South African Health Products
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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.

All the relevant forms to be completed in conjunction with this guideline are accessible on the SAHPRA Website.

Document History

Final Version	**Reason for Amendment**	**Effective Date** [dd Month yyyy]
1	First issue	August 2021
2	Updates published for implementation	26 April 2022
3	− Content structured on the latest SAHPRA Guideline Template − New document number allocated	29 August 2022
4	− SAHPRA Service desk implementation − Inclusion of the application form (GLF-PEM-BIO-01A) for Lot release	8 June 2023

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Contents

Glossary

Abbreviation/ Term	Meaning
EDQM	European Directorate for the Quality of Medicines
EPI	Expanded Program on Immunization
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
GMP	Good Manufacturing Practices
HCR	(Holder of the Certificate): of Registration 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.
ISO	International Organization for Standardization
Local Manufacture	a process that includes the formulation of the drug product and/or filling of a primary container.
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.
NCL	National Control Laboratory
NRA	National Regulatory Authority
OCABR	Official Control Authority Batch Release
OOS	(Out of specification): result is generated when a vaccine is tested and fails to meet a predefined registered specification.
Product Labelling information	(PLI): Printed materials that accompany a prescription medicine and refers to all labelling items as per the 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 • PIL

PIL	Patient Information Leaflet
PMS	Post-marketing surveillance
QC	Quality Control
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.
SAHPRA	South African Health Products Regulatory Authority
SANA	South African National Accreditation System
SANCLBP	South African National Control Laboratory for Biological Products
SSDS	SAHPRA service desk system
Specifications	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 the specific lot of vaccine, which is certified and signed by the responsible person of the manufacturing company.
UFS	University of Free state
Vaccine	Preparations containing antigens capable of specific and active immunity in humans against an infectious agent or toxin.
VAR	Vaccine arrival report
WHO	World Health Organization
WHO-NNB	WHO National Control Laboratory Network for Biologicals

1. INTRODUCTION

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

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 marketed.

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 NRA or NCL and, in some circumstances, by testing that is independent of the manufacturers' quality-control testing.

1.1 Purpose

The purpose of this Guideline is to provide guidance on the SAHPRA Lot Release application process as well as the requirements to be fulfilled when making a lot release request to SAHPRA for lot release of all human vaccines.

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, 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. GENERAL INFORMATION

SOUTH AFRICAN NATIONAL CONTROL LABORATORY FOR BIOLOGICAL PRODUCTS

The SANCLBP is located in Bloemfontein on the campus of the UFS and is contracted by SAHPRA through the UFS to perform the lot release testing. The SANCLBP complies with the expected standards and is accredited to perform the lot release testing as per the stipulated regulatory standards. SAHPRA will exercise the regulatory decision including the issuance of Lot release certificate or rejection note.

PRINCIPLES

3.1 SAHPRA Lot release

SAHPRA currently makes provision for first release and further release.

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 3.9.

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.

3.2 Summary Protocol review

Manufacturers' summary protocols summarize 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 finalized and approved by the NRA/NCL during the review of the -registration 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 the EDQM OCABR model protocol format (https://www.edqm.eu/en/human-ocabr-guidelines) or the WHO-recommended format. The HCR must include in the application 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.

3.3 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, efficacy 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 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,

[1] Note any variation should obtain prior approval from SAHPRA before including it in summary protocol

adopted the testing scope for final containers as detailed in the EDQM OCABR product- specific guidelines (https://www.edqm.eu/en/human-ocabr-guidelines).

3.4 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- NNB or a NRA with which SAHPRA is aligned with, and the outcome of the risk assessment.

3.5 Cold Chain review

The SANCLBP reviews the integrity of the cold chain for all vaccine shipments to South Africa. A VAR must be submitted to the SAHPRA for each lot and shipment to be released and must comply with the format requirements as detailed in section 4.3.2 The HCR should provide the SAHPRA 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.

3.6 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 with the application.

3.7 Evaluation of the lot and the decision-making process

If a vaccine lot conforms with the release requirements, the SAHPRA will notify the HCR through the SSDS and provide an electronic copy of the lot release certificate. The initiator of the task on the Service desk will receive a copy of the release certificate corresponding to that task.

If a vaccine lot does not conform to the release requirements due to an OOS test result, and after investigation, a quality defect is confirmed, a rejection note is issued to the HCR. HCR will be allowed to appeal decision made by the regulator within 30 working days.

