GUIDELINES ON THE CONDUCT OF SURVEYS OF THE QUALITY OF MEDICINES

(June 2015)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (koppins@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by 20 August 2015.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/15.630:

Guidelines on the conduct of surveys of the quality of medicines

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1. INTRODUCTION

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

- Authorisation/registration for marketing with the assessment of products documentation, inspection of manufacturers’ compliance with the principles of good manufacturing practices (GMP) and approval of products’ information;
- Post-marketing surveillance activities including maintenance of products’ authorisation/registration through variations or renewals, regular inspections of manufacturers, wholesalers/distributors/retailers, quality control testing, and pharmacovigilance; and
- Implementation of regulatory actions should any quality problem be found.

Quality surveys may serve as an important source of information about the quality of medicines available to patients. They can be organized by NMRAs, international organizations, procurers, non-governmental organizations or academic and research groups. Not all countries have a stringent system of medicines regulation in place and information from quality surveys is specifically important for countries with weaker systems.

Data on the quality of medicines, if properly collected, interpreted and used, are vital for the planning of effective interventions to improve the quality of medicines. Surveys give snapshots of the medicine quality situation but 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 available resources may restrict the number of collected samples, tested parameters, 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 medicines and parameters that pose higher risk to patients and apply risk analysis during planning of the survey. Also co-operation 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. It provides recommendations and examples of various methodological approaches with discussion of their advantages and disadvantages, and suggestions on preparation of reports from such surveys.

2. GLOSSARY

Sample collected within a quality survey. A sample means a product in given presentation (identified by its name, content of active pharmaceutical ingredient/s (API), dosage form, strength, batch number and manufacturer) 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 must consist of the number of dosage units (e.g. tablets, capsules, ampoules, vials, bottles) required by the sampling plan.
pharmaceutical outlet. A pharmaceutical outlet means any point (licensed or unlicensed) of sale or provision of medicines for individual patients or other medicine providers.

sampling plan. A sampling plan 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 contains also detailed instructions for sample collectors.

3. OBJECTIVES OF THE SURVEY AND INITIAL PLANNING

Detailed objectives must be set at the start of planning since all the activities and requirements within the survey should be derived from its objectives. Objectives for a quality survey should reflect the reasons why the survey is conducted and should be formulated in a way enabling to identify medicines to be surveyed, sites of sample collection, surveyed areas/regions/countries and tests to be conducted. Clearly defined objectives are essential for setting up conditions for sampling and testing which should be described in detail in the survey protocol.

There is a wide range of possible objectives, just to mention a few examples:

- to evaluate quality of selected medicines available in the market in selected areas/regions/countries at various levels of distribution/supply chain with the aim to assess the exposure of patients to poor-quality medicines and propose appropriate actions;
- to compare quality of domestically produced medicines with imported ones in order to recommend appropriate regulatory actions and adjust pharmaceutical policy in the country;
- to identify possible causes of inferior quality of specific products to which patients are exposed. To propose possible strategies and implementation plans to address the problems identified by the survey;
- to test quality of selected medicines in order to support the national medicines regulatory authorization (NMRA) in identification of manufacturers non-compliant with quality standards and in adoption of regulatory measures;
- to find out if within a selected category of medicines any spurious/falsely labelled/falsified/counterfeit products penetrate to the market in selected areas/regions/countries, and what may be the health impact for patients. To propose possible strategies and implementation plans to prevent harm to patients.

To ensure that a survey provides the requested information it is useful, in addition to a primary objective, to set questions to be addressed within the survey. Some examples of such questions may be:

- 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 at 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?
• What is the registration status of 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 which influence quality of sampled medicines?
• Are there poor-quality medicines in the selected area, border checkpoint, etc.?
• What is the proportion of poor-quality medicines being sold and/or 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 the quality changed for a medicine, or medicine category, or in an area (in case of repeated random surveys with consistent design)?

