

REPUBLIC OF RWANDA



**GUIDELINES FOR POST-MARKETING SURVEILLANCE OF
PHARMACEUTICAL PRODUCTS**

RWANDA FDA
Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

[Handwritten signatures/initials]

[Handwritten signature/initials]

TABLE OF CONTENT

TABLE OF CONTENT	i
FORWARD.....	iii
ABBREVIATIONS	iv
DEFINITIONS.....	v
1. INTRODUCTION.....	1
2. OBJECTIVES OF POST MARKETING SURVEILLANCE	2
2.1. General Objectives	2
2.2. Specific objectives.....	2
3. ORGANIZATION OF POST MARKETING SURVEILLANCE	2
3.2.2 Post-marketing surveillance committee	3
3.2.3 Post Marketing Surveillance stakeholders	4
3.3 Planned Post-Marketing surveillance activities	4
3.4 Ad hoc PMS activities.....	4
3.5 Surveys/studies by external parties	4
3.6 Implementing teams.....	5
4. IMPLEMENTATION OF PMS USING RISK-BASED APPROACH	5
Figure 1: Risk based post marketing surveillance.(Reference:PQM, 2018).....	6
4.1. Planning.....	6
4.2. Development of PMS protocol using risk-based PMS approaches:.....	6
Steps in PMS planning.....	7
Protocol for Post marketing surveillance.....	7
4.2.1.SamplingSamplingdesigns ² :8	8
4.2.1.1. Convenience sampling	8
4.2.1.2. Simple random sampling.....	8
4.2.1.3. Stratified random sampling	9
4.2.2 Types of sample collection sites	9
4.2.3 Selection of medicines to be surveyed.....	10
4.3Sampling tools	10
4.4 Storage and transportation of samples	10
4.5 Receipt and testing of samples by a testing laboratory.....	11
4.6Testing	12
Level-1: Visual inspection.....	12
Level-2: Advanced screening whenever applicable	13
Level-3: Compendial testing.....	13
Figure 2.Guidance for Visual and Field-based screening(Level 1 and 2). (Reference: PQM, 2018)..	14
Figure3. Suggested prioritization for compendialtesting(level 3). (ReferencePQM,2018).....	15
4.7 Data management.....	16
4.8 Reporting	16
4.8.1. Internal reporting:	16
4.8.2.External reporting:	16
4.8.3. Third party PMS reporting.....	16
4.9 Regulatory action taking	16
4.10 Communication/Sharing of information	16
5. MONITORING AND EVALUATION.....	17
5.1. Indicator types and definition.....	17

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

<i>Guidelines for Post-Marketing Surveillance of Pharmaceutical products</i>	
Structural (STL) Indicators:.....	17
Process/Input (PRS) Indicators:.....	18
Output (OUT) Indicators:	18
Outcome (OUE) Indicators:.....	18
Impact Indicators (IMT):	19
Continuous improvement Indicators (COI):.....	19
Annex 1:SAMPLE COLLECTION FORM.....	20
Annex 2: Suspected Poor Quality Reporting Form	21
Annex 3: Test Request Form	23
REFERENCES.....	24



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

FORWARD

The Rwanda Food and Drugs Authority (RWANDA FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. According to the law, especially in its article 8 paragraph 9, the authority is mandated to conduct pharmacovigilance and post marketing surveillance for quality of products regulated.

These guidelines have been developed to provide guidance to stakeholders and Rwanda FDA in carrying out post marketing surveillance for quality of pharmaceutical products. It also provides guidance on dissemination of information on the quality of pharmaceutical products to health professionals and other stakeholders.

Rwanda FDA acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines. These guidelines were developed under the support of USAID/PQM in the spirit of promoting quality of medicines.



Director General
RWANDA FOOD AND DRUGS
AUTHORITY

RWANDA FDA

Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

ABBREVIATIONS

1. PMS : Post Marketing Surveillance
2. GMP : Good Manufacturing Practices
3. ISO/IEC : International Standardisation Organisation and International Electrotechnical Commission
4. PQM : Promoting the Quality of Medicines
5. USAID : United States Agency for International Development
6. Rwanda FDA : Rwanda Food and Drugs Authority
7. WHO : World Health Organization
8. SOP : Standard Operating Procedures
9. QA : Quality Assurance
10. MAH : Marketing Authorization Holder

RWANDA FDA
Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

DEFINITIONS

Pharmaceutical products: any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared or stored, cleaning hospitals, equipment and farm houses;

Unregistered/unauthorised Pharmaceutical products: Pharmaceutical products that have not undergone evaluation and/or approval by the Rwanda FDA for the market in which they are marketed/distributed or used, subject to permitted conditions under national regulation and legislation;

Substandard Pharmaceutical products: Also called “out of specification”, these are authorized Pharmaceutical products that fail to meet either their quality standards or their specifications, or both;

Falsified Pharmaceutical products: Pharmaceutical products that deliberately/fraudulently misrepresent their identity, composition or source;

Non-compliant products: Non-registered products or non-conform with specifications including substandard and falsified products;



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

1. INTRODUCTION

The burden of substandard and falsified medicinal products is a global public health problem causing loss of confidence in health systems leading to treatment failure, increase of treatment cost and may lead to drug resistance, disability, injury and/or death. The estimated burden of substandard and falsified (SF) pharmaceutical products within the East African region is not known but around 10% of globally traded medicines are estimated to be falsified with an even higher number in low-income countries¹.

