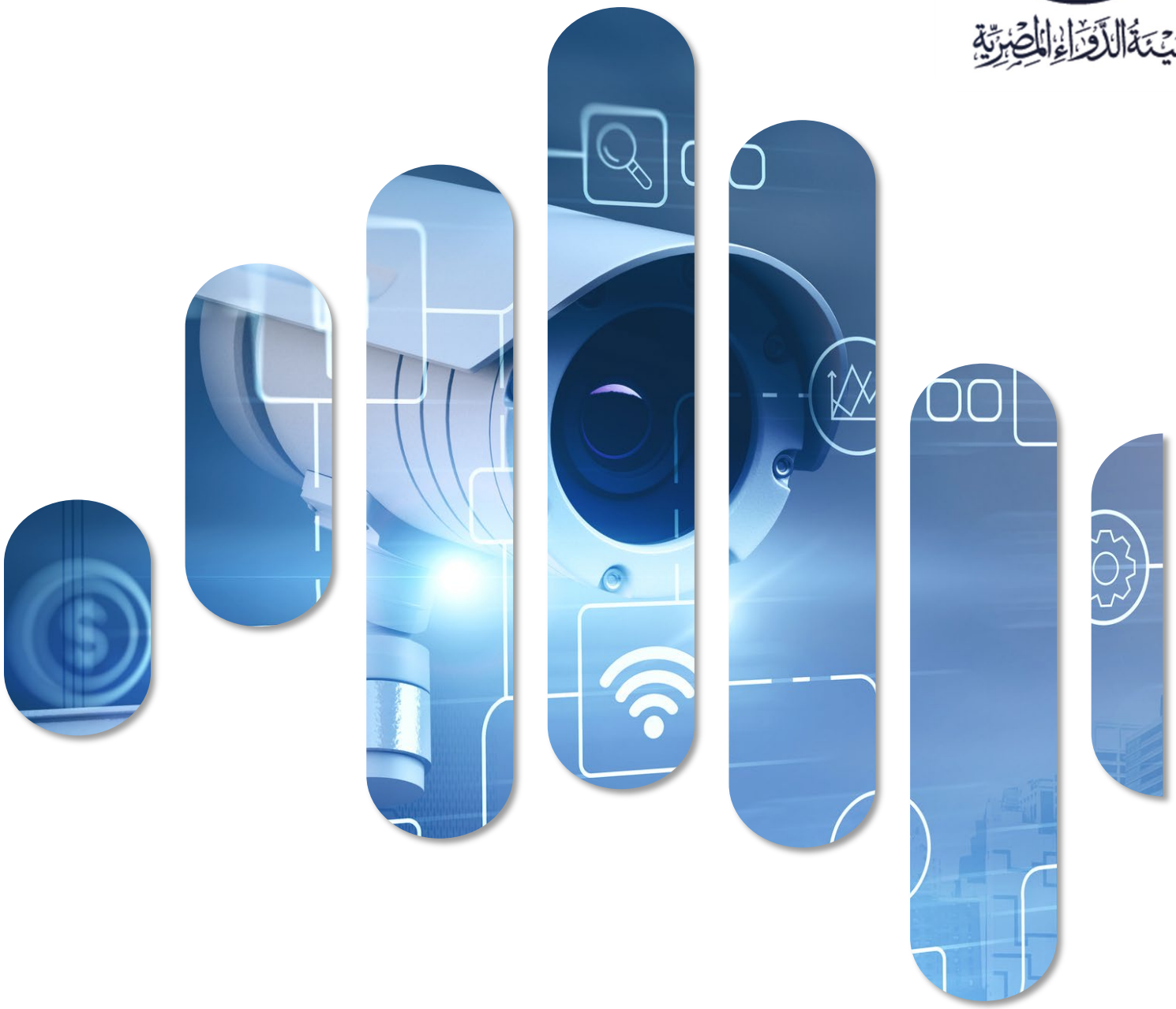

Guideline for Conducting Risk-Based Post Market Surveillance Plan within the Egyptian Market

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1. Introduction

Post-marketing monitoring is one of the important monitoring activities that occur after the market approval of the drug. Due to the adoption by the Egyptian Drug Authority of a new approach to reduce the number of batches subject to analysis, both for biological and pharmaceutical products, as well as the vitality of the importance of trading products, monitoring after marketing has become one of the important activities for quality control of those products through developing a risk-based plan depending in the first place on the extent to which the products are subjected to analysis before trading.

