Ethiopian Food and Drug Authority (EFDA)

Risk-based Guideline for Post-Marketing Quality Surveillance of Medicines in Ethiopia

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Table of Contents

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Acronyms

ADE	Adverse drug effect
API	Active pharmaceutical ingredient
EFDA	Ethiopian Food and Drug Authority
FMoH	Federal Ministry of Health
GMP	Good Manufacturing Practice
GSMS	Global Surveillance and Monitoring System of WHO
ICT	Information communication technology
ISO/IEC	International Organization for Standardization and the International Electrotechnical Commission
LQAS	lot quality assurance sampling
OOS	Out of specification
PMS	Post-marketing surveillance
PQM	Promoting the Quality of Medicines program
QA/QC	Quality assurance and quality control
RB-PMS	Risk-based post-marketing surveillance
RDV	Rural drug vendor
SOP	Standard operating procedure
USAID	U.S. Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Glossary

For this document, the following terms and definitions are used.

Administrative measure	The range of actions taken against regulated persons or products by the Authority including denial, corrective notification, warning letter, suspension, revocation, detention, seizure and disposal of products, recall, and recommendation for prosecution.
Authority	The Ethiopian Food and Drug Authority
Convenience sampling	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.
Efficacy	The maximum ability of a medicine to produce the purported effect as determined by scientific methods, regardless of dosage forms.
Epidemiology	The study of the various factors influencing the occurrence, distribution, prevention, and control of disease, injury, and other health-related events in a defined population in an effort to understand the etiology (causes) and course of illness and/or disease.
Falsified	Medical products that deliberately/fraudulently misrepresent their identity, composition, or source.
Lot quality assurance sampling	Sampling technique designed to determine whether a lot of goods meets the desired specifications without having to inspect the entire lot. This technique can be used to determine whether the prevalence of outlets selling poor-quality medicines exceeds a certain threshold.
Marketing authorization	An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy, and quality of the product.
Pharmaceutical outlet	A pharmaceutical outlet means any point (licensed or unlicensed) of sale or provision of medicines for individual patients or other medicine providers.
post-marketing surveillance	Surveillance activities that occur following market approval of a

	medicine, including: maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products. Post-marketing surveillance is typically considered a key regulatory function and refers to the set of comprehensive quality surveillance activities.
Quality assurance	An integrated system of activities involving planning, quality control, quality assessment, reporting, and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence.
Quality control	All measures taken, including the setting of specifications, sampling, testing, and analytical clearance, to ensure that raw materials, intermediates, packaging materials, and finished pharmaceutical products conform with established specifications for identity, strength, purity, and other characteristics.
Quality survey	Serves as a source of information about the quality of medicines available to patients at a point in time. However, quality surveys rely on laboratory testing and cannot offer complete assurance that medicines are safe and effective.
Safety	The medicine should not present risks that are disproportionate to its benefits.
Sample	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.
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.
Sentinel sites	Communities from which in-depth data are gathered and the resulting analysis is used to inform programs and policies affecting a larger geographic area. Sentinel sites are a limited number of selected reporting sites from which the information collected may be extended to the

	general population. Sentinel surveillance systems are useful because a rich source of data collected from the sentinel sites enables more accurate estimation of a risk than that available from broader passive surveillance programs.
Simple random sampling	Random sampling is a probability-based sampling technique whereby a group of subjects is selected (a sample) for study from a larger group (a population). Each subject is chosen entirely by chance, and each has an equal (or non-zero in the case of complex random sampling) chance of being included in the sample. This technique differs from convenience sampling, which is a non-probability sampling technique and is therefore prone to biases. Convenience sampling may, however, be suitable for identifying potential areas with a high risk of poor-quality medicines so that further sampling can be conducted.
Stratified random sampling	A probability sampling method in which the population is divided into non-overlapping subgroups (strata) and then a probability sample (often a simple random sample) is drawn proportionally from within the different strata.
Substandard	Also called “out of specification,” this term refers to authorized medical products that fail to meet either their quality standards or specifications, or both.
Suspension	An administrative measure taken against regulated person or product when the Authority has a reason to believe that any of the grounds for suspension exist.
Unregistered	Medical products that have not undergone evaluation and/or approval by a national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

1 Introduction

1.1 Background

Good quality medicines are essential for efficient disease management. Substandard and falsified medicines can cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to the development of drug resistance. Vulnerable populations and patients with comorbidities are at particular risk of being harmed from receiving substandard or falsified medicines. Poor-quality medicines also increase health care costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health.

Medicines regulation is a complex process which is comprised of various regulatory instruments like 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. It can also include post-marketing surveillance (PMS) activities, such as maintenance of products' authorization and/or registration through variations or renewals, regular inspections of manufacturers, wholesalers and retailers, quality control testing, use and disposal of medicines, pharmacovigilance, and implementation of regulatory actions in the event any quality problem being found. When a product is publicly available, it is not possible to anticipate every conceivable side effect or adverse event that could occur in broad and diverse populations, and it may not be realistic for manufacturers to foresee every manufacturing issue that could appear during full-scale operation.

Quality of medicines may easily deteriorate through improper handling during distribution or storage before they reach patients. Quality control/quality assurance (QA/QC) of medicines in the distribution system according to proper specifications is, therefore, an important prerequisite in ensuring optimal outcomes. Noting this, introducing quality surveys of marketed products are thus vital in ensuring quality of medicines. It provides information on handling, storage and manufacturing conditions that affect quality of products so that corrective actions can be implemented.

For these reasons, the Ethiopian Food and Drug Authority (EFDA) is serious about post-market surveillance. It is an inherent responsibility for the Authority, which is clearly stated in the Proclamation No. 1112/2019, article 4-section 9. The Authority's mission is to ensure that all medicinal products are safe, effective and of good quality so that the public's health is protected. On the other hand, the Authority alone could not create a robust post-marketing surveillance infrastructure. Post-marketing surveillance is, therefore, a multidimensional activity with shared responsibilities for EFDA, pharmaceutical manufacturers, importers, wholesalers, retailers and end users. It encompasses a litany of regulations linked to product safety, efficacy, and quality and labeling, all of which must be considered as a holistic path to compliance. Because of the complex nature of this activity, manufacturers are highly encouraged to begin structuring their post-

marketing surveillance programs even before they make a regulatory submission because of the amount of details needed to create a robust program.

Regulation of prescription and non-prescription medicines is critically important in protecting the health and safety of citizens. However, the approval process for new medicines cannot adequately predict the full extent of harmful or unexpected effects of a drug once it is on the market. Consequently, a post-marketing surveillance system is necessary for medicines. Such a system will be able to detect harmful and unexpected effects of medicines in a timely manner to avoid delay in follow-up and intervention measures. It also helps to improve the protection of health and safety of patients, users and others by reducing the likelihood of the same type of adverse incident being repeated in different places at different times.

Post-marketing surveillance of medicines, therefore, plays an important role in discovering the actual status of products in terms of their safety, quality and efficacy that might present a risk to the users. As a result, the Authority may take appropriate measures of risk prevention or propose studies to further investigate the hazard and frequency of its occurrence related to safety, quality and efficacy of the products studied. This is very important to monitor continued safety, quality and efficacy of medicines. Thus, PMS is critical in ensuring that medicines in the Ethiopian market meet specifications.

This Guideline succeed and supersede the first Guideline implemented in 2015, which was in use for conducting post-marketing quality surveillance of medicines. It has been revised based on the following main benefits:

- To incorporate the role of pharmaceutical importers and manufacturers in PMS;
- To introduce risk-based PMS principles in conducting PMS of medicines;
- To incorporate the guide from the new WHO's Guidelines on the conduct of surveys of the quality of medicines, which was published in 2016; and
- To incorporate new developments in conducting PMS.

Therefore, this Guideline was revised with the intention of having a standard and consistent way of conducting post-marketing quality surveillance of medicines to give information related to why, who, how, when and where to conduct the survey and take appropriate measures based on the PMS findings following a risk-based approach. As the study methods in this field continue to develop, there will be a need to regularly review the Guideline to ensure that new methodologies are adapted in the assessment of EFDA regulated product quality, safety and efficacy.

1.2 Risk-Based Approach to Post-Marketing Surveillance (RB-PMS)

Moving from sporadic medicines quality monitoring activities toward robust risk-based post-marketing surveillance programs is critical for Ethiopia to ensure the quality of medicines. Effective RB-PMS programs can also optimize the use of resources and create sustainable post-marketing surveillance programs that are integrated and implemented as a core regulatory function. Figure 1

depicts the key aspects of developing and implementing a risk-based post-marketing surveillance program.

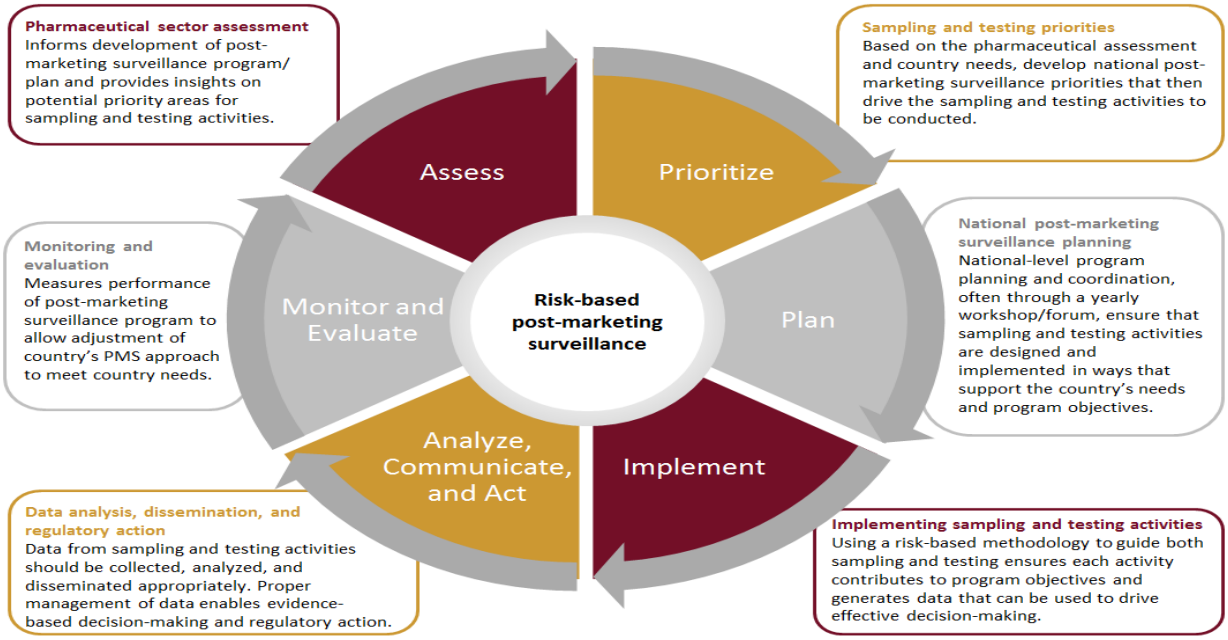


Figure 1: Framework for developing and implementing post-marketing surveillance programs adopted from Guideline for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries. 2017. USP/PQM. Rockville, Maryland.

1.3 The post-marketing surveillance system

Post-marketing surveillance encompasses the pro-active and reactive collection of information on quality, safety and performance of medicines, medical devices, complementary medicines, cosmetics, and related substances after they have been introduced in the market.

Thus, greater involvement of all actors and consumer will considerably improve the effectiveness of the post-marketing surveillance system. PMS can be conducted in three different ways.

Safety studies: Safety is a measure of the probability of an adverse or untoward outcome occurring and the severity of the resultant harm to health of individuals in a defined population associated with use of a medical technology applied for a given problem under specified conditions of use and helps to detect adverse reactions of medicines and which were not observed on the development/formulation phase of a particular product on population subgroup which are not normally exposed during the clinical trial.

Efficacy studies: Efficacy is benefit or utility to the individual of the treatment regimen, drug, preventive or control measure advocated or applied. The factors to be studied in this type of PMS are benefits to be achieved, medical problem giving rise to use of the technology, Population affected, and Conditions of use under which the technology is applied.

Quality studies: Quality study of medicines stands for testing the collected samples in a proper quality control laboratory to identify the presence of substandard and counterfeited products. It can be achieved by chemical, physical or biological testing of the collected samples.

1. Scope of the Guidelines

This Guideline applies to conducting PMS, which evaluates the quality of marketed medicines through laboratory testing and gathering sufficient data on the regulatory and usage status of the medicines in the market. Though the study design used must be adopted on a case-by-case basis for products using specifically designed PMS protocols, the Guidelines define the essential principles to be applied in a varity of situations.

3. Objectives

3.1 General objective

The general objective of this Guideline is to guide survey of the quality of selected medicines available in the market in selected areas at various levels of the distribution channel with the aim of assessing the quality status of medicines and proposing appropriate actions.

3.2 Specific objectives

- To provide recommendations and various methodological approaches in conducting a survey of the quality of medicines
- To provide suggestions on the preparation of surveys' reports
- To provide guidance in taking appropriate actions based on the PMS findings
- To provide scientific evidences to enhance evidence based regulatory decisions

4. Management of PMS Programs

4.1 Main activities of PMS

PMS needs a collaborative and coordinated system to achieve the best results at the end of the program. It involves the pro-active and reactive collection of information on quality products after they have been released into the market. It is a post-registration procedure system to maintain the quality of the medicines. The main activities expected from the PMS system are the following:

1. Collection of samples for selected medicines from the formal and/or informal market as per the protocol or in response to complaints;

2. Testing of sampled medicines;
3. Writing of reports for each PMS activity;
4. Taking administrative measures;
5. Implementation of corrective and preventive actions; and
6. Follow up on the administrative measures taken and recommendations.

4.2 Survey Management Task Force

Noting the poor quality or substandard medicines and counterfeit medicines has a direct and huge effect on the public health. A well-structured PMS system is very important. As a result, a PMS system requires collaboration and coordination activities among different departments and stockholders, such as different Directorates of EFDA, the Ministry of Health (MOH), disease programs, manufacturers, importers, and other relevant partners and stakeholders.

Depending on the type of products under surveillance, the study design will be determined by the objectives of the study, which must be clearly defined and detailed in the study protocols. Any specific quality concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods.

The process of conducting PMS needs coordination to ease the effectiveness of the activities. For this reason, a national PMS task force will be established to coordinate the overall PMS activities. The task force will involve all key players in the activities of the PMS.The task force consists of representatives of the following directorates and organizations. This task force is directly responsible to Medicine Facility Inspection Directorate. The PMS task force will adopt its own rules of procedures.

1. Medicine Facility Inspection Directorate
2. Medicine Quality Control Directorate
3. Medicine Registration and Licensing Directorate
4. Concerned programs of Ministry of Health (MOH)
5. Stakeholder or partners who provide technical and financial assistance.
6. Other Directorates or Offices of EFDA as appropriate

4.3 Roles and Responsibilities

4.3.1 PMS management task force

The PMS task force will carry out the following responsibilities:

- Supervise all PMS activities.
- Develop a detailed action plan based on the annual work plan.
- Develop and/or revise protocols for PMS as necessary.
- Map medicine outlets.
- Select study area for collection of samples.

- Select medicinal products to be sampled.
- Select people who will collect samples in each sentinel site.
- Arrange training programs and trains sample collectors, sample analysts and mystery clients as required and also provides relevant inputs for training.
- Prepare sampling strategies (number of samples per site/sector/source).
- Ensure that all input for sample collection and testing are fulfilled.
- Collect and analyze data and information generated through the PMS system.
- Ensure design of PMS database.
- Write and submit final report to EFDA and donors and ensure use of evidence for action.
- Monitor and evaluate implementation of the PMS system.
- Manage logistics, including transportation to and within the sites.
- Assist in dissemination of the PMS results and taking relevant regulatory actions.

4.3.2 Medicine Facility Inspection Directorate

The Directorate will oversee the following responsibilities.

- Coordinate the national PMS task force.
- Manage oversight of PMS activities in collaboration with the PMS task force.
- Ensure that all samples collected conforms to sampling protocols.
- Ensure that samples collected are delivered to Medicine Quality Control Directorate.
- Take appropriate administrative measures based on the PMS results.
- Serve as a member of the national PMS task force.

4.3.3 Medicine Quality Control Directorate

The Directorate will oversee the following responsibilities.

- Receive and store samples in conformance to the protocols.
- Provide method validation and verification, if necessary.
- Conduct analysis on timely basis.
- Prepare and submit the summary of analysis report of the raw data to the PMS committee.
- Perform additional testing if this is required.
- Store retained samples for reference and future use.
- Serve as a member of the national PMS task force.

4.3.4 Medicine Registration and Licensing Directorate

- Provide reported quality defect medicines with necessary information to the PMS task force
- Identify which medicines are registered or unregistered.
- Be involved in the implementation of the administrative measures.
- Identify each product label with data base label bank (label comparison).

- Compare the sample information with the specification obtained during pre-marketing data
- Serve as a member of the national PMS committee.

4.3.5 Ministry of Health (concerned programs)

- Provide program-related medicines information and of quality defective medicines.
- Play a role in the selection of sentinel sites.
- Provide information on newly introduced programs.
- Support the implementation of the administrative measures taken on specific public health programs.
- Serve as a member of the national PMS task force.

4.3.6 Partners who provide technical and financial assistance

- Provide technical and financial assistance in the implementation of PMS programs.
- As per the agreement with EFDA, share reports with appropriate partners.
- Provide supervisory visits and trainings.
- Support logistics, including transportation to and within the sites.

4.3.7 Role of medicine manufacturers, importers and wholesalers

EFDA has been conducting PMS activities with its budget and in collaboration with development partners. But now it is also important to include manufacturers and importers to the PMS activity. Hence, the following are roles of importers and manufacturers in the PMS:

- Perform periodic monitoring of quality, safety, and efficacy of its manufactured or imported medicine.
- Perform PMS that would enable it to continuously monitor its medicine when required by the EFDA or on its own will.
- EFDA may periodically undertake PMS of medicine and may require manufacturers or importers, as appropriate, to cover the associated cost.
- Be responsible for damages caused as a result of quality and safety problem associated with the product.
- Cooperate during sample collection.
- Report results of the PMS conducted by themselves to EFDA

5. Methodology

5.1 Selection medicines to be surveyed

Fully regulating the quality of all medicines circulating in the country is extremely difficult and often unfeasible. Hence, applying risk-based approaches to select medicines for sampling and testing as part of a post-marketing surveillance program is imperative. Even within the same disease, risk-based approaches must be applied in selecting the type of medicines to target. The authority may use the following criteria:

- Newly introduced medicines on the market,
- Branded medicines with limited safety and efficacy data,
- Medicines with complex formulations,
- Medicines known to have stability issues,
- Medicines to which antimicrobial resistance is increasing,
- Medicines in high demand,
- Manufacturers or suppliers with previous quality issues,
- The likelihood that poor-quality medicines exist, and
- Potential health impact on patients.

