Central Administration of biological and innovative products and clinical studies
General Administration of biological products

Guideline

Guideline for Lot Release of Biological Products in Egypt 2022

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1. Introduction

This guideline is issued based on decree of Egyptian Drug Authority's president No. 425/2022 for lot release of biological products to provide assistance to marketing authorization holders (MAHs), Importers and distributors with respect to the official lot release program of the Egyptian Drug Authority (EDA).

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. It should be noted that EDA has the right to request any biological product batch to be subjected to a lot release within the context of this guideline.

In the interest of harmonization with international standards, EDA considers the batch to be released without performing lot release testing if such tests have been performed by well-established regulatory authorities.

Biological therapeutics, also referred to as Biologicals, are Products containing one or more active ingredients produced or derived from a biological source.

Biologicals are a diverse group of medicines which includes vaccines, Plasma-Derived Medicinal products (PDMPs), as well as biotechnology–derived therapeutic proteins such as growth factors,immune modulators, and monoclonal antibodies. What distinguishes Biologicals from other medicines is that these are generally proteins purified from living culture systems or from blood, whereas other medicines are considered as 'small molecules' and are either made synthetically or purified from plants [1].

Vaccines are biological products used for healthy populations. The impact of using sub-standard lots may not be known for a very long time (years). Similarly, safety issues with a particular lot may not be known immediately (within a few hours) after administration, and could have a drastic impact on a large number of healthy individuals receiving vaccines before the problem is recognized. For these reasons, a careful independent review

of manufacturing and QC data on every lot is necessary before it is marketed. Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programs, thus potentially compromising public health strategies. Therefore, it is essential to ensure the consistent quality of each lot before it is released to the market [2].

Plasma-Derived Medicinal Products (PDMPs) are prepared from human plasma and include products such as albumin, coagulation factors and immunoglobulins, which are life-saving for several chronic and acute life-threatening diseases. They are complex in nature and their quality and safety rely heavily on source of materials as well as subsequent manufacturing processes including infectious marker testing and viral removal and inactivation [3].

In addition to manufacturing complexity inherent to biological products, proper storage conditions and efficient supply chain management must be ensured to preserve the sensitivity and limited shelf-life properties of these products. For the reasons as stipulated above, a careful independent review of manufacturing and quality control data on every lot of products as stated is therefore necessary before use. Lot release program will enable National Regulatory Authority (NRA) to ascertain the safety and efficacy of every lot of these products before releasing to the market.

The independent lot release of biological products by EDA is part of the regulation of these products and involves independent assessment of each lot before it is released to the market.

As per WHO guideline 'Guideline for independent lot release of vaccines by regulatory authorities' [2], there are currently different approaches to conducting lot release including

1) Review of summary protocol only,

2) Review of summary protocol with independent testing (full or selected testing)

3) Recognition/acceptance of lot release certificates from the responsible NRA/NCL

These approaches are not mutually exclusive and may be product specific. Where appropriate, strategy for each product shall be established by taking into consideration

aspects such as nature of the product and post-marketing experience including production history and safety profile.

2. Scope

This guidance applies to all biological products, whether imported or locally manufactured, received by the EDA Lot Release Administration.

This document is intended to provide guidance to MAHs, importers and Distributors with respect to the official lot release program of EDA.

3. Definitions

Certificate of Analysis (CoA): a document 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: the process of NRA/ NCL evaluation of an individual lot of a licensed vaccine before giving approval for its release into the market.

Lot Release Certificate: an official document that authorizes the manufacturer to release the specific lot into the market.

Lot Summary Protocol (LSP): as defined by WHO Guidelines, lot summary protocol is 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. The test results shall include the test specification and date of test conducted.

Plasma Derived Medicinal Products (PDMP): Biological products derived from human blood plasma components, for example albumin and clotting factors and other plasma derivatives.

Risk-Based Approach: NRA reliance approach that consider factors, such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country, and opportunities for reliance [4].

Vaccine: A vaccine contains an active component (the antigen). A vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection

Annual Product Quality Review: 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

Non-Compliance: failure or refusal to comply with a standard or a set of limits.

4. Procedures

4.1. Lot release in Egypt

This guideline is largely based on the recommendation outlined in 'the guidelines for independent lot release of vaccines by regulatory authorities' [1].

The lot release for biological products in Egypt will follow one of the following pathways:

a) Normal release pathway: in which all biological products will be categorized into three risk groups Low, moderate and high risk groups.

b) Expedited release pathway: which will be applied for any biological product under

certain exceptional cases.

c) Recognition pathway: in which LR will be performed by recognition of release certificate from responsible stringent authority.

4.2. Normal release pathway:

Each lot of a biological product is subject to the lot release program before marketing in Egypt through risk-based approach (**Annex I**). The assessment for the documents and sample testing of biological products are based on the degree of risk associated with the product. The graduated risk-based approach to testing and oversight allows EDA to focus on ongoing testing of product for which enhanced surveillance is needed.

4.2.1. Criteria upon which batches will be released on Egyptian market:

A. Biological products will be categorized into three different evaluation groups according to the following risk factors:

- **Product Indication** (age of target population, health status, population size)
- **Nature of the Product** (small molecule, complex molecule human origin)
- **Product qualifications** (Regulatory authority, Registration status, prequalification……)
- **Inspection History (**quality or safety issues found during on site evaluationsand other inspections**)**
- **Testing History** (non-conformity -insufficient lot to lot consistency)
- **Post-marketing experience** (REMS listing- adverse drug reactions reports, product complaints, product recalls and withdrawals)
- **Regulatory compliance** (MAH's obedience to the EDA's laws, regulations, and other rules that govern biological products in Egypt).

Review of relevant documents & summary protocol (Documents that should be submitted with each batch):

a) Documents to be submitted with each batch according to product type illustrated in **Annex II**

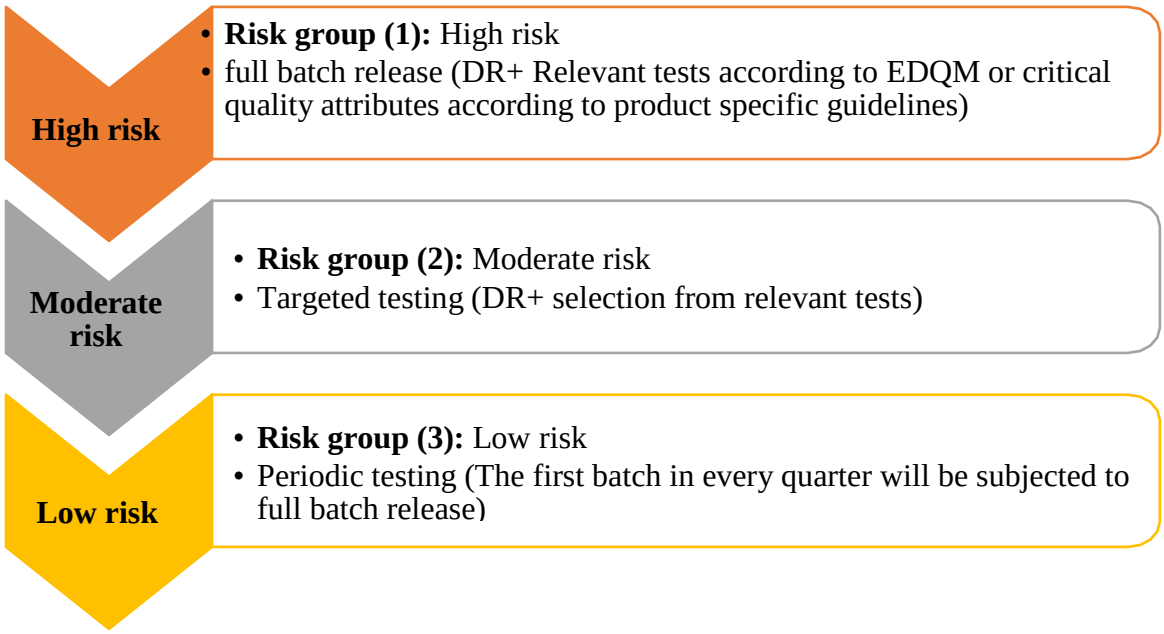
b) Documents to be submitted annually or when required:
1-Annual product quality review.
2-GMP certificates (for all manufacturing sites).

c) The manufacturer's summary protocol (SP) summarizes information taken from the production and testing records according to GMP requirements and CoA that contains all release tests and its specification based on product marketing authorization file which has been evaluated and approved by EDA during product registration to ensure that the lot meets the specifications in the marketing authorization. In addition, the summary protocol & CoA submitted to EDA have to be approved by appropriate QA or QC of the manufacturer. EDA qualified person should review the protocol & CoA in order to:

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

B. Testing policy requirements based on risk level:

EDA conduct independent testing to monitor key products parameters, consistency of production and to verify test results of the manufacturer. Therefore, LR in EDA will assign products into one of three risk groups based on the outcomes of risk assessment.



- **High risk group:**

Product will fall into high-risk group if it is:

- High risk products based on risk assessment outcomes.
- New registered biological product (first 3 batches after registration).
- Major variation to already registered products in accordance to the technical committee decision dated on 15th July 2021.
- Product that failed to achieve consistency in production and testing.

(The targeted time frame for products in this group to be released is 29 WD after receipt of all required information and samples. The timeframe for some products, such as those with long bioassays, may be longer but not more than 60 days).

- **Moderate Risk group:**

Product will fall into Moderate risk group if it is:

- Moderate risk products based on risk assessment outcomes.

(The targeted time frame for products in this group to be released is 22 WD after receipt of all required information and samples).

- **Low risk group**

One batch to be analyzed every quarter and the rest of batches released after evaluation of documents only

Product will fall into low-risk group if it is:

- Low risk products based on risk assessment outcomes.
- Product has demonstrated batch consistency and good compliance (not less than 20 batch)

(The targeted timeframe for products in this group to be released is 18 WD after receipt of all required information and samples in case of sample analysis and 5-7 WD in case of documents review only).

➢ **General considerations:**

- Concerning batches derived from the same final bulk, only one batch will be tested according to each product risk level and for the other batches some test items could be omitted.
- In case of imported biological products, for all incoming batches with the same batch number for a batch that had been subjected to LR process previously and batch 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 batch is valid within its shelf life.
- When it is considered necessary by the Egyptian drug authority, testing items may be added or omitted independently according to the risk levels of each product.

4.2.2. Evaluation of results:

Results from the national lot release process which involves laboratory testing and relevant document review will be compared / checked with the approved specification in the product marketing authorization file and all approved variations. This is performed by LR administration under the EDA.

4.2.3. Change between risk groups:

-LR may review and update product risk assessment to high-risk group if there are reports of significant or sever problems with GMP, adverse events, repeated testing failure or product recalls.

-Product assignment to risk groups is reviewed annually. Products assigned in risk groups (1 &2) will be reassigned to the next risk group with lower risk after demonstration of batch consistency and compliance (not less than 20 batches) with the

exception of vaccines, antisera and PMDPs which should remain in the risk group (2).

4.2.4. Risk-Based Post-market monitoring program

In order to control the quality of all biological products after the implementation of risk based lot release policy, low risk products will be subjected to post marketing monitoring program (PMP) (**Annex III**) as part of a post-marketing surveillance program using risk based prioritization. The frequency of sampling is determined according to the risk assessment tool, that has been mentioned in the Egyptian guideline for conducting risk based post market surveillance plan in accordance to EDA chairman decree no (120) of 2022.

4.3. Lot release in exceptional case (Expedited Release)

Expedited release may be granted in exceptional cases and upon appropriate justification such as:

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

Batches will be released after evaluation of relevant documents and performing the minimum test items that assure product safety & quality.

For other situations in which a product is needed to be released immediately, it will be handled on a case-by-case basis, see **Annex IV.**

4.4. Recognition of Lot Release by Other NRAs/NCLs

Lot release administration shall accept a batch for release based on the existing release certificate from one of the competent authorities listed in **Annex V**, through unilateral recognition process. In this case, the batch release process is performed on the basis of the existing NRA/NCL release certificate and laboratory testing is minimized to visual inspection test.

4.5 Data monitoring

LR request an APQR from the manufacturer to verify the consistency of the process, to assess the ongoing safety and quality of the product and to highlight any trends, as well

as trend analysis which will be performed by LR administration concerning the results of quality control testing submitted by the manufacturer.

