Guideline for Post Market Quality Monitoring of Biological Products in Egypt

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1. Introduction

Strong post-marketing surveillance (PMS) programs capable of monitoring the overall quality and safety of medicinal products (e.g., medicines, vaccines, etc.) and responding to public health risks are required to help protect the markets from the threats posed by substandard and falsified medicines with efficient management of surveillance activities within a logical timeframe.

Risk Based Post-Marketing Surveillance (RB-PMS) testing program is established to monitor and confirm that the medicinal products available in the market meet appropriate quality requirements. It is considered an effective tool for monitoring the quality of medicines in resource-limited countries.

Additionally, other reactive tools are utilized for targeted investigations and complaints in response to information about suspected quality issues with drugs on the market.

The legal provision under which the PMS lays is: Egyptian Drug Authority's (EDA) Chairman Decrees No. 781/2022 and No. 425 /2022

This document should be read in conjunction with guidelines for conducting a risk-based post-marketing surveillance plan within the Egyptian market for medical and biological products (Code: EDREX: GL.CAO.014), Guidelines for Lot Release (LR) of Biological Products (Code No.: EDREX.GL.Bioinn.003), and Guidelines on Recall and Rapid Alert System for Medicinal Products (Code: EDREX: GL.CAO.008).

2. Scope

This document pertains to the implementation of RB-PMS plan for all licensed biological products in Egypt and is conducted by Bio Inn at EDA in collaboration with other stakeholders. It describes the measures taken to ensure the compliance of biological products with the requirements for safety, quality, and performance after they are placed on the market. Also this document describes the process of dealing with information about suspected quality issues for biological products through complaint samples or temperature deviation cases.

3. Abbreviation

CA	Central Administration
CPMP	Complains and Post Marketing Program
EDA	Egyptian Drug Authority
LR	Lot Release
MC	Market Control
NCL	National Control Laboratory
OOS	Out Of Specification
PMS	Post Marketing Surveillance
RB-PMS	Risk Based -Post Marketing Surveillance
WHO	World Health Organization
3LA	Three level approach

4. Definitions

Post Marketing Surveillance: The practice of monitoring quality, safety and efficacy of medicines after they have been registered and released into the market.

Critical quality attributes: A physical, chemical, biological, or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Substandard products: According to WHO, also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both.

Falsified product: Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Biological products: They are products that contain one or more active ingredient produced or extracted from biological origin. For instance, they may include human vaccines, antisera, blood products and plasma derivatives, biotechnology-manufactured products and the like as well any products or materials that may be created according to science developments and/or international standards and references.

Complaints: Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a biological product after it is released for distribution.

Temperature excursion: Any temperature reading outside the ranges specified by the manufacturers.

Recall: Removal of marketed products for reasons of lack of quality, safety, or efficacy, including labeling that is against the law.

5. Main topic

5.1. Risk – Based Post Marketing Surveillance (RB-PMS) testing program (proactive approach)

Biological manufacturers, no matter where they are located, are responsible for guaranteeing that only quality products reach Egyptian patients. Product testing is the responsibility of manufacturers of all marketed biological products, to make sure their products conform to the appropriate quality standards. Bio Inn's mission is to assure that quality biological products are available to patients by protecting them from poor-quality biological products by determining whether companies are fulfilling their responsibilities and initiating appropriate action or not.

Sampling and testing complement other surveillance approaches to ensure product quality including inspecting manufacturing facilities, evaluating post-market quality reports, and using data analytics. The outputs obtained from RB-PMS testing program are analyzed to understand the state of quality for particular products or classes of products, identify defective or potentially harmful products, and provide evidence for compliance actions.

It should be noted that biological products that do not undergo official lot release testing (routine lot release testing) will be subjected to RB-PMS testing program according to LR guideline.

The Developed RB-PMS plan will be designed by setting a criterion for the selection of products as mentioned in guidelines for conducting a risk-based post-marketing surveillance plan within the Egyptian market for medical and biological products.

PMS sampling protocol will include a well-designed sampling plan that contains information such as: name(s) of the samples to be collected, unit pack, dosage form, number of unit per sample, number of collected samples depending on volume of sample) and sample site information.

5.1.1. Procedure for conducting the RB-PMS testing program

Samples withdrawal is performed according to the annual RB-PMS plan by Market Control (MC) administration. Where the MC - inspectors will perform the sampling according to established and approved plan as per guideline for conducting Risk-based post market surveillance plan within the Egyptian market for medical and biological products.

The testing of biological products that are subjected for RB-PMS testing program will follow the following phases within a timeframe of 22 working days.

Sample screening

The importance of this phase is reflected in its ability to detect the falsified product from genuine product before jumping to quality testing and avoid misuse of resources. This phase is initiated by the reception of required documents (sample analysis request, record for sample collection, and good storage and distribution practices report issued by EDA inspectors) and include the following actions:

- Verification of the legal entry of the sampled batch into market through reviewing LR data base.
- Checking the following data on the received sample:
    - Registration status
    - Expiration date
    - Labeling
    - Inner and outer packaging
- Performing visual check for the outer packaging and inner label of the product by comparing the label and package of the samples against the approved packaging in marketing authorization file.

Parameters to be tested during RP-PMS

Tests are conducted using compendial methods and validated approved methods during RP-PMS targeting selected critical quality attributes (CQAs) which have added value to the RP-PMS program decisions and regulatory actions as mentioned in **Table 1**.

Table 1: Selected tests to be detect product quality issues.

Test	Possible product Quality issue
Visual inspection /particulate matter	Poor quality product lead to safety issue
Identification	Falsified product
Assay	Quantity of active ingredient inconsistent with claim on label
Purity profile	Unsuitable storage lead to product degradation and impaired efficacy and immunogenicity issues

The testing strategy is based on a tiered approach (three-level approach) to testing as part of post marketing surveillance .This approach uses three interlinked approaches with increasing level of complexity, to strengthen the quality assurance systems of biological products.

- The first level includes a visual and physical inspection to assess the packaging conditions and the physical characteristics of the actual biological products.
- The second level consists of some targeted tests to be selected from the previously mentioned table.
- The third level involves quality control testing for all tests parameters that are mentioned in the previous table.

Result evaluation and report preparation

The obtained results throughout the program are analyzed in order to prepare the report which will be shared with stakeholders among EDA. The analysis result in addition to other factors will be the base by which the next year plan will be settled.

5.2. Complaint handling (reactive approach)

5.2.1. Procedure for handling of complaints samples

1- Receiving the complaint samples of biological products from the market in response to complaints or for technical investigation about suitability for human use after certain events.
2- Screening of submitted documents attached with complaint samples and communicating with relevant stakeholders as required.
3- Verification of the received complaint batch in EDA- LR data base to check batch number presence in the market through a legal supply chain channel.
4- Evaluation and comparisons of label and package of the complaint samples against the approved packaging and artwork at product's marketing authorization file available at EDA.
5- Review stability studies if required (in case of the deviation from the product's storage temperature).
6- Testing of complaint samples according to the complaint case following testing strategy scheme as illustrated below.
7- Reporting for the investigation results through a technical report containing a summary of the results, possible conclusions and recommendations.
8- Report submission to MC administration at EDA to take the appropriate regulatory action. In case of non-conform result, the product should be subjected to withdrawal or batch recall.

5.2.2. Testing strategy scheme for product complaints

Step 1 (Visual inspection)

The complaint sample is inspected visually to check that it is free from any foreign particles. If the sample does not meet the visual inspection criteria, testing will be stopped and out of Specification (OOS) result will be issued.

Step 2 Product identification

The complaint sample will be tested for identification of active substance to ensure that it is the genuine product not falsified products. If the product cannot be identified, testing will be stopped and OOS result will be issued.

Step 3 (Assay/purity)

The complaint sample will be tested to determine its assay or purity. If the product does not meet the assay/purity criteria, OOS result will be issued.

5.3. Temperature excursion

The quality, effectiveness, and ultimately the safety of the product can be impacted by temperature deviations or improper storage conditions. Therefore, it is recommended that all products be kept under constant observation and in their respective recommended conditions at all times. Temperature excursions may occur during transportation and storage during supply chain cycle. The entire batch may be rejected if the traceability of temperature monitoring and appropriate storage conditions cannot be demonstrated.

Electronic temperature monitoring equipment is required in all shipments to document temperature limits exceeded during cold chain inspection, ensuring product safety and preventing potential harm.

5.3.1 Procedure for handling temperature excursion cases for biological products.

1. Documents attached with the case such as (fridge tag report and description report of the complaint case) are assessed and evaluated, in addition to supporting documentation available at EDA and submitted by company, such as:

- Stability studies (e.g. accelerated and stress studies)
- Freeze thawing cycling study (if applicable)
- Transportation stability studies

- Any additional studies or information shall be submitted in the case where stability data is lacking.