Setting reasonable objectives and appropriate design of a survey needs initial planning. Some examples of questions which should be considered in the planning phase are:

• What is already known about the quality and risk of inferior quality of the target medicines?
The information may be sought in scientific literature, alerts of medicines quality, and published studies through searches, e.g. in PubMed or Google Scholar. In the case that an NMRA is involved in the survey, it is important to gather information from inspectors, assessors, laboratory and pharmacovigilance experts and design the survey in cooperation of such a multidisciplinary team. Also discussions with pharmacists and other health-care professionals may help to prioritize surveys.

• What is the distribution/supply system of the target medicines?
Distribution/supply chains vary in individual countries and even in one country may be different for various medicines categories. 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 sampling sites best serving the survey objectives. Complex supply chains pose higher risk of quality deterioration and should be prioritized in market surveillance activities. Information on distribution/supply chains should be available to NMRA, ministries of health, provincial health departments and health centres or other governmental organizations. In the public domain some information can be found at the World Health Organization (WHO) Essential Medicines and Health Products department website (http://www.who.int/medicines/areas/coordination/partnerscoordination/en/). Several international nongovernmental organizations are mapping pharmaceutical outlets in various areas and publishing the information on their website, e.g. Population Services International - PSI (http://www.psi.org/) or, specifically for antimalarials, ACTWatch (http://www.actwatch.info/). If the survey should focus on unlicensed outlets, it may be necessary to perform an initial pre-survey to map their locations.
• **What is health-seeking behaviour for the target medicines?**
  For some surveys it may be important to also 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 of different spending power and ethnicity. For example, the wealthier people may go to pharmacies or private clinics, whilst the poorest go to grocery shops or street peddlers and people of middle income may go to hospitals. There will also be brands of the same product at different prices aimed at different market segments. If such information is needed, an initial pre-survey should be performed.

• **What is the patients’ exposure to the target medicines?**
  The higher volumes of medicines used the bigger impact the inferior quality will have on patients. Therefore medicines with high consumption volumes should be prioritized in market surveillance activities. It may be difficult to obtain consumption volumes in some countries but some 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 are available to NMRAs or ministries of health and sometimes are published on their websites. It should be taken into account that most countries also apply a policy of making available unregistered medicines under certain conditions, e.g. specific medicines used in public health programmes or donated may not be necessarily registered.

• **What brands for the target medicines are available in the surveyed area/in the selected outlets?**
  If the objectives of the survey require a wide picture of the quality of medicines available on the market, samples produced by as many manufacturers as possible should be collected and more sampling sites may be necessary to visit. It is normally very difficult to know in advance how many brands of a specific medicine (containing the same API in the same dosage form) are sold on the market and which their market share is. A pilot study asking for a product list at the selling points may help to collect the data needed to better plan the survey.

For correct understanding of all parties involved in the survey and proper interpretation of its results, any limitations of the survey should be always stated and explained.

4. **SURVEY MANAGEMENT AND TIME FRAME**

Ideally, the authorities (ministry of health/NMRA) of surveyed countries should be involved or should agree with the survey plan before it commences. Responsibilities and tasks of persons having key roles in the survey organization (e.g. survey coordinator, focal persons in individual areas/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. Communication lines and means should be agreed in advance.
It is recommended before starting the sample collection to organize a meeting with participation of focal persons to explain and discuss the project, survey protocol and 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 and the actions needed.

It is important to take into consideration when the samples will be collected. There is no information on seasonal changes in the frequency of poor-quality medicines, but they may occur. For example, it is possible that falsified antimalarials are more common during the malaria season. Access to outlets in rural areas may be impaired in the rainy season due to floods and landslides. In addition, seasonal environmental conditions may have an influence on the quality of the medicine collected. Humidity and temperature may influence specific products and should be considered when planning the timing of the survey.

Issues such as the utilization of results and their public availability should be clearly understood by 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 (falsified medicines or criminal negligence). Therefore, if an NMRA does not organize the survey directly, it should be provided with the results before 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 which might be considered confidential. The default position should be to distribute as widely and openly as possible.