Prior to issuing a destruction note, SAHPRA SANCLBP will engage with the HCR and the manufacturers QC laboratory to investigate the cause of the 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 a rejection note from SAHPRA with the instruction to destroy the affected doses and provide a copy of the destruction certificate to SAHPRA. It is the responsibility of the HCR to submit the destruction certificate to the regulator within 30 working days from the date of notice.

3.8 Expedited release process

Under exceptional circumstances, e.g., in case of an outbreak, or a critical vaccine stock shortage supported by NDoH, the lot release for a particular lot can be prioritized 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 via application form for lot release. The review outcome of the expedited review request will be recorded on the SSDS within 3 working days of the request. Any communications regarding expedited review outcomes must be directed to dedicated lot release email Lotrelease@sahpra.org.za and copy biological medicine unit manager, with subject line “Expedited review request outcome”. Note that expedited reviews will not be considered in the absence of the required motivation and/or supporting documents.

3.9 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 uploaded to SSDS. It is important that the HCR use the appropriate reference generated by the SSDS upon applying. This is a requirement to ensure traceability. 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

4. REQUIREMENTS AND ADMINISTRATIVE PROCEDURE FOR LOT RELEASE SUBMISSION

4.1 Application for lot release

A completed **Application Form for Release of Human Vaccines (GLF-PEM-BIO-01A)** as accessible on SAHPRA Website, or lot release based on SAHPRA requirements must be signed, dated and submitted to SSDS with all the supporting documents uploaded thereon.

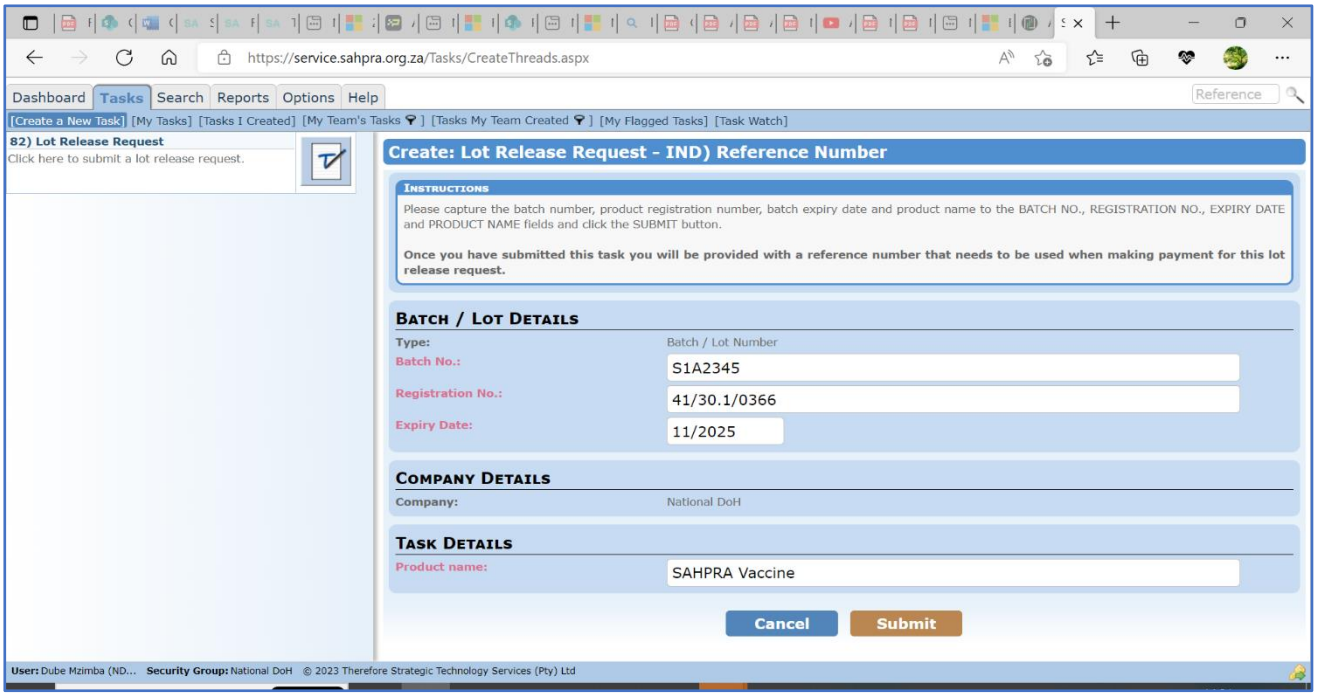
4.2 Submission of Lot Release Applications

All Applications for lot release should be submitted via the SAHPRA Service Desk system at https://service.sahpra.org.za. Note that you are to upload all the supporting documentation for your Lot release application on the SAