may be necessary. Collaborating with other actors, such as national disease control programmes, may help to identify products commonly used.

Selection of medicines is driven by the survey objectives and public health considerations. The potential public health impact of poor-quality medicines should be a key guide for selection. To optimize use of available resources the survey should focus on medicines posing most risk to patients, e.g. where the therapeutic index is narrow, substandard quality could lead to a significant change in the health outcome, or certain categories may be particularly vulnerable to counterfeiting. To estimate risks posed by individual medicines an analysis should be performed. Aspects to consider may include:

- probability of occurrence of a quality problem, taking into account:
    - complexity of manufacture,
    - stability of the medicine – risk of quality deterioration under local conditions of storage, distribution and use,
    - compliance of manufacturers of the target medicines with GMP principles,
    - complexity of distribution chain for the target medicines and likelihood of non-compliance with good distribution practices (GDP) principles and approved storage conditions during distribution and storage;

- exposure of patients to the medicine and seriousness of potential health impairment, considering:
    - extent of exposed population – number of patients and length of treatment, and volumes used,
    - vulnerability of target population – susceptibility of treated population to the undesired effects of the medicine,
    - complexity of the dosage form in relation to the route of administration,
    - therapeutic properties and risk, such as safety margins and risk of side effects, risk of therapeutic failure, acute versus chronic exposure, and risk of development of resistance.

Instructions should be provided to sample collectors with regard to the dosage forms and strengths of the selected medicines to be collected. Unless the objectives of the survey require a focus on a particular brand or brands, instructions should be given to the collectors on how to select samples if several brands are available at the sample collection site.

The number of medicines that should be selected for the survey depends on available resources (both financial and human) and care should be taken to keep the survey manageable.

5.3 Selection of sample collection sites

5.3.1 Types of sample collection sites

Types of pharmaceutical outlets vary greatly both within and between countries and may be classified according to the countries' medicine legislation. To allow comparison between regions and/or countries, outlets can be classed as:

- public (government);
- formal (licensed), i.e. registered private for profit and private not for profit (nongovernmental organizations (NGOs));
- informal (unlicensed).

Another way to classify sample collection sites is according to their level in the supply chain:

- Level 1 – points of entry to the market, e.g. warehouses of importers or manufacturers, central medical stores, NGO central stores, procurement centres or other facilities supplied directly within various programmes, central wholesalers and/or distributors;
- Level 2 – wholesalers and/or distributors, pharmacies and other regulated retailers, dispensing facilities, hospitals, health centres, sub-health centres, district hospitals, clinics, polyclinics, cabinets, treatment centres, health posts and community health workers;
- Level 3 – informal outlets selling medicines outside the approved distribution system, e.g. kiosks, street vendors, grocery shops, drug stores and itinerant sellers;
- Level 4: virtual outlets, e.g. sales of medicines via the Internet.

Sampling should usually be performed in both the public and private sectors as well as in the "informal market", i.e. both licensed and unlicensed outlets should be included. Types of sites for sample collection should be selected in the way that will best serve the survey objectives and the selection should be explained.

Quality of samples collected in the supply chain close to the point of sale to patients (Levels 2 and 3) may be influenced by distribution and storage conditions. However, these samples will be the closest in terms of quality to the medicines that patients actually take. When a medicine at Level 2 or 3 is found to be substandard, possibly due to degradation, subsequent sampling of that medicine at Level 1 may identify the source of the problem in the supply chain.

Samples collected at points of entry to the market (Level 1) should be less affected by the conditions they may encounter during in-country distribution, but are relatively distant from the actual quality of medicines that patients will have access to and take. Sampling at this point in the supply chain has the advantage of determining the quality of products as supplied by manufacturers and allowing quality issues to be detected before the products reach patients. Corrective actions may be more easily taken if the results are quickly available.

Once the types of sample collection sites have been selected, the areas, regions or countries to be sampled need to be mapped and the sites where samples will actually be collected during the survey should be identified (by address and facility type). Good local knowledge of the distribution and supply chain structure for the target medicines and information on where patients obtain medicines is needed. Cooperation with NMRAs and relevant disease control programmes in this respect is crucial. If the survey objectives require collection of samples offered by itinerant sellers, it may not be possible to map their "territory" and a pre-survey investigation, e.g. in households, may be needed. Another option would be to include a list of the outlets where itinerant vendors buy their medicines.

5.3.2 Sampling designs

Various designs can be used for selection of sample collection sites. The choice depends on the objectives of the survey, the risks and consequences of inherent decision errors and biases, and available resources.

5.3.2.1 Convenience sampling

Convenience sampling is a non-probability sampling technique based on the judgement of the survey organizer. The sites, however, should not be selected just because of their convenient accessibility and proximity. There should be defined rules guiding the selection so as to best reflect the survey objectives. Whenever convenience sampling is used, it is necessary to report how the sites were identified and which types and what proportion of the outlets the selection represents.