Medicines quality surveys aim primarily to enforce medicines quality standards and reduce harm to patients, and represent market surveillance or generation of new scientific knowledge. Normally, they are not subject to an ethical approval. But as the requirements for ethical clearance vary between countries, they should be checked in target countries before planning a specific survey.

The survey plan with key milestones and persons responsible for individual steps should be predefined together with an estimated timeframe (Table 1). It is necessary to plan the financial resources expected for the whole survey before commencing.

Table 1. Example of the plan of survey activities

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<tr>
<th>Activity</th>
<th>Timeframe</th>
<th>Responsible person</th>
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<tr>
<td>Selection of areas/region/countries and medicines to be surveyed</td>
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<tr>
<td>Preparation of survey protocol</td>
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<tr>
<td>Agreement with authority/ies in surveyed country/ies</td>
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<td>Selection of testing laboratory/ies</td>
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Working document QAS/15.630

5. METHODOLOGY

Medicines quality survey methodology and conduct may pose important challenges due to, e.g. insufficient sample size, incorrect sampling and/or testing. This may lead to inaccurate results and policy recommendations. Survey results may influence national policies and have a direct impact on individuals and public health. Therefore careful methodological and ethical considerations should guide the survey preparation and the people involved should comply with the instructions and appropriate ethical standards.

Any survey should be conducted according to a predefined survey protocol. In principle, the survey protocol should, apart from the background and explanation of the survey objectives and limitations, contain the following information.

5.1 Selection of areas to be sampled

Different geographical areas should be sampled unless the objectives expressly justify targeting one area only. Samples should not usually be collected only in the capital city, as situations in rural and suburban areas often differ. Depending on the survey objectives, the following variables may be considered for area selection:
• population density;
• incidence/prevalence of the disease for which the target medicines are indicated;
• level of risk of poor-quality medicines, e.g. higher risk can be at trade routes across country borders, areas where poor-quality medicines have been previously found, areas where formal health services are limited, areas where the NMRA has little 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.

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

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. by the content of APIs, therapeutic group classification, formulation, specific programme under which they are supplied, 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 sectors, such as national disease control programmes, may help to identify products used commonly.

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

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

• exposure of patients to the medicine and seriousness of potential health impairment, considering:
  o extent of exposed population – number of patients and length of treatment, and volumes used,
  o vulnerability of target population – susceptibility of treated population to the undesired effects of the medicine,
  o 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, risk of development of resistance.

Sample collectors should be provided with instructions as regards the dosage forms and strengths of the selected medicines to be collected. Unless the objectives of the survey require to focus on the particular brand/s, it should be defined how to select samples if more brands are available in the sample collection site.

The number of medicines 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

Pharmaceutical outlets vary greatly in type both within and between countries and may be classified according to the countries’ medicine legislation. To allow comparison between regions/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 classification of sample collection sites may be according to the level of 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/distributors;
- Level 2 – wholesalers/distributors, pharmacies and other regulated retailers, dispensing facilities, hospitals, health centres, sub-health centres, district hospitals, clinics, polyclinics, cabinets, treatment centres, health posts, community health workers;
- Level 3 – informal outlets selling medicines outside the approved distribution system, e.g. kiosks, street vendors, grocery shops, drug stores, itinerant sellers.

Sampling should usually be performed in both the public and private sectors as well as in the "informal market", i.e. include both licensed and unlicensed outlets. Types of sites for sample collection should be selected in a way to best serve best 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 will be the closest in terms of quality to the medicines that patients actually take. If medicine quality problems are found and suggest degradation, collection of additional samples of the same product at higher levels of the chain, e.g. in central wholesalers and central medical stores, may highlight the importance of supply chain management.
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 identifying the quality of products as supplied by manufacturers and detecting quality issues before the products reach patients. Corrective actions may be more easily put in place if the results are quickly available.

Once the types of sample collection sites are selected, the areas/regions/countries to be sampled need to be mapped and the sites where samples will be actually collected in the survey should be identified (by address and facility type). Good local knowledge of the distribution/supply chain structure for the target medicines is needed and cooperation with NMRAs and relevant disease control programmes in this respect is very important. 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 associated with 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 identified just because of their convenient accessibility and proximity. There should be defined rules guiding the selection to best reflect the survey objectives. Whenever convenience sampling is used it should be reported how the sites were identified and which types and proportion of the outlets the selection represents.

