



National Agency for Food & Drug Administration & Control (NAFDAC)

Vaccines, Biologicals and Medical Devices Laboratory Services Directorate (VBM-LSD)

NAFDAC Guidance Document And Guideline For Lot Release Of Human Vaccines And Other Biologicals 2024

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1. Introduction

The lot release of human vaccines and other Biologicals is performed in compliance with the WHO Guidelines for independent lot release of vaccines by regulatory authorities. The lot release of vaccines and other Biologicals by regulatory authorities is part of the regulation of vaccines and other Biologicals and involves the independent assessment of each lot of a licensed vaccine and other Biologicals before it is released into the market. This assessment is based, as a minimum, on the review of manufacturers' summary protocols. It may be supplemented by other documents such as the release certificate from the responsible national regulatory authority (NRA) or national control laboratory (NCL) and, in some circumstances, by testing.

It is the responsibility of the National Agency for Food and Drug Administration and Control (NAFDAC) to ensure that the products available in the Nigerian market adequately meet the requirements of safety, efficacy and quality. It should be noted that NAFDAC has the right to request for any human vaccine and other biologicals batch to be subjected to lot release process within the context of this guideline.

Human vaccines are biological products used in 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 if many healthy individuals receive a vaccine before the problem is recognized.

In addition to manufacturing complexity inherent to biological products, proper storage conditions and efficient supply chain management should 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 effectiveness of every lot of these products before releasing to the market.

The independent lot release of biological products by NRA is part of the regulation of these products and involves independent assessment of each lot before it is release into the market. As per WHO guideline [1], for biological products independent assessments may be based on:

- i. As a minimum, review of manufacturers' summary protocols
- ii. recognition/acceptance of release certificate from responsible NRA or National Control Laboratory (NCL)
- iii. Testing that is independent of manufacturers' quality control testing

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 human vaccine and other biological products, whether imported or locally manufactured, received by NAFDAC.

This document is intended to provide guidance to manufacturers, MAHs and importers with respect to the lot release program.

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 several sub-lots, which are later accumulated to form a final homogeneous lot. In continuous manufacture, the lot should 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.

Summary Protocol (also called "lot summary protocol"): 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

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 Report (APQR): a report submitted annually by manufacturers to the NRA/NCL containing production information on both bulk and final lots, including test methods and results, reasons for any recalls and corrective action taken, as well as other pertinent post-market information.

Other Biological Products: Biologicals Products except human vaccines.

Out of specification (OOS): an OOS result is generated when a vaccine is tested and fails to meet a predefined registered specification

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

4. Procedures

4.1 Lot release in Nigeria

This guideline is based on the recommendation outlined in the guidelines for independent lot release of vaccines by regulatory authorities (WHO, TRS No 978, Annex 2). The lot release approach for human vaccines and other biologicals products in Nigeria will include all the following:

- i. Inspection on arrival and sample collection in the warehouses
- ii. Review of manufacturer's summary protocol based on product marketing authorization file which has been approved by NAFDAC during product registration phase.
- iii. Review of recognized lot release certificate from National Regulatory Agency (NRA) of Country of Origin.
- iv. Review of Certificate of Analysis.
- v. The test is conducted on the products (according to Laboratory testing policy).

4.2 Policy statement:

Each lot of a human vaccines and other biologicals product is subject to the lot release program before marketing in Nigeria through risk-based approach. The assessment and testing of biological products is based on the degree of risk associated with the product.

The risk-based approach to testing and oversight allows NAFDAC to focus on ongoing testing on product for which enhanced surveillance is needed.

4.2.1 The applicant should submit the following documents with batches subjected to independent lot release.

4.2.1.1 Documents to be submitted with each batch:

- i. Summary protocol
- ii. NRA lot release certificate of country of origin
- iii. Plasma Pool Certificate (For Plasma Derived Medicinal Products only)
- iv. Certificate of analysis of finished product
- v. Certificate of analysis of solvent (if applicable)
- vi. Proof of cold chain integrity
- vii. In case of products using albumin as stabilizer, the applicant should submit:
 - Batch release certificate for albumin batch used from country of origin
 - Declaration on link between albumin batch used in the production and the batch of finished product

4.2.1.2 Documents to be submitted annually or when required:

- i. Annual product quality report
- ii. GMP certificates.