Ensuring that Pharmaceutical products available to the patients are of good quality and maintaining the quality throughout the supply chain requires a robust quality assurance(QA) system. The regulatory system is an important component of QA. Under the law N° 003/2018 of 09/02/2018, the mission of Rwanda FDA is to “regulate pharmaceutical products, vaccines, human and veterinary processed foods and other biological products used in clinical as drugs, food supplements, food fortificants, fortified foods, poisonous substances, herbal medicines, medicated cosmetics, medical devices, tobacco and tobacco products, management of unfit pharmaceutical and food products and clinical trials on pharmaceutical products for human and veterinary use ensuring that Pharmaceutical products are of good quality”. Chapter II, article 8, section 9 of the law stipulates that the authority has the mandate to conduct pharmacovigilance and post-marketing surveillance for safety and quality of products. Post-marketing surveillance (PMS) of Pharmaceutical products is a regulatory function implemented by the Rwanda FDA to protect public health. An effective PMS system requires strong legislation, transparency, accountability, adequate human and financial resources, structured PMS planning, adequate quality control capacity, mechanisms for managing and communicating results and taking regulatory actions.

1.1 Purpose of the PMS guidelines

The purpose of this Post-marketing guidelines is to:

- Define the PMS program;
- Provide information, guide Rwanda FDA and stakeholders on how to plan and execute PMS activities;
- Set the ground for the development of PMS standard operating procedures(SOP).

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

Rwanda FDA will strive to build a strong PMS program that is comprehensive, inclusive, efficient, and sustainable. The authority will put in place the processes and use the tools and the resources that will help to implement the PMS. Rwanda FDA will aspire to continuously monitor and evaluate the efficiency of the PMS activities implementation and make necessary changes and adjustments to meet obligations toward ensuring that the medicines available to the patients are of good quality. Effective implementation of PMS guidelines will enable Rwanda FDA to generate scientific evidence on the quality and safety of medicines and medical devices for improved health outcomes.

1.2 Scope of PMS guidelines

The PMS guidelines are designed to cover a wide range of pharmaceutical products marketed in Rwanda in order to strengthen and improve their quality and safety.

2. OBJECTIVES OF POST MARKETING SURVEILLANCE

2.1. General Objectives

Post-marketing surveillance of Pharmaceutical product quality is implemented to safeguard access of the public to quality products by detecting and removing non-compliant products. PMS activities also allow periodic diagnosis of the Pharmaceutical quality assurance (QA) system that is in place to identify any gaps.

2.2. Specific objectives

PMS activities are carried out to:

- Evaluate the quality of Pharmaceutical products available throughout the supply chain;
- Remove noncompliant products from the market;
- Initiate actions to address the source cause of noncompliant products;
- Prevent noncompliant products from entering the supply chain;
- Identify gaps in the quality assurance system

3. ORGANIZATION OF POST MARKETING SURVEILLANCE

3.1 Rwanda FDA strategies for PMS

Rwanda FDA strategies for PMS include the following:

- Control of products at the port of entry: this includes verification of documents and products, visual inspection, screening of products and sampling for compendial testing whenever necessary.
- Sampling and testing of products available in supply chain.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

3.2 Structure of PMS program

The structure of PMS program is composed by Regulatory authority (Rwanda FDA), PMS committee and PMS stakeholders with the following role and responsibilities:

3.2.1 Rwanda FDA

Rwanda FDA coordinates all Post-marketing surveillance activities but mainly two divisions are dedicated including Quality control Laboratory division and Pharmacovigilance and Food safety monitoring Division.

Quality Control Laboratory Division

- To conduct quality control tests on the samples obtained using validated and/or approved methods;
- To provide evidence-based test results to inform regulatory action against identified substandard products.

Pharmacovigilance & Food Safety Monitoring Division

- To develop sampling protocol and sampling plan;
- To carry out sampling of selected products;
- To report on PMS activities;
- To conduct customer complaint survey, identify products to be included in the PMS sampling plan;
- To inspect the implementation of a regulatory action taken like product recalls and products in quarantine;
- To analyze and follow up on reports related to suspected poor quality pharmaceutical products.

3.2.2 Post-marketing surveillance committee

The committee is composed:

- Managers of Pharmacovigilance and Safety Monitoring Division,
- Managers of Drugs and Food Inspection and Compliance Division,
- Managers of Quality Control Laboratory Division.
- Other members including but not limited to Public Health Programs:
 - Central Medical Store,
 - National Pharmacy Council,
 - One representative from a private pharmaceutical establishment,
 - Complementary and alternative medicine practitioners shall be invited when needed.

The committee has the following roles and responsibilities:

- Set the priorities for PMS activities;
- Plan PMS activities;
- Provide recommendations on actions to be taken on non-compliant Pharmaceutical products.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

3.2.3 Post Marketing Surveillance stakeholders

The PMS stakeholders include pharmaceutical industries, MAH, pharmacy wholesales, retail pharmacies, health facilities, research institution(s), Public Health Programs, Central Medical Store and National Pharmacy Council, Health professional Organizations, Complementary and alternative medicine practitioners, etc.

PMS stakeholders have the following responsibilities:

- To report any suspected or confirmed poor quality product issues to Rwanda FDA (**using Annex 2**);
- To implement any regulatory action taken from PMS activities;
- Research institution(s) has (ve)the responsibility to submit research protocol related to post-marketing survey or study to Rwanda FDA for approval. The results from the survey or study shall be submitted to the Authority before publication.

3.3 Planned Post-Marketing surveillance activities

The Rwanda FDA will plan periodic surveillance of target medicines (once or twice a year). The periodicity of PMS activities will be determined based on quality-related information collected and the needs that may arise. The authority may conduct PMS activities for Health Programs sponsored by donors. For effectiveness and good resources management, PMS activities for Health Programs could be planned and carried out in combination with other PMS activities. These PMS activities should be defined in one protocol.

