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Guideline for Lot release of human vaccines

This document is intended to provide guidance to applicants for lot release requirements for all human vaccines. This will be a "living document" and will be updated on a regular basis. It is important that applicants adhere to the prescribed requirements in order to avoid delays during processing.

Document History

Final Version	Reason for Amendment	Effective Date [dd Month yyyy]
1	Date of implementation	August 2021
2	Date of implementation	26 April 2022
3	New number and new guideline template.	29 August 2022

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Contents

Glossary

Abbreviation/ Term	Meaning
EDQM	European Directorate for the Quality of Medicines
EPI	Expanded Program on Immunization
GMP	Good Manufacturing Practices
HCR	Holder of the Certificate of Registration
ISO	International Organization for Standardization
NCL	National Control Laboratory
NRA	National Regulatory Authority
OCABR	Official Control Authority Batch Release
OOS	Out of specification
PMS	Post-marketing surveillance
SAHPRA	South African Health Products Regulatory Authority
SANA	South African National Accreditation System
SANCLBP	South African National Control Laboratory for Biological Products
UFS	University of Free state
VAR	Vaccine arrival report
WHO	World Health Organization
WHO-NNB	WHO National Control Laboratory Network for Biologicals

1. INTRODUCTION AND SCOPE

1.1 Introduction

The lot release of human vaccines is performed in compliance with the WHO Guidelines for independent lot release of vaccines by regulatory authorities1.

Vaccines are biological products used in healthy populations, and the impact of using substandard 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 there could be a drastic impact if a large number of healthy persons receive a vaccine to prevent infection or minimize disease severity. For these reasons, a careful, independent review of manufacturing and quality control data on every lot is necessary before it is marketed1.

The lot release of vaccines by regulatory authorities is part of the regulation of vaccines and involves the independent assessment of each lot of a licensed vaccine before it is released onto 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 that is independent of the manufacturers' quality-control testing1

1.2 Scope

This document focuses on vaccines registered for human use and vaccines supplied under Section 21 approval. The document is intended to provide guidance to the holder of the certificate of registration (HCR) and vaccine suppliers on the requirements and administrative procedures to be followed for lot release. It may also be relevant to public health authorities, such as a national immunization programme, Expanded Program on Immunization (EPI).

2. LEGAL BASIS

Lot release of human vaccines is conducted within the framework of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965) as amended and Act 14 of 2015, regulations 15(1), 15 (2) and 15(3).

3. DEFINITIONS

Lot: a defined quantity of starting material, packaging material or product, processed in a single process or series of processes so that the quantity is expected to be homogeneous. The lot size can be defined either as a fixed quantity or as the amount produced in a fixed time period.

Lot release: the process of NRA/NCL evaluation of an individual lot of a licensed vaccine before giving approval for its release to the market.

First release: the first lot release issued for a final labelled lot.

Further release: the case where additional consignments of a vaccine previously released by SAHPRA are imported for lot release, and the final primary container lot number and expiry date are identical to that previously released by SAHPRA.

Holder of the Certificate of Registration (HCR): a person or legal entity in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality, safety and compliance with conditions of registrations.

Local manufacture: a process that includes the formulation of the drug product and/or filling of a primary container.

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

Product Labelling Information: Printed materials that accompany a prescription medicine and refers to all labelling items Medicines and Related substances Act 101 of 1965, General Regulation # 10, #11 and # 12:

- Professional Information (PI), including prescribing information: that provides product information on indication, dosage and administration, safety and efficacy results, contra- indications, warnings, and a description of the product for health care providers
- Inner label or container label
- Outer label or carton
- Patient information Leaflet (PIL)

Registration Application: A formal application to SAHPRA for approval to register and market a new medicine. The purpose of the Registration Application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information, chemistry, manufacturing and control.

Responsible NRA/NCL: the NRA/NCL taking responsibility for regulatory oversight of a product with regard to 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 among the Member States.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described in the marketing authorization dossier. Specifications are critical quality standards proposed and justified by the manufacturer and approved by the regulatory authorities.

Summary protocol: (also called "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.

Vaccine: Preparations containing antigens capable of specific and active immunity in humans against an infectious agent or toxin.

4 GENERAL INFORMATION

SOUTH AFRICAN NATIONAL CONTROL LABORATORY FOR BIOLOGICAL PRODUCTS

The South African National Control Laboratory for Biological Products (SANCLBP) is located in Bloemfontein on the campus of the University of the Free State (UFS) and is contracted by SAHPRA through the UFS to perform the lot release function. The SANCLBP complies with the expected standards and is accredited to perform the lot release function as per the stipulated regulatory standards. The issuing of the lot release certificate however remains the responsibility of SAHPRA.

PRINCIPLES

4.1 SAHPRA Lot release

4.1.1 SAHPRA Lot release pathways

SAHPRA currently makes provision for two lot release pathways (which can include expedited release and the parallel testing procedure):

First Release

In the case where a vaccine lot is submitted to SAHPRA for the first time, a full lot release is performed consisting of a review of the manufacturers lot summary protocol, review of the cold chain data for the shipment/s, review of the product labelling information and possible selected independent retesting. A first lot release certificate is issued for a final labelled lot. The first lot release is subject to payment of a lot release fee to SAHPRA as detailed in section 3.1.9.

Further Release

If additional consignments of a vaccine previously released by SAHPRA are imported and where the final labelled primary container lot number and expiry date is identical to that previously released, a further lot release is issued. The further lot release process is limited to reviewing the cold chain data for the shipment/s and a review of the product secondary packaging labelling information (if different from the first release). A further lot release certificate is issued for a final labelled primary container lot with the same lot number and expiry date.

4.1.2 Summary Protocol review

Manufacturers' summary protocols summarise information taken from the production and test records, according to GMP requirements, to ensure that the lot meets the specifications in the product registration dossier. In addition, summary protocols submitted to the NRA/NCL should be approved by the person designated as responsible for quality assurance or quality control of the manufacturer. In general, the format and content of the protocol are finalised and approved by the NRA/NCL during the review of the license application. The format of the protocol should be amended in response to changes in the approved production process and should be approved by the NRA/NCL[1].

The lot summary protocol submitted by the HCR for review should therefore reflect all appropriate production steps and controls as outlined in the registration dossier for the product. SAHPRA will accept manufacturer summary protocols compiled to comply with an EDQM OCABR model protocol format (https://www.edqm.eu/en/human-ocabr-guidelines) or a WHO-recommended format. The HCR must notify the SANCLBP of any approved amendments relevant to the lot under review at the time of submission.

An independent review of critical data from each lot of vaccines is essential to:

- assure the consistency of quality of each manufactured lot.
- obtain confidence in the claimed strength of active components.
- assess the validity and accuracy of the tests performed.

This review encompasses the traceability of critical source materials, active and critical components used in the manufacture of the product, and the results from tests performed by the manufacturer at various stages of production, including tests performed on critical components, intermediates, final bulk and final product[1].

4.1.3 Independent testing

SAHPRA applies a risk-based testing policy to reduce redundant testing and promote reliance between releasing authorities. However, the risk-based approach must still guarantee that SAHPRA meets its obligation, which is to ensure the safety and quality of all released vaccine lots, i.e., imported and locally manufactured. As far as practically possible, the same methods, equipment, reagents, and reference standards used by the manufacturer are used in the tests to ensure comparability of test results.

It is the responsibility of the HCR to facilitate technology transfer to the SANCLBP if required for lot release testing or post-marketing surveillance (PMS). It is recommended that the proposed HCR engage with the SANCLBP during the registration application process to determine the need to transfer analytical methods.

SAHPRA strives to align itself with the current best international practice for lot release and, as such, adopted the testing scope for final containers as detailed in the EDQM OCABR product- specific guidelines (https://www.edqm.eu/en/human-ocabr-guidelines).

Parallel testing procedure

The HCR of a locally manufactured vaccine can request lot release testing through the Parallel Testing Procedure. In this case, the SANCLBP will start independent testing before the manufacturer's Quality Control has completed the analytical testing on the finished product. The request for parallel testing must be indicated on the application form for lot release. Labelled samples must be submitted to the SANCLBP, and the approved lot summary protocol is then sent to the SANCLBP at the completion of the tests by the Quality Control of the manufacturer.

SAHPRA will only issue a lot release certificate after testing the samples and reviewing the lot summary protocol has been completed by the SANCLBP.

Should the HCR want to withdraw the lot during the Parallel Testing Procedure due to non- compliance with the specifications during the analytical testing or any other reason, SAHPRA and the SANCLBP must be notified, and the procedure is stopped.

4.1.4 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 a National Regulatory Authority (NRA) with which SAHPRA is aligned and the outcome of the risk assessment.

4.1.5 Cold Chain review

The SANCLBP reviews the integrity of the cold chain for all vaccine shipments to South Africa. A vaccine arrival report (VAR) must be submitted to the SANCLBP for each lot and shipment to be released and must comply with the format requirements as detailed in section 4.5. The HCR should provide the SANCLBP with validated transport stability data that would support transport temperature guidelines. Note: Containers in which the temperature monitoring devices have malfunctioned or have been omitted must be separated from the rest of the consignment. SAHPRA will not release the vaccines in these containers unless proof can

be provided that all the shippers were transported as a unit until unpacking by the recipient (e.g., cling-wrapped on a pallet), as consignment homogeneity cannot be guaranteed.

4.1.6 Product labelling information review

The SANCLBP also reviews the printed materials that accompany the vaccine batch to ensure that all labelling items comply with the relevant General Regulations (i.e., 10, 11 and 12) of the Medicines and Related substances Act 101 of 1965, as amended. In the case where SAHPRA granted an exemption from these conditions, the approval letter must be submitted to the SANCLBP.

4.1.7 Evaluation of the lot and the decision-making process

If a vaccine lot conforms with the release requirements, the SAHPRA will notify the HCR by email and provide an electronic copy of the lot release certificate. It is the responsibility of the HCR to inform SAHPRA who should be on the mailing list and receive copies of the release certificate. The communication with HCR will be through the Lotrelease@sahpra.org.za

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, a rejection note is issued to the HCR with the instruction to destroy the lot and to provide a copy of the destruction certificate to the SANCLBP and SAHPRA.

Prior to issuing a destruction note, however, the SANCLBP will engage with the HCR 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 will be compiled and submitted to SAHPRA with a recommendation for rejection of the lot.

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, and the temperature deviation impacted the quality of the product, the affected doses will not be released. The HCR will be instructed, through an appendix to the lot release certificate, with the instruction to destroy the affected doses and provide a copy of the destruction certificate to the SANCLBP and SAHPRA.

4.1.8 Expedited release process

Under exceptional circumstances, e.g., an emergency situation or a critical vaccine stock shortage, the lot release for a particular lot can be prioritised and expedited, but will at a minimum still include a review of the manufactures lot summary protocol, review of the cold chain data for the shipment/s, and review of the product labelling information. An expedited release however, is subject to the availability of a lot release certificate issued by the responsible NCL. A request for expedited release must be submitted to SAHPRA. The applicant will therefore submit a request for expedited review to Lotrelease@sahpra.org.za cc Biological Medicines Unit Manager with adequate motivation and communication subject Expedited Release request. If expedited review is approved SAHPRA will notify SANCLBP to expedite the review process.

4.1.9 Fees

SAHPRA requires payment of a lot release fee (https://www.sahpra.org.za/fees-2/) for the first release of each vaccine final lot. The release fee must be paid directly to the SAHPRA account, and proof of payment must be sent to SAHPRA and the SANCLBP. It is important that the HCR use the appropriate reference (i.e., product name, registration number and the final lot number) that will reflect on the payment advice. This is a requirement to ensure traceability for audit purposes. Please consult the guideline for payment of fees to

SAHPRA, https://www.sahpra.org.za/wp- content/uploads/2021/01/SAHPRA-Payment-Guideline-Nov-2020.pdf

5 REQUIREMENTS AND ADMINISTRATIVE PROCEDURE FOR LOT RELEASE SUBMISSION

5.1 Application for lot release

A completed application form for lot release based on SAHPRA requirements must be signed and dated and submitted to as follows with the notification of proof of upload submitted to Lotrelease@sahpra.org.za cc Biological Medicine Unit Manger and HPA ;

A copy of the application form must also be submitted to the SANCLBP (see 4.2 for further guidance).

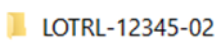
5.2 Submission of Lot Release Applications

Naming the folders that will contains the lot release application files should follow the below naming conversion, or naming format

LOTRL- AppNo- BatchNo

Example of how the file might look like using the above format LOTRL-12345-02

Or



LOTRL – Lots Release

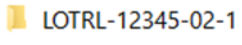
AppNo – Application number

BatchNo – Batch Number

Should there be corrections or follow-up documents on the same LOTS RELEASE APPLICATION , the following format must be followed in the previous folder name please add -1 when you resubmit for the first time, and -2, for the second time, and so forth.

The folder should look like the below example, for the first resubmission LOTRL-12345-02-1

Or



5.2.1 Samples

The following samples must be supplied to the SANCLBP for each lot to be released:

- For imported vaccines, thirty (30) vials/syringes of the single or multi-dose final container;
- For locally manufactured vaccines forty (40) vials/syringes of the single or multi-dose final container per sampling point;
- For BCG culture, four (4) vials of the final container;
- If more than the required containers are sent to the SANCLBP, the excess containers cannot be

returned;

- Samples should be sent at the correct transport temperatures to the SANCLBP. Appropriate cold chain monitor(s) must accompany each consignment of vaccine samples to the SANCLBP. Samples received without monitor(s) or with alarmed monitors will not be accepted and will be destroyed. Replacement samples will need to be provided;
- The SANCLBP will receive samples from Monday to Friday during office hours (07:30 to 16:00);
- Final labelled and packaged containers are preferred for testing.
- For the Parallel Testing procedure and under exceptional circumstances and with good motivation, final labelled containers without packaging are also accepted;
- Provisionally labelled containers will be accepted, provided that this is pre-arranged with the Director of the SANCLBP. A lot release certificate will only be issued once proof of final packaging and labelling has been provided.

5.2.2 Sampling must be performed as follows

- Quarantined shippers, i.e., where a temperature excursion has occurred, must not be sampled;
- The samples taken must represent the commercial consignment as far as practically possible, i.e., sampled from different shippers at different locations. The SANCLBP acknowledges that the sampling procedure could be constrained due to different shipping configurations;
- Clearly indicate on the receiving documents from which shipper(s) sampling was performed;
- If resampling is required for retesting, the SANCLBP will provide guidance on which shippers must be sampled;
- For locally manufactured lots, samples must be taken from three 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 HCR will be informed by SAHPRA, of any change/reduction of the number of samples and sampling points subject to sufficient data confirming the consistency of production.

5.3 Documentation submission

- All lot release documentation must be uploaded to the SANCLBP Cloud. Document names should include the type of vaccine, the corresponding batch no. and a short description without special characters. Avoid sending large files by email as they can get lost or corrupted. Each supplier has a dedicated library for uploading documents, which is password protected. The SANCLBP can be contacted if passwords have been forgotten or lost;
- The SANCLBP needs to be notified via email at nclfhs@ufs.ac.za after files have been uploaded. The email should contain a list of files uploaded and the upload date
- Multiple copies of the same documents should not be sent. If more than one supplier handles a vaccine lot, they must coordinate with each other;
- If an incomplete document was sent to the SANCLBP or uploaded to the SANCLBP Cloud, the complete new document must have a different file name than that initially submitted. Send an email to the

SANCLBP to notify them that a new file has been uploaded;

- Documentation can also be submitted to the SANCLBP via the HCR or the manufacturer's own SharePoint site. It is the responsibility of the HCR or the manufacturer to arrange access to the site for SANCLBP staff. The SANCLBP needs to be notified via email at nclfhs@ufs.ac.za after files have been uploaded. The email should contain a list of files uploaded and the upload date.

5.4 Lot summary release protocol submission

- Lot summary protocols (not Certificates of Analysis) must accompany each lot. Electronic copies must be sent before or at the time that the samples are submitted;
- The lot release certificate from the releasing NRA must be included. Where possible, it should be accompanied by the respective test report;
- File names must contain the vaccine name and lot number(e.g., Vaccine_ABC123_protocol.pdf). Avoid using spaces or special characters in file names;
- Testing will not commence until both the samples and protocols have been received, except for the case of the Parallel Testing Procedure.

5.5 Proof of cold chain integrity

A vaccine arrival report (VAR) must be submitted to the SANCLBP for each lot to be released. In those instances where a lot is imported in multiple shipments, each shipment's documentation must be clearly distinguished. This report must include the following:

- The product name and lot number must be clearly visible on all documents;
- The date, time and location of dispatch and receipt of shipment;
- A copy of the air waybill;
- The quantity per shipment;
- A packing list indicating the number of containers/shippers per shipment and the number of doses per container/shipper;
- A temperature monitor check sheet indicating the number of temperature devices per container/shipper, 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;
- The vaccine lot number and the number of the container/shipper must be clearly indicated on the document displaying the temperature monitor data. Alternatively, supporting documentation must be attached showing the serial numbers of electronic monitors used in each shipper/container of the shipment;
- Raw data from electronic temperature monitoring devices (including QTag WHO Type 1 monitors) is required, except for devices where a summary is automatically generated. In these cases, the summary is preferred;

- File names must contain the vaccine name and lot number (e.g., Vaccine_ABC123_VAR.pdf, Vaccine_ABC123_AWB.pdf, etc.);

Collate all the documents for a shipment and verify that it is complete before uploading to the SANCLBP Cloud.

5.6 Proof of payment of the lot release

- Proof of payment must be sent to the SANCLBP and SAHPRA;
- No release certificate will be issued without proof of payment.

5.7 Acknowledgement of the receipt

- The SANCLBP will acknowledge receipt of samples and or documentation confirming that they are for a first or further release;
- Acknowledgements will also be sent to SAHPRA;
- It is the responsibility of the HCR to inform the SANCLBP who should be on the mailing list and receive the acknowledgement of receipt for samples and documentation;
- The HCR is advised to follow up with the SANCLBP if an acknowledgement of receipt has not been received within two (2) working days.

5.8 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) and proof of secondary packaging is required;
- A copy of the lot summary protocol as detailed in section 4.4 is required;
- Clearly indicate in the application form for lot release to SAHPRA that this is a further lot release and provide the first lot release certificate number (if already available);
- A lot release performed through the further release process will be processed within five (5) working days.

5.9 Lead times

- As a SANAS accredited laboratory, the SANCLBP must maintain impartiality at all times. The vaccine lot release process will be performed on a “first in, first out” basis with strict adherence to lead times, as detailed in Appendix I. In the case of an unexpected delay due to retesting or delays in the availability of reference materials, delays will be communicated to the HCR and SAHPRA;
- The lead time is determined by the nature and scope of independent testing required. The lead time will be communicated to the HCR at the time of product licensing (Appendix I);The lead time countdown will start once the lot release application form, samples and a complete summary protocol have been received by the SANCLBP;
- For the Parallel Testing Procedure the lead time is five (5) working days after receipt of the approved lot

summary protocol;

- It remains the HCR's responsibility to keep a record of all samples and information submitted to the SANCLBP. The vaccine arrival report and/or final proof of packaging/labelling can be submitted later, but this will result in the lead time extension of five (5) working days after receipt;

- Lead times have been approved by SAHPRA and will be shortened only under exceptional circumstances, as detailed in section 3.1.8.

6 REFERENCES

Guidelines for independent lot release of vaccines by regulatory authorities, WHO Technical Report Series, 978, Annex 2 https://www.who.int/biologicals/areas/vaccines/lot_release_of_vaccines/en/ (accessed 04 January 2021)

7 VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces (SAHPGL-PEM-BIO-01_Guideline for lot Release of Human Vaccine April 2022_v2). It will be reviewed on this timeframe or as and when required.

APPENDIX I Product-specific lead times for lot release

Vaccine	Lead time
BCG Culture	4 weeks
BCG Vaccine	8 weeks
Cholera	3 weeks
Corona Virus Vaccine	2 weeks
Hepatitis A	3 weeks
Hepatitis B, Hepatitis A and B	3 weeks
HPV	3 weeks
Influenza	2 weeks
Measles	4 weeks
Meningococcal	3 weeks
MMR	3 weeks
OPV	4 weeks
Pneumococcal	3 weeks
Rabies	3 weeks
Rota	4 weeks
Rubella	3 weeks
T, dT, DTaP, DTaP-IPV, DTaP-IPV-Hib, DTaP-IPV-Hib-Hep B	4 weeks
Typhoid	3 weeks
Varicella	3 weeks
Yellow fever	6 weeks
Zoster	3 weeks