4.6 In case of batch non-conformity:

If the batch is not complying with the specification of any test that mentioned in MA file in EDA, LR administration will schedule a meeting with both inspection team and the applicant to discuss this result, and complete investigation will be requested to be performed by the applicant regarding the root cause and its impact on product safety, quality and efficacy. This investigation will be revised by LR and inspection teams to take the final decision about the batch non-conformity, see **Annex VI**. Further decisions will be taken as per chairman decree number 343 / 2021, article 5.

4.7 Lot Release Timelines

- The timeline for each activity in the lot release process are as follow:

Activity	Duration
Submission of batch data form and required relevant documents	10 working days before product arrival at warehouse
Issuance of lot documents review report	Within a duration range from 7-10 WD according to product type
Submission of samples of lots inspected to LR for testing	Within 2 working day from cold chain inspection for warehouses
Issuance of lot release certificate	Within 5 days from receiving all lot testing results.
Submission of non-conformity appeal by the applicant	Within 10 working day form the date that it was informed with non-conformity case.

4.8 Processing Fees

- Every application for lot release shall be charged
- Applications without the correct fees will not be processed.

A. Fees for lot release (Document evaluation according to chairman decree no 193 year 2020)

Type of biological product	Fees
Imported biological product	3000 L.E./Lot
Locally produced biological product	2000 L.E./Lot

B. Fees for lot release (sample analysis according to EDA Law executive regulation no 777 year 2020)

Type of biological product	Fees
Imported biological product	5000 L.E./ Lot
Locally produced biological product	3000 L.E./Lot

4.9 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 email: Bio.lr@edaegypt.gov.eg

5. Glossary:

APQR	Annual Product Quality Review
CA	Central administration
CoA	Certificate of Analysis
DR	Document Review
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
MOH	Ministry of health
NCL	National Control Laboratory
NONC	Notice of non-compliance
NRA	National Regulatory Authority
REMS	Risk Evaluation and Mitigation Strategy
OOS	Out of specification

PDMPs	Plasma-Derived Medicinal Products
PMP	Post Marketing Program
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
SP	Summary Protocol
WD	Working Day
WHO	World Health Organization

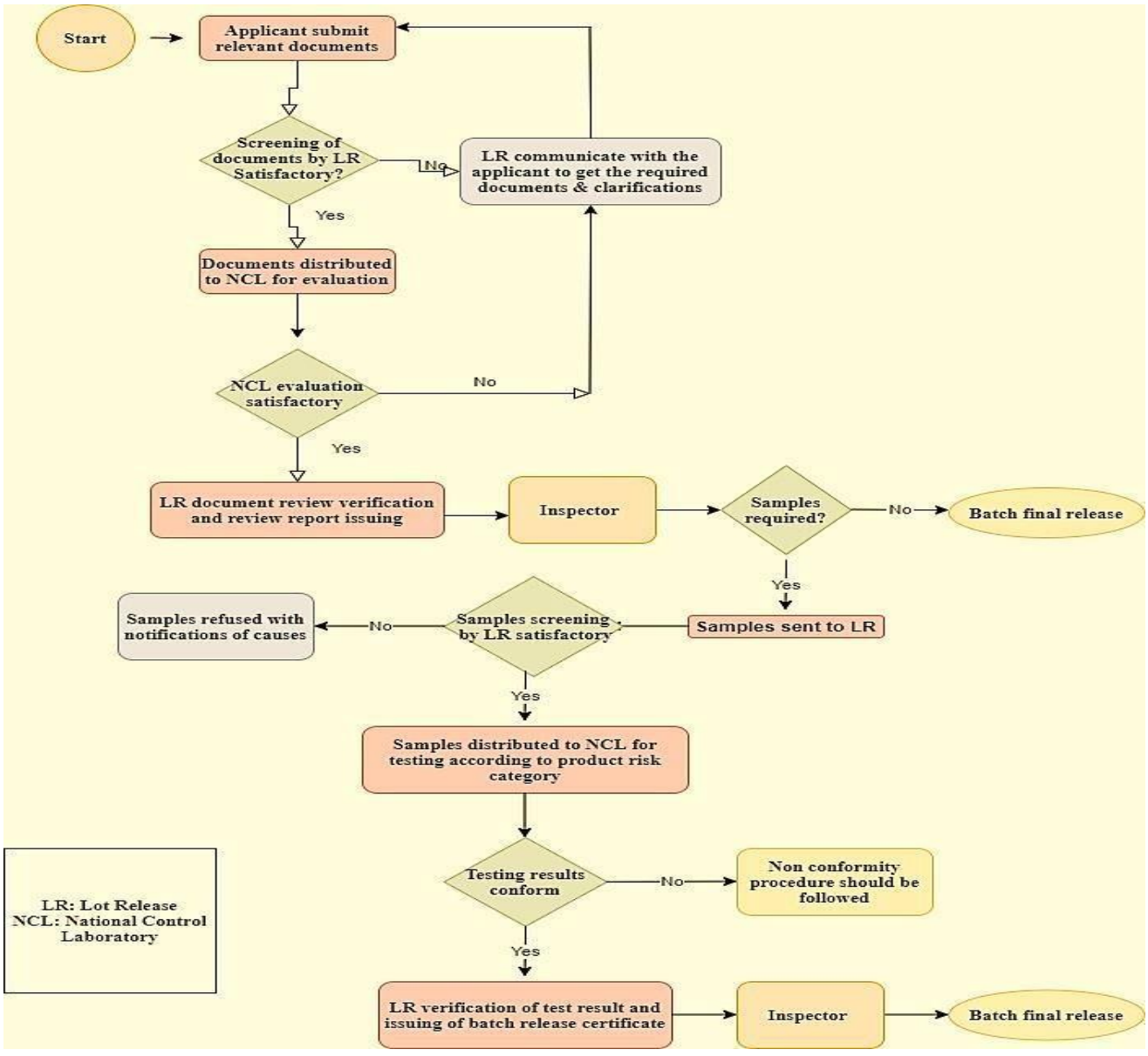
6. References:

1-https://www.who.int/health-topics/biologicals
2-WHO. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Geneva,World Health Organization, 2013 (WHO Technical Report Series, No.978).
3-WHO. Assessment Criteria for National Blood Regulatory Systems. Geneva, World HealthOrganization, 2012
4-World Health Organization. (2020). Good reliance practices in regulatory decision-makinghigh-level principles and recommendations. 2020-06.

7. Annexes

Annex I: Normal Lot release process flow
Annex II: Documents to be submitted with each batch according to the product type & Documents in case of sampling
Annex III: Process Flow of the Post marketing monitoring program (PMP)
Annex IV: Lot release process for exceptional case
Annex V: List of Competent Regulatory Authorities
Annex VI: Process Flow of the decision-making process of non-compliance batch release

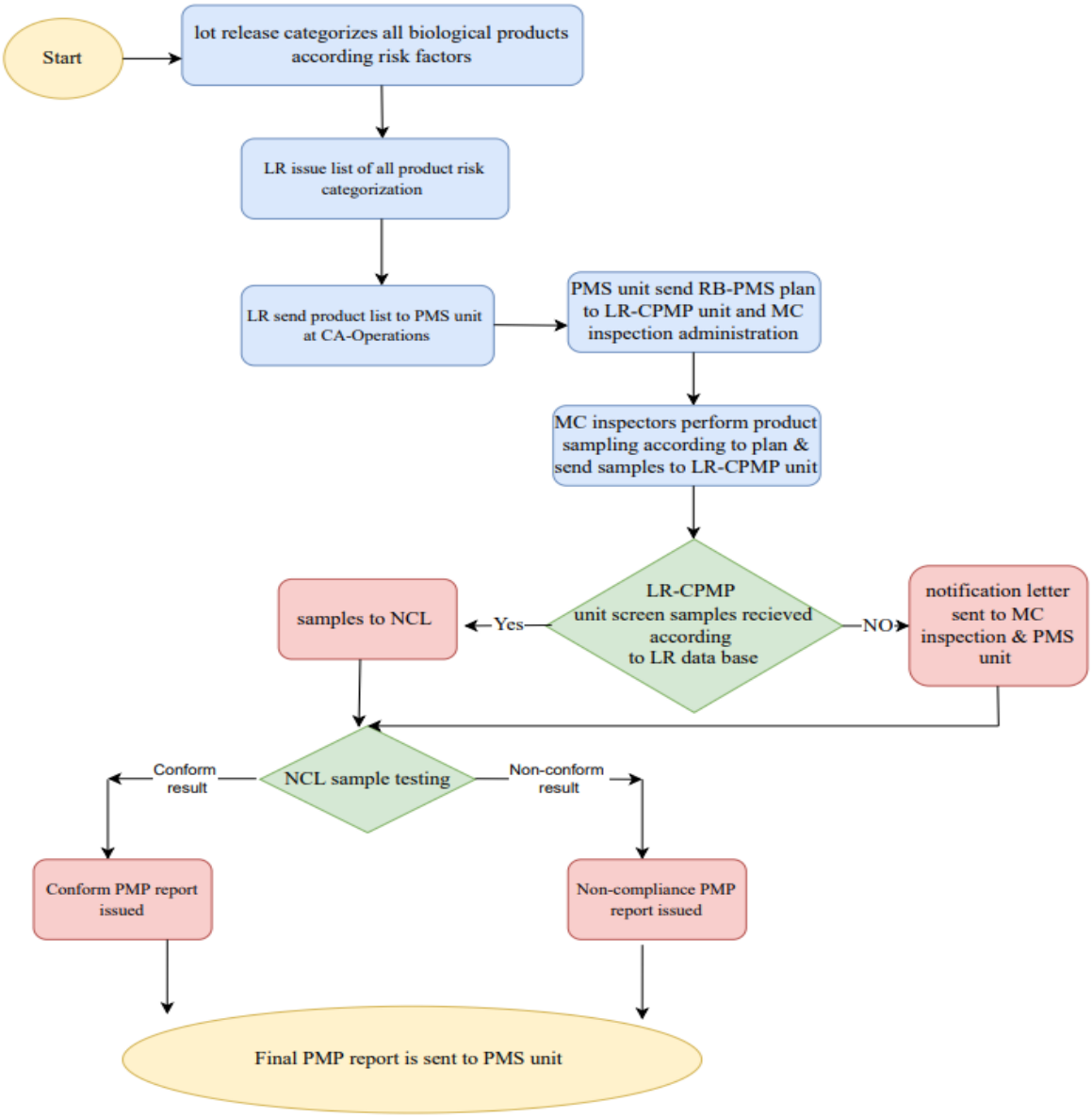
Annex I – Normal Lot release process flow