Convenience samples are simple and do not necessarily need complete lists of outlets in defined areas, which may be difficult to obtain especially for unlicensed or mobile outlets. However, they are inherently prone to biases that have to be considered when interpreting the survey outcomes. Such surveys are predominantly used for selection of sample collection sites, e.g. by NMRAs for market surveillance. To utilize resources in the most efficient way NMRAs focus on outlets where the risk of poor-quality medicines being found is high. When selecting such sites the risk analysis should take into account, for example, how medicines are distributed to the site, transport conditions, storage conditions

and handling of products at the site, and experience of the NMRA with the distribution chain and sites.

The results of convenience sampling cannot be generalized to other areas, even within the same country, or reliably interpreted over time. However, such surveys may provide the evidence necessary to support regulatory actions or to signal a quality problem. If convenience sampling does indicate a medicine quality problem, further investigation or regulatory actions can be initiated. If a wider picture is needed, subsequent surveys using probability sampling can be designed. If convenience surveys do not reveal a problem one should bear in mind that this may be a false-negative result. It is important to explain the limitations of this technique in reports and scientific papers.

Despite its limitations, convenience sampling is most suitable for NMRAs to identify high-risk areas for further regulatory actions.

Examples of convenience sampling include some surveys conducted in Africa (*1*, *2*) and South East Asia (*3*, *4*).

5.3.2.2 Simple random sampling

Random sampling is a probability sampling technique that, if the sample size is sufficient, will give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor-quality medicines. Formulas for calculation of sample size for random sampling can be found in the literature (*5*, *6*). The disadvantages of random sampling are the large sample sizes needed, the necessity for complete lists of the locations of the target outlets and the additional costs in terms of labour and time. In addition, it is important to recognize that a random survey will only produce reliable and useful information if the list of outlets and actual within-outlet sampling is consistent with the primary aims of the survey. For example, a random survey of the quality of a medicine in the private sector, when most patients obtain this medicine in the public sector would not be useful, nor would a random survey using overt shoppers for a medicine which the outlet staff know should not be sold to patients. Comparisons with subsequent estimates using this same sampling design should, however, be valid and will allow the evaluation of interventions.

5.3.2.3 Stratified random sampling

Stratified sampling is a probability sampling technique wherein the researcher divides the entire group of subjects to be investigated (e.g. outlets) into different subgroups (layers or strata), then randomly selects the final subjects proportionally from the different subgroups. Stratified sampling can be used to adjust for potential differences, e.g. sales volume, type of customers, or geographical, trade and socioeconomic variables (such as rural versus urban, private versus public outlets and one geographical area versus another) may

be considered. Stratification requires adjustment of the sample size calculation. Sampling that is proportional to the number of outlets will be more efficient than simple random sampling. It is important that the randomization procedure is done using formal random number tables or statistical software. This technique has been used in a stratified random survey in Lao People's Democratic Republic (*7*). Other examples of random surveys come from Nigeria (*8*) and the United Republic of Tanzania (*9*).

5.3.2.4 Lot quality assurance sampling

An alternative approach to formal random sampling that is simpler and less expensive, and needs smaller sample sizes, is lot quality assurance sampling (LQAS). This technique can be used to determine whether the prevalence of outlets selling poor-quality medicines exceeds a certain threshold.

LQAS is designed to find out whether a lot of goods meets the desired specifications without having to inspect the entire lot. Thus, the sample size in LQAS is defined as the number of outlets or medicines ("goods") that are selected for each site or region ("lot") and the only outcome is that the site or region is "acceptable" or "unacceptable". Setting the level of risk taken by not inspecting each and every item enables the researcher to accept or reject an entire lot after inspecting a randomly selected sample of items. Therefore the sample size in LQAS is based on defined threshold values that classify good and bad outcomes and the probability of error that the researchers are willing to tolerate.

Acceptable probabilities of error must be specified, i.e. the risk of accepting a "bad" lot (consumer risk) and the risk of not accepting a "good" lot (provider risk). These risks are commonly referred to as Type I (alpha) and Type II (beta) errors, respectively. The former is often set to 0.05. This means that if the null hypothesis (that the site has fewer outlets selling poor-quality medicines than the specified value) is true, there is a 5% chance that a site with an unacceptable proportion of outlets selling poor-quality medicines will be "accepted" or go undetected. In general, Type I risk is set lower than the Type II risk.

