FOOD AND DRUGS AUTHORITY

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Technical Advisory Committee on Safety of Vaccines and Biological Products

GUIDELINE ON LOT RELEASE OF VACCINES AND/OR OTHER BIOLOGICAL PRODUCTS IN GHANA

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No. 17 Indian Ocean Street, Nelson Mandela Avenue, Shiashie ● Greater Accra ● Ghana
P. O. Box CT 2783, Accra ● GPS: GA-237-7316 ● (+233) 302 233200 / 235100 ● fda@fda.gov.gh

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Executive Summary

Lot release is essential for ensuring the quality, safety, and efficacy of biological products, including vaccines, antisera, blood products, and therapeutic proteins. Marketing Authorization Holders (MAHs) must submit specific documentation and, in some cases, product samples for evaluation before a lot can be distributed. This process ensures compliance with approved specifications, protecting public health, maintaining manufacturing consistency, and verifying adherence to Good Manufacturing Practices (GMP).

The FDA adopts a risk-based approach, performing full testing, surveillance-based testing, or exempting certain products if consistent quality is proven. These guidelines, under the Public Health Act 851 (2012), apply to vaccines and biological products, whether manufactured locally or imported, and align with WHO standards.

The scope includes human vaccines (for prophylactic and therapeutic use) and other biological products like antisera and plasma-derived medicinal products (PDMPs). The FDA requires rigorous quality control and continuous monitoring by manufacturers to safeguard patient and healthcare provider trust. The guidelines outline procedures for lot release applications, ensuring compliance before products are released onto the Ghanaian market.

Products subjected to lot release are categorized into high, moderate, or low risk based on factors like product complexity, compliance history, manufacturing consistency, and post-market safety data. Testing and documentation requirements vary accordingly, with annual or situational reassessment of the risk category.

MAHs must submit complete LR applications, provide necessary samples, documentation, reagents, and collaborate on discrepancies. Applications must include a Lot Summary Protocol (LSP), which are evaluated independently for compliance by the FDA.

The FDA reviews test results and documentation, issuing a lot release certificates for conforming products. Non-conforming products require corrective actions or rejection. Noncompliant lots or rejected lots must be safely disposed of or returned to their origin, with proof submitted to the FDA.

The FDA continuously monitors production and market data of products subject to lot release to ensure consistency and safety. Appeals against decisions can be submitted within 60 days, and regulatory actions for non-compliance may include suspension or withdrawal of products.

1.0 Introduction

Lot release is a critical component of ensuring the quality, safety, and efficacy of biological products, such as vaccines, antisera, blood products, and certain therapeutic proteins. Marketing Authorization Holders are required to submit specific documentation and, in some cases, physical product samples for evaluation (testing) before a lot (batch) can be distributed or released onto the market. The lot release process ensures that each lot of these biological products meet the stringent standards outlined in the product's approved specifications at the time of their registration.

Lot release serves several key purposes, including protecting public health, ensuring consistency in manufacturing, and verifying compliance with Good Manufacturing Practices (GMP). Depending on the risk profile of the product, the FDA may perform relevant full testing, surveillance-based testing, or exempt certain products from some routine lot release requirements if consistent quality is demonstrated.

In pursuant to the Public Health Act, Act 851, these guidelines apply primarily to vaccines and/or other biological products. They emphasize a risk-based approach, balancing oversight with efficiency. By requiring manufacturers to maintain rigorous quality controls and continuously monitor production, the FDA lot release process upholds the quality, safety and efficacy of critical medical products, safeguarding the trust of healthcare providers and patients.

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

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 other related recommendations/guidelines for vaccines and biological products guidelines published on the FDA's website.

1.1 Legal Basis

This guideline applies to lot release process of registered human vaccines and/or other biological products in accordance with Section 118 of the Public Health Act 851, of 2012.

1.2 Scope

This guideline is applicable to the following category of biological products registered by the FDA for human use:

a) Human Vaccines for both prophylactic and therapeutic use.

b) Other biological products (antisera, PDMPs)

The guideline is applicable to both vaccines and/or other biological products manufactured locally and imported from other countries.

This guideline is intended to provide guidance to marketing authorization holders (MAHs), importers and distributors in addition to other relevant stakeholders on the FDA's lot release procedures and the conditions that must be met when submitting a lot release application to the FDA, prior to the products release onto the Ghanaian market.

2.0 Definitions and Abbreviations

2.1 List of abbreviations

APQR: Annual Product Quality Report
COA: Certificate of Analysis
EDQM: European Directorate for the Quality of Medicines & HealthCare
FDA: Food and Drugs Authority
cGMP: current Good Manufacturing Practices
LSP: Lot Summary Protocol
LR: Lot Release
LRC: Lot Release Certificate
MAH: Marketing Authorization Holder
MA: Marketing Authorization
NRA: National Regulatory Authority
NCL: National Control Laboratory

OOS: Out of specification

OCABR: Official Control Authority Batch Release

PDMPs: Plasma Derived Medicinal Products

UN: United Nations

2.2 Definitions of Terms

- **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 products to highlight any trend, deviation, change control, market complaints and to identify the product and process development.

- **Biological Products:** Products in which the active ingredient is a biological substance including antisera, antivenins, plasma derived medicinal products.

- **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 release:** The process of National Regulatory Authority (NRA)/ National Control Laboratory (NCL) evaluation of an individual lot of a registered vaccine, antisera, Plasma Derived Medicinal Products (PDMPS), or other biological products before giving approval for it to be released onto the market.

- **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:** A document summarizing all manufacturing steps and test results for a lot of vaccine, which is certified and signed by the responsible person of the manufacturing company.

- **Marketing Authorization Holder (MAH):** The company or corporate or legal entity in the field of pharmaceuticals on whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization and is subject to legislation in the country that issued the marketing authorization.

- **Out of specification (OOS):** An OOS result is generated when a product is tested and fails to meet predefined specification limits or acceptance criteria.

- **Out of Trend (OOT):** A result of a sequence of 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 considers 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.

- **Responsible NRA/NCL:** The regulatory Authority or laboratory taking responsibility for regulatory oversight of a product regarding the critical regulatory functions defined by WHO, including independent lot release. The responsible NRA/NCL is usually that of the country of manufacture, unless specific agreements exist within defined territories, such as in the European Union, where the “country” of manufacture is the European Union and the activity of the responsible NRA/ NCL is designated from among the Member States.

- **Vaccine:** 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.

3.0 Requirements

3.1 General Overview of Lot Release

The lot release system requires that each lot of a registered human vaccine and/or other biological products is subjected to the LR process before it is allowed for use in Ghana. The FDA is responsible for ensuring that independent lot release is performed for vaccines and/or other biological products registered for use in Ghana.

MAHs are fully responsible for ensuring the products comply with the product registration information. If there are any changes to the products, MAHs are expected to obtain approval for variation prior to submission of LR applications. Please refer to the FDA Variation Guideline for Biologics for further details.

The LR process will apply to all vaccines and/or other biological products including those imported through self-procurement or supplied through UN agencies, or vaccines procured for public health emergency and to other biological products lots before releasing to the market for use.

3.2 Shelf-life of imported vaccine and/or other biological products

Any vaccines and/or other biological products arriving in Ghana should have at least 60%-80% of its shelf-life remaining excluding vaccines donated and vaccines and/or other biological products intended for use during public health emergencies.
In the case of donations and emergencies, the FDA may release for use vaccines and/or biological products supplied through UN agencies and vaccines having not less than 50% remaining of the proposed shelf-life at the point of arrival into the country.

3.3 Regulatory pathways for Lot Release

There are currently three (3) main pathways to conduct lot release of vaccines and/or other biological products in Ghana. These are routine/full, non-routine (Reliance) and non-routine (Exceptional Case/Expedited) release pathways.

3.3.1 Routine/Full lot release pathway

The routine pathway involves the independent assessment of each lot of a vaccine and/or other biological product before it is released unto the market. Each lot of the product shall undergo document assessment (including LSP) and /or sample testing, which shall be determined by the degree of risk associated with the product.

3.3.2 Non-routine (Reliance) lot release pathway

Full or partial exemption of independent testing may be granted to a vaccine and/or other biological product upon submission of a lot of release certificate issued by a well-resourced or reference NRA / NCL. The list of acceptable FDA's well-resourced or reference National Regulatory Authority or Entity is available in FDA Reliance Guideline on Regulatory Decision-making published on the FDA's website.

The lot release pathway for vaccines and/or other biological product originating from FDA reference NRA/NCL or entities may be changed from non-routine (reliance) to routine (full) lot release pathway based on factors such as recalls, non-conformity, or regulatory non-compliance, and others, which may impact the degree of risk associated with the product.

3.3.3 Non-routine (Exceptional Case/Expedited) lot release pathway

Non-routine (exceptional case/expedited) lot release pathway may be granted in exceptional cases and upon appropriate justification according to the following cases:

- Product stock shortage in Ghana
- Crises or public health emergency (PHE) situations such as pandemics or epidemics
- An urgent need due to changes in national health policy recommendation
- Vaccines and/or other biological products donated from international organizations

Lots will be released via this pathway after evaluation of relevant documents and performing the minimum testing items (as applicable) that assure product safety & quality. Other circumstances that require a vaccine and/or other biological product to be released via the non-routine (exceptional case/expedited) pathway will be handled on a case-by-case basis by the FDA.

3.4 Risk-based approach

The FDA uses a risk-based methodology/assessment for lot release. Depending on the results of the risk assessment and the following considerations, more thorough testing might be required. This risk-based strategy ensures that the FDA fulfils its responsibility to guarantee the quality, safety, and efficacy of all biological products that are released into the market.

3.4.1. Factors considered for risk-based categorization

The FDA's risk - based lot release assessment and categorization consider risk factors for individual vaccine and/or other biological products. These may include:

- **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 reviewed in the APQR in addition to the tests results obtained by manufacturer or FDA 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 FDA's guidelines, and other guidance that govern the regulation of vaccines and/or other biological products in Ghana. Examples of product non-compliance include but not limited to:
    - Failure / continuous delay to provide requested data.
    - Release of products (including quarantined products) without previous approval from the FDA.
    - Inconsistent product documentation system.

3.4.2 Categorization of Risk Groups

The FDA categorizes all human vaccines and/or biological products (imported and locally manufactured) submitted for lot release into the following groups:

- **High Risk**: The FDA performs lot release for this category of products by performing thorough document review in addition to performing all relevant tests according to product specific critical quality attributes and EDQM human OCABR guidelines.

- **Moderate Risk**: The FDA performs lot release for this category of products by performing targeted testing through selection of some relevant tests to be conducted in addition to document review.

- **Low Risk**: 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 as applicable. It should be noted that vaccines and/or biological products where lot samples are not routinely submitted for targeted testing will be subjected to market surveillance and control.

3.4.3 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:

- FDA 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, among others.

- FDA may review and update products of lower risk to higher risk group if the regulatory non-compliance from applicant was evident.

3.5 The Responsibility of the MAH in Lot Release

- Submission of lot complete release application to the FDA
- Submission of samples in an appropriate condition as applicable including packaging and product information as needed.
- Submission of the lot release certificate of the responsible NRA in the case of imported products into Ghana.
- Provision of product specific reagents and working reference materials as may be needed by the FDA for testing purposes.
- Collaboration with FDA to resolve any discrepancy on test results.

- Take appropriate action on the issues related to any non-compliance. In the event of non-compliance of certain lots, the MAH may submit lot release application of other lots of the biological product.
- Take appropriate action (s) on any rejected lots according to GMP requirements.
- Provide any documents or other information regarding the quality of the vaccine and/or other biological products, required by the FDA.

Manufacturers have the responsibility to provide technical support needed for a successful analytical method transfer including but not limited to relevant training, preparation of transfer protocol, supply of adequate quantities of critical reagents and reference materials and standards. Manufacturers shall submit enough reference standards, critical reagents and materials specified in the MA dossier for testing. All reference standards and critical reagents shall be submitted along with their certificate of analysis.

3.6 Sampling and Testing

The FDA will follow the testing strategy based on the outcomes of risk assessment as illustrated in 3.4.2. Samples needed for LR testing as applicable shall be taken during the conduct of cold-chain verification of imported products.

Manufacturers where applicable have the responsibility to provide technical support needed for a successful analytical method transfer including but not limited to relevant training, preparation of transfer protocol, supply of adequate quantities of critical reagents and reference materials and standards. Manufacturers shall submit enough reference standards, critical reagents and materials specified in the MA dossier for testing. All reference standards and critical reagents shall be submitted along with their certificate of analysis.

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 Ghana, taking into consideration the product risk categorization, release pathways, and good reliance practices.

Notes:

- Concerning finished products lots derived from the same final bulk, only one lot will be tested according to each product risk level.

- In the 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 FDA, it will be released by the FDA if 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 FDA.
- For locally produced products, under certain circumstances, FDA may agree to receive samples from manufacturers before they complete their own test procedures so that testing by the FDA is done in parallel with manufacturers. In such cases, the lot cannot be released by the FDA 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).

3.7 Application for Lot Release

- An application for lot release for a vaccine and/or biological product, either locally manufactured or imported, shall be made in writing.
- An application form shall be completed in accordance with the sequence of appendices and shall be dated, signed and stamped by the Marketing Authorization Holder.
- Application shall be accompanied by:
    - A duly signed covering letter
    - Two (2) soft copies (preferably on one CD-ROM and a DUPLICATE CD-ROM) of completed application forms and lot release regulatory documents (Lot summary protocol, LRC issued by the NRA/NCL from the country of origin, Importing packing List,
    - All supporting documents as specified on the application form
    - Non-refundable application fee as specified in the FDA's fee schedule.
    - Representative product samples

- Alternatively, the application form shall be submitted together with other required documentation for lot release to the FDA via email (vbpd@fda.gov.gh).
- The submission of the required documents shall be in a period of not less than the stipulated timeline of the shipment arrival. Applications will be acknowledged.

3.8 Lot Summary Protocol Review

In general, the format and content of the Lot Summary Protocol (LSP) are approved by FDA during the marketing authorization process. The format of the LSP may be amended by the FDA 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 FDA. The LSP submitted by MAH for individual products shall be consistent with LSP templates provided by the FDA on its website. In the absence of LSP templates on the FDA website, LSP submitted by MAHs shall follow the current LSP templates provided by the EDQM OCABR guidelines for human biologicals, and/or Model protocol for the manufacturing and control templates in the current WHO Technical Report Series (TRS) that pertains to the vaccine and/or biological product. An independent review by the FDA 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

3.9 Lot Release Application Evaluation and Decision making

The FDA shall evaluate all data/results from the 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.

- **Conform decision**: If the lot conforms to the lot release requirements, the FDA will notify and provide the applicant with a decision letter and/or lot release certificate as applicable, will be issued.
- **Non-conform decision:** If the lot is not complying with the approved specifications from document review or for any test, the outcome detailing the non-compliances will be communicated to the MAH. In instances where critical non-compliances are noted or post-approval changes are made without the FDA's approval, the necessary regulatory decision will be taken. In the specific situations where an arrangement has been made between FDA and the manufacturer to perform lot testing in parallel, any

lots failing tests or out of specifications shall be addressed in line with relevant procedures. The FDA may request applicants to provide a complete report regarding the root cause of OOS results and its impact on product safety, quality and efficacy. The review of this investigation reports by the FDA may inform the FDA on the final decision of the lot. It is however the responsibility of the MAH to perform an investigation to determine the root cause of the issues, including steps for corrective and preventive actions to avoid similar problems in the future. This shall be verified by the FDA during GMP inspections.

- **Rejection of lot release application**: A lot may be rejected under conditions including but not limited to the following:
    - Inadequate supporting documentation
    - Results not meeting specification (out of specification after review of Lot Summary protocol data).
    - Failure to include temperature monitoring device. Failure of the temperature monitoring device to monitor the temperature of whole journey. No supporting data for temperature excursion.
    - Deviation of information from the approved product specification with prior approval by FDA for such changes
    - unreliable data and out of trend during trend analysis.

3.10 Lot Release certificate withdrawal

The FDA shall withdraw a released lot certificate if:

- The information on which the lot release of the product was given is later found to be false
- The circumstances under which the lot release of the product was given no longer exist
- Any of the provisions under which the product was registered has been contravened

The FDA may take further regulatory actions which may include cancelation of the marketing authorization of the product if deemed necessary.

3.11 Safe disposal of non-conforming and rejected lots

The MAH shall ensure that non-compliant and rejected lots are not released onto the market and shall be safely disposed in Ghana where applicable pursuant to the Public Health Act, 2012, (Act 851) and/or should be transported back to the country of origin for disposal.

The MAH shall provide the proof of collection for disposal within 30 days after issuance of non-compliance notification and proof of disposal within 90 days after the date of collection

3.12 Continuous Monitoring of Data for Products Subject to Lot Release

- The FDA may request the APQR for products subject to lot release from the manufacturer to verify the consistency of the process, and to assess the ongoing safety and quality of the product and to highlight any trends, as well.

- Trend analysis shall be performed by the FDA concerning the results of quality control testing submitted by the manufacturer to assess production consistency.

- Reports for products experience from market control and surveillance as well as pharmacovigilance reports shall be considered during reassignment of biological products risk categories.

3.13 Appeal of Decision

An appeal against the decision of the FDA may be submitted to the CEO of the FDA within sixty (60) days after the date of rejection notification of lot release application.

Where the lot release certificate of the product is suspended, withdrawn or cancelled, the FDA shall cause the withdrawal from circulation of that product lot and shall accordingly cause the suspension, cancellation or withdrawal to be published in the Gazette.

4.0 Timelines for Processing Lot Release Application

Activity	Duration
Submission of application form and applicable documents	10 working days before the lot of product lot arrival at the port of entry. The FDA upon receipt of application shall process documentation within 5 working days
Submission of cover letter and payment of lot release application fee	At the point of submission of application
Cold-chain verification.	The FDA has within two (2) days to inspect the consignment upon arrival in-country. Where applicable, samples shall be taken by the FDA for testing at the FDA's laboratory.
Submission of evidence of disposal in the event of non-compliance	The MAH shall provide the proof of collection for disposal within 30 days after issuance of non-compliance notification and proof of disposal within 90 days after the date of collection.
Non-routine (Exceptional Case/Expedited) lot release pathway	Expedited release pathway shall be completed within 10 working days of receiving the complete application which consists of the needed documents, samples and the fees, where required
Non-routine (Reliance) lot release pathway	Reliance release pathway shall be completed within 5 working days of receiving of the complete application which consists of the needed documents, samples and the fees, where required
High risk group	The timeline of this category is 30 working days. However, some products with long bioassay tests may take longer timeline but not more than 60 working days of receiving the complete application.
Moderate risk-group	Timeline of this category is 24 working days
Low risk group	Timeline of this category is 18 working days

5.0 References

1. WHO. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No.978).

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

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

4. CBER. Providing Lot Release Protocol Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format: Guidance for Industry, Center for Biologics Evaluation and Research, February 2019.