3.4 Ad hoc PMS activities

The Rwanda FDA may also conduct impromptu PMS activities. The authority may also conduct sampling and testing of pharmaceutical products following complaints from health professionals or consumers due to lack of concern about efficacy or apparent adulteration. The Rwanda FDA may also decide to sample and test products that were reported to be non-compliant with quality specifications by other countries. It may also sample and test products for which severe adverse events have been reported. Rwanda FDA inspectors may collect samples at inspection sites if the facility inspected raises concern.

3.5 Surveys/studies by external parties

The Rwanda FDA is the only entity mandated to carry out PMS activities in the country. The authority will participate in the development, review of protocols and approval for studies/surveys on Pharmaceutical products quality sponsored by external parties (Universities and Non-GovernmentalOrganizations). The Rwanda FDA shall oversee the implementation of the protocols and the approval of study reports before publication.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

3.6 Implementing teams

Inspectors from the Rwanda FDA are responsible for sampling Pharmaceutical products following a sampling plan. If needed, Rwanda FDA may delegate some sampling activities to staff from other institutions provided that they received adequate training and the delegation is officially documented. Each sampling team will have at least one inspector from the authority.

4. IMPLEMENTATION OF PMS USING RISK-BASED APPROACH

A risk based approach to post market surveillance is a method which concentrates limited resources on the areas considered most likely to pose a risk of quality defects due to limited resources.

PMS is one of the most challenging regulatory function to implement, which calls for close collaboration within the regulatory authority and among the authority and stakeholders. Considering that the number of Pharmaceutical products available in the market is very large, the high cost of sampling and testing, and the human resource needed, it is not conceivable to control the quality of all products on the market. Applying risk-based approach in the implementation of PMS has become a necessity. Rwanda FDA will adopt risk-based PMS (RB-PMS) approach at all levels starting from the planning to sampling, testing, and regulatory action taking, (See figure 1).



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date: 10/12/2022
Revision No.:0	Effective Date: 17/12/2019	



Figure 1: Risk based post marketing surveillance.(Reference:PQM, 2018)

4.1. Planning

Setting the objectives of PMS activities:

- Gathering of information regarding the quality of medicines and possible/potential challenges in the supply chain
- Identifying priority targets for post-marketing surveillance in consultation with stakeholders (Health programs, Central Medical Store, Pharmacists Association, etc...). Risk-based approach should be used to determine priority target products. The priority will be determined based on risk factors for the products to be surveilled and it should be given to products that are at high risk of presenting quality issues. High risk products may be for example those reported in pharmacovigilance, reported in other countries etc.....

4.2. Development of PMS protocol using risk-based PMS approaches:

Once the objectives of the round of PMS activities have been defined, development of PMS protocol can be initiated.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

- Develop sampling plan using MedRS (Medicine Risk based Sampling) or other tool/approach based on the objectives of PMS activities. A set of risk factors should be used for medical products selected for surveillance. Similarly, risk factors relating the sector (public, private, ..), geographical area, and location should be considered. The mapping of all pharmaceutical establishment, updated on regular basis, will be used to develop the sampling plan. As per PMS good practice, during each round of surveillance activities, the protocol should include the products/batches that have been reported to be falsified or substandard (e.g. WHO Rapid Alert reports). Inspectors should verify if these products are available at the sampling site.
- Gather information on the availability of target products before finalizing the sampling plan. This is important to avoid deviating too much from the sampling plan once in the field and realize that there are not enough units of a given medicine at a given facility to sample from. Consult with the stakeholders including supply chain managers
- Testing strategy for targeted products (3-Level approach, tiered-compendial testing). Once the sampling plan has been finalized, the testing plan can be developed. Targeted testing could be used based on the quality risk for a given product. For instance, if a given product can potentially have contaminants/impurities then priority will be given to impurities test;
- Budgeting

Budget should be developed to cover the cost of PMS activities.

Steps in PMS planning.

The steps in PMS planning include the following:

- Step 1: Preparation of PMS protocol
- Step 2: Preparation of sampling plan
- Step 3: Training of sample collectors
- Step 4: Procurement of samples/Sampling
- Step 5: Dispatch of samples to the laboratory
- Step 6: Analytical screening of samples
- Step 7: Identification of samples for full analysis
- Step 8: Collation and evaluation of result for analysis
- Step 9: Evaluating results (in case you detect poor quality, it is required to report immediately to the surveillance study coordinator for urgent actions on quarantining and recalls)
- Step 10: Preparation of Draft report of survey
- Step 11: Presentation of the draft report to relevant stakeholders
- Step 12: Preparation of final report
- Step 13: Dissemination and Publication of report

Protocol for Post marketing surveillance

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

Protocol for post marketing surveillance is a written detailed document that clearly outlines/describes how the surveillance should be carried out. In principle, the protocol should, contain information such as

- i. (i) Background and significance of the study,
- ii. Study objectives,
- iii. Methodology
 - a) Design of the study,
 - b) Selection of areas to be sampled
 - c) Selection of sample sites
 - d) sampling design
 - e) Number of sample units to be collected
 - f) sample collection
 - g) Storage and transportation of samples
 - h) Data management
 - i) Brief description of the Quality control Laboratory, and testing parameters.
- iv. Budget
- v. National Health Research committee/ ethics committee and Rwanda FDA approvals

4.2.1. Sampling Sampling designs²:

4.2.1.1. 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.

If a wider picture is needed, subsequent surveys using probability sampling can be designed. If convenience surveys do not reveal a problem one should bear in mind that this may be a false-negative result. It is important to explain the limitations of this technique in reports and scientific papers. Despite its limitations, convenience sampling is most suitable to identify high-risk areas for further regulatory actions.