Once the threshold values and probabilities of error have been considered, a sample size and decision value can be obtained. The decision value is the number of outlets selling poor-quality medicines that need to be found before an area is considered unacceptable. LQAS still requires random sampling and preparation of complete lists of the locations of the outlets, and has the disadvantage that it does not estimate an exact prevalence. The advantage is that it requires relatively smaller sample sizes. Sampling can stop once the number of outlets selling poor-quality medicine is exceeded, greatly reducing sampling time and costs.

As LQAS will only provide a binary result, formal random sampling may be required to examine longitudinal changes in the prevalence of poor-quality medicines accurately. It can also be useful as a way to monitor the situation when the exact prevalence of poor-quality medicines is known.

There has been almost no discussion as to what proportion of outlets selling poor-quality medicines should be regarded as unacceptable. Ideally there should be zero-tolerance for outlets selling poor-quality medicines, as even a 1% prevalence of such medicines for potentially fatal diseases, such as malaria, tuberculosis and HIV, is disastrous for individual patients.

Examples of this approach are described in several publications (*10*, *11*). Sampling procedures and tables for lot acceptance by parties who receive goods manufactured by others can be found in the international standards, e.g. ANSI/ASQ Z1.4 and Z1.9 or ISO 2859 and ISO 3951 series.[1]

5.3.2.5 Sentinel site monitoring

Sentinel site monitoring involves following the quality of medicines in a particular locality over time. There are no common rules as to whether these sites should be chosen on the basis of potentially important variables such as rural versus urban and private versus public outlets, or as to sampling design (i.e. convenience or random samples or LQAS). The power of this methodology resides in allowing longitudinal changes to be followed in one place, but data from fixed sentinel site monitoring should be interpreted with caution. Sentinel site monitoring suffers from the disadvantage that shop owners may soon realize that they are being sampled, change their behaviour accordingly and thus cease to be representative. Examples of this approach include the survey in the Mekong region (*12*).

5.4 Sampling plans

Sampling plans should be prepared for each area, region or country involved in the survey and should be in compliance with requirements identified in the survey protocol. They should specify the:

- individual sites where collectors should collect samples (by facility type and address, possibly including global positioning system (GPS) coordinates);
- medicines to be sampled (by APIs, dosage form, strength, and, if needed, also by package size);

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[1] http://asq.org/knowledge-center/Z14.Z19/index.html;
http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=39991;
http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=57490.

- minimum number of dosage units to be collected per sample;
- number of samples to be collected per medicine;
- total number of samples to be collected in the relevant area, region or country.

Sampling plans should also contain detailed instructions for collectors. Examples of sampling plans for surveys organized by WHO can be found in the published survey reports.[2]

5.4.1 Number of dosage units to be collected

The number of dosage units that should be collected per sample depends on the survey objectives, surveyed medicines, tests to be conducted, testing methods to be employed and available resources. To protect the integrity of the samples and avoid quality deterioration before testing, dosage units should normally not be taken out of the original primary and secondary packaging, and only intact and unopened packages should be collected. Sampling plans usually define the minimum number of dosage units to be collected per sample. The appropriate number of packages is collected in relation to the available package size.

In surveys aiming to provide evidence to support regulatory actions, which are often organized by NMRAs or with their participation, pharmacopoeial tests performed in compliance with pharmacopoeial procedures are commonly used. In such surveys the principles of good practices for pharmaceutical quality control laboratories (*13*) should be followed and the number of dosage units per sample should allow:

- the planned tests to be conducted;
- investigation and confirmatory testing of samples found to be out-of-specification (OOS);
- sufficient retention samples to be used in case of dispute.

To fulfil these requirements, suitably large numbers of dosage units per sample should be collected (e.g. 100 tablets, 40 injection solution ampoules or powder for injection vials, depending on the medicine and the requested tests), which may be difficult to obtain from some outlets. Requests for such large quantities of products may also suggest to the outlet owner that the buyer is not an ordinary shopper, in cases where the survey objectives require a mystery-shopper approach. The minimum number of dosage units of each selected medicine to be collected should be agreed with the testing laboratory.

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[2] World Health Organization Prequalification of Medicines Programme. Quality Monitoring (http://www.who.int/prequal/).

The advantage of surveys using pharmacopoeial procedures is the possibility to apply quality acceptance criteria as defined in pharmacopoeias. The disadvantage is that the rather time- and resource-intensive laboratory testing leads to fewer samples that can be included in the survey.

Other types of surveys include quality screening surveys using basic, simple tests, non-destructive techniques (such as Raman and infrared (IR) spectroscopy) or unofficial testing methods (i.e. non-pharmacopoeial or not approved by the NMRA during the registration process) to assess the identity of the API and estimate its content. Such surveys cannot be used as a basis for regulatory actions but may prompt further investigations with appropriate protocols. The advantage is that only a few dosage units need to be collected per sample, a higher number of samples can be collected and the mystery-shopper approach can be used, if needed. The disadvantage is that when testing only a few individual dosage units, the usual pharmacopoeial quality acceptance criteria are difficult to apply, e.g. when estimating the content of the API by testing only a few individual tablets, pharmacopoeial criteria for the assay cannot be used.