4.2.2 **Criteria for batches release:**

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

- i. Product Indication (age of target population, health status, population size).
- ii. Nature of the Product
- iii. Product qualifications (Country of origin, Registration status, prequalification)
- iv. Inspection History (quality or safety issues found during on site evaluations and other inspections)
- v. Testing History (non-conformity -trend analysis)
- vi. Post-market Experience (Adverse drug reactions reports, product complaints, product recalls and withdrawals)
- vii. Regulatory compliance

4.2.3 **Review of document & summary protocol**

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 NAFDAC during product registration to ensure that the lot meets the specifications in the marketing authorization. In addition, the summary protocol & CoA submitted to NAFDAC should be approved by appropriate QA or QC of the manufacturer. Vaccines, Biologicals and Medical Devices Laboratory Services Directorate (VBM-LSD) qualified person should review the protocol, NRA Lot release certificate & CoA.

4.2.4 **Testing policy requirements based on risk level:**

- 4.2.4.1. NRA has been recommended by WHO to conduct independent testing to monitor key products parameters, consistency of production and to verify test results of the manufacturer. Therefore, VBM-LSD will assign products into one of three risk groups based on the outcomes of risk assessment. Testing of vaccines is done as per the assigned rating of the product. Products are classified into three risk groups based on the outcomes of risk assessment of the product. The following are considered during product risk assessment;
- i. Nature of the Product
 - ii. Product qualifications (Country of origin, Registration status, WHO prequalification)
 - iii. Inspection History (quality or safety issues found during on site evaluations and other inspections).
 - iv. Testing History (non-conformity, trend analysis).
 - v. Post-market Experience (Adverse drug reactions reports, product complaints, product recalls and withdrawals)
 - vi. Regulatory compliance

| Risk group | Risk Rating | Requirements | LR Actions | Reliance |
|-------------------|--------------------|--|---|---|
| 1 | High Risk | i. Imported vaccines that have failed any parameter during testing. ii. Vaccines that show Out of trend results during trending or have no trended data. iii. Newly registered product (Except products that are WHO prequalified). iv. Unsatisfactory documents. v. New registered biological product (first 3 batches after registration). vi. Variation to the manufacturing process or already registered products. vii. Product that failed to achieve consistency in production and testing. | Document Review and Laboratory Testing(as defined in procedure for risk-based testing) | No |
| 2 | Medium risk | Product that failed to achieve consistency in production and testing for 5 years. i. Products that have not shown consistency in trending data and have not failed any parameter during testing. ii. WHO prequalified products (New Registration). iii. iii. Products submitted for renewal of registration. | Document Review and Laboratory Testing (as defined in procedure for risk-based testing) | Yes Availability of proof of cold chain integrity. |
| 3 | Low Risk | i. Products that consistently have satisfactory laboratory reports have a consistent trend. ii. WHO prequalified products. iii. Products with satisfactory required documents. iv. Product has demonstrated batch consistency and good compliance (not less than 20 batches). | Document review only. Periodic Laboratory testing (One batch to be analyzed every five (5) batches for imported human vaccines) will be done. | Yes Availability of proof of cold chain integrity. |

4.2.5 Change between risk groups

- 4.2.5.1 Product risk assessment may be reviewed to high-risk group if there are local or overseas reports of significant or severe problems with GMP, adverse events, repeated testing failure or product recalls.
- 4.2.5.2 Products in high and medium risk groups may be re-assigned to the next risk group with lower risk after demonstration of batch consistency and compliance (not less than 20 batch) except for vaccines which could remain in the medium risk group indefinitely.

4.2.6 **General consideration:**

- 4.2.6.1 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.
- 4.2.6.2 When it is considered necessary, testing items may be added or subtracted independently according to the risk levels of each product.

4.3 **Evaluation of the lot and decision-making process**

- 4.3.1. Results from testing and document review performed by VBM-LSD should be compared to the specification in the product marketing authorization file and all approved variations. If the results are found to be satisfactory, Lot release certificate will be issued for each lot verified (see Annex 1 for lot release flow chart).
- 4.3.2. If a vaccine lot conforms with the release requirements, VBM-LSD will notify the relevant directorates electronically and provide a hard copy of the lot release certificate.
- 4.3.3. If a vaccine lot does not conform to the release requirements due to an out of specification (OOS) test result, and after investigation, a quality defect is confirmed, VBM-LSD will engage with the MAH and the manufacturers QC laboratory to investigate the cause of the out of specification (OOS) test result. If the quality defect is confirmed after the investigation, a report by the manufacturer will be compiled and submitted to VBM-LSD, and a Lot Rejection Notice will be issued to the MAH (copying all relevant directorate) with the instruction to destroy the lot.
The destruction exercise should be supervised by the Enforcement and Investigation Directorate. A Certificate of destruction should be issued to the MAH and a copy submitted to VBM-LSD.
- 4.3.4. In the case where there is evidence that the cold chain of a shipment or part of a shipment was not adequately maintained or controlled, the affected doses will not be released. The MAH will be instructed to destroy the affected doses as stated in 4.3.3.

4.4 **Lot release in exceptional case**

- 4.4.1. Expedited Lot release: Expedited release may be granted in exceptional cases and upon appropriate justification such as:
 - i. Product shortage in Nigeria
 - ii. Public health emergency
 - iii. Biological products donated from international organizations.

- iv. Urgent need e.g., due to changes in national health policy recommendations.

An expedited release, however, is subject to the availability of a Lot release certificate issued by the responsible NRA/ NCL. A request for expedited release should be submitted to NAFDAC. The applicant will submit a request for expedited review to the responsible directorate. If expedited review is approved the responsible directorate will notify VBM-LSD to expedite the Lot release process. All other situations will be handled on a case-to-case basis, (see Annex 2 for exceptional LR pathway).

4.4.2. Further lot release: If consignments with the identical final labelled primary container lot (including identical expiration dates) are imported after the release of the first consignment/s, it is regarded as a further lot release; A vaccine arrival report (VAR), proof of secondary packaging and a copy of the lot summary protocol should be submitted to VBM-LSD. The importer should clearly indicate in the communication to VBM-LSD and other relevant directorate that the shipment is a further lot release and provide the first lot release certificate number.

Batch will be released after evaluation of relevant documents.

4.5 Risk-Based Post-market monitoring program

To control the quality of all human vaccines and other biologicals products registered after lot release, products will be subjected to post market surveillance (PMS) as using risk-based prioritization.

4.6 Reliance

The requirement for routine independent lot release testing will be based on a risk assessment and whether reliance can be applied. The risk assessment considers the post-marketing experience related to the safety and quality of the product. Reliance on some or all tests or reduced independent testing may be considered subject to the availability of a Lot release certificate issued by a releasing NCL that is a full member of the WHO National Control Laboratory Network for Biologicals (WHO-NNB) or as detailed in NAFDAC policy on regulatory reliance (See annex 3).

4.7 Data monitoring

All critical quantitative data from quality-control test results, and especially potency, from the manufacturer or VBM-LSD test results will be used for trend analysis as an essential part of lot release. Statistical analysis will be conducted once sufficient data have been accumulated. The alert or warning limits and action limits of consistency trends should be defined on statistical. The variability and precision of the test will be considered when defining the limits.

5. Requirements and Administrative Procedure for Lot Release

5.1 Samples Submission

Note that the number of samples requested is determined by the number of tests to be performed and if pooling of samples is required. Refer to NAFDAC Website Sampling Guide.

5.1.1 Samples should be transported and submitted at the appropriate temperatures to VBM-

LSD. Appropriate cold chain monitors (minimum Data Logger) should accompany

each consignment of vaccine and other biologicals.

5.1.2 The VBM-LSD will receive samples from Monday to Friday during office hours (09:00 to 14:00).

5.1.3 Samples submitted should follow NAFDAC's Regulation on Labelling.

5.2 Sampling should be performed as follows

5.2.1 No sampling shall occur where a temperature excursion (cold chain breakage) has occurred.

5.2.2 The samples collected should be a representation of the commercial consignment, i.e., samples from various shipments at different locations.

5.2.3 If resampling is required for retesting, the VBM-LSD will provide guidance on sampling location.

5.2.4 For locally manufactured, lots samples should be taken from each of the sampling points, i.e., from the beginning, middle, and end of the filling run. Containers should be clearly labelled to distinguish from which part of the filling run the samples originate. The MAH will be informed by the VBM-LSD of any change/reduction in the sampling points subject to sufficient data confirming the consistency of production.

5.3 Cold Chain Monitoring

The VBM-LSD and Drug Evaluation and Research (DER) directorate review the integrity of the cold chain for all human vaccine and other biologicals shipments to Nigeria.

A vaccine arrival report (VAR) should be submitted to the Port Inspection directorate (PID) and VBM-LSD for each lot and shipment to be released.

Note: Containers in which the temperature monitoring devices have malfunctioned or have been omitted should be separated from the rest of the consignment. VBM-LSD will not release the vaccines in these containers unless proof can be provided that all the shipments were transported as a unit until unpacking by the recipient. vaccines in these

containers unless proof can be provided that all the shipments were transported as a unit until unpacking by the recipient.

5.4 Proof of cold chain integrity

A vaccine arrival report (VAR) should be submitted to PID and VBM-LSD for each lot to be released. In instances where a lot is imported in multiple shipments, each shipment's documentation should be clearly distinguished.

The VAR should include the following:

- i. The product name and lot number should be clearly visible on all documents.
The date, time and location of dispatch and receipt of shipment.
- ii. A copy of the air waybill.
- iii. The quantity per shipment.
- iv. A packing list indicating the number of containers/shipment and the number of doses per container/shipment.
- v. A temperature monitor check sheet indicating the number of temperature devices per container/ shipment, serial number, location [e.g., inside (top or bottom) or outside the container], and status of each temperature monitor, i.e., a temperature excursion noted or whether it malfunctioned or not. Freeze tag information should be provided in instances where vaccines are not allowed to freeze.
- vi. The vaccine lot number and the number of the container/shipment should be clearly indicated on the document displaying the temperature monitor data. Alternatively, supporting documentation should be attached showing the serial numbers of electronic monitors used in each container of the shipment.
- vii. Raw data from electronic temperature monitoring devices (including Q Tag WHO Type 1 monitors) is required, except for devices where a summary is automatically generated.
In these cases, the summary is preferred.

5.5 Product Labelling information review

VBM-LSD reviews the printed materials that accompany the vaccine batch to ensure that all labelling items comply with NAFDAC Drug and Related Product Labelling Regulations.

5.6 Lead times

The human vaccine and other biological product lot release process will be performed on a "first in, first out" basis with strict adherence to stipulated timelines.

5.6.1 Lot Release Timelines: The timeline for each activity in the lot release process are as follow:

| ACTIVITY | DURATION |
|--|--|
| Submission of batch data and required relevant documents | 7 working days before product arrival |
| Review of Lot documents and report | Within a duration range from 7-10 working days according to product type |
| Inspection and sampling of Lots for testing | Within 2 working day from Arrival of Shipment |
| Laboratory Testing | Within 30 – 40 working days according to product type |
| Issuance of lot release certificate | Within 5 working days from receiving Lot testing results. |
| Submission of non-conformity appeal by the applicant | Within 10 working day form the date of receipt of non-conformance. |

6. **Tariff**

Please refer to the appropriate section at www.nafdac.gov.ng for NAFDAC Approved Tariffs. Note that all fees attract 7.5% VAT.

7. **Acronyms and Glossary**

The following acronyms and definitions are used in this document:

| | |
|---------|---|
| GMP | Good Manufacturing Practice |
| LR | Lot Release |
| MAH | Marketing Authorization holder |
| PR | Protocol Review |
| QA | Quality Assurance |
| QC | Quality Control |
| SP | Summary Protocol |
| TRS | Technical Report Series |
| VBM-LSD | Vaccines, Biologicals and Medical Devices Laboratory Services Directorate |
| WHO | World Health Organization |