4.2.1.2. Simple random sampling

Random sampling is a probability sampling technique that, if the sample size is sufficient, will give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor-quality medicines. The disadvantages of random sampling are the large sample sizes needed, the necessity for complete lists of the locations of the target outlets and the additional costs in terms of labour and time. In addition, it is important to recognize that a random survey will only produce reliable and useful information if the list of outlets and actual within-outlet sampling is consistent with the primary aims of the survey. Comparisons with subsequent estimates using this same sampling design should, however, be valid and will allow the evaluation of interventions.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

ed q

ll

4.2.1.3. Stratified random sampling

Stratified sampling is a probability sampling technique wherein the entire group of outlets is divided into different subgroups (layers or strata), then randomly selects the final outlets 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. 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.

Rwanda FDA will use one of the above mentioned sampling designs depending on the objectives of the PMS activity.

4.2.2 Types of sample collection sites

Sample collection sites in Rwanda are classified as follow:

- Public (government): including Central medical stores, District Pharmacies, Pharmacies for health facilities (Hospitals, Health centers etc)
- Private: including Manufacturers/Industries, small scale manufacturers, Pharmacy Wholesale, Private hospitals and clinics, Retail Pharmacies
- Non-governmental Organizations (NGOs)

The other type of classification for sample collection sites are based on the level of activity in the supply chain:

Level 1: Points of entry to the market, e.g. warehouses of importers or manufacturers, central medical stores, NGO central stores, other facilities supplied directly within various programs, central wholesalers/distributors;

Level 2: District Pharmacies, Retail Pharmacies, hospitals, health centers, Health posts/Clinics, community health workers;

Level 3: Informal outlets selling medicines outside the approved distribution system, e.g. street vendors, grocery shops, drug stores, patent stores.

Sample collection should be performed in both the public and private sectors as well as in the "informal market". Types of sites for sample collection should be selected in a way to best serve the study 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. If the medicines quality are compromised due to degradation from distribution and storage problems, collection of additional samples of the same product at level 1 may highlight the bridge in the quality assurance system of supply chain management.

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Samples collected at points of entry to the market (Level 1) may be less affected by storage and distribution conditions they may encounter during in-country distribution. 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 to be sampled need to be mapped. The sites where samples will be actually collected in the study should be identified according to address and type of facility.

Good knowledge of the distribution/supply chain structure for the target medicines is needed and cooperation with Public Health program 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.

4.2.3 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 public health programmes, may help to identify products used commonly. Selection of medicines is driven by the PMSobjectives 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.

4.3 Sampling tools

Sampling form(Annex 2), office supplies, devices to record temperature and relative humidity, cool boxes, Ice packs for collecting samples of temperature sensitive products, Containers and other supplies as needed.

4.4 Storage and transportation of samples

Storage and transportation of the samples to the Quality control laboratory should be done according to the Rwanda FDA requirements. Handling of samples should be done as quickly and straight as possible so as not to jeopardize the quality of collected samples

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

- a) Storage and handling conditions of samples should comply with all national regulatory procedures.
- b) Storage conditions for the pharmaceutical products to be sampled should be in compliance with the recommendations of the manufacturer.
- c) Storage areas should be clean and free from accumulated waste and vermin. Sample collectors must ensure that premises and storage areas are cleaned regularly.
- e) 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.
- f) 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.
- g) In case of temperature-sensitive medicines, temperature data loggers may be included within shipments to document adequate temperature in prolonged transit
- h) Medicines and other health product samples should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors.
- i) In the case that sample collectors are not transporting samples directly to the testing laboratory, samples with the accompanying documents should be sent by a courier service or as determined by the PMS management team. 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". 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.

4.5 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;

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

- Conduct quality testing in line with the testing protocol and in compliance with Good Practices for Pharmaceutical Quality Control Laboratories, including investigation and documentation of each Out of Specification result according to the laboratory SOP. If the Out of specification result is confirmed, it should be reported within 24 hours to the surveillance study coordinator providing both results and investigation report to protect the population from using the poor quality products
- Complete analytical test reports/certificates of analysis containing information established by Rwanda FDA, The study coordinator should define the format of the outcome (e.g. separately for each sample or as a tabulated report);
- Keep documents received with samples, records of testing of each sample including all raw data and retention samples according to the requirements defined by the study coordinator (e.g. for at least six months if the sample complied with the specifications, or until the expiry date, if it did not comply) and archive data according to the agreed conditions

4.6 Testing

Testing methodologies would be decided based on the products sampled. Whenever possible 3-level methodology will be used.

Level-1: Visual inspection

All samples will undergo visual inspection using a formal check list, (it should be Annex 3) to detect any defect or indication of adulteration or non compliance with good manufacturing practices. The visual inspection should refer to the information related to the specific product registration in Rwanda. Types of defect may include the following:

Wrong labelling

Particulates

Crumbling tablets

Underfill

Glass particulates

Mould contamination

Discoloration

Wrong fill

Odor

The visual inspection is an important test that may reveal noncompliance without further testing.

Sample selection for testing: visual inspection along with storage conditions recorded will help

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

determine the samples that need further testing. If several samples of the same products are collected they will be visually compared to one another.

Level-2: Advanced screening whenever applicable

Advanced screening may involve the use of Minilab™ or other screening technology available to the Rwanda FDA laboratory(See figure 2). Current spectroscopy-based technologies involving the use of handheld spectrometers could be used as screening tools to detect falsified medicines in the field. Rwanda FDA will determine the handheld spectrometers to be used to support its PMS activities. The quality control laboratory may be tasked to develop methods and methodologies for the implementation of handheld spectrometers in the field. Minilab™ should be used in the Rwanda FDA laboratory.

Level-3: Compendial testing

In case a product was deemed noncompliant, the lab will confirm the results following compendial methods and internal standard operating procedure(s), (See figure 3).

Note:For the tests which can not be done locally, samples can be sent to ISO/IEC 17025 Accredidited or WHO prequalified laboratories for the analysis of medical products.



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

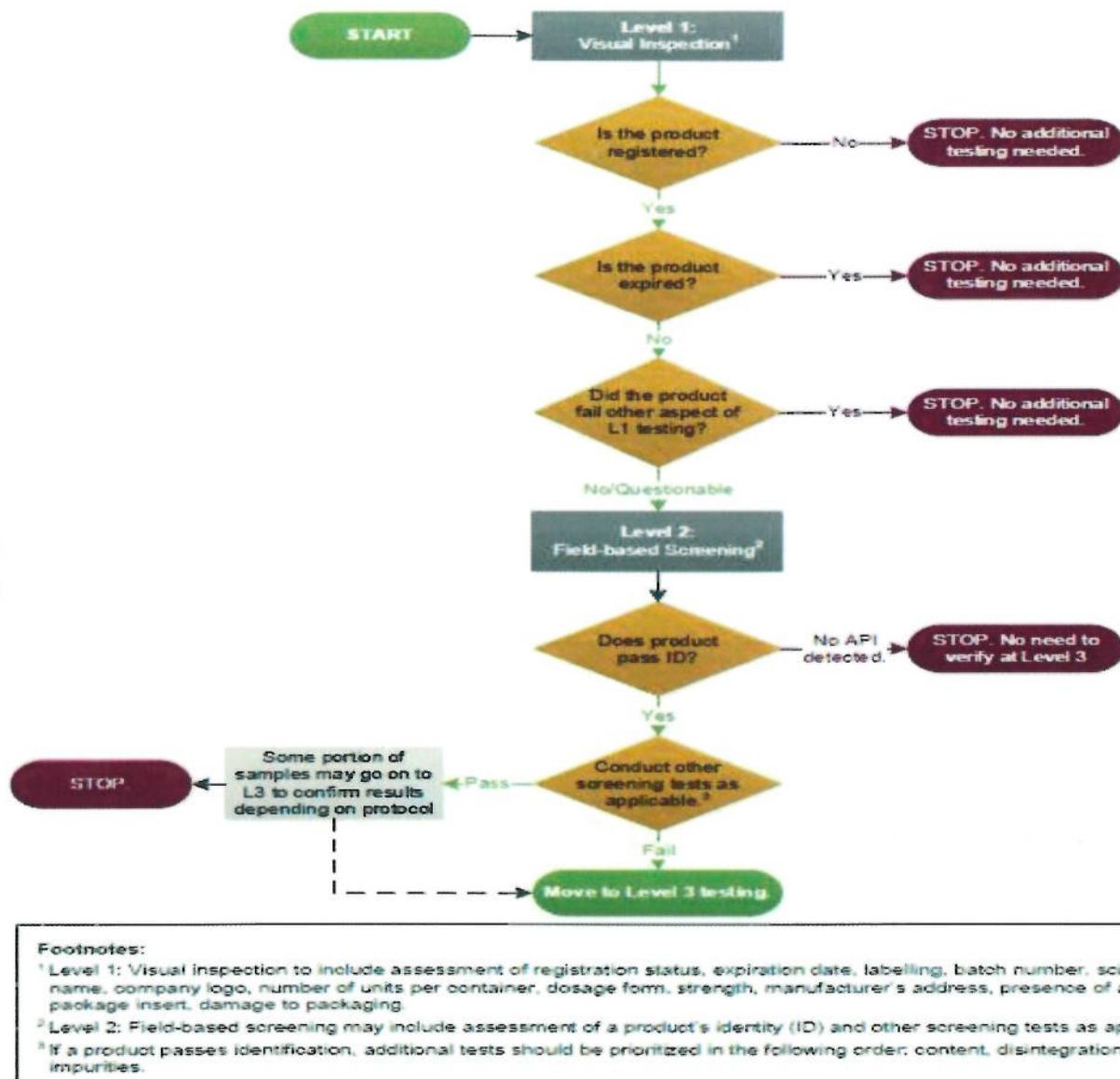


Figure 2. Guidance for Visual and Field-based screening (Level 1 and 2). (Reference: PQM, 2018)