Testing of individual dosage units to assess the content of API raises the question of how many dosage units, within a specific medicine sample, need to be analysed. The variability of individual units can be very high, especially within a sample of poor-quality medicine. Various statistical approaches to representative medicine sampling, especially for forensic analysis purposes, have been described. These are published, e.g. by the United Nations (UN) Office on Drugs and Crime (*14*), Scientific Working Group for the Analysis of Seized Drugs (*15*), European Network of Forensic Sciences Institutes,[3] and in other publications (*16*).

Sampling procedures to ensure that representative samples are taken by authorities, procurement agencies, manufacturers or customers, for acceptance of consignments, batch release testing, in-process controls, special controls, inspection for customs clearance, deterioration and adulteration, or for obtaining a retention sample are described in the WHO guidelines for sampling of pharmaceutical products and related materials (*17*).

5.5   Sample collection

5.5.1   Overt sampling versus mystery-shopper approach

The decision on who should collect samples will depend on the survey objectives, the regulatory status of the target medicines and what is known about the knowledge and attitude of the sellers (i.e. whether they know that the outlet

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[3]   Calculator for qualitative sampling of seized drugs (http://www.enfsi.eu/documents/enfsi-dwg-calculator-qualitative-sampling-seized-drugs-2012).

is selling poor-quality medicines and understand the health, legal and ethical implications). If outlet staff are anxious to avoid poor-quality medicines and are informed about the survey objectives, overt sampling with feedback would allow more data to be collected on poor-quality medicines and their risk factors and lead to a direct improvement in the medicine supply. Overt sampling may be the only possible method in some circumstances, such as when collecting samples at locations where people are seen first by clinicians, or in the public sector.

However, many outlets in countries with weak medicines regulation sell expired or unregistered medicines, which may make outlet staff suspicious and anxious about investigations. If the seller knows or is concerned that his or her stock contains illegal or poor-quality medicines and that the buyer is potentially linked to the NMRA, this may influence which medicines are offered. An additional concern is that in many resource-poor countries the medicine market is heavily segmented with different markets for people with different spending power and ethnicity. Even within a single outlet there will often be several different brands of the same medicine at different prices aimed at different market segments. In such cases a covert, mystery-shopper approach may be appropriate (*18*). The identity and purpose of the buyer should not be generally known by the outlet being evaluated. Sampling should usually be performed by nationals of the country concerned although there may be some situations, such as suspicion that migrant workers may take inferior medicines, where this would not be applicable. It may not be safe for people living in the same wider community to act as purchasers. In contrast, in some remote rural locations, it would be difficult for someone who is not local to request medicines as this would cause suspicion. The safety of those acting as mystery shoppers should be considered, a risk assessment performed and instructions appropriate to local conditions need to be developed.

The mystery shopper mimics a "normal shopper" from the community in which the outlet is located and should dress, speak and behave appropriately for that community. Shoppers should use a standard scenario, e.g. pretending to be a visitor from another part of the country who needs some medicines for a specified disease, for a specific reason and for a stereotypical patient. Mystery shoppers should be prepared to explain the real purpose of their visit to protect themselves if their identity is revealed.

After leaving the survey site the mystery shopper should record details of each purchase. Price, name of the provider and/or outlet, and an estimation of temperature at the site should be documented as well as the conditions of the purchase, e.g. how many people were in the outlet, how long the purchase took, the nature of the interaction between the mystery shopper and outlet staff, whether it was easy to convince the provider to sell medicines, and any other information needed to meet the survey objectives. All medicines collected

should be properly identified and stored, e.g. in a plastic bag labelled with the name of the outlet.

The mystery shopper should brief the local coordinator for the surveyed area upon his or her return from each outlet. The local coordinator should transcribe the reported interaction together with a translation if appropriate. Translations should use a meaning-based method, rather than a literal or interpretative approach. The original text with translation should be double-checked for accuracy by other members of the team and kept.

Examples of overt sampling include some surveys in Asia (*19*, *20*) and an example using the mystery-shopper approach can be found in the report of a survey conducted in Lao People's Democratic Republic (*7*).

5.5.2 Instructions to sample collectors

The local coordinator for each area, region or country will arrange for training of collectors to familiarize them with the project, survey protocol, sampling plan and instructions for collection of samples. Staff from the NMRA and different national disease control programmes may provide a useful insight into the survey planning. Instructions and procedures for data collection should be well understood by the collectors (translated into the language of the collectors, pilot-tested and revised, if needed). The following principles should be stated in detailed instructions for collectors.