Convenience surveys 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 which have to be considered when interpreting the survey outcomes. It is a technique predominantly used for selection of sample collection sites by, e.g. NMRAs for market surveillance. To utilize resources in a most efficient way NMRAs focus on outlets where the risk of poor-quality medicines occurrence is high. When selecting such sites the risk analysis should consider, e.g. the way of medicines distribution to the site, transport conditions, storage conditions and handling products in the site, 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, convenience surveys may provide the evidence to support regulatory actions or signal of 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 with probability sampling can be designed. If convenience surveys do not demonstrate 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.
Examples of convenience sampling include some surveys conducted in Africa\(^3,4\) and South East Asia\(^5,6\).

### 5.3.2.2 Random sampling

Random sampling is a probability sampling technique that, with sufficient sample size, will give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor-quality medicines. Formulas for calculation of a sample size for random sampling can be found in the literature.\(^7\) The disadvantages of random sampling are the large sample sizes needed, necessity of complete lists of the locations of the target outlets and the additional costs in 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 in concordance with the primary aims of the survey. For example, a random survey of the quality of 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 the same sampling design should be valid and will allow the evaluation of interventions.

Stratified sampling is a probability sampling technique wherein the researcher divides the entire group of investigated subjects (e.g. outlets) into different subgroups (layers/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 geographic area versus another) may be considered. Stratification requires adjustment of the sample size calculation. Sampling proportional to number of outlets will be more efficient compared to simple random sampling. It is important that the randomization procedure uses formal random number tables or statistical software. Examples of this technique are described in a stratified random survey in Lao People’s Democratic Republic.\(^8\) Other examples of random surveys are from Nigeria\(^9\) and the United Republic of Tanzania\(^10\).

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5.3.2.3 Lot quality assurance sampling

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

LQAS is designed to allow determination as to whether a lot of goods meets 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/region (“lot”) and the only outcome is that the site/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, 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 when the exact prevalence of poor-quality medicines is known as a way to monitor the situation.

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 in various areas can be found in several publications,\(^{11,12}\) a LQAS toolkit is available from the Liverpool School of Tropical Medicine.\(^{13}\)

### 5.3.2.4 Sentinel site monitoring

Sentinel site monitoring involves following the quality of medicines in a particular locality through 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 are no longer representative. Examples of this approach include the survey in the Mekong region.\(^{14}\)

### 5.4 Sampling plans

Sampling plans should be prepared for each area/region/country involved in the survey and should in compliance with requirements of the survey protocol identify:

- 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 package size);
- 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/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.\(^{15}\)

#### 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 integrity of samples and avoid quality deterioration before testing, dosage units should not be taken out of the original primary and secondary packaging and only intact and unopened packages should be collected. Sampling plans normally define

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the minimum number of dosage units to be collected per sample. In relation to the available package size the appropriate number of packages is collected.

In surveys aiming to provide evidence to support regulatory actions, which are often organized by NMRA 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\footnote{Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report. Geneva, World Health Organization. WHO Technical Report Series, No. 957, 2010, Annex 1: http://www.who.int/prequal/info_general/documents/TRS957/GPCL_TRS957_Annex1.pdf.} should be followed and the number of dosage units per sample should allow:

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

To fulfil these requirements, quite high 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 requested tests), which may be difficult to obtain in some outlets. It may also suggest to the outlet owner that the buyer is not an ordinary shopper in cases when the survey objectives request a mystery-shopper approach. The minimum number of dosage units to be collected per each selected medicine should be agreed with the testing laboratory. The advantage of surveys using pharmacopoeial procedures is the possibility to apply quality acceptance criteria as defined in pharmacopoeias. The disadvantage is rather time- and resource-demanding laboratory testing leading to lower numbers of samples which can be included in the survey.