RWANDA FDA

Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

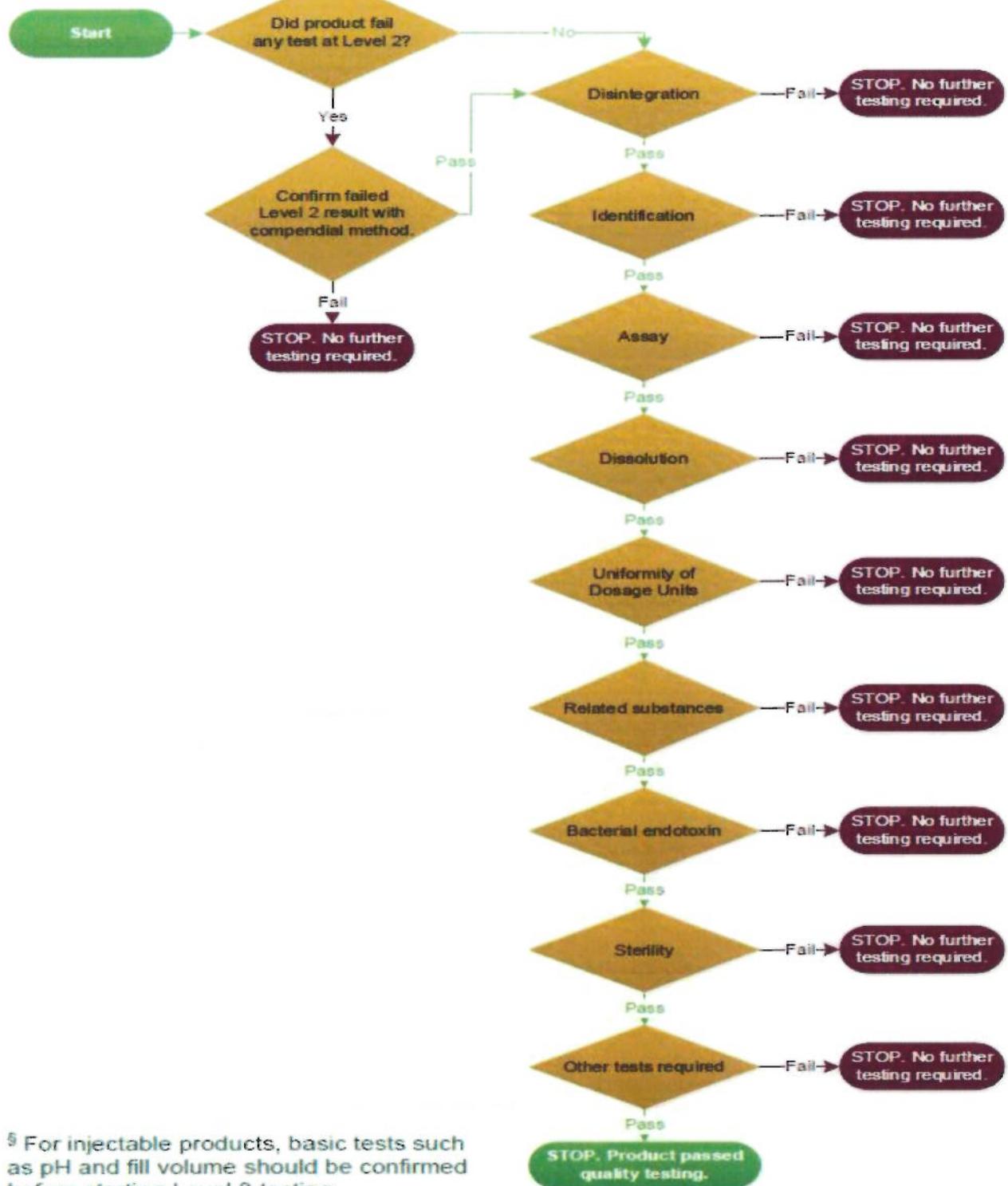


Figure3. Suggested prioritization for compendial testing (level 3). (Reference PQM, 2018)

Note: For more safety and public health interests some cases should be selected for further investigations with advanced analytical techniques to identify the nature or toxicity of detected poor

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date: 10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products
quality products.

- i. In case the market authorization holder contests the test results, he/she will be responsible for re-testing costs by an independent ISO/IEC accredited or WHO pre-qualified laboratory and Rwanda FDA with MAH will mutually select the laboratory. In case the results of retesting do not confirm the results of testing, Rwanda FDA and MAH will decide the second retest and Rwanda FDA reserves the right to take final decision.

4.7 Data management

Data generated through PMS activities will be recorded in a database that is linked to inspection and registration. Rwanda FDA will analyze the data and report the analysis to stakeholders. Prior to the establishment of the database, PMS teams may use other means to store the data (Excel sheet template).

4.8 Reporting

4.8.1. Internal reporting:

The Rwandan FDA will keep its departments personnel informed about PMS activities. The authority may have several departments involved in PMS planning and implementation. Internal reporting will follow the authority's internal communication procedures.

4.8.2. External reporting:

The Rwanda FDA will inform stakeholders on PMS activities and results through official and formal channels. The authority will issue reports to stakeholders using report template.

4.8.3. Third party PMS reporting

After completion of a PMS activity by third party, results will not be published without approval of Rwanda FDA.

4.9 Regulatory action taking

Falsified products: the Rwanda FDA will take immediate action to remove falsified products from the market nationwide. Investigations on how the product reached the supply chain will be carried out by the authority.

For substandard products, through the PMS committee, the authority may decide the level of corrective and preventive actions. The level of corrective actions should be proportional to the severity of noncompliance. The authority will follow up with the manufacturer producing the noncompliant product until it addresses the cause of the noncompliance of its product.

4.10 Communication/Sharing of information

In its commitment to transparency, Rwanda FDA will make information on PMS activities publicly available on its website and through official channels. Prior to the publication, Rwanda

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

FDA will inform the market authorization on the non-conformance detected. The authority may share the results of PMS activities including any regulatory actions taken.

5. MONITORING AND EVALUATION

In seeking continuous improvement of its processes, Rwanda FDA monitors and evaluates its PMS program. The monitoring and evaluation office will work closely with PMS team to collect data on the implementation of PMS program. The data collected shall be analyzed and recommendations formulated to address any shortcoming in the implementation of PMS or explore opportunities for its improvement. PMS indicators shall be monitored and measured quarterly, and annually-to review the trend of PMS performance.

5.1. Indicator types and definition

Indicator types	Definition
Structural	Measure key aspects of regulation, infrastructure, National Regulatory Authority functions and structure, Quality Assurance/Quality Control systems, supply chains, storage, and distribution in the pharmaceutical sector.
Process/Inputs	Measure the resources needed for the implementation of an activity or intervention and may include policies, human resources, materials, and financial resources needed to measure whether planned activities took place or not.
Output	Measure the direct results of an intervention and are mainly quantitative. Output indicators add more detail on the product ("output") of the activity.
Outcome	Measure the achievement of common objectives of Rwanda FDA to address poor-quality products. Outcome indicators are used to demonstrate the degree to which post-marketing surveillance objectives are being met.
Impact	Measure the extent to which post-marketing surveillance program objectives contribute to safeguarding the public from harmful products. Measuring these indicators can be difficult due to multiple factors, interventions, and externalities that also affect impact.