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

EDA ensuring that a post-marketing surveillance program is supported by appropriate legal frameworks, staffed with a qualified and proficient regulatory workforce and financed through regular and adequate national budget appropriations; helps ensure continued operational sustainability.

Regular strategic planning efforts with key stakeholders are also critical in ensuring that approaches, assumptions, and priorities for the post-marketing surveillance program remain relevant over time.

2. Purpose

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

1- Monitoring the safety, quality and efficacy of both biological and pharmaceutical products available in the market in different region at different levels of supply chain with a view to assessing patients' exposure to poor quality biological and pharmaceuticals suggesting appropriate actions.

2- To identify potential causes of low quality of certain products to which patients are exposed.
3- To test the quality of both biological and 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 what the health impact may be on patients.
5- To identify medicinal products SF that reached consumers and evaluated pharmacovigilance reports by healthcare professionals and patients.
6- To raise awareness of the importance of reporting an unusual deficiency in the effectiveness of medicinal products.
7- To improve and enhance safety measures, which include statistical analysis of adverse drug reactions (ADRs) have also been reported by healthcare institutions and patients, thus revealing signs of adverse drug interactions that may require further investigation.

EDA is considering what is achieved from these goals is a factor to evaluate the provisions of market control and the strengths and weaknesses of the system are identified and the ability to continuously develop.

Adoption of a risk-based approach to market surveillance would 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.

3. Scope

This guide will be applied to both biological and pharmaceutical products. Covering all points of the supply chain, whether distribution companies, warehouses or pharmacies, whether public or private and given the presence of other parties that have entered the supply chain, such as vaccination centers or even vaccination campaigns, this has been taken into account in the development of the risk-based plan.

Criteria for exclusion based on risk:

1- These products are independently tested by EDA and released for all batches for both the biological and pharmaceutical registered products.

2- Vaccines in Egypt are categorized into:

- National immunization vaccines (EPI and COVAC) where all these vaccines undergone full testing of 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.
- Non-National immunization vaccines (private market) since these are imported from registered authority with no history of non-compliance in testing or as SF product in market.

3- Antisera & Antitoxins are not marketed but are for governmental use only.

4- All products restricted for hospital use only; eg: Albumin & Anti-RH.

5- Pharmaceutical products that are intended for specific diseases; eg: Amyotrophic lateral sclerosis (ALS).

6- Pharmaceutical products sampled by 100% of their produced batches from their manufacturers.

7- All products represent shortage in the Egyptian market.

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

4. Methodology

4.1. This Post marketing surveillance risk-base (PMS-RB) plan will be divided along the 4 quarters of the year; every quarter will target different groups of products with different risk category.

4.2. Four groups of targeted products categories [A, B, C, D] will be designed to ensure effective control of medicinal products based on the risk-based approaches.

4.3. The Product *Category 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 respectively for each quarter.

5. 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 under the EDA is coordinated with all sharing stakeholders.

The 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.

The EDA leads sampling, testing activity and finalizes the plan of each program. The 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 with all relevant stakeholders. The EDA carries out follow-up actions.

Substitution criteria for the sampling site should be developed to address the following scenarios when they occur:

Since on designing the risk-based plan, distribution list will be requested from the license and distribution companies and this data will be analyzed to determine a primary/ secondary or tertiary sampling site and substitution will take place in the following cases:

- The selected sampling outlet is closed, then the outlet can be substituted by the nearest pharmaceutical institute found in the same area.
- The medical product being sampled is not found either unavailable or insufficiency, then exchange the product with another available product planned to be sampled from another governorate with same risk level, then the outlet can be substituted by the nearest pharmaceutical institute found in the same area.

- The pharmaceutical product in the outlet has less than six month's shelf life or minimum quantity of sampling is not available during sampling.

In all cases, the supply chain of this pharmaceutical product will be investigated by the EDA inspectors.

6. The Designing of plan

Developed PMS-RB 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 pharmaceutical products it was started from pooling all products mentioned in the PMS complaints and those recalled within the previous two years in addition to those highly sold within the last two years. As well as, products used in the treatment of critical diseases and consumed by a high sector of population according to their Anatomical Therapeutic Chemical (ATC).

Regarding the 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 via these data.

All technical information to be collected for each sample is complete and accurate.

The PMS-RB plan defines the governorates and sampling sites at which samples will be collected, the medical products to be sampled. It also contains detailed instructions for sample collectors.

This PMS-RB scheduled plan of the biological and 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 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.

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

7.1 Selection of products

The number of authorized and licensed biological and pharmaceutical products to be on the market varies from one country to another. Controlling the quality of these products registered is extremely difficult and often unfeasible, so applying risk-based approaches to select both biological and 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 the EDA's lot release risk factors for biological products or the EDA's Information Management System (IMS) data and the Drug Factory inspection (DFI) manufacturer assessments for both local and imported manufacturer's products which is implemented to the set timetable of the annual plan. According to these factors both biological and pharmaceutical products will be classified into:

Group (1) High-risk products
Group (2) Medium-risk products
Group (3) Low-risk products

7.2 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.

Follow-up of the cold chain for the stores of biological and vaccines products in all the places they pass through 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.

7.3 Collection Site

-Collection of samples from ports of entry are excluded since verification of consignments is done by inspectors from EDA, & 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.

-Withdrawals are made from main outlets ***(Level 1)*** like the stores of distribution companies and/or private stores and warehouses (medical stores - drug stores - regional stores of the governorate, Intermediate vaccine stores and medical districts) and secondary outlet ***(Level 2)*** like local pharmacies and pharmacies inside general and specialized hospitals and health care units.

7.4 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.

7.5 Level testing approach

This guideline was developed to ensure monitoring the medicinal market which was initially implemented via the regulatory aspects. This guideline adopts the Promoting the Quality of Medicines (PQM) program in cooperation agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeia Convention (USP). 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 PMS-RB 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.

7.6 Frequency of sampling

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

Group (1) High-risk products:

- These products are withdrawn and analyzed three times annually twice from the main outlets (distribution companies, stores and warehouses) and once from a secondary outlet.
- At least one sample Withdrawn from one of the sites of a governorate with high and one 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 withdrawn and analyzed twice a year, once from one of the main outlets (distribution companies, stores and warehouses) and once from a secondary outlet.
- At least one sample Withdrawn from one of the site of a governorate with high 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 withdrawn and analyzed twice a year, twice from a secondary outlet.
- Samples will be withdrawn twice during the year from any governorate at least one medium risks governorate, with follow-up of the good storage and distribution practice including cold chain investigation (if required) in all governorates.

8. 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 PMS risk-based (PMS-RB) process and start sampling after making an inspection report for the pharmaceutical 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 withdrawn 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 to mention any notes in case there are any changes while matching the drawn sample to an original sample. Visual examination of the drug is carried out to monitor the presence of impurities, the appearance of mold, or a change in the physical properties of the product and take notes, if there are any.

9. 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.

10. Product Information Review and confirmatory testing

- Results of the product information review and confirmatory testing will be completed via the EDA's NCL.
- Testing results will be shared with Market control & Post marketing surveillance (PMS) unit in EDA for sharing information with relevant stakeholders and taking further regulatory actions.

11. Analyze, Communicate & Act:

Regular meetings are held with all interested parties that will be in direct or indirect contact and will be affected by the risk-based plan by mean or another to clarify all the vague points for instance refunding the pharmaceutical institutions for the withdrawn products and the response in case of non-conform sample.

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.

12. 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.

13. References:

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