2. International standards for cold chain and temperature sensitivity of biological products are consulted to take the appropriate decision.

- If the supporting documents or information are insufficient to demonstrate product stability, the product lot must be rejected.
- Final report is issued with the regulatory decision either to continue using the samples or to reject them.

6. References:

- Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low-and Middle-Income Countries.
- WHO Guidelines on the conduct of surveys of the quality of medicines, 2016.

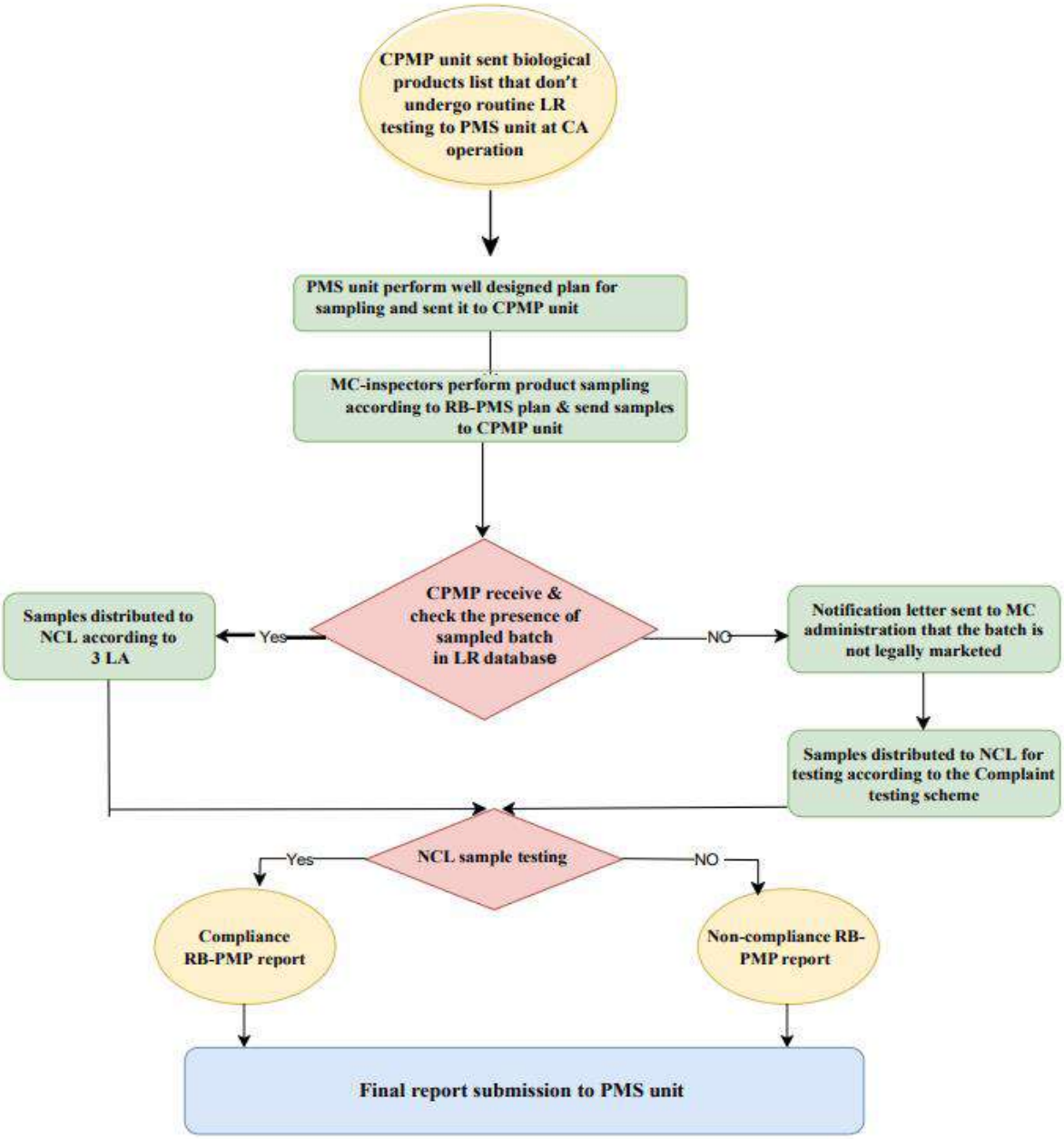
7. Annexes

Annex I: Process flow of the RB-PMS testing program

Annex II: Process flow of complaints samples handling

Annex I

Process Flow of the RB-PMS testing program



Annex II

Process flow of complaints samples handling