Other types of surveys are quality screening surveys using basic, simple tests, non-destructive techniques (such as Raman and infrared (IR) spectroscopy) or unofficial testing methods (non-pharmacopoeial or not approved by the NMRA during 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 precipitate further investigations with appropriate protocols. The advantage is that only a few dosage units can 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, usual pharmacopoeial quality acceptance criteria are difficult to apply, e.g. when estimating the content of the API by testing a few individual tablets only, 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 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 are described by, e.g. United Nations (UN) Office on Drugs and Crime\footnote{United Nations Office on Drugs and Crime. Guidelines on Representative Drug Sampling, Laboratory and Scientific Section, Editor. 2009: http://www.unodc.org/documents/scientific/Drug_Sampling.pdf.}.
Scientific Working Group for the Analysis of Seized Drugs, European Network of Forensic Sciences Institutes, or in some publications.

Sampling procedures ensuring 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/adulteration or for obtaining a retention sample are described in the WHO guidelines for sampling of pharmaceutical products and related materials.

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, regulatory status of the target medicines and what is known about the knowledge and attitude of sellers (whether he/she knows that the outlet is selling poor-quality medicines and understands 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 direct improvement in the medicine supply. Overt sampling may be the only possible method in some circumstances, such as if samples are collected 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/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 of 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. 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, the risk assessment performed and instructions appropriate to local conditions developed.

The mystery shopper mimics a “normal shopper” for the community in which the outlet is located and should dress, speak and behave appropriately for the community. They 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 stereotyped patient. The mystery shopper should be prepared to explain the real purpose of the visit to protect himself/herself in case that his/her identity is revealed. After leaving the surveyed place the mystery shopper should record details of the purchase. Price, name of the provider/outlet, estimation of temperature at the place should be documented as well as conditions of the purchase, e.g. how many people were in the outlet, how long it took, what was the interaction between the mystery shopper and outlet staff, was it easy to convince the provider to sell medicines, and other information requested by the survey objectives. Collected medicines 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 focal person for the surveyed area after return from each outlet. The focal person should transcribe the reported interaction with translation as appropriate. Translations should use a meaning-based translation 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 and the example of mystery-shopper approach can be found in the survey conducted in Lao People’s Democratic Republic.

5.5.2 Sample collection

The focal person for each area/region/country will arrange for training of collectors to be familiar with the project, survey protocol, national sampling plan and instructions for collection of samples. Staff from the NMRA and the different national disease control programmes may provide a useful insight into the survey planning.

Data collection instructions and procedures should be well understood by the collectors (translated in the language of collectors, piloted and revised, if needed). The following principles should be included 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, 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 if a selection has to be made. It should be taken into consideration that mystery shoppers requesting a very specific

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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 afflicted 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 raising suspicion of a verbal request. Using the written prescription format may also enable studying the quality of dispensing, labelling directions and counselling;

- all units of one sample must be of the same batch number;
- the medicine samples should not be taken out of the original primary and secondary packaging (though removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened. In cases 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 to 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 it should be indicated 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 (legible and not covering 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 envelope marked with the appropriate sample code and trade name of the product). For large surveys, bar-code systems may be helpful and reduce errors;
- when overt sampling is used, manufacturer’s batch certificates of analysis should be collected with samples, if available, and kept with the sample collection form;
- storage conditions at the site (temperature, humidity, access of light, any other observation) should be described in the sample collection form. When overt sampling is used collectors can measure temperature if not controlled in 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 put in place; medicine boxes should be kept in a locked area.

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

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 in outlets, and potential difficulties of replenishment of 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 in that outlet should be omitted.

In case of surveys seeking the proportion of poor-quality medicines sold to patients, outlet product-specific sales volumes may be necessary. Collection of these data can be conducted after sampling, especially when the mystery-shopper approach is used, and sellers should be informed about the survey. This approach requires NMRA support as 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.* It should be done as quickly and straight as possible so as not to jeopardize the quality of collected samples.