The following indicators may be used and expanded:

Structural (STL) Indicators:

STL1 Existence of Regulatory framework on PMS program.

STL2 Existence of defined roles, responsibilities, and structure for post-marketing surveillance program.

STL3 Existence of mechanism for collaboration with key stakeholders (e.g., police, customs)

STL4 Existence of post-marketing surveillance activities targeted to national priority health programs/products.

STL5 Existence of evidence-based decision-making practice using post-marketing surveillance data

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date: 10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

(e.g., evidence of regulatory actions taken against poor quality medicines based on post-marketing surveillance data).

STL6 Existence of written SOPs for post-marketing surveillance related to planning, execution, and reporting PMS activities

STL7 Existence of key tools used in post-marketing surveillance

STL8 Existence of sampling strategies

STL9 Existence of annual PMS plan

STL10 Existence of reporting and disseminating mechanisms of results from PMS activities.

STL 11 Existence of screening and testing equipped facilities

Process/Input (PRS) Indicators:

PRS1 Number of procedures implemented to perform post market surveillance and control

PRS2 Number of skilled and experienced staff for post-marketing surveillance program

PRS 3 Percentage change in financial resources for post-marketing surveillance activities

Output (OUT) Indicators:

OUT1 Number of reports received for suspected falsified and substandard Pharmaceutical products

OUT2 Number of follow-up done and feedback provided on reports about pharmaceutical products suspected to be falsified or substandard

OUT 3 Number of feedback provided to reporters about the pharmaceutical products suspected to be falsified or substandard

OUT4 Percentage of pharmaceutical product samples that failed Level 1 (visual inspection) and underwent confirmatory analysis

OUT5 Number of individuals trained on topics related to post-marketing surveillance by year

OUT6 Percentage of total post-marketing surveillance reports attributed to product quality defect are recorded in database compared to the previous calendar year

OUT7 Percentage of licensed pharmaceutical establishments covered by post-marketing surveillance program in public and private sector

Outcome (OUE) Indicators:

OUE1 Cost savings attributed to risk-based post-marketing surveillance activities

OUE2 Percentage change in the number of licensed pharmaceutical establishments that sell falsified and substandard Pharmaceutical products (each year there should be a decrease in percentage compared to previous years)

OUE3 Percentage of substandard or falsified Pharmaceutical products circulated in the market identified in the current year (each year there should be a decrease in percentage compared to previous years)

OUE4 Percentage change in the number of post-marketing surveillance inspections in terms of frequency from high-risk to low-risk areas as a result of effective risk-based post-marketing surveillance

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

Guidelines for Post-Marketing Surveillance of Pharmaceutical products
OUE5Percentage of non-compliance samples followed by the Rwanda FDA with regulatory actions

Impact Indicators (IMT):

IMT1 Percentage change over time in medicine-related hospital admissions resulted from product quality defects

IMT2 Percentage change in medicine-related deaths caused by medicines quality defects

IMT3 Change in behavior of supplier, distributor, and retailer handling pharmaceutical products to embrace the quality and safety as a key criterion in their practice

Continuous improvement Indicators (COI):

COI1 Existence of a mechanism to promote transparency, accountability and communication in post-marketing surveillance program

COI2 Existence and implementation of continuous improvement processes (Plan > Do > Check > Act)



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	



P O. Box 84 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

SAMPLE COLLECTION FORM

1. Sample code:
(Region/product/sequence number/sampling date...../..../.....)
2. Name & Address of Premises where sample was taken:
 - a. Physical Address.....
 - b. Postal address.....
 - c. Telephone No.....
 - d. Email address..... (if applicable)
3. Product name of the sample:
 - a. Description/identification (colour).....
 - b. Name of active pharmaceutical ingredient(s) (INN)
 - c. Strength
 - d. Dosage form (tablet, oral powder, etc):
 - e. Package size & type:
 - f. Batch/lot number:
 - g. Date of manufacture:Expiry date.....
4. Name and physical address of the manufacturer:
5. Number of units collected (tins, packet).....
6. Is the product registered in the country? Yes/ No.
 - a. If Yes, indicate the registration number:
7. Storage condition of product at the premises:.....
8. Details of representative of the premises and Drug Inspector (s)/Sampling officer(s)

