

**GUIDELINE FOR POST MARKETING SURVEILLANCE  
OF MEDICINES**

**National Medicines Regulatory Authority**

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DRAFT FOR COMMENTS

## 1. Definitions

For the purpose of this document, the following definitions (adapted from the World Health Organization) are used.

**Falsified**- Medical products that deliberately/fraudulently misrepresent their identity, composition, or source.

**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.

**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.

### **screening tests**

The qualitative and/or quantitative tests that could rapidly acquire preliminary analytical information or data on the quality of medical products in the field.

**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.

**substandard** Also called “out of specification,” refers to authorized medical products that fail to meet either their quality standards or specifications, or both.

## 2. Introduction

The National Medicines Regulatory Authority Act No. 05 of 2015 empowers the National Medicines Regulatory Authority (NMRA) to carry out post marketing surveillance programs. Post-marketing surveillance is a key standalone regulatory function of the NMRA with a legal basis in the national laws and regulations.

Approval of post marketing surveillance from government health institutions was granted by the Ministry of Health, Nutrition and Indigenous Medicines by the circular No. NMRA/PMS/01. This circular was attached in the NMRA website.

Strong national post-marketing surveillance programs is focused quality, safety and efficacy of medical products and responding to public health risks can help protect citizens from the threats posed by substandard and falsified (SF) medicines. The majority of post -marketing surveillance concern adverse drug reactions (ADRs) monitoring and evaluation and other quality complaints.

This guideline defines the regular sampling and surveying of both the regulated and unregulated supply chains to identify SF medical products and adverse events monitoring. Different methodologies are used to sample the market and range from random sampling through targeted sampling of particular products and outlets. Risk-based approaches are used to determine the types of medicines that will be sampled, the sampling locations, the sample size, and the appropriate analytical tests to perform.

This guideline will assist National Medicines Quality Assurance Laboratory (NMQAL), Pharmacovigilance Division as well as Authorized Officers in Enforcement division including those working in the periphery to effectively carry out relevant duties.

## 3. Purpose

This guide provides information for NMRA to begin executing post-marketing surveillance as a core regulatory function.

## 4. Objectives

- 4.1 To monitor safety, quality and efficacy of medicines available in the market in different areas/region at various levels of distribution/supply chain with the aim to assess the exposure of patients to poor-quality medicines and propose appropriate actions;
- 4.2 To identify possible causes of inferior quality of specific products to which patients are exposed.
- 4.3 To test quality of medicines in order to support the NMRA in identification of manufacturers non-compliant with quality standards and in adoption of regulatory measures;

- 4.4 To detect and report any spurious/false labelled/falsified/ counterfeit products penetrate to the market and what may be the health impact for patients.
- 4.5 To identify SF medical products that have reached consumers and to evaluate pharmacovigilance reporting by healthcare professionals and patients.
- 4.6 For raising awareness concerning the importance of reporting an unusual lack of efficacy of medical products
- 4.7 To improve and enhance safety measures, which involve statistical analysis of adverse drug reactions (ADRs) as reported by healthcare institutions and patients, thereby detecting signals of ADRs that may warrant further investigation.

## **5. Procedure for Post-Marketing Surveillance**

- 5.1 Sampling plan is prepared according to the requirements of NMRA.
- 5.2 Initial planning under the NMRA is coordinated with other stakeholders.
- 5.3 NMRA Officers/Authorized Officers carry out sampling according to an established and approved plan.
- 5.4 NMQAL and other selected laboratories whenever requires carry out tests according to regulations and guidelines (pharmacopeial methods or official verified/validated test methods in product dossiers,).
- 5.5 Data are analyzed by the NMQAL and reported to the NMRA which is responsible for sharing with all relevant stakeholders.
- 5.6 NMQAL and enforcement divisions carry out follow-up actions as appropriate.
- 5.7 Reporting of suspected ADRs to Safety and Risk Evaluation Committee (SAFREC) and evaluation and monitoring safety of reported suspected ADRs.
- 5.8 NMRA conduct workshops relevant post market surveillance activities to stakeholders.

## **6. Sampling and Testing Priorities**

6.1 NMQAL involves in the planning stage of any sampling and testing activity. The role of NMQAL is to provide all technical information about the tests to be used, the specifications of the products, the number of units per sample to collect for each medicine and key information related to the stability and proper handling of medicines during sampling. The NMQAL should contribute and review the sampling form and ensure that all technical information to be collected per each sample is complete and accurate.

6.2 The type of testing and the specifications for each medicine are used to develop risk based sampling and testing steps as given below.

- a) Monitoring medicines that are new to the market.