- The minimum number of dosage units per sample and number of batches to be collected from each collection site for each selected medicine as indicated in the sampling plan should be adhered to.

- The target medicines, their dosage forms, strengths and package sizes should be defined. As outlets may have more than one brand of a particular medicine available, instructions should be provided on how to decide which to choose if a selection has to be made. It should be taken into consideration that mystery shoppers requesting a very specific brand or product may alert sellers. However, such an approach may be required if evidence suggests that only one brand of an essential medicine is affected by falsification or substandard production. It may be useful to consider using a specific written prescription for a number of items including the target medicine. This can reduce the suspicion that might be raised by a verbal request. Using the written prescription format may also enable the quality of dispensing, labelling directions and counselling to be studied.

- All units of one sample should have the same batch number.

- The medicine samples should not be taken out of the original primary and secondary packaging (although removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened. Where medicines are sold without package leaflets, or in unlabelled plastic bags coming from large-sized boxes (locally repacked), or as individual dosage forms, this should be recorded.

- Ideally, samples collected should have at least six months remaining before expiry to allow sufficient time for chemical analysis. However, the frequency of expired medicines is also an important outcome measure and any expired medicine found in the outlet should be recorded.

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

- Each sample should be recorded separately using the sample collection form (for an example see Appendix 1). Whenever the required information is not available this should be noted in the appropriate space on the sample collection form; any observed abnormalities should also be recorded.

- Each sample should be identified by a unique sample code, defined on the sample collection form and specified on all original packages belonging to the respective sample. It should be written legibly and should not obscure the basic product information. The sample collection form and all packages belonging to one sample should be kept together (e.g. blisters inserted in a dedicated zip-lock plastic bag or an envelope marked with the appropriate sample code and trade name of the product). For large surveys, barcode systems may be helpful to reduce errors.

- When overt sampling is used, manufacturer's batch certificates of analysis should be collected with the samples, if available, and kept with the sample collection form.

- Storage conditions at the site (temperature, humidity, access of light and any other observations) should be described in the sample collection form. When overt sampling is used collectors can measure the temperature if it is not controlled at the site. Mystery shoppers can estimate and record the temperature.

- Samples should be collected and kept under controlled conditions in line with the product label requirements. The cold chain has to be maintained, where required. Samples should be kept protected from light, excessive moisture or dryness. Safety measures against theft should be taken; medicine boxes should be kept in a locked area.

The period within which samples should be collected and the deadline for sending the last sample to the testing laboratory should be clearly indicated and adhered to.

Normally samples of collected medicines should be paid for by collectors. The cost of collected samples needs to be taken into account when determining the numbers of samples to be collected. In some countries, NMRA inspectors have legal power to collect samples from the market without reimbursement.

Collectors should be mindful of the stock of sampled products held in outlets, and of the potential difficulties of replenishing sampled medicines through the supply chain, so as not to jeopardize the availability of these medicines to patients. If there is a risk of product shortage after sampling, replacement of the sampled amount should be arranged immediately after the survey or, less desirably, collection of that particular product from that outlet should be omitted.

For surveys seeking to determine the proportion of poor-quality medicines sold to patients, data on product-specific sales volumes from the outlets may be necessary. These data can be collected after sampling, especially when the mystery-shopper approach is used, and sellers should be informed about the survey. This approach requires the support of the NMRA as data on sales volumes are better collected by inspectors or by officers of the authority.

5.6 Storage and transportation of samples

Storage and transportation of the samples to the testing laboratory should be done according to the requirements set out in paragraph 2.3 of *WHO Guidelines for sampling of pharmaceutical products and related materials* (*17*). Transportation should be as quick and direct as possible so as not to jeopardize the quality of the collected samples.

- The samples should be kept in their original packaging and stored under the conditions specified on the label; freezing should be avoided and, where required, the cold chain should be maintained.

- For transport, all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination. Any residual space in the container should be filled with a suitable material.

- For temperature-sensitive medicines, temperature data loggers may be included within shipments to document maintenance of an appropriate temperature during prolonged transit.

- A covering letter, copies of sample collection forms and, if available, copies of the manufacturer's batch certificate of analysis should accompany the samples.

- Where collectors do not transport samples directly to the testing laboratory, samples, with the accompanying documents, should be sent by a courier service. The documentation with each shipment should clearly indicate that the samples are being 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. If the country where the laboratory is located requires permission for importation of samples, the laboratory or NMRA of that country may be able to assist to avoid long clearance procedures. The staff of the testing laboratory should be informed of the shipment and provided with the tracking number assigned by the courier service to enable them to follow the shipment and arrange collection as soon as possible.

- Copies of sample collection forms and, if available, copies of manufacturer's batch certificates of analysis should also be sent to the principal survey coordinator or the person preparing the survey report.