- The samples should be kept in their original packaging and under storage conditions as specified on the label; freezing should be avoided and, where required, the cold chain should be retained.
- 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.
- In case of temperature-sensitive medicines, temperature data loggers may be included within shipments to document adequate temperature in prolonged transit.
- A covering letter, copies of sample collection forms and, if available, copies of manufacturer’s batch certificate of analysis should accompany the samples.
- In the case that collectors are not transporting samples directly to the testing laboratory, samples with the accompanying documents should be sent 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. If the country, where the laboratory is located, requires permission for importation of samples, the laboratory or NMRA of the country may be able to assist to avoid long clearance procedures. The testing laboratory should be informed of the shipment, with the tracking number as provided by the courier service, to be able 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 survey coordinator or person preparing the survey report.
5.7 Testing

5.7.1 Testing laboratory

It is important that only quality control laboratories which demonstrate capability to produce reliable testing results are used in quality surveys. Therefore laboratories for testing should be properly selected and should meet the three following criteria:

- The laboratory works in compliance with WHO *Good practices for pharmaceutical quality control laboratories*\(^{14}\) – preferably a WHO prequalified laboratory\(^{25}\) or a laboratory where other evidence of equivalent working standards is available;
- the laboratory is capable and competent to perform tests required by the testing protocol;
- the laboratory has sufficient capacity and agrees to test the required number of samples within the specified period for the cost within the available budget.

The choice of the testing laboratory/ies should be explained in the survey protocol, reports and publications. There can be one or more laboratories used for testing of samples collected within the survey. If more laboratories are testing collected samples, samples should be divided among laboratories in a way that all samples containing the same APIs are assigned for testing to one laboratory. Many countries do not have a fully functioning quality control laboratory and should consider making arrangements with a laboratory abroad.

The appropriate arrangement with the laboratory has 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, financial arrangements etc.):

- medicines and numbers of samples to be tested, tests to be conducted and specifications to be used according to the testing protocol. If there are more testing laboratories 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 of the laboratory;
- acceptance of a possible audit of the laboratory, access to records and retained samples.

Once agreement/s is/are concluded, the survey coordinator should inform the focal persons in areas/regions/countries participating in the survey about the name and address of the laboratory/ies, the contact person/s in the laboratory and medicines assigned for testing to the particular laboratory. The laboratory normally starts testing only when all samples containing the same API in the same dosage form are 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

\(^{25}\) The list of WHO-prequalified laboratories can be found at [www.who.int/prequal](http://www.who.int/prequal).
laboratory/ies. Depending on the survey objectives, target medicines and available resources, the tests to be applied to samples collected in the survey may include:

- verifying the identity;
- performing complete pharmacopoeial or analogous testing;
- performing special or specific tests.

In the case that testing should 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 in case of dispersible tablets;
- for liquid dosage forms – pH value and volume in containers/extractable volume;
- for parenteral products – sterility and bacterial endotoxins tests.

Inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial endotoxins tests, which are costly, time demanding and need more dosage units to be collected, should be considered in relation to 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.

Packaging of each collected sample, labelling and package leaflets should be inspected visually for any signs of a spurious/falsely-labelled/falsified/counterfeit (SFFC) product. The World Health Professionals Association published a checklist which may be used for this purpose. Laboratory analysis is not always successful in identifying falsified or substandard medicines and any identified suspicious product should be further examined in cooperation with the NMRA in the country of collection and the manufacturer declared on the label of suspicious sample (for guidance on such investigation see WHO guideline QAS/15.631: Testing of substandard/spurious/falsely-labelled/falsified/counterfeit medicines (draft in preparation)).

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 countries are involved in the survey it should be kept in mind that requirements on information to be provided on medicines labels and package leaflets may differ.

Screening methods do not provide a full picture of the quality of medicines and may underestimate non-compliant findings in comparison with laboratory testing. However, they enable testing of large number of samples in the field, e.g. to search for spurious, falsely-labelled, falsified or counterfeit medicines. It is recommended to verify outcomes of screening

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 a way to serve best to the survey
objectives. In general, when samples from different manufacturers are collected within 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 individual countries.
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 the need
to look at the product and conditions of regulatory approval more closely and further actions
should be considered by the respective NMRA.

Wherever they are appropriate, pharmacopoeial methods and specifications should be used. A
national pharmacopoeia may be applicable if a survey is organized in one country. If more
countries are involved widely accepted pharmacopoeias (such as the International
Pharmacopoeia, British Pharmacopoeia or United States Pharmacopeia) may be appropriate.
In spite of efforts to harmonize pharmacopoeias there are still many differences. When a
monograph for the particular medicine is available in more pharmacopoeias the ability of the
respective methods and specifications to reveal quality problems should be considered and the
monograph selected accordingly.

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

If samples suspicious to be an SFFC product should be tested, pharmacopoeial methods may
not be sufficient and further examination should be conducted (for guidance on such
investigation see WHO guideline QAS/15.631: Testing of substandard/spurious/falsely-
labelled/falsified/counterfeit medicines (draft in preparation)).

Once tests to be performed and methods and specifications to be used are selected, the testing
protocol should be finalized. For each of the target medicines it 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.13

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 conformance with the information
  contained in the sample collection form or test request; an electronic databank (e.g.
  scanned pictures or photographs of the medicines, such as of the tablets, packaging,
  and package leaflet) is recommended;
store the samples in line with the conditions on 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,\(^{14}\) including investigation and documentation of each OOS result according to the laboratory SOP. If the OOS result is confirmed, it should be reported without delay to the survey coordinator providing both results and investigation report;

- complete analytical test reports/certificates of analysis containing information listed in Appendix 2. The 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 samples, records of testing of each sample including all raw data and retention samples according to the requirements defined by the survey 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 well-arranged in a database (using Excel sheets or software for epidemiological studies), linking each sample with all the gathered data and ensuring consistency and security. Any errors should be avoided. For analysis of large sets of data statistical software may be used. If relevant, personal identification of individuals who participated in the survey (buyers, sellers, etc.) should be entered in the database using codes only.

NMRA\(s\) of countries involved in the survey should be informed forthwith about confirmed OOS results to be able to investigate in line with regulatory practice and legislation with the relevant manufacturer or other party. It should be kept in mind that if testing methods and specifications approved during registration process differ from those used in the survey, it may be necessary to retest the particular product using the approved manufacturer’s method, where available. Once survey results are compiled, evaluated and summarized they should be shared with the NMRA\(s\) involved as they may provide information on medicine quality problems that will alert NMRA\(s\) 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 a public health emergency.

A detailed survey report should be prepared including all testing results for collected samples with interpretation. An example of the outline of the survey report content is provided in Appendix 3. Recommendations for items to be addressed in reports of medicines quality surveys can be also found in published literature.\(^{27}\)

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 the public will lose faith in medicines or the health-care system should be reduced by careful wording. Also any potential harm that

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can be caused to manufacturers, suppliers or outlets should be considered to avoid any legal actions.

Appendix 1

Example of the sample collection form

SURVEY TITLE

Area/Region/Country: ___________________________ Sample code: ___________________________

(Area/region/country code/medicine abbreviation/sequence number/sampling date ddmmyy)

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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28 The sample collection form should always be kept with the collected sample.
29 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/country.
Quantity collected (number of tablets/ampoules/vials and number of packages):

Initialize first page:

Product name: ________________________ Sample code: ______________

Date the batch was received at the location: ______________________________

Storage/climatic conditions at sampling site:

Conditions controlled: Yes ☐ No ☐

Temperature and humidity at 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/country where the sample was collected.
- Sample product name (trade name as 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 (both description of the product and of primary and secondary packaging, type and packaging material of primary container); if there is any sign of bad handling during the transportation, it should be mentioned.
- Batch number of the sample, expiry date and, if available, manufacturing date.
- Quantity 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.
- In the case that a reference substance was used for quantitative determination, the substance should be specified (e.g. British Pharmacopoeia or United States of America Pharmacopoeia 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), average and the relative standard deviation (RSD); in case of an OOS result and retesting also the investigation report and results of retesting.
- Conclusion whether or not the sample complies with the specifications set for the survey.
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/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