S.No	Name	Organization	Signature	Date

Note: Samples collected must remain in their original containers

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

set 2

H

Annex 2: Suspected Poor Quality Reporting Form



RWANDA FDA

Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	



P O Box 84 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

SUSPECTED POOR QUALITY PRODUCT REPORTING FORM

I. PRODUCT CATEGORY (Tick as appropriate)					
Medicinal product <input type="checkbox"/> Vaccine <input type="checkbox"/> Other Biological Products <input type="checkbox"/> Herbal product <input type="checkbox"/> Other (Please Specify): _____					
II. PRODUCT DETAILS					
Brand name			Generic Name		
Batch/Lot No.	Manufacturing Date		Expiry date		Date of receipt
Name of manufacturer			Physical Address and Country of Origin		
Name of Distributor/Supplier			Distributor/Supplier's Address		
III. PRODUCT FORMULATION			IV. DESCRIPTION OF PRODUCT COMPLAINT		
<input type="checkbox"/> Tablets /capsules <input type="checkbox"/> Suspension/Syrup <input type="checkbox"/> Injectable Infusions <input type="checkbox"/> Creams/Ointment/Liniment/Paste <input type="checkbox"/> Pessaries <input type="checkbox"/> Suppository <input type="checkbox"/> Powder for reconstitution of oral suspension <input type="checkbox"/> Powder for reconstitution of injection <input type="checkbox"/> Ear/Eye drops <input type="checkbox"/> Diluents <input type="checkbox"/> Nebulizing solutions <input type="checkbox"/> Other (Please Specify): _____			<input type="checkbox"/> Color/odor change <input type="checkbox"/> Molding <input type="checkbox"/> Turbidity <input type="checkbox"/> Mislabelling <input type="checkbox"/> Poor Packaging/ lack of patient leaflet/ lack measuring devices <input type="checkbox"/> Therapeutic ineffectiveness <input type="checkbox"/> Particulate matter <input type="checkbox"/> Seal integrity of packs and/ or Leakage <input type="checkbox"/> Caking <input type="checkbox"/> Separating <input type="checkbox"/> Incomplete packs <input type="checkbox"/> Powdering/crumbling <input type="checkbox"/> Suspected falsified/ Substandard <input type="checkbox"/> Others(Specify): _____		
Describe the Complaint in details:					
V. PRODUCT STORAGE CONDITIONS					
Does product require refrigeration?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>	<i>Other Storage details (if necessary):</i>			
Does product require protection from light?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>				
Does product require protection from Moisture?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>				
Was it stored following manufacturer/Rwanda FDA guidelines?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>				
VI. CIRCUMSTANCE AND TIME OF THE POOR QUALITY DETECTION					
When did you notice the poor-quality problem?	<input type="checkbox"/> Before taking/administering the product <input type="checkbox"/> While taking/administering the product <input type="checkbox"/> After taking/administering the product <input type="checkbox"/> When the patient returned the product		<input type="checkbox"/> After a complaint of the patient <input type="checkbox"/> After Visual inspection <input type="checkbox"/> After quality control <input type="checkbox"/> Other(specify): _____		<input type="checkbox"/> Stop Taking/Administration of the product <input type="checkbox"/> Quarantining the product <input type="checkbox"/> Returning the product to the supplier <input type="checkbox"/> Other (specify): _____
Have you experienced any adverse event after taking this medicine? YES <input type="checkbox"/> NO <input type="checkbox"/> If YES, please complete the ADR/AEFI Reporting Form.					
VII. REPORTER INFORMATION					
Name of reporter:		Qualification:		Phone number:	
Name of Health Facility		District:		Report Reference No:	
E-mail Address:		Contact/Tel No:		Date of report:	
<i>All information is held in strict confidentiality and will not disclose reporter's identity in response to any public request. Information supplied will contribute to the improvement of safety and vigilance of Medical Products in Rwanda. Once completed please send it to Rwanda FDA.</i>					
Revision No.:0	Effective Date: 17/12/2019				

Guidelines for Post-Marketing Surveillance of Pharmaceutical products

Annex 3: Test Request Form

 RWANDA FDA <small>Rwanda Food and Drugs Authority</small>	Division : Quality Control Laboratory Doc Title : Test Request Form	Doc. N° QCL/FOM/001 Revision N°: 0 Effective Date: 13 Mar 2019 Ref Doc: QMS SOP 001
--	--	--

1. Full Description <i>(Generic name / Trade name if any other names)</i> Composition: Strength and Dosage form	10. Would you like QCL to choose the Appropriate test method(s) to be used in above tests? Yes / No if no suggest:
2. Manufacturer Names and Address: Batch No _____ MFG Date: _____ EXP Date _____ Retest date (APIs and Pharmaceutical excipient)	11. Source of the sample Institution / Company _____ Country _____ Address / Tel _____
3. Size of submitted sample: _____	12. Marketing Authorization number _____
4. Size of the consignment package: _____	13. Date sample collected: _____
5. Required storage condition: _____	14. Sample Submitted by: Institution _____ Position _____ Address / Tel _____ Signature & Date:
6. Physical condition of the sample upon arrival: State: Frozen, Chilled, Room temp Packaging: Sealed, Unsealed, Damaged, Un-damaged General appearance : Good, Poor Discrepancies: _____	15. Receiver's name & signature: _____ Date and time of submission _____
7. Reason for analysis request: _____	16. Laboratory Sample registration number: _____
8. Specification to be used for testing: _____	17. Turnaround time: _____
9. Parameters to be tested: _____	18. Note, if any: _____

19. For Laboratory use only.....

Received by		Date & signature
Assigned Analyst		Date & signature

20. Sample transfer

Quantity (mg, ml...)	Transferred by	Received by	Time and date	Signature

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	




REFERENCES

1. Guidelines on the conduct of surveys of the quality of medicines accessed on <http://apps.who.int/medicinedocs/documents/s22404en/s22404en.pdf>
2. Guidelines for post marketing surveillance in Nigeria, 2016 accessible on https://www.nafdac.gov.ng/wpcontent/uploads/Files/Resources/Guidelines/PVG_GUIDELINES/Guidelines-for-Post-Marketing-Surveillance-Nigeria.pdf
3. :<https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products>
4. Guidance for Implementing Risk-Based Post_Marketing Quality Surveillance in Low and Middle Income Countries



Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	

[Handwritten signature]

[Handwritten signature]

	Author	Authorized by	Approved by	Change made and reason for revision
Title	Division Manager PV-FSM	Head of Inspection and Safety unit Department	Af, DG.	
Names	NTIRENGANYA Bazare	ALEX GISAGACIYA	Dr Karangwa Charles	
Signature				
Date	10/12/2019	10/12/2019	17/12/2019	



RWANDA FDA

Rwanda Food and Drugs Authority

Doc. No.:PSM/GDL/015	Revision Date: 10/12/2019	Review Due Date:10/12/2022
Revision No.:0	Effective Date: 17/12/2019	