5.7 Testing

5.7.1 Testing laboratory

It is important that only quality control laboratories with demonstrated capability to produce reliable test results are used in quality surveys. Therefore laboratories for testing should be carefully selected and should meet the following criteria:

- the laboratory works in compliance with WHO *Good practices for pharmaceutical quality control laboratories* (*13*), is preferably a WHO prequalified[4] laboratory or is a laboratory where other evidence of equivalent working standards is available;

- the laboratory is capable and competent to perform the tests required by the testing protocol;

- the laboratory should have sufficient capacity and should agree to test the required number of samples within the specified period for the cost specified according to the available budget.

The choice of the testing laboratory or laboratories should be explained in the survey protocol, reports and publications. One or more laboratories may be used for testing the samples collected during the survey. If several laboratories are testing collected samples, samples should be divided in such a way that all

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[4] The list of WHO-prequalified laboratories can be found at www.who.int/prequal.

samples containing the same APIs are assigned for testing to the same laboratory. Many countries do not have a fully functioning quality control laboratory and should consider making arrangements with a laboratory abroad. The appropriate arrangements with the laboratory have to be made in advance.

Within the usual selection procedure and the resulting agreement the following should be clearly specified in addition to the usual elements of such agreements (such as deadlines and financial arrangements):

- medicines and numbers of samples to be tested, tests to be conducted and specifications to be used, according to the testing protocol. If more than one testing laboratory is selected, a specific testing protocol should be prepared for each laboratory;

- responsibilities of the laboratory during the survey as specified in section 5.7.4;

- confidentiality declaration made by the laboratory;

- acceptance of a possible audit of the laboratory, access to records and retained samples.

Following conclusion of the agreement(s), the principal survey coordinator should inform the local coordinators in the areas, regions or countries participating in the survey about the following:

- name and address of the laboratory or laboratories;

- the contact person(s) in the laboratory; and

- medicines assigned for testing to the particular laboratory.

The laboratory normally starts testing only when all the samples containing the same API in the same dosage form have been received. Therefore it is important to set and adhere to the deadline for sending samples to the testing laboratory.

5.7.2 Tests to be conducted

Laboratory testing of all collected samples should be performed according to the testing protocol, which is a part of the survey protocol, and should be agreed with the testing laboratory or laboratories. Depending on the survey objectives, target medicines and available resources, the tests to be done on samples collected in the survey may include:

- verifying the identity;

- performing complete pharmacopoeial or analogous testing;

- performing special or specific tests.

If testing is expected to provide a full picture of the quality of target medicines, it should be performed according to a pharmacopoeial or analogous monograph and the following tests are, in principle, included:

- appearance, visual inspection;
- identity;
- assay for APIs declared on the label;
- test for related substances;
- for solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), fineness of dispersion, for dispersible tablets;
- for liquid dosage forms – pH value and volume in containers or extractable volume;
- for parenteral products – sterility and bacterial endotoxins tests.

Inclusion of tests for uniformity of content for single-dose dosage forms, or for sterility and bacterial endotoxins, which are costly and time consuming, and necessitate the collection of more dosage units, should be considered in relation to the target medicines and available resources. It is impossible to achieve 100% certainty about sterility of the product through testing only and inspections and enforcement of compliance with GMP principles may be more efficient tools for verification in some cases.

The packaging of each collected sample, labelling and package leaflets should be inspected visually for any signs of being an SFFC product. The World Health Professionals Association has published a checklist that may be used for this purpose (*21*). Laboratory analysis is not always successful in identifying falsified or substandard medicines and any suspicious product that is identified should be further examined in cooperation with the NMRA in the country of collection and the manufacturer declared on the label of the suspicious sample (for guidance on conducting such investigations see the WHO guidelines[5]).

Information on labels and in package leaflets can also be checked for quality and completeness of essential information, and compliance with requirements and approved product information in the country of collection can be verified. However, when more than one country is involved in the survey, it should be kept in mind that requirements for information to be provided on medicines labels and package leaflets may differ between countries.

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[5] Testing of "suspect" substandard/spurious/falsely-labelled/falsified/counterfeit medicines (QAS/15.634) (draft in preparation).

Screening methods do not provide a full picture of the quality of medicines and may be more likely to underestimate non-compliant findings than laboratory testing methods (*1*). However, they do enable testing of a large number of samples in the field, e.g. to search for SFFC medicines. It is recommended that outcomes of screening are verified by laboratory testing, at least for a random selection of those samples that pass screening and for all those that fail.