- b) Monitoring medicines based on the risks associated with manufacturing complexity, dosage form, stability (e.g., temperature sensitivity), safety/efficacy (e.g., narrow therapeutic window), demand (e.g., high-burden diseases), therapeutic indication (e.g., infectious diseases), or other factors.
- c) Monitoring the quality of medicines at key ports of entry. This type of monitoring serves as a first-line intervention, has been shown to deter the trading of poor-quality medicines, and requires close collaboration among the regulatory, customs, and law enforcement authorities.
- d) Coordinating with ongoing sampling and testing initiatives, such as: Sampling and testing activities conducted by national health programs (e.g., Anti malaria, TB, HIV/AIDS, and family health Bureau).

### **6.3 Sampling plan.**

The quantity of the sample required for testing is prepared by NMQAL and the amount of pharmaceutical dosage units required for the testing is posted in the NMRA website as Quantity of Samples required for Analysis-Guidance Document- GN-PR-01-GD 01. The sample size may be a case-by-case decision depending on the number of pharmaceutical dosage units needed per test procedure, the number of presentations of the dosage forms to be tested, the availability of the product, the size of the market, the clinical use of the product, etc.

NMQAL prepares a sampling plan which 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.

### **6.4 Information needed for risk based sampling and testing**

6.4.1 Selection of area to Sample-Administrative and health structure, updated demographic information, disease prevalence, medicines supply chain, pharmaceutical sector information (number of outlets for each sector).

6.4.2 Selection of medicines- Most-used medicines according to the essential medicines list, complaint investigations, quality failures, most-sold medicines, higher risk medicines (stability, storage), medicines imported from countries with stringent regulations, supply system of targeted medicine, known points of distribution

6.4.3 Selection of collection sites- Complete and up-to date information about the pharmaceutical sector in the area (number of outlets, levels of distribution, type of outlets, type of available sectors for supplies, geographical and administrative structure (e.g., number of provinces, number of districts), demographic information Government health institutions e.g.

government hospitals, medical supplies division(MSD), regional medical supplies divisions (RMSDs), etc and private sector institutions (e.g. whole sale pharmacies and drug stores, community/retail pharmacies, pharmacies and dispensaries at private hospitals).

6.4.4 No. of dosage units/sample, No. of samples/ medicine, Total number of samples/area- Based on the objectives and testing methodology of the activity, data on the specifications for the medicine and its dosage form are required and should be available at the NMRA. The number of samples is determined based on the objectives and availability at the collection site.

6.4.5 Sample testing- Test to be applied or selected must be determined by NMQAL based on objectives of the sampling and testing activity according to the pharmacopoeial specifications or manufacturers' specifications.

Manufacturer's/Market authorization holders should provide necessary information related to the quality of their products.

### **6.5 Handling, storage, and transportation of samples**

NMRA officers, other relevant authorized officers and healthcare institutions who involve in sending samples to laboratory should observe the following best practices throughout the chain of custody of the products:

- 6.5.1 Avoid excessive mechanical vibration during transportation.
- 6.5.2 Store in original container, where available, and label accordingly.
- 6.5.3 Store away from sunlight and excessive humidity.
- 6.5.4 Collect all the information required for each sample with the location of collection, number of samples collected, name of the sample and any observation at the time of collection in the sample collection form – GN-PR-01-F02. Product complaints should be submitted with the form-Submission of Products complaints to NMQAL-GN-PR-01-F03. Both forms are posted in the NMRA website. NMQAL Officers who involve in sample collection should use the Government Surveillance Sample Collection form-GN-PR-01-F01.
- 6.5.5 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.
- 6.5.6 In the case that collectors are not transporting samples directly to the laboratory, samples with the accompanying documents should be sent by a courier service with required storage conditions. 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.

### **6.6 Testing**

6.6.1 NMQAL perform medicines quality testing to comply with international standards (ISO 17025) to ensuring the reliability and accuracy of test results and carry out the tests according to the pharmacopoeia/validated tests submitted in market authorization document.

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- 6.6.2 Officers authorized by Ministry of Health at Field-level also be trained appropriately by the NMRA and/or NMQAL to perform field-level visual inspection and appearance.
- 6.6.3 Following tests are, in principle, included: appearance, visual inspection; identity; assay for APIs declared on the label; test for related substances, microbial quality testing; for solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), for liquid dosage forms – pH value and volume in containers/extractable volume; for parenteral products – sterility and bacterial endotoxins tests. Table 1 provides a summary of these tests and the potential product quality issues that can be detected by each test.
- 6.6.4 Inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial endotoxins tests, which are costly, time demanding and need more dosage units to be collected, should be considered in relation to target medicines and available resources. It is impossible to achieve 100% certainty about sterility of the product through testing only and inspections and enforcement of compliance with GMP principles may be more efficient tools for verification in some cases.

