Central Administration for Operations
General Administration For Market Control

Guideline for Conducting Risk-Based Post Market Surveillance Plan within the Egyptian Market For Medical and Biological Products 2023

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1. Introduction

Post-marketing monitoring is an important monitoring activity, among others, that takes place after approving market circulation for either both a medical or biological products. According to EDA's approach; mandating the reduction of number of batches subject to analysis, both for medical and biological products; Post-marketing monitoring became a crucial activity for quality control regarding the aforementioned products through developing a risk-based plan depending in the first place on the extent to which the products are subjected to analysis pre-trading.

The post-marketing control process is not limited to regular inspections of manufacturers, distribution companies, warehouses, pharmacies, and risk-based products for analysis, but also extends to following up on any reports related to the safety of products and reporting the same to pharmacovigilance. In addition to monitoring the promotion of poor-quality products; dealing with market complaints; removal and destruction of SF products.

EDA enacted a post-marketing surveillance program according to EDA's Chairman Decree no. 120 for 2022 and EDA's Chairman Decree no. 781 for 2022 in order to control the quality of all pharmaceutical products (medical and biological products). In addition to, availability of a qualified and proficient regulatory workforce; helps ensure continued operational sustainability.

2. Scope

This guide will be applied to all Pharmaceutical Products. Covering all points of the supply chain, whether distribution companies, warehouses or pharmacies, whether public or private, as well as; other establishments introduced to the supply chain, which is taken into account in developing of the risk-based plan.

3. Abbreviations:

3.1. **COVAC**: Covid Vaccine.

3.2. **EDA:** Egyptian Drug Authority

3.3. **EPI:** Expanded Program for Immunization.

3.4. **GSDP**: Good Storage and Distribution Practice.
3.5. **SF**: Sub-standard and Falsified.
3.6. **PMS**: Post Marketing Surveillance.
3.7. **PMS-MC**: Post Marketing Surveillance within the Market Control General Administration in the Central Administration of Operations.
3.8. **RB-PMS**: Risk-Based Post Marketing Surveillance.
3.9. **NCL**: National Control Laboratories.
3.10. **QC**: Quality Control.
3.11. **ADR**: Adverse Drug Reaction.
3.12. **ATC**: Anatomical Therapeutic Chemical.
3.13. **IMS**: EDA's Information Management System.
3.14. **DFI**: Drug Factory inspection.

4. Definitions:

4.1. **Medical Products:** Any product of formula or article containing a substance or a group of substances used for the purpose of treatment or prevention or diagnosis in humans or animals or which can be described as having another medical effect or which aims to restore, correct or modify physiological functions through having a pharmacological, immunological, or metabolic effect on general health, all of which in accordance to the applicable references and standards, as well as, any products or formulae or substances that may be created through advances in science and/or international references and standards.

4.2. **Biological Products:** Products containing one or more active ingredients produced or derived from a biological source, including but not limited to, human vaccines, serums, blood and plasma products and derivatives, and also products manufactured using biotechnology and the like, as well as, any products or substances that may be created based on science updates and/or international standards and references.

4.3. **Pharmaceutical Products:** Shall mean for purposes of this guideline medical and biological products.

4.4. **Drug Shortage Product*:** Drug shortage products are defined as products when its demand or expected demand for a medically necessary drug doesn't met its supply.

5. Purpose

The objectives of post-marketing sampling and testing programs are derived from the legal requirements:

1- Monitoring the safety, quality and efficacy of all Pharmaceutical Products available in the market in different regions at different levels of supply chain.

2- To identify potential causes of low quality of certain products to which patients are exposed.

3- To test the quality of all Pharmaceutical Products in order to identify non-compliant manufacturers with quality standards and in adopting regulatory measures.

4- To detect and report any counterfeit products penetrating the supply chain and the health impact on patients.

5- To identify SF Pharmaceutical Products that reached consumers and evaluated pharmacovigilance reports by healthcare professionals and patients.

6- To raise awareness regarding the importance of reporting an unusual deficiency in the effectiveness of Pharmaceutical Products.

7- To improve and enhance safety measures, which include statistical analysis of adverse drug reactions (ADRs) have also been reported by

* According to European Medicines Agency (EMA)

healthcare institutions and patients, thus revealing signs of adverse drug interactions that may require further investigation.

EDA shall evaluate among others the provision of MC –strengthens and weakness- according to the achieved goals, ensuring the ability to continuously develop.

EDA's risk-based approach to market surveillance shall allow the National Control Laboratories (NCL) to optimize the use of their limited resources on those areas considered most likely to pose a risk of quality defects.

6. Criteria for exclusion based on risk:

1- Products independently tested by EDA and released for all batches regarding all registered biological products.
2- National immunization vaccines (EPI and COVAC) where all these vaccines undergone full testing for all batches during lot release, in addition being trade in governmental hospitals, health care units or vaccination centers where tight supply chain is provided and GSDP and cold chain is provided.
3- Antisera & Antitoxins intended for governmental use only.
4- All pharmaceutical products restricted for hospital use only.

Based on risk; these products may be targeted for PMS surveillance at any time.

7. Methodology

7.1 This Risk-Based Post Marketing Surveillance (RB-PMS) plan will be divided along the 4 quarter groups [A, B, C, D] of the year; every quarter will target different groups of products with different risk category.

7.2 The Products of Group A that was chosen to start with during the first quarter, and then will be joined by other Groups B, C and D which will be formulated and put into the plan by end of each quarter respectively.

8. The Designing of plan

Developed RB-PMS plan will be designed by setting a criterion for the selection of products as for biological products, the selection should be matching with the lot release plan which is implemented according to the set timetable. While, for the medical products it was started from pooling all products used in the treatment of critical diseases and consumed by a high sector of population according to their Anatomical Therapeutic Chemical (ATC) Code from the IMS database. All pharmaceutical products, will be subjected to categorization according to PMS complaints and any incident for non-conformity within the previous two years.

Regarding Pharmaceutical Products, EDA's NCL upon the risk-based plans provide all technical information about the tests to be used, product specifications, the number of units per sample to collect for each drug and basic info and inform the PMS-MC unit with the required data.

All technical information to be collected for each sample is complete and accurate. The RB-PMS plan defines the governorates and sampling sites at which samples will be collected, the Pharmaceutical Products to be sampled. It also contains detailed instructions for sample collectors.

This RB-PMS scheduled plan of the Pharmaceutical Products is made based on PMS risk factors according to the products type as:

1. Monitoring **new drugs** on the market.
2. Drug monitoring based on risks associated with **manufacturing complexity**, **dosage form**, **stability** (e.g., temperature sensitivity), **safety/efficacy** (e.g., narrow therapeutic window), **demand** (e.g., high burden disease), and **therapeutic indications** (e.g., infectious diseases), or other factors.
3. Quality control of the Pharmaceutical Products at the **main entry points**. This type of monitoring acts as a first-class intervention, has been shown to prevent the circulation of poor quality imported Pharmaceutical Products, and requires close cooperation between regulatory, customs and law enforcement authorities.

4. Regarding facing emergency cases, RB-PMS factor will be added to the current plan concerning:
   a. The newly marketed products or
   b. Newly recorded product's shortage or
   c. Newly recorded SF reports or
   d. Received complaint for any of these marketed products.

PMS subject the aforementioned products to in-field investigation and either:

a. If the products weren't included in the current RB-PMS plan, the products shall be evaluated according to the RB-PMS risk factors.
b. If the products were included in the current plan, the products' risk factors shall be re-evaluated within the current plan and its testing level may be upgraded if required.

9. Preparing to Implement Post-Marketing Surveillance Programs

The sampling and testing plan must ensure that sampling is unbiased, and the data produced are meaningful and accurate in order to be used for decision-making.

Sampling and testing activities conducted at least once per year. The initial planning shall be circulated within EDA's concerned organizational administrations.

EDA establishes clear procedures and guidelines on how to execute all steps of sampling and testing, including clear definition of roles and responsibilities of all parties involved.

EDA leads sampling, testing activity and finalizes the plan of each program. EDA inspectors carry out sampling according to an established and approved plan. The Official NCL carry out quality control (QC) tests according to regulations and guidelines (official verified/validated test methods in product dossiers, or pharmacopeia methods). Analysis reports are reported to the PMS unit, in which it is responsible to analyze and report the findings and share it with all relevant stakeholders. EDA's different administrations –according to jurisdiction- carry out

follow-up actions to ensure the marketed products' quality within the Egyptian market.

In all cases, the supply chain / storage requirements of all Pharmaceutical Products will be investigated by EDA inspectors.

10.Framework for risk-based post-market surveillance tool

10.1 Selection of products

The number of authorized and licensed Pharmaceutical Products to be on the market varies from one country to another. Sampling and analysis of these products registered is extremely difficult and often unfeasible, so applying risk-based approaches to select any of the Pharmaceutical Products for sampling and testing as part of a post-marketing surveillance program is imperative that is why categorizing these products was done according to PMS risk factors mentioned previously following to either EDA's lot release risk factors for biological products or EDA's Information Management System (IMS) data and the Drug Factory inspection (DFI) manufacturer assessments for both local and imported manufacturer's medical products which are implemented to the set timetable of the annual plan.

According to these factors the underlined Pharmaceutical Products will be classified into:

Group (1) High-risk products

Group (2) Medium-risk products
Group (3) Low-risk products

10.2 Selection of geographical area for sampling

The governorates will be classified using their geographical regions and based on the following classification PMS risk factors: Population Size, Border zone / ports, Supply chain, transportation from the central stores to regions, Storage performance and history of cold chain complaints and history of counterfeit and sub-standard incidents recorded.

10.3 Collection Site

- Collection of samples from ports of entry are excluded since verification of consignments is done by inspectors from EDA and consignments are released under restricted release conditions to warehouses of distributers, wholesalers,…etc. and is checked by inspectors from EDA for final release or sampling for testing.
- Sampling is made from main outlets **(Level 1)** among which the stores of distribution companies and/or warehouses and secondary outlet **(Level 2)** among which public and private pharmacies.

- **Follow-up of the cold chain for the stores of pharmaceutical products and vaccines in all sites of inspections and sampling wherever in all the governorates is a must. In-addition to that, the GSDP inspection checklist is a must to be implemented for the evaluation of the sampling storage sites for all products type.**

10.4 Number of collected samples

Required quantity of samples which needed for issuing complete report should be collected with reference to the NCL guidance document. The number of samples withdrawn according to the product type, size, dosage form and risk-based testing from the same batch number.

10.5 Level testing approach

This guideline was developed to ensure monitoring the pharmaceutical market, based on what was initially implemented via the regulatory aspects.

The PMS-MC within EDA looks for implementing the three-level approach. It is a cost-effective mechanism to avoid resources consumptions during monitoring implementing the RB-PMS plan. The approach strengthens medicines quality assurance systems by allowing better regulation of the pharmaceutical market, which ultimately reduces the prevalence of poor-quality medicines.

10.6 Frequency of sampling

According to the previous factors a PMS risk-based sampling matrix will be done according to the following Groups:

Group (1) High-risk products:

- These products are sampled and analyzed **three times annually twice from the main outlets** (stores of distribution companies and/or warehouses) **and once from a secondary outlet (**public and private pharmacies).
- At least sampled **once from one of the sites of a governorate with high risk and once medium risks**, with follow-up of the good storage and distribution practice including cold chain investigation (if required) in all governorates.

Group (2) Medium-risk products:

- These products are sampled and analyzed **twice a year at least once from one of the main outlets.** At least sampled **once from one of the sites of a governorate with high or medium risk,** with follow-up of the good storage and distribution practice including cold chain investigation (if required) in all governorates.

Group (3) Low-risk products:

- These products are sampled and analyzed **twice a year.**

- At least sampled **once from one of the sites of a governorate with medium risk,** with follow-up of the good storage and distribution practice including cold chain investigation (if required) in all governorates.

11. Implementation of Plan

After developing the PMS risk-based plan which provide all technical information about the tests to be used, product specifications, the number of units per sample to collect for each drug and basic information regarding the stability of the drugs and proper handling during sampling and the notification of all concerned parties of the risk-based plan.

The drug authority inspectors will implement the risk-based PMS (RB-PMS) process and start sampling after making an inspection report for the pharmaceutical establishments or institution, from which the risk-based will be made, indicating the availability of good storage requirements for the institution, as well as describing the storage conditions of the sampled product, in addition to the necessity and quality of documents indicating a source of supply of the product indicating the supplier, batch number and date of supply.

Visual check is done for outer packaging and inner leaflet of the product and report any notes in case there are any changes while matching the drawn sample to an original sample. Visual examination of the drug is conducted to monitor the presence of impurities, the appearance of mold, or a change in the physical properties of the product and submit a report, if there are any.

12. Sampling collection

The number of samples corresponding to the risk-based plan is drawn randomly from the same batch number, in preparation for sending them for analysis. The PMS sampling form shall be filled out showing all the technical information (including the location of collection, the number of samples collected, the name of the sample and any note at the time of collection) that will be collected for each complete and accurate sample, and it shall be signed by the authority's

inspectors as well as the director of the pharmaceutical establishment or institution.

13. Product Information Review and confirmatory testing

- Results of the product information review and confirmatory testing will be completed via EDA's NCL, to be delivered to.
- Testing results will be shared with EDA's Market control & Post marketing surveillance (PMS) unit to act accordingly.

14. Analyze, Communicate & Act:

Depending on the data presented to the NCL and 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 and requesting additional information or clarification from market authorization holders, or other appropriate regulatory action such as recall.

15. Conclusion:

Data from sampling and testing activities within post marketing surveillance programs can be used to strengthen the programs themselves and should be used to continuously shape, refine, and improve future activities and national post-marketing surveillance priorities.

16. References:

1. WHO Technical report series 996 Annex 7, Guidelines on the conduct of surveys of the quality of medicines, 2016.

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3. Risk-Based Post-Marketing Surveillance of Medicines: Implementation Resources for Low- and Middle-Income Countries. USP, October 2021.
4. EDA's Chairman Decree no. 120 for 2022.
5. EDA's Chairman Decree no. 781 for 2022