5.7.3 Test methods and specifications

Test methods and specifications should be selected in the way that will best serve the survey objectives. In general, when samples from different manufacturers are collected in a quality survey, all samples containing the same APIs in the same dosage form are tested using the same method and 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 the survey. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products and those specifications and methods may be approved by regulatory authorities in the countries concerned. Non-compliance with the specification selected for the survey does not therefore necessarily imply non-compliance with the specifications approved in the country but it indicates to the respective NMRA the need to look at the product and conditions of regulatory approval more closely and discuss these with the manufacturer or registration holder.

Wherever appropriate, pharmacopoeial methods and specifications should be used. A national pharmacopoeia may be applicable if a survey is organized in one country. If several countries are involved, widely accepted pharmacopoeias (such as the *British Pharmacopoeia*, *European Pharmacopoeia*, *The International Pharmacopoeia* or the *United States Pharmacopeia*) may be appropriate. In spite of efforts to harmonize pharmacopoeias there are still many differences between them. When a monograph for the particular medicine being tested is available in more than one pharmacopoeia the ability of the different methods and specifications to reveal quality problems should be considered and the monograph selected accordingly. Suitability of test methods for the intended use should be appropriately verified.

If no monograph for the target medicine exists in a pharmacopoeia or the existing monographs do not cover the desired tests, a validated method of the laboratory should be used.

When samples from one manufacturer only are tested in a survey, that manufacturer's methods and specifications can be used, if available to the testing laboratory. The performance of such methods under the conditions of the testing laboratory should be verified.

If samples suspected of being an SFFC product are tested, pharmacopoeial methods may not be sufficient and further examination should be conducted (for guidance on such investigations see WHO guidelines[6]).

Once the tests to be performed and the methods and specifications to be used have been selected, the testing protocol should be finalized. For each of the target medicines the protocol should contain the list of tests to be conducted, reference to methods to be used and specifications to be employed. Examples of testing protocols used for surveys organized by WHO can be found in the published survey reports.[7]

5.7.4 Receipt and testing of samples by a testing laboratory

When samples are received, the testing laboratory should:

- inspect each sample to ensure that the labelling is in conformity with the information provided in the sample collection form or test request; an electronic databank (e.g. scanned pictures or photographs of the medicines, e.g. of the tablets, packaging and package leaflet) is recommended;

- store the samples according to the conditions set out on the product labels, including compliance with any cold chain requirements;

- conduct quality testing in line with the testing protocol and in compliance with WHO *Good practices for pharmaceutical quality control laboratories* (*13*), including appropriate verification of test methods, investigation and documentation of each OOS result according to the laboratory standard operating procedure. If the OOS result is confirmed, it should be reported without delay to the principal survey coordinator who should receive both the results and the investigation report;

- prepare complete analytical test reports and certificates of analysis containing the information listed in Appendix 2. The principal survey coordinator should define the format of the outcome (e.g. separately for each sample or as a tabulated report);

- keep document(s) received with the samples, records of testing of each sample including all raw data, and retention samples according to the requirements defined by the principal survey

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[6] Testing of "suspect" substandard/spurious/falsely-labelled/falsified/counterfeit medicines (QAS/15.634) (draft in preparation).

[7] For details of the various studies carried out using the protocol referred to, see: http://apps.who.int/prequal/

coordinator (e.g. for at least six months if the sample complied with the specifications, or for at least one year or until the expiry date (whichever is longer) if it did not comply) and archive data according to the agreed conditions.

6. Data management and publication

To allow proper interpretation, the data obtained during collection and testing of samples should be summarized and appropriately organized in a database (using Excel sheets or software for epidemiological studies), linking each sample with all the data gathered and ensuring consistency and security. Suitable precautions should be taken to avoid errors. For analysis of large sets of data, statistical software may be used. If relevant, personal identification of individuals who participated in the survey (e.g. buyers and sellers) should be entered in the database using codes only.

The NMRAs of countries involved in the survey should be informed immediately about confirmed OOS results. NMRAs should carry out their investigations with the involvement of the relevant manufacturer, registration holder or other party (e.g. procurement organizations). It should be kept in mind that if the testing methods and specifications approved during the registration process differ from those used in the survey, it may be necessary to retest the product concerned using the approved manufacturer's method, where available. Appropriate measures should be taken to ensure the accuracy of the results.

Once survey results have been compiled, evaluated and summarized they should be shared with the NMRAs involved as they may provide information on medicine quality problems that will alert NMRAs and manufacturers. Before publication of the results, it is useful to hold a meeting with appropriate stakeholders to discuss the results and the actions needed. The WHO Rapid Alert System should be informed when results are considered to constitute a public health emergency.

A detailed survey report should be prepared that includes all test results on the collected samples together with their interpretation. An example outline for the survey report content is provided in Appendix 3. Recommendations for items to be addressed in the reports of medicines quality surveys can also be found in the published literature (*22*).

