بسم الله الرحمن الرحيم

Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline on Post Market Surveillance

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Definitions

a. **Authority**- Maldives Food and Drug Authority

b. **Efficacy**- The maximum ability of a medicine to produce the purported effect as determined by scientific methods, regardless of dosage forms.

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

d. **Marketing authorization**- An official document issued for the purpose of marketing of a product after evaluation of safety, efficacy, and quality of the product.

e. **Pharmaceutical outlet**- A pharmaceutical outlet means any point (licensed or unlicensed) of sale or provision of medicines for individual patients or other medicine providers.

f. **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; 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.

g. **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.

h. **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.

i. **Safety**- The medicine should not present risks that are disproportionate to its benefits.

j. **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.

k. **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

l. **Substandard product-** Also called "out of specification," this term refers to authorized medical products that fail to meet either their quality standards or specifications, or both.

m. **Unregistered product-** Medical products that have not undergone evaluation and/or approval by MFDA for the market in which they are marketed/distributed or used, subject to permitted conditions under national regulation and legislation

Guideline on Post Market Surveillance

1 INTRODUCTION

Good quality medicines are essential for efficient disease management. Substandard and falsified medicines can cause treatment failure, 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 and/or falsified medicines. Poor-quality medicines also increase health care costs to both patients and the healthcare system, wasting resources that could otherwise be used to benefit public health

Medicines regulation is a complex process which is comprised of various regulatory instruments such as, 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.

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. Therefore, 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. Therefore, MTG considers PMS an important activity of the regulatory function. PMS is inherent responsibility for the Authority stated in the health service Act (29/2015) and medicine regulation (R-46). The Authority's aim is to ensure that all medicinal products available in the country are safe, effective and of good quality so that the health of the public is protected. On the other hand, the Authority alone could not create a robust post-marketing surveillance program. Post-marketing surveillance is, therefore, a multidimensional activity with shared responsibilities for the ministry of Health, MTG,

pharmaceutical manufacturers, importers, wholesalers, retailers and end users. It encompasses a litany of national legislations linked to product safety, efficacy, and quality and labeling, all of which must be considered as a holistic path to compliance.

Post-marketing surveillance of medicines 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.

The post-marketing surveillance system

Post-marketing surveillance encompasses the pro-active and reactive collection of information on quality, safety of medicines, once they have been introduced in the market. PMS program shall be carried out by Enforcement Section.

2 Purpose

This Guideline is developed with the intention of having a standard and consistent way of conducting post-marketing quality surveillance of medicines. This guideline provide information related to why, who, how, when and where to conduct the survey and take appropriate measures based on the Post Marketing Surveillance (PMS) findings following a risk-based approach

3 Scope

These Guidelines applies to all the activities related with post market surveillance, 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 enforcement of PMS program varies from case-by-case, the guidelines define the essential principles to be applied in a variety of situations. The guideline provides guidance for PMS activities involving human medicines, vaccines marketed in the country

4 Responsibilities

As a coordinator of the PMS program the enforcement section shall carry out the following responsibilities.

a. Monitor and coordinate all PMS activities.
b. Develop a detailed PMS plan with timeline (this plan should be developed for one year)
c. Develop and/or revise protocols for PMS as necessary.
d. Select medicinal products to be sampled and submit for approval for MTG Technical Committee.
e. Develop sampling plan and select sampling location
f. Carry out sampling as per sampling plan and sampling protocol
g. Conduct training for sample collection team and provide comprehensive information
h. Collect and analyze data and information generated through the PMS system.
i. Write and submit final report to MTG management review meeting
j. Monitor and evaluate implementation of the PMS system.
k. Manage logistics, including transportation and other relevant arrangements
l. dissemination of the PMS results and enforcement of relevant regulatory actions

5 Guideline Content

5.1 Main activities of PMS

5.1.1 PMS needs a collaborative and coordinates 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 an important post registration activity to maintain the quality and safety of medicines.

5.1.2 The main activities expected from the PMS system are the following:

a. Collection of samples for selected medicines from the market as per the protocol or in response to complaints
b. Evaluation and comparisons of label and product appearance (cross-checking of market samples against samples submitted for registration).

c. Testing of sampled medicines.
d. Writing of reports for each PMS activity.
e. Taking administrative/regulatory measures.
f. Implementation of corrective and preventive actions.
g. Monitor the implementation of corrective and preventive measures.

5.2 Technical Committee

5.2.1 PMS system requires collaboration and coordination activities among different departments and stakeholders. To effectively conduct PMS process, and decisions regarding PMS will be made by MTG Technical Committee.

5.3 Selection of medicines to be surveyed

5.3.1 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 PMS program is imperative. The authority may use the following criteria for selecting medicine:

a. Newly introduced medicines on the market,
b. Branded medicines with limited safety and efficacy data,
c. Medicines with complex formulations,
d. Medicines known to have stability issues,
e. Medicines to which antimicrobial resistance is increasing,
f. Medicines in high demand or high consumption
g. Manufacturers or suppliers with previous quality issues,
h. The likelihood that S&F medicines exist,
i. Medicines which require prolonged administration to a larger population
j. Medicines imported under Hospital agreement

5.3.2 The following are some risk factors to be considered during selection of the medicines:

a. Stability of medicines
b. GMP compliance (of manufacturers if known)
c. Distribution chain complexity

d. Extent of population exposure
e. Patient vulnerability
f. Dosage form complexity
g. Therapeutic risk
h. Extent of harm due to poor quality
i. Availability of the medicine during the survey period.
j. Safety and quality history of the product (prior pharmacovigilance (PV) or medicine quality information, from prior studies)
k. Distribution chain complexity.
l. 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

5.4 Selection of areas to be sampled

5.4.1 Based on the sampling and testing plan, risk-based selection should first be applied to the areas where the sampling of medicines will be conducted. Such criteria could include poor storage conditions, poor access, high disease burden, population size, 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 the knowledge of the medicines supply chain in the country.

5.5 Sample collection sites (sampling level)

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

a. Level 1: port of entry
b. Level 2: Warehouse of Importers
c. Level 3: Retailers: pharmacies, hospitals, health centers, clinics and health posts who purchase and store medicine from Authorized importers.

5.6 Sampling Plans

5.6.1 A Sampling plan is prepared and approved for each year in compliance with the requirements identified in this guideline. The sampling plan specifies the:

- Individual sites where collectors should collect samples
- Medicines to be sampled (by APIs, dosage form, strength)
- Number of dosage units to be collected per sample
- Number of samples to be collected per medicine.
- Total number of samples to be collected in the relevant collection area.

5.6.2 Sampling plans will also contain detailed instructions for collectors. 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.

5.7 Substitution criteria

5.7.1 In case where the sample collectors cannot get samples from the already selected collection outlets, then the sampling plan 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 criterion:

a. If the 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 enough quantity of medicines in the collection outlet.

5.7.2 On a such scenario the head of enforcement Section shall substitute sampling outlets by replacing the randomly selected sampling outlet by the nearest similar level facility found in the same criteria

5.8 Storage and transportation of samples

5.8.1 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:

a. Avoid excessive mechanical vibration during transportation.

b. Store in original container, where available, and label accordingly.

c. Label each sample with the location of collection, number of samples collected, name of the sampler and any observation at the time of collection.

d. 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.

e. 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.

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

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

5.9 Evaluation and comparisons of label and product appearance

5.9.1 A thorough visual inspection could be an important screening step for product quality. An evaluation shall be carried out by sample collection team. in the evaluation the product label should 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. for unregistered product, international websites and manufactures information from the manufacture's website can be use.

5.9.2 To perform the visual inspection, Use Relevant parts of Port inspection checklist is used as a guided document.

5.10 Laboratory Testing

5.10.1 Medicines quality testing is an important component of a PMS. National Health laboratory is the designated testing laboratory for the national PMS program. After the visual inspection all samples shall properly deliver to NHL. Once the testing is completed a report of analysis will be granted to MTG. The findings is published by MTG and feedback is given to the outlets the samples were collected from.

5.11 Data analysis

5.11.1 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. After all the assessments, the PMS Committee shall prepare a report based on the findings. Every report will contain a summary of the results and recommendations to guide the Authority. The final report is presented at MTG Management review meeting to discuss further actions.

5.12 Results dissemination

5.12.1 Publication of test report (The information should be made available to the public) and reports to be delivered to the sample provider (the pharmacy /warehouse owner). The information may also be shared with other regulatory agencies, WHO and harmonization initiatives

5.13 Enforcement of PMS

5.13.1 The objective of post market surveillance is to determine the quality of medicines and adherence to the legally set standards. Every post-marketing surveillance report should contain a summary of the results and recommendations

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

a. Further testing of samples
b. Requesting additional information or clarification from market authorization holders
c. Withdrawal of products
d. Recall of batches (Guideline for Quality Defects and Product Recall)
e. Re-registration of products
f. Institution of disciplinary proceedings as regulation
g. Any other necessary legal action(s)

5.13.3 All the regulatory Actions shall be approved and authorized by national pharmaceutical board and ministry of health legal or policy

6 References

a. Health Services Act 29/2015
b. Medicine Regulation R-46/2014