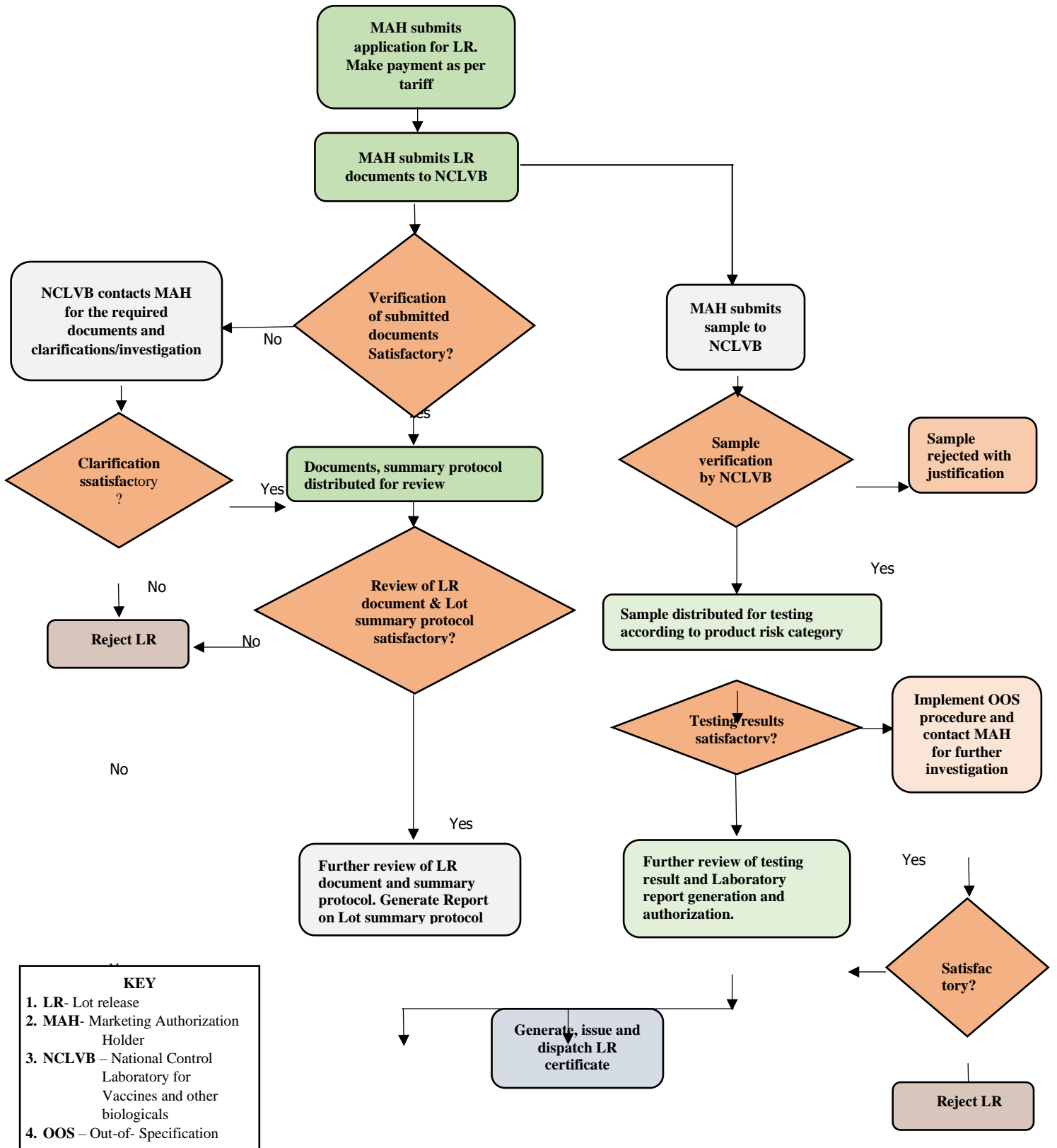
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1. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities, Annex 2, TRS No 978. (<https://www.who.int/publications/m/item/guidelines-for-independent-lot-release-of-vaccines-annex-2-trs-no-978>).
2. WHO good practices for pharmaceutical quality control laboratories https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs957-annex1-goodpractices-harmaceuticalqualitycontrol-laboratories.pdf?sfvrsn=ca0c211c_0