The report should be published as widely and openly as possible. The conclusions and wording should be prepared with caution so as not to cause embarrassment or panic. The risk that patients will stop taking genuine medicines and that the public will lose faith in medicines or the health-care system should be reduced by careful wording. Also any potential harm that might be caused to manufacturers, suppliers or outlets should be considered to avoid any legal actions.

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Appendix 1

Example of a sample collection form[1]

SURVEY TITLE

Area/region/country: _____ **Sample code:** _____
(Area/region/country code/medicine abbreviation/
sequence number/sampling date dd/mm/yy)[2]

Name of location/place where sample was taken: _____

_____

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

_____

_____

Organization and names of people who collected the sample:
1. _____
2. _____

Product name of the sample: _____

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

_____

Dosage form (tablet, injection, 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: _____

_____

_____

_____

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[1] The sample collection form should always be kept with the collected sample.

[2] *Area/region/country code*: e.g. for countries, the two-letter code is used for the Internet country top-level domains; *medicines abbreviations* to be established; sample code system can be extended to be appropriate for a collection system in a particular area, region or country.

Quantity collected (number of tablets/ampoules/vials and number of packages): _____

Initial first page:

Product name: _____ **Sample code:** _____

Date the batch was received at the location: _____

Storage and climatic conditions at sampling site:

    Conditions controlled?   Yes ☐   No ☐

    Temperature and humidity in the place where the sample was stored at the time of sample collection: _____

_____

Comments on suitability of premises where products are stored, abnormalities, remarks or observations that may be considered relevant, if any:

_____
_____
_____
_____
_____
_____
_____
_____

Date:

Signature of person(s) taking
samples

Signature of representative of the
facility where sample was taken
(*only for overt sampling, optional*)

1. _____   _____

2. _____

Note: Samples collected must remain in their original primary and secondary packaging, intact and unopened.

Appendix 2

Content of the analytical test report/certificate of analysis

- Name and address of the laboratory performing the sample testing
- Name and address of the originator of the request for testing
- Number/code of the analytical test report/certificate of analysis
- Sample reference number assigned by the laboratory and sample code assigned at the time of sampling (specified in the sample collection form and packages belonging to one sample)
- Date on which the sample was received
- Name of the area, region or country where the sample was collected
- Sample product name (trade name as it appears on the label), dosage form, APIs, strength, package size (e.g. number of tablets in one blister and number of blisters in the secondary packaging, volume in one ampoule and number of ampoules in secondary packaging)
- Description of the sample (describing both the product and the primary and secondary packaging, type and packaging material of primary container); if there is any sign of unsatisfactory handling during transportation, this should be mentioned
- Batch number of the sample, expiry date and, if available, date of manufacture
- Number of units received for the sample
- Name and full address of the manufacturer (as specified on the label or in the package leaflet)
- Reference to the specifications used for testing the sample, including the limits
- If a reference substance was used for quantitative determination, this substance should be specified (e.g. *The International Pharmacopoeia*, *British Pharmacopoeia* or *United States Pharmacopeia* reference substance or working standard)
- Results of all the tests performed; for the evaluation and interpretation of results it is useful to request numerical results wherever possible, any observation made during testing, and the following details:
  - for content uniformity, all results for individual units,
  - for dissolution test, results for all tablets tested,

- for assay, results of each individual sample preparation (usually 3 sample preparations), the average and the relative standard deviation; in the case of an OOS result followed by retesting, also the investigation report and results of retesting

- Conclusion as to whether or not the sample complies with the specifications set for the survey
- Date on which the test was completed
- Signature of the head of the laboratory or authorized person

Appendix 3

Outline of the content of a survey report

Glossary and abbreviations

Executive summary

1. Introduction
    1.1 Background
    1.2 Objectives of the survey

2. Methodology
    2.1 Survey period
    2.2 Selection of medicines for sampling and testing
    2.3 Selection of areas, regions or countries
    2.4 Sampling design and selection of sample collection sites
    2.5 Sample collection and transportation
    2.6 Testing laboratories
    2.7 Quality tests performed and test methods and specifications used
    2.8 Definition of compliance of samples with standards

3. Results
    3.1 Overview of samples collected
        3.1.1 Medicines
        3.1.2 Manufacturers and batches
        3.1.3 Sites of sample collection
        3.1.4 Storage and transportation conditions
    3.2 Registration status of sampled products
    3.3 Compliance with specifications
        3.3.1 Overall results
        3.3.2 Results of specific quality tests for individual products

4. Discussion
    4.1 Testing methods and data quality
    4.2 Limitations of methodology
    4.3 Interpretation of the results
    4.4 Recommendations

5. Conclusions

6. Other information (conflict of interests, funding)

References

Attachments – Detailed test results tabled for individual samples