The medicines to be sampled and 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 importers or wholesalers declared on the label).

Therefore, the medicine selection for a survey is made based on the survey objective and potential public health impact using a series of risk factors. For example, a medicine risk assessment tool (**MedRS)** developed by USP/PQM can be used to select medicines to be surveyed. If collection of commonly used products is required, a pre-survey investigation of treatment-seeking behavior may be necessary. Collaborating with other actors, such as national disease control programmes, may help to identify products commonly used. The following are some risk factors to be considered during selection of the medicines:

- ✓ Stability of medicines
- ✓ GMP compliance (of manufacturers if known)
- ✓ Distribution chain complexity
- ✓ Extent of population exposure
- ✓ Patient vulnerability
- ✓ Dosage form complexity
- ✓ Therapeutic risk
- ✓ Extent of harm due to poor quality

- ✓ Availability of the medicine during the survey period.
- ✓ Safety and quality history of the product (prior pharmacovigilance (PV) or medicine quality information, from prior studies)
- ✓ Extent of distribution and use of the medicine in the region
- ✓ Manufacturing and distribution chain complexity
- ✓ 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

5.2 Selection of areas to be sampled

5.2.1 Selection of geographical area

Based on the sampling and testing plan, risk-based selection should first be applied to the geographical areas where the sampling of medicines will be conducted. Such criteria could include poor storage conditions, poor access, high disease burden, population size, porous border zone, level of drug resistance, presence of illicit market, complexity of supply chain, and specific issues reported by prior inspections. Areas with a high risk of compromised medicines quality and/or patient safety should be prioritized. Selection criteria should be identified and applied during the initial planning in collaboration with key stakeholders and based on EFDA's knowledge of the medicines supply chain in the country.

5.2.2 Types of sample collection sites (sampling level)

Sample collection will be done at the different levels within the drug distribution chain in Ethiopia and the following are different levels to be considered during sample collection.

Level 1: Points of entry to the market: Warehouse of Importers/ manufacturers, central and district medical stores, NGO central stores, procurement centers or other facilities supplied directly within various programs, central wholesalers and/or distributors

Level 2: Wholesale, regional stores, districts stores

Level 3: Retailers: pharmacies, drug stores, RDVs, hospitals, speciality centres, health centres, clinics and health posts

Level 4: Illegal outlets: Sites selling medicines outside the approved distribution system and includes Informal or unauthorized markets.

Level 5: virtual outlets -sales of medicines via the Internet.

Note: Using the medicine risk assessment tool, risk levels are attributed to each level with the highest risk at level 4 and lowest at level 1.

Sampling should usually be performed in both the public and private sectors as well as in the "informal market"; that is, 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 in the study protocol.

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.Specific sample collection outlets will be selected using PMS risk-based screening tool based on the list prepared from each sentinel site before collection starts.

5.2.3 Mapping sample collection sites/areas

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 or regions 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 relevant disease control programmes, regional regulatory bodies and also importers of the product in this respect is crucial.

The following factors could be considered while determination of sample collection areas:

- Epidemiological data demonstrating the prevalence of the disease in the area
- Probability of getting the product at the site;
- Presence of either of medicine outlets (private or public or informal);
- Adverse drug event (ADE) reports;
- Climatic condition to affect the stability of medicines; and
- The potential for product smuggling and illegal border trade to take place in the site and; and
- Oother relevant criteria, if any.

5.3 Selection of sample collection outlets

A risk-based medicine assessment tool such as MedRS may be used to identify the actual outlets from which the samples are going to be collected. Those tools should integrate and automate the science and practice of a risk-based post-marketing surveillance into a single platform.

It enables to consistently implemented risk-based approaches to answer important questions for post-marketing surveillance, including:

(1) Which geographical locations and outlets should be sampled?
(2) How many geographical locations and outlets should be sampled?
(3) How many samples should be collected?

5.4 Sampling Designs

Various designs can be used for the 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.

5.4.1 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.

5.4.2 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 medicine. A valid sample size calculation should be used to determine a representative sample size for random sampling.

5.4.3 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, such as sales volume, type of customers, or geographical, trade and socioeconomic variables. 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.

5.4.4 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.

5.4.5 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, private versus public outlets, or sampling design, such as convenience or random samples or lot quality assurance sampling (LQAS).

5.5 Sampling Plans

Sampling plans should be prepared for each sample collection area involved in the survey and should be in compliance with the 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);
- ✓ 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 relevant collection area.

Sampling plans should also contain detailed instructions for collectors.

5.5.1 Number of dosage units to be collected

Use of the risk-based approaches discussed in previous sections reduces the potential number of samples to collect. However, the number of units to collect per sample depends on the objectives of the sampling and testing activity, the type of medicine, the planned tests to be applied, and the approved medicine specification. 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 in the survey protocol 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 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) as per EFDA's OOS Procedure; and
- ✓ 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 and should be detailed in the specific survey protocol.

5.5.2 Substitution criteria

In case where the sample collectors cannot get samples from the already randomized collection outlets, then the survey protocol should have a substitution criterion to get the planned number of samples. The following are possible scenarios that will force the survey to have a substitution criteria:

a. If the randomly selected sampling outlet is closed.

b. If the medicine is not available or the dispenser/seller is not willing to offer.

c. If the available medicine in the outlet has less than five months shelf life.

d. When the stock available are limited and that medicine is important for life of the patient.

e. When there is possibility of not getting minimum quantity of medicines in the collection outlet.

e.g of a substitution criteria could be: Sample collectors will substitute sampling outlets by replacing the randomly selected sampling outlet by the nearest similar level facility found in the same stratum.

5.6 Sample collection

The survey protocol should identify the type of sampling technique to be followed depending 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 it is known that the outlet is selling poor-quality medicines and understand the health, legal and ethical implications). Basically, two kinds of sampling techniques are used: **overt** and **covert**:

5.6.1 Overt sampling versus mystery-shopper approach

Overt sampling: 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.

Covert sampling: In covert sampling, a mystery shopper mimics a "normal shopper" from the community where the outlet is located and should dress, speak and behave appropriately for that community. Mystery 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.

Hence overt sampling technique will be used in public/private level I health establishment while covert sampling (mystery shoppers) will be used in private/public level II-IV establishment as applicable.