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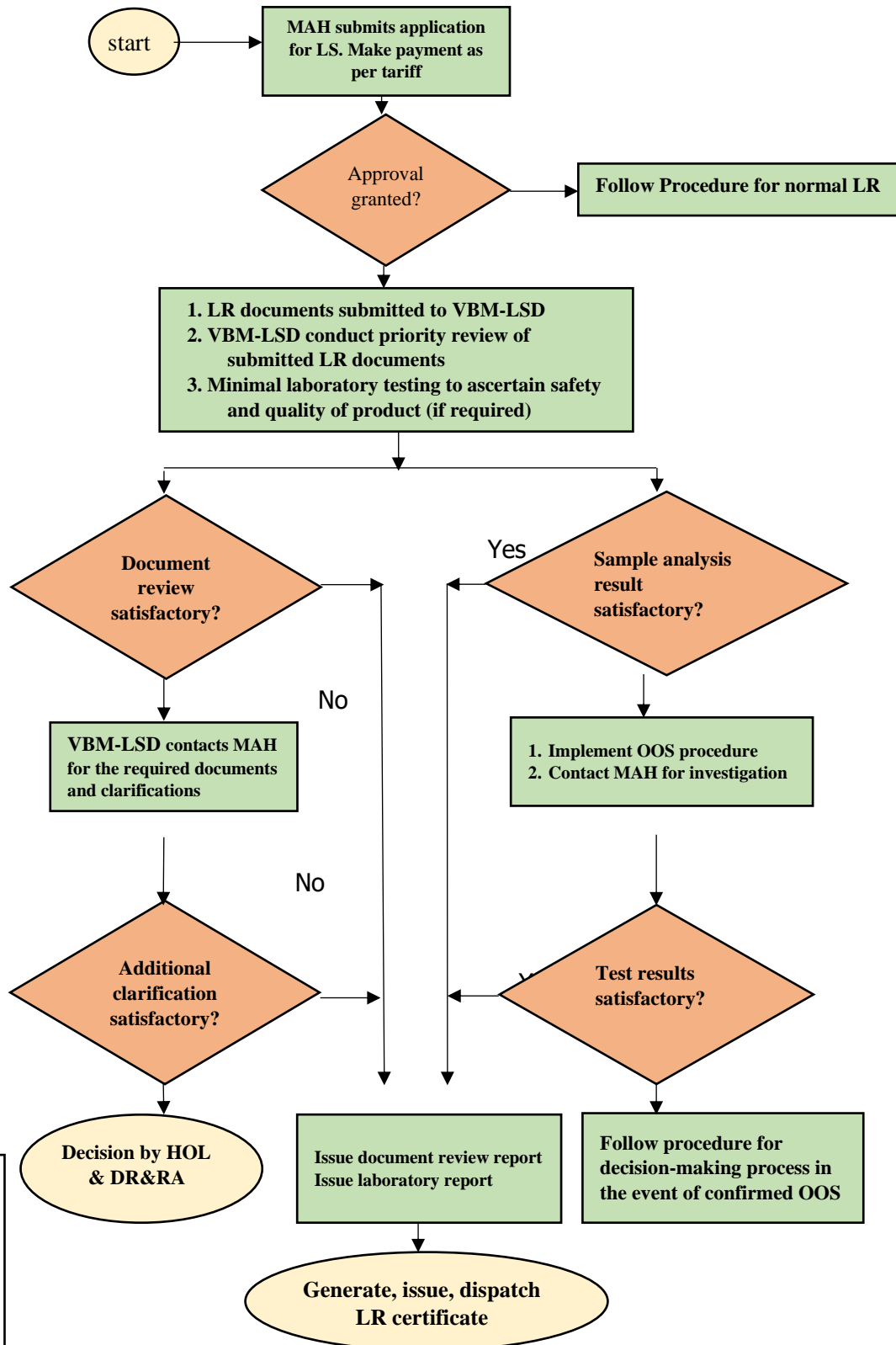
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Annex 1 - Lot release flow chart



KEY
 1. LR- Lot release
 2. MAH- Marketing Authorization Holder
 3. NCLVB – National Control Laboratory for Vaccines and other biologicals
 4. OOS – Out-of- Specification

Annex 2- Lot release in exceptional case



Key

- 1. LR- Lot release
- 2. HOL – Head of Laboratory
- 3. DR&R- Drug Registration and Regulation
- 4. NCLVB – National Control Laboratory for Vaccines and other biologicals

Annex 3-List of Stringent Regulatory Authorities and National Control Laboratories

1. Stringent Regulatory Authorities (SRAs): NRAs who are members or observers or associates of the ICH/VICH: USA (USFDA), Europe (EMA), Japan, Swiss Medic, Health Canada, Australia, Norway, Iceland, Liechtenstein, Article 58, WHO Listed Authorities, USA-EPA.
2. International bodies: World Health Organization (WHO), World Organization for Animal Health (OIE)
3. Regional bodies: West Africa Health Organization (WAHO), ECOWAS Medicines Regulatory Harmonization (MRH)
4. WHO Pre-Qualified Laboratories or ISO/IEC 17025 accredited
5. African Medicines Regulatory Harmonization (AMRH)
6. Full members of WHO National Control Laboratory Network for Biologicals (Australia; Austria; Belgium; Brazil; Bulgaria; Canada; Cuba; Denmark; France; Germany; India; Indonesia; Italy; the Netherlands; Norway; Republic of Korea; Russian Federation; Senegal, South Africa; Sweden; Switzerland; Thailand; United Kingdom).