Guideline for Lot Release of Biological Products in Egypt

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1. Introduction

Lot release (LR) process is a crucial part of regulatory system of biological products in order to ensure the acceptable quality and safety of each manufactured lot. It is the responsibility of EDA to ensure that the products available in the Egyptian market adequately meet the requirements of safety, efficacy, and quality.

LR involves the confirmation that each lot meets the specifications in the approved marketing authorization file of the product. Under defined circumstances, laboratory testing by a National Control Laboratory (NCL) can provide added value to this confirmation. The need for testing should be justified according to the criteria specified in this document and the laboratory should operate under an appropriate quality assurance system.

It should be noted that EDA has the right to request biological products lots to be subjected to a LR within the context of this guideline.

The legal provisions under which the LR for vaccines and other biologicals lies are the EDA establishment law (151/2019); and its executive regulations (777/2020) article no 17, as well the EDA chairman decree no 425/2022.

This guideline is performed in compliance with WHO guidelines for independent lot release of vaccine by regulatory authority and should be read in conjunction with Guideline for post market quality monitoring of biological products in Egypt (EDREX.GL.Bioinn.009).

2. Scope

This guideline is intended to provide guidance to marketing authorization holders (MAHs), importers and distributors in addition to other relevant stakeholders (as Egyptian unified purchasing authority and the national immunization program), on the EDA lot release procedures and the conditions that must be met when submitting a lot release request to EDA. It applies to all biological products prior their release to the market.

3. Abbreviation

APQR	Annual Product Quality Review
CA	Central administration
CoA	Certificate of Analysis
EDA	Egyptian Drug Authority
EDQM	European Directorate for the quality of medicines
GMP	Good Manufacturing Practice
LR	Lot Release
LSP	Lot summary protocol
MAHs	Marketing Authorization holder
NCL	National Control Laboratory
NONC	Notice of non-compliance
NRA	National Regulatory Authority
OOS	Out of specification
OOT	Out of Trend
RB-PMS	Risk Based -Post Marketing Surveillance
PDMPs	Plasma-Derived Medicinal Products
WD	Working Day

4. Definitions

Annual Product Quality Review (APQR): Regular periodic review of all licensed commercial drug products conducted annually by the companies with the objective of verifying the consistency of the existing manufacturing process, the rightness of the current specification for both starting materials and finished product to highlight any trend, deviation, change control, market complaints and to identify the product and process development.

Certificate of Analysis (CoA): a document prepared by the manufacturer that contains all release tests and its specification based on product marketing authorization file, which has been evaluated and approved by NRA during product registration.

Lot: a defined quantity of starting material, packaging material, or product processed in a single/ series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a lot into a number of sub-lots, which are later accumulated to form a final homogeneous lot. In continuous manufacture, the lot must correspond to a defined fraction of the production, characterized by its intended homogeneity. The lot size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Lot Release Certificate: an official document issued by the competent national drug regulatory authority that authorizes the manufacturer to release the specific lot into the market.

Lot Summary Protocol (LSP): a document summarizing all manufacturing steps and test results for each producing lot which is certified and released by the responsible person of the manufacturing company.

Out of Specification (OOS): An OOS result is generated when a biological product is tested and fails to meet a pre-defined specification.

Out of Trend (OOT): A result of a sequence of the analytical results which conform to the specifications but not in the expected trend with respect to the initial or expected result.

Reliance: The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

5. Main topic

5.1. General Principals

5.1.1. Lot release pathways

5.1.1.1. Normal pathway

This pathway involves the independent assessment of each lot of a biological product before it is released to the market. Each lot of the product must undergo document assessment and /or sample testing, which is determined by the degree of risk associated with the product.

Normal track timeframe will depend on the risk group as mentioned below

5.1.1.2. Expedited Release pathway

Expedited release may be granted in exceptional cases and upon appropriate justification according to the following cases:

- Product shortage in Egypt
- Public health emergency
- Biological products donated from international organizations

Lots will be released after evaluation of relevant documents and performing the minimum testing items that assure product safety & quality. For other situations in which a product is needed to be released in expedited pathway, it will be handled on a case-by-case basis.

*Expedited release pathway shall be completed within **10 WDs** of receiving of the complete set which consists of the needed documents, samples and the fees, where required.*

5.1.1.3. Reliance Release pathway

Full or partial exemption of independent testing may be granted to vaccine / plasma derived products upon submission of lot release certificate issued by a reference NRA / NCL. The list of the approved reference NRAs is published on EDA website.

For biotechnology products imported from reference countries, full exemption from lot release testing will be applied. These products will follow PMS testing in accordance with 'post marketing quality monitoring on biological products in Egypt' guideline (code: EDREX.GL.Bioinn.009). In case these products were subjected to recall, non-conformity, or regulatory non-compliance, normal LR testing track will be conducted.

*Reliance release pathway shall be completed within **5WDs** of receiving of the complete set which consists of the needed documents, samples and the fees, where required.*

5.1.2. Risk-based approach

EDA applies a risk-based lot release approach. More extensive testing may be needed based on the outcome of the risk assessment according to the following factors. This risk-based approach must guarantee that EDA meets its obligation of ensuring the safety, efficacy and quality of all released lots of biological products.

5.1.2.1 Factors considered for risk-based categorizing:

EDA risk - based lot release approach considers the following risk factors:

- **Product Indication:** (age of target population, health status, population size).
- **Nature of the Product:** (complexity and origin of the molecule)
- **Product qualifications:** (Regulatory authority, Registration status, prequalification……)
- **Inspection History:** quality or safety issues found during on site evaluations or any observations related to GMP that could affect the quality of the biological product

- **Consistency of manufacturing processes:** as reviwed in the APQR in addition to the tests results obtained by manufacturer or EDA-NCLs including out of trend and non-conformity lead to insufficient lot to lot consistency.
- **Post-marketing experience:** Information related to adverse drug reaction reports, product complaints, product recalls, and withdrawals contribute to the post-market safety profile of the drug product
- **MAH Regulatory compliance:** with EDA's laws, regulations, and other rules that govern biological products in Egypt.
  Examples of product non-compliance include but not limited to:
  - Failure / continuous delay to provide requested data.
  - Release of product (including quarantined products) without previous approval from the EDA.
  - Inconsistent product documentation system.
  - Failure to comply with the RB-PMS testing strategy

5.1.1.2. Risk-based categories

EDA categorize all biological products (either imported or locally manufactured) submitted for lot release into the following groups:

- High risk group: where lot release is performed through document review in addition to performing all relevant tests according to product specific critical quality attributes and EDQM guidelines. *The timeline of this category is **29 WDs however, some products with long bioassay tests may take longer timeline but not more than 60 WDs** of receiving of the complete requirements.*

- Moderate risk-group: where targeted testing is performed by selection of some relevant tests to be conducted in addition to document review. *Timeline of this category is **22 WDs**.*

- Low risk group: In this group, all batches are subjected to document review before release. Lot samples may be requested for periodic testing by maximum of one batch per quarter. It should be noted that biological products where lot

samples are not routinely submitted for targeted testing will be subjected to market surveillance and control. *Timeline of this category is **18 WDs**.*

5.1.1.3. Change between risk groups

Product assignment to risk groups is reviewed annually or when required within the year. Risk groups assessment for each product are performed and re-categorization can be changed as follow:

- LR team may review and update products of low and moderate risk to high-risk group if there are reports of significant or sever incompliance with GMP, adverse events, repeated testing failure or product recalls.
- LR team may review and update products of lower risk to higher risk group if the regulatory non-compliance from applicant was evident.
- Products assigned in risk groups (high, moderate, and low) will be reassigned to the lower risk group after demonstration of lot consistency and compliance (not less than 20 lots to be subjected to LR testing after registration or remaining in the higher group for a period of two years or by evaluating APQR for imported products), except for vaccines and plasma derived products, which may remain in moderate risk group indefinitely.

5.2. Conducting lot release

5.2.1. Document review

To apply for LR process, the applicant must submit a complete application with all required documents as published on EDA website, using the designated submission LR automation system (Bio release system) on EDA website in addition to paying the requisite service consideration.

The submission of the required documents shall be in a period of not less than **10 WDs** of the shipment arrival. The LR staff will then check the completeness of the submitted application. If the application form is incomplete, the applicant will be informed within **1WD** from the application receipt. Any missing documents or clarifications should be submitted by the applicant within **10 WDs** after

receiving LR comment. In case the applicant didn't satisfy the needed documents, the application will be cancelled and a new one will be needed. The LR administration, through the designated communication system, will notify the applicant with any raised comments within **5WDs** and the evaluation results for the submitted documents will be within **10 WDs** after receiving complete required documents.

Summary protocol review (for vaccines & PDMPs)

In general, the format and content of the LSP are approved by EDA during the registration process. The format of the LSP may be amended in response to post approval changes. The summary protocol is certified and released by the manufacturer and is evaluated based on the product marketing authorization file approved by EDA. An independent review by EDA staff for the critical data from each lot is essential to ensure product quality and compliance with regulatory requirements. Independent review of each lot LSP shall ensure:

- The consistency of quality or manufacturing process of each manufacturing lot.
- Obtain confidence in the potency and identity of active ingredient (s).
- Assess the validity and accuracy of the tests performed

5.2.2. Independent testing

5.2.2.1. Lot release testing

LR-units at EDA will follow the testing strategy based on the outcomes of risk assessment as illustrated in 5.1.1.2. Samples needed for LR testing should be submitted within **5WDs** from cold chain inspection for warehouses.

Some practical considerations:

- Concerning finished products lots derived from the same final bulk, only one lot will be tested according to each product risk level.
- In case of imported biological products, for all incoming lots with the same lot number for a lot that had been subjected to LR process previously and lot release certificate had been issued for it by EDA, it will be released through the EDA inspectors according to their regulations as long as the lot is valid within its shelf life.
- According to the risk group of each product, testing items may be added or omitted independently as required by LR administration.
- It may be necessary to obtain product specific reference materials or reagents from the manufacturer. The amount requested should be relevant to the number of tests that will be performed.
- ***For locally produced products***, under certain circumstances, EDA may agree to receive samples from manufacturers before they have completed their own test procedures so that testing by the NCL is done in parallel. In such cases, the lot cannot be released by the LR administration until all the test results from the manufacturer have been received (including the completed and signed final CoA and summary protocol with their test results).

5.2.2.2. Testing for post approval changes

Certain major quality changes require re-analysis after the implementation of the change on the first upcoming batch on which the change is implemented in accordance with guideline for lot release of biological products in Egypt, taking into consideration the product risk categorization, release pathways, and good reliance practice where imported products from reference countries will not undergo retesting for variation according to technical committee decision.

5.3. Data monitoring

- LR administration request the APQR from the manufacturer to verify the consistency of the process, in order to assess the ongoing safety and quality of the product and to highlight any trends, as well.
- Trend analysis which is performed by LR administration concerning the results of quality control testing submitted by the manufacturer in order to assess production consistency.
- Reports for products experience from Market control and surveillance as well as pharmacovigilance reports should be considered during reassignment of biological products

5.4. Data evaluation and decision making

It is the responsibility of LR administration at the EDA to review all results from the national lot release process which involves relevant laboratory testing and document review that will be compared / checked with the approved specification of the product in the marketing authorization file and all approved post approval changes.

5.4.1. Conform decision

If the lot conforms to the release requirements, the LR administration will notify the applicant through the automation system (Bio-release system) and provide the applicant with an electronic copy of lot release certificate within **3WDs** from receiving all lot testing results.

5.4.2. Non-conform decision

If the lot is not complying with the approved specifications for any test, LR administration will schedule a meeting with the applicant to discuss this result, and complete investigation report will be requested from the applicant regarding the root cause of this OOS and its impact on product safety, quality and efficacy. This investigation will be revised by LR administration to take the final decision

about the lot non-conformity

The applicant may request to submit a non-conformity appeal **within 10 WDs** from LR final decision. Further decisions shall be taken as per chairman decree number 343 / 2021, article 5.

5.5. Communication with LR team:

All MAHs could communicate with LR team in case of any required clarification regarding LR process and procedures through the official emails of LR Units:

Biolr.pb@edaegypt.gov.eg
biolr.vac@edaegypt.gov.eg
biolr.cpmp@edaegypt.gov.eg

6. References:

1. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Annex 2, Technical Report Series, No.978, WHO 2013.

2. Assessment Criteria for National Blood Regulatory Systems, WHO, 2012.

3. Good reliance practices in regulation of medical products: high-level principles and considerations, Annex 10, Technical Report Series, No.1033, WHO 2021.

4. Official control authority batch release (OCABR) for human biologicals: vaccines, blood and plasma derivatives, EDQM, 2013.

7. Annexes

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