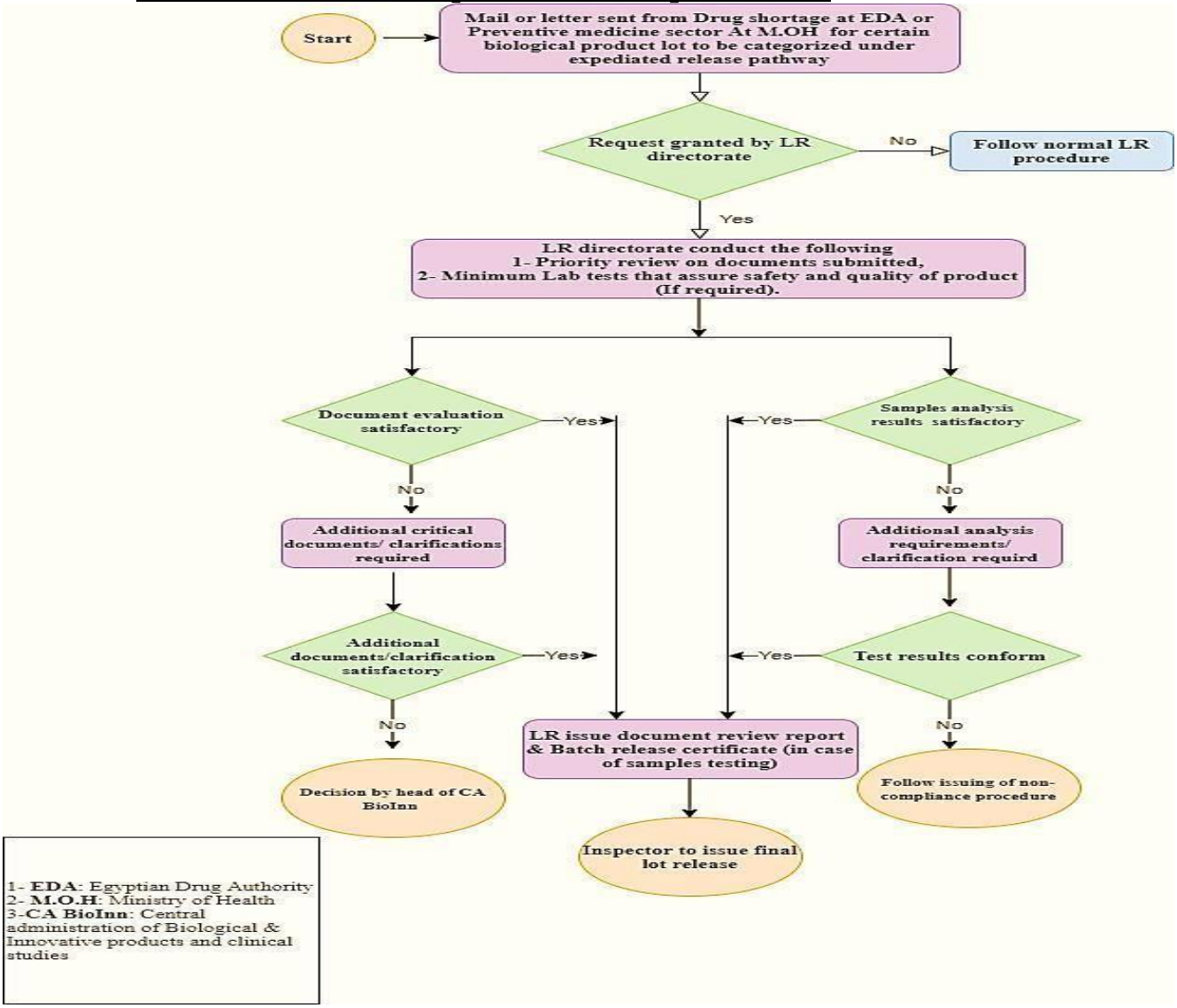
Annex II- Documents to be submitted with each batch according to the product type & Documents in case of sampling

A)Documents according to the product type
First: Vaccines
1-Lot release summary protocol
2-NRA lot release certificate of country of origin
3-Certificate of analysis of finished product
4-Certificate of analysis of solvent (if applicable)
5- In case of products using albumin as stabilizer, the applicant should submit: -NRA batch release certificate for albumin batch used from country of origin - Certificate of analysis of finished product for the batch used from the manufacturing company -Declaration on link between albumin batch used in the production and the batch of finished product
Second: Plasma Derived Medicinal Products (PDMP):
1-All documents that mentioned under vaccines should also be submitted, besides the following: -Certificate of release of plasma Pool form the country of origin -Viral Inactivation Certificate for the product -TSE Certificate of the batch, in case of products extracted from animal origin.
Third: Products Prepared by Recombinant DNA Technology:
1-Certificate of analysis of finished product
2-Certificate of analysis of the Active Pharmaceutical Ingredient that used in the final produced batch received from the manufacturing company
3-Certificate of analysis of solvent (if applicable)
5- In case of products using albumin as stabilizer, the applicant should submit: -NRA batch release certificate for albumin batch used from country of origin - Certificate of analysis of finished product for the batch used from the manufacturing company -Declaration on link between albumin batch used in the production and the batch of finished product
Fourth: Extractable Products:
1-All documents that mentioned under Products Prepared by Recombinant DNA Technology should also be submitted, besides the following: -TSE Certificate of the batch, in case of products extracted from animal origin.
B- Documents in case of sampling
1-Sample analysis request
2-Cold chain assurance report (for imported products only)

Annex III- Process Flow of the Post marketing monitoring program (PMP)