Table 1. Select tests to detect product quality issues

| Test  | Possible product quality issue                                 | Comments  |
|---|--|---|
| Visual inspection   | Falsely or incorrectly labeled, poor appearance, unregistered  | Comparison with innovator or registered products in the country. Medicines Registration Database is a good source of information. |
| Identification  | Incorrect or absent active ingredient                          | Techniques vary depending on capacity and technology.   |
| Assay Uniformity of dosage unit                             | Quantity of active ingredient inconsistent with claim on label | See Pharmacopeia sections on uniformity of dosage units, QAS 15.635.  |
| Disintegration Dissolution                                  | Dosage form performance  | Harmonized across pharmacopeias – USP, EU, etc  |
| Related substances/ Impurities                              | Degradation or impurities                                      | Product specific Refer to pharmacopeial or other standards  |
| Endotoxin Sterility Foreign particulate matter Viscosity pH | Toxicity or contamination of liquid and sterile formulation    | Microbial testing may necessary when available or outsourced  |



## 7 Data analysis and reporting

- 7.1 Field inspectors and NMQUAL should report results to the NMRA as soon as confirmed data or results are available.
- 7.2 Depending on the data presented to the NMRA and the potential public health importance of the findings, the authority may take a variety of actions, including further testing of samples and requesting additional information or clarification from market authorization holders, or other appropriate regulatory action such as recall published in NMRA website.
- 7.3 NMRA share results with other stakeholders, both those involved in the sampling and testing activities, and other relevant groups, and the general public.
- 7.4 Results from post-marketing surveillance program can be captured through online publicly available NMRA web site. Sharing this information publicly can have a direct impact on the health and wellbeing of patients and populations.

## 8. Adverse Events of Medicines

8.1 In active post-marketing surveillance programs drug adverse events monitoring is also essential. When a new drug (NCE) is first marketed, it would have been tested only in a limited number of patients. Rare adverse drug reactions could be identified only after the drug is marketed and used by a much larger population. Safety information in use in special groups such as children, elderly, pregnant women etc. are not often available at the time of first marketing of a new drug.

8.2 Healthcare professional such as doctors, dentists, pharmacists and nurses are encouraged to report suspected adverse events encountered in their day to day practice.

8.3 Adverse drug events can be reported to the NMRA by completing the relevant forms available in NMRA website. The NMRA database for adverse event reporting is a computerized information database designed to support the NMRA's post-marketing safety surveillance program for all approved drugs. The ultimate goal of this system is to improve the public health by providing the best available tools for storing and analyzing safety reports.

8.4 These reports are evaluated by the Safety and Risk Evaluation Sub-Committee (SAFREC) which consists of multidisciplinary staff (Pharmacologists, Immunologist, Physician etc.) to detect safety signals and to monitor drug safety. As a result, the NMRA may take regulatory actions to improve product safety and protect the public health, such as updating a product's labeling information, or re-evaluating an approval decision and also product recall. For further details refer the guideline for Adverse Reaction monitoring.

### 8.4 Reporting of Adverse Events

Using the ADR form available in the NMRA web site, adverse events can be reported to,

Address : Director General /CEO

National Medicines Regulatory Authority

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No. 120, Norris Canal Road

Colombo 10

Telephone : +94112698896, +94112698897

Fax : +94112689704

Adverse Events reporting forms Available in NMRA website:

Suspected Adverse Reaction to Medicines/Borderline Products: Case Reporting Form

Anaphylaxis Case Reporting Form (pink form)

A copy of the form shall be forwarded to the Adverse Drug Reaction Monitoring Unit of the Department of Pharmacology, Faculty of Medicine, Kynsey Road, Colombo 08. (TP/ Fax: +94 112 697 483)

### **9. Related Documents and forms**

- 9.1 Quantity of Samples required for Analysis-Guidance Document- GN-PR-01-GD 01
- 9.2 Government Surveillance Sample Collection form-GN-PR-01-F01.
- 9.3 Submission of Products complaints to NMQAL-GN-PR-01-F03
- 9.4 Private sector sample collection form – GN-PR-01-F02
- 9.5 Suspected Adverse Reaction to Medicines/Borderline Products: Case Reporting Form
- 9.6 Anaphylaxis Case Reporting Form (pink form)

### **10 References**

- 1. Guidance for Implementing Risk-Based post marketing Quality Surveillance in low and middle income countries. PQM. Promoting the Quality of Medicines USAID and USP, February, 2018
- 2. WHO GUIDELINES ON THE CONDUCT OF SURVEYS OF THE QUALITY OF MEDICINES Working document QAS/15.630 June 2015 Draft document for comment