5.6.2 Training (instructing) sample collectors

Sample collectors should be trained or orientated on sampling procedures and techniques and on how to approach medicine outlets and how to request medicinal products. The composition of the sample collectors should be determined in each protocol and such a training should be organised by EFDA's Medicine Facility Inspection Directorate.

Staff from EFDA Medicines Facility Inspection Directorate, Medicines Quality Assessment Directorate, Medicines Registration Directorate, regional regulatory bodies, branch EFDA offices and different national disease control programmes may provide useful insight into the survey planning. Instructions and procedures for data collection should be well understood by the collectors and also translated into the language of the collectors when required, pilot-tested and revised, if needed.

5.7 Storage and transportation of samples

Inappropriate handling, storage, and transportation of samples affect the overall integrity of medicines and can compromise results. This is particularly true for medicines that have poor stability profiles and/or require cold chain transportation. It is important to observe the following best practices throughout the chain of custody of the products:

- Avoid excessive mechanical vibration during transportation.
- Store in original container, where available, and label accordingly.
- Label each sample with the location of collection, number of samples collected, name of the sampler and any observation at the time of collection.
- Samples that are light or heat sensitive may require special handling, transportation, and storage conditions. If cold storage is indicated, store in an appropriate container and monitor the temperature during transportation.
- 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 completed sample collection forms (annex 2) and, if available, copies of the manufacturer's batch certificate of analysis should accompany the samples.

- There should be a strong collaboration between the sample collection team and the Laboratory in transporting and storing the samples in the laboratory.

Note: Details of sample storage and transportation conditions should be included in the study protocol and the sample collectors should also be trained appropriately.

5.8 Testing

5.8.1 Laboratory Testing

Medicines quality testing is an important component of a PMS system. After the collected samples are properly delivered to the quality control laboratories, the laboratories should test the collected products on a timely basis, according to the protocol, to clearly identify quality, substandard and falsified products. The collected samples should not be expired before testing. The specific tests to be carried out depend on the products collected and the specific objectives of the study. The test could be in full or selected tests as per approved pharmacopoeia or in-house specifications. Relevant procedures (monographs) used to test the product, a method submitted at the time of registration for registered products or monograph as labeled on the unregistered products, should be followed to evaluate quality of the product through laboratory testing. The test result should be filled to the laboratory certificate of analysis (Annex 3) and submitted to the PMS task force for preparing the final PMS report. If different laboratories of EFDA or other competent laboratory are testing collected samples, then the samples should be divided in such a way that all samples containing the same APIs are assigned for testing to the same laboratory.

If outsourcing the testing to a competent external testing laboratory is required, within the usual selection procedure and the resulting agreement, then 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, then a specific testing protocol should be prepared for each laboratory.
- Responsibilities of the laboratory during the survey.
- 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;
- 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.

This guideline also recommends the use of a tiered approach to testing as part of PMS and builds upon and refines the Three-Level Approach, which proposes that testing can occur at three levels: in the field, initially through visual inspection; then through field-based tests (using the Minilab™ or other screening tools); and finally, at the laboratory as required (using compendial
or other methods accepted by the EFDA).

5.8.2 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 upon 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; and
- Performing special or specific tests (e.g., microbial test).

If testing is expected to provide a full picture of the quality of target medicines, then it should be performed according to a pharmacopoeial or analogous monograph or manufacturers' method. The following tests are, in principle, included but selection should follow the risk-based approach:

- Appearance, visual inspection;
- Identity;
- Assay for APIs declared on the label;
- Test for related substances;
- Solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), fineness of dispersion, for dispersible tablets;
- Liquid dosage forms – pH value and volume in containers or extractable volume; and
- Parenteral products – sterility and bacterial endotoxins tests.

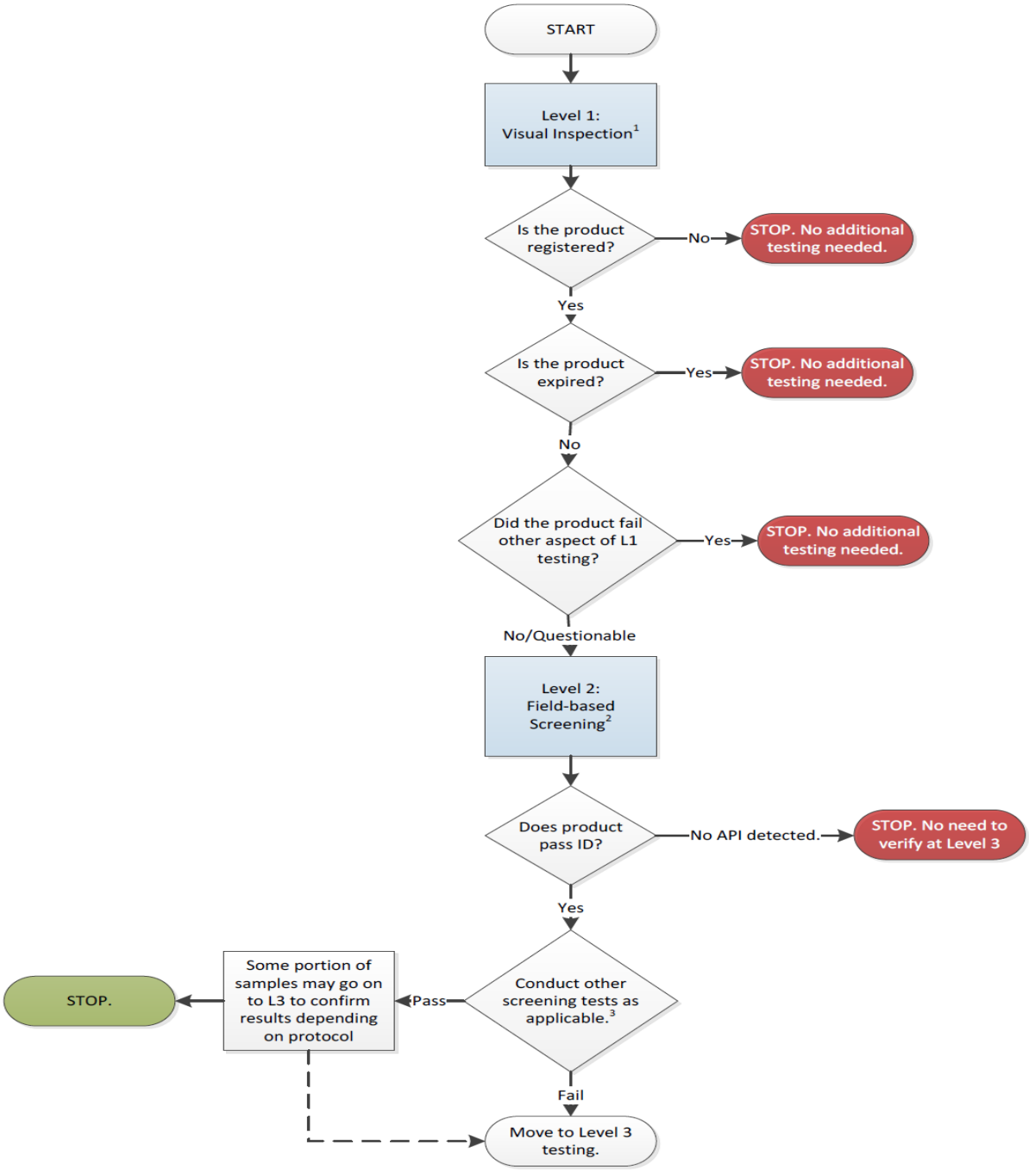
Inclusion of tests for uniformity of content for single-dose dosage forms, or for sterility and bacterial endotoxins, which are costly and time-consuming, and necessitate the collection of more dosage units, should be considered in relation to the target medicines and available resources. It is impossible 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.

Pharmacopeial /manufacturer's methods should be used to give information for EFDA to take relevant measures but other types of surveys include quality screening surveys using basic, simple tests, non-destructive techniques (e.g. Raman and infrared [IR] spectroscopy, minilab technique) or unofficial testing methods (e.g., non-pharmacopoeial or those not approved by the NMRA during the registration process) to assess the identity of the product 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).

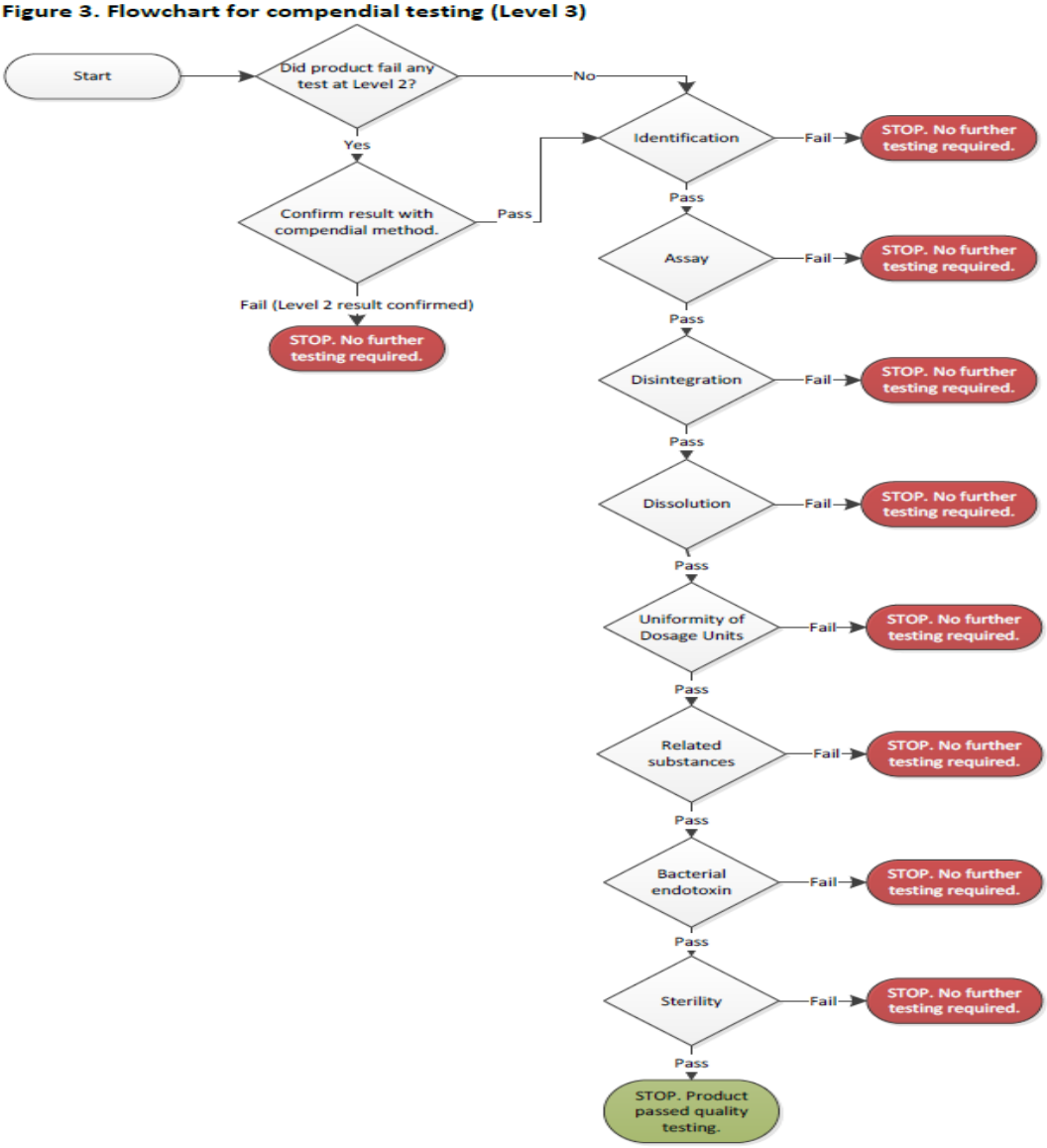
Figure 2 provides a flow diagram for conducting visual screening. Before assessing other aspects of quality, inspectors should confirm that the product is registered with the appropriate and relevant regulatory authority and has not expired. When unregistered or expired products are detected, inspectors should discuss the findings with the regulatory authority to determine appropriate next steps. Depending on the objective of the study, further assessment of the quality of the product may be warranted.

Figure 2. Guidance for visual and field-based screening (Levels 1 and 2)



Compendial testing should be carried out on suspected samples that fail field-based screening tests and, depending on the protocol, on a portion of samples to confirm the results from Level 2. Figure 3 proposes a scheme for prioritizing compendial testing based on the type of product being tested, the risk associated with samples, the costs associated with particular tests, and the technical complexity. The use of Pharmacopeial methods or other validated methods approved by the NRA is recommended. Note that if a product fails a test at Level 2 (for example, the sample does not pass disintegration), the same test should be performed at Level 3 using compendial methods before initiating tests for other quality attributes. If the result from Level 2 is confirmed at Level 3, then no further testing is needed. If, on the other hand, conducting the same test using compendial methods does not confirm the result from Level 2 testing, it is recommended that the analyst proceed with the suggested prioritization of compendial tests as outlined in Figure 3.

Figure 3. Flowchart for compendial testing (Level 3)



5.8.3. 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 and label 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. Wherever appropriate, pharmacopoeial methods and specifications should be used. 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. 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.

5.8.4 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, such as 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;
- Confirm proper storage condition was used during sample transportation;
- Conduct quality testing in line with the testing protocol and in compliance with the Laboratories Quality Management system;
- Prepare complete analytical test reports and certificates of analysis containing the information listed in Annex 3;
- 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 coordinator 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) did not comply; and
- Archive data according to the agreed conditions following the internal procedure of EFDA on sample management.

5.8.5 Regulatory status studies

Registration status of the collected samples will be studied using the EFDA database of registered products and the label of the collected products should also be evaluated against the original label provided from the product manufacturer at the time of registration. Evaluation of the product label against the standard label may not be relevant for products that are not registered by authority.

6.0 Data analysis, communication and action

6.1 Data analysis

To allow proper interpretation, the data obtained during collection and testing of samples should be summarized and appropriately organized 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.

After all the assessments, the PMS task force shall prepare a standard report based on the findings. Every report will contain a summary of the results and recommendations to guide the Authority. Finally, the report shall be officially submitted to the Medicine Facility Inspection Directorate for review and any relevant measures.

6.2 Communication

The findings from PMS, including measures taken, must be communicated to the relevant stakeholders and the public. This should be accomplished, considering their mandates, by the Public Relation and Communication Office, Legal Drafting and Medicolegal Directorate and ICT team of the Authority. Different mechanism can be used to disseminate/communicate the PMS findings results. The following should be taken into consideration:

- Present results in different forums to raise awareness on quality of medicines;
- Publish in different bulletins, newsletters, magazines and other relevant printed materials;
- Use different electronic medias, including radio and television;
- Upload results to the Authority's website and other recognized websites;
- Write and disseminate a press release with the results and contact information for follow-up; and
- Capture and collate results through online publicly available databases such as the Medicines Quality Database (http://www.usp.org/global-health/medicines-quality-database) or WHO's Global Surveillance and Monitoring System (GSMS; http://www.who.int/medicines/regulation/ssffc/surveillance/en/).

6.3 Action

Depending on the data and results found by PMS, the potential public health importance of the findings, the Authority may take a variety of actions, including, but not limited to:

- Further testing of samples;
- Requesting additional information or clarification from market authorization holders;
- Recall of products according to the EFDA's SOP or guidelines for recalling substandard and counterfeit medicines. Manufacturers and importers have the responsibility to conduct the recall process;
- Suspension of a product's marketing authorization;
- Warning in EFDA's national bulletins or separate warning sent out to a list of institutions and any key persons dealing in /or prescribing the product;
- Adequate and proportional sanctions, penalties and prosecution upon conviction for violations of the applicable legislation;
- Communicate with relevant stakeholders like regional health bureaus, neighboring countries and other relevant organizations;
- Take administrative actions in collaboration with relevant regulatory bodies and police;

- Take relevant legal actions in accordance with the administrative measures and complaint handling guidelines and other national laws. (Note: Flow of the PMS is mapped in annex 1)
- the administrative measures and complaint handling guidelines and other national laws. (Note: Flow of the PMS is mapped in annex 1)

7. References

1. WHO Guideline on the Conduct of Surveys of the Quality of Medicines (WHO-TRS number 996, 2016, Annex 7). World Health Organization: http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_web.pdf

2. Promoting the Quality of Medicines (PQM) Program: Guidance for implementing Risk-Based Post-Marketing Quality Surveillance in Low-and -Middle -Income -Countries: https://www.usp-pqm.org/sites/default/files/pqms/article/risk-based-post-marketing-surveillance-feb-2018.pdf

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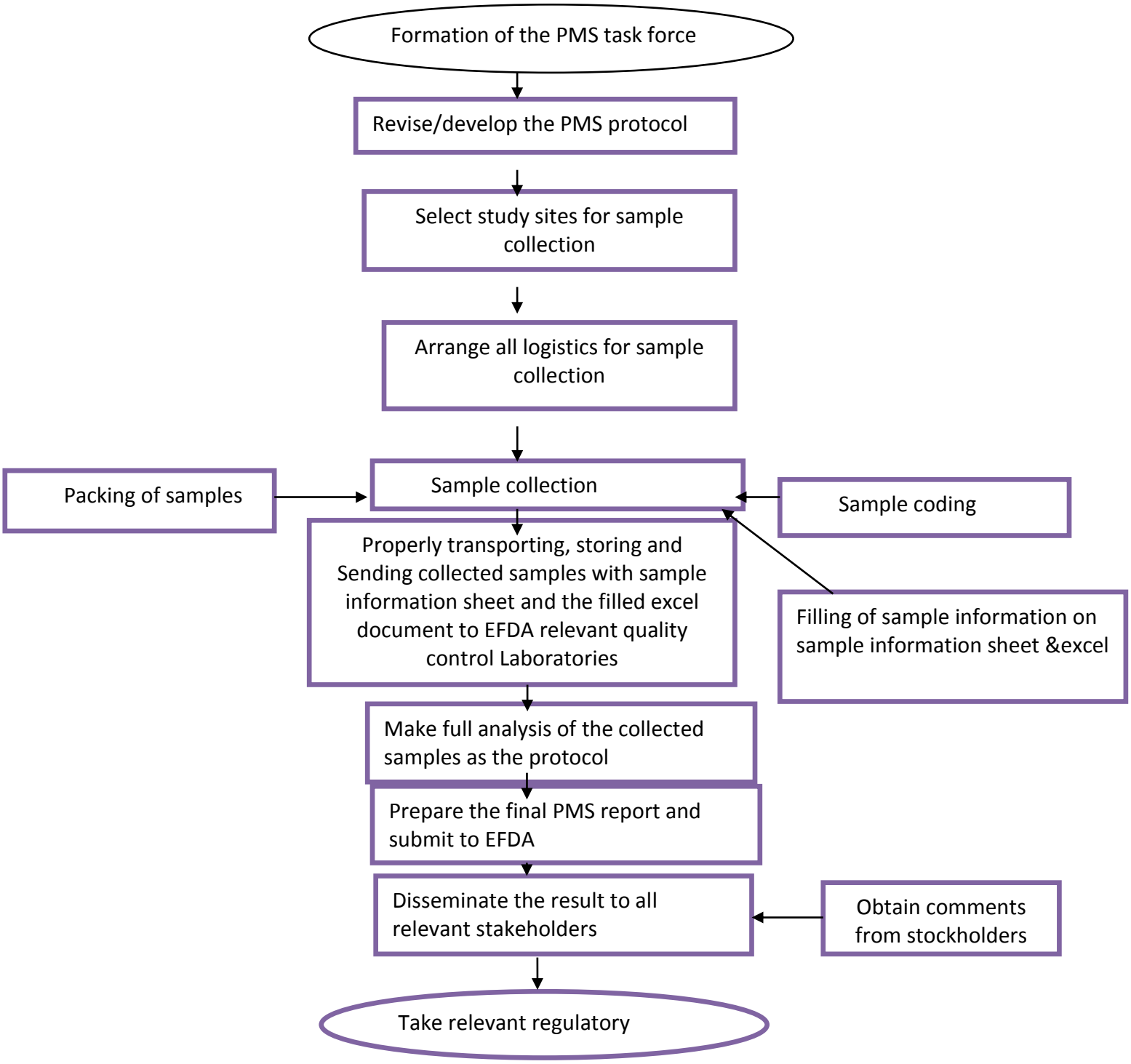
6. Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies: http://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex3.pdf

7. A Risk-based Identification of Essential Medicines for Local Manufacturing in Low- and Middle-Income Countries. World Health Organization: http://www.who.int/medicines/areas/quality_safety/quality_assurance/Local-manufacturing-risk-QAS16-682_24082016.pdf?ua=1

8. A Risk-Based Resource Allocation Framework for Pharmaceutical Quality Assurance for Medicines Regulatory Authorities in Low- and Middle-Income Countries: https://www.usp-pqm.org/sites/default/files/pqms/article/risk-based_resource_allocation_framework_june2018.pdf

Annexes :

Annex 1: Post Market Quality Surveillance of medicines flow chart



Annex 2: Sample information filing form

	Ethiopian Food, Medicine and Health Care Administration and Control Authority	Page 1 of 1
	Inspection and Surveillance Directorate	FORM_ISD_001
Sample information filing sheet (form) for PMS of medicines circulating in Ethiopia		

Sample code· _____
(Site name / Type of the product/ Sampling date MM-YY / Sample sequential number: A/B/C/D)
Type of collection premise: Private: _____; Public: _____; NGO: _____
Name of drug outlet/ location/place where sample was taken: _____
Address (with telephone, fax number and email address, if applicable): _____
_____
Organization and names of people who took samples:
1. _____
2. _____
Product name of the sample: _____
Name of active pharmaceutical ingredient(s) (INN) with strength: _____
Dosage form (tablet, capsule, powder for injection, etc)· _____
Package size, type and packaging material of the container: _____
Batch/lot number: _____
Date of manufacture: _____ Expiry date: _____
Regulatory status in the country, registration number, if applicable: _____
Name and address of the manufacturer· _____
_____
Quantity collected (number of sample units or of multidose containers taken)· _____
Storage/climatic conditions at sampling site/point (temperature and humidity, indication of conditions during daytime only is acceptable, comments on suitability of premises where products are stored at the particular site for the NDRA information):_____

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

Date· _____

Name & Signature of person(s) taking the samples	Name &Signature of Sample collection Supervisor
1._____	1. _____
2._____	

Note:

- ✓ Samples collected must remain in their original containers, intact and unopened.
- ✓ This Sample Collection Form should always be kept with the sample collected.
- ✓ Proper sampling procedures should be followed.

Annex 3: Certificate of Analysis-template

	FOOD, MEDICINE AND HEALTHCARE ADMINISTRATION AND CONTROL AUTHORITY OF ETHIOPIA	FORM-PQAD-034.003
	PRODUCT QUALITY ASSESSEMENT DIRECTORATE *Tel. 251-011-2776984* *P.O. Box 5681* *e-mail qctlab.daca@*	**Certificate No.**

Physico-chemical Certificate of Analysis

Sample Information

Sample ID:		Client Ref No.:	
Brand Name:		Generic Name:	
Formulation:		Presentation:	
Composition:		Batch No.:	
Mfg. Date:		Exp. Date:	
Manufacturer:		For the account of:	
Submitted by:		Method of Analysis:	
Analysis Request date:		Date Report prepared:	

Physico-chemical Test Results

Date of Test	Test Parameter	Specification	Observation	Conclusion
	Condition of the Sample			
	Description			
	Identification [by HPLC or UV-VIS]			
	Uniformity of Dosage Units [by HPLC or UV-VIS]*			
	Disintegration Test			
	Dissolution Test by [UV-VIS or HPLC]*			
	PH*			
	Loss on Drying (LOD)*			
	Water Determination By Karl Fischer (KF)*			
	Fill Volume/ extractable volume			
	Assay by [by HPLC or UV-VIS]*			

General Conclusion: The sample [**meets, does not meet]** the requirements as per …….

Remark

1. The test result is based on the tests carried out on the samples submitted to the laboratory by the customer.
2. * tests accredited for ISO 17025:2005

Analyst: - *Sign.* *Date:*

Reviewed by (Case team coordinator): - *Sign.* *Date:*

Approved by (Laboratory Director): - *Sign.* *Date:*

Ethiopian Food and Drug Authority (EFDA)

Mission

To promote and protect the public health by ensuring safety,efficay and quality of health and health-related products and services through product quality assessment &registration; licensing and inspection of health professionals, health institutions, pharmaceutical and food establishments, and provision of up-to-date regulatory information while promoting proper use of health and health-related products and services including proper use of medicines, pharmaceuticals & food establishments, and health facilities and provision of up-to-date regulatory information while promoting rational medicines use

Objectives

To protect the health of consumers by ensuring food safety and quality, safety, efficacy and performance of medical device, safety, quality and performance of medical device.

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