Annex IV: Lot release process for exceptional case

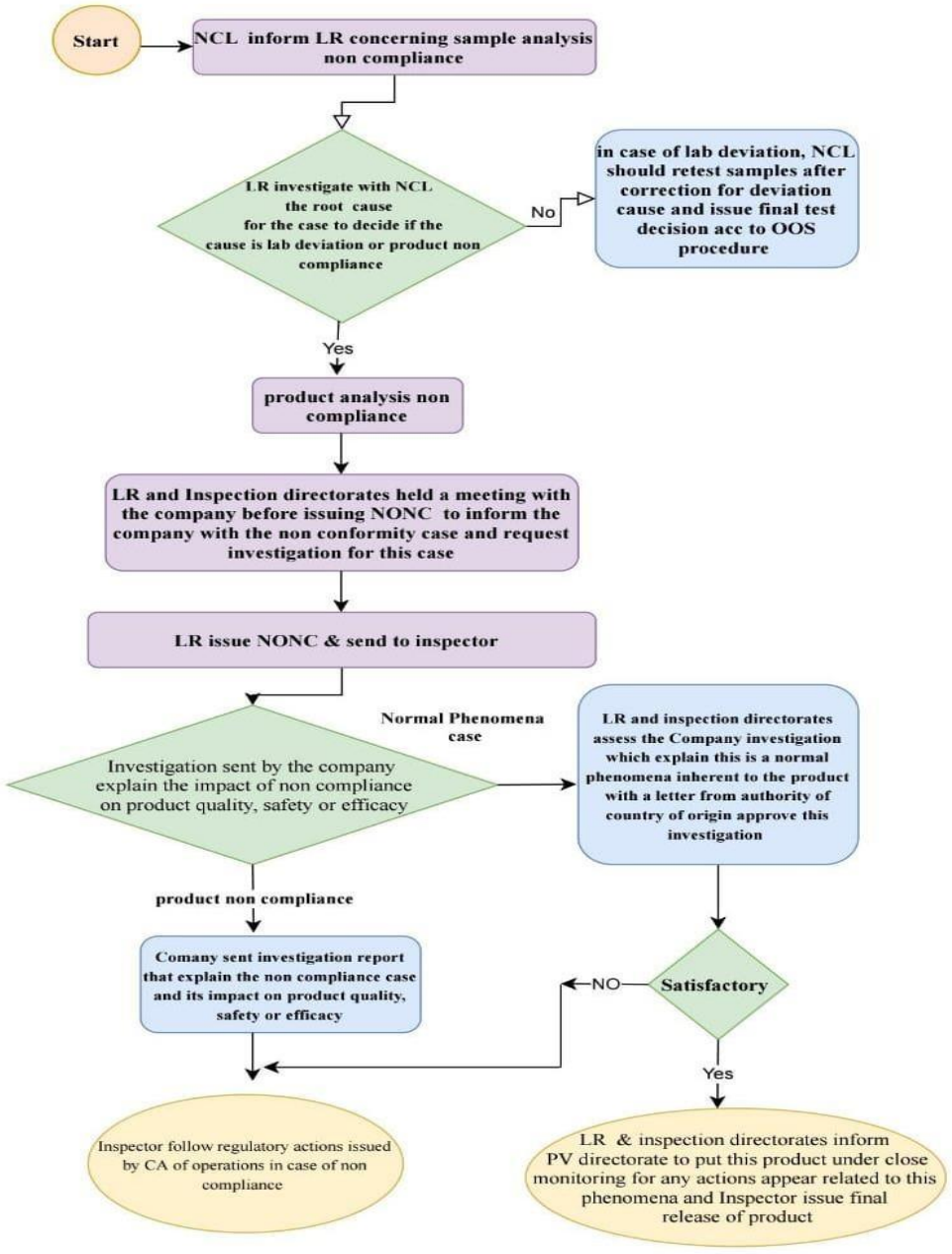


Annex V- List of Competent Regulatory Authorities:

Australia	**Portugal**
Austria	**Romania**
Belgium	**Slovakia**
Bulgaria	**Slovenia**
Canada	**Spain**
Croatia	**Sweden**
Cyprus	**Norway**
Czech Republic	**Malta**
Denmark	**Netherlands**
Estonia	**Poland**
Ireland	**Finland**
Italy	**France**
Japan	**Germany**
Latvia	**Greece**
Liechtenstein	**Hungary**
Lithuania	**Iceland**
Luxembourg	**Switzerland**
United State of America	**United Kingdom**

* This list is based on Technical committee decision dated 16/9/2021

Annex VI- Process Flow of the decision-making process of non-compliance batch release



1-**NCL**: National Control Laboratory
2- **NONC**: Notice of non-compliance
3- **OOS**: Out of Specification
4- **PV**: Pharmacovigilance
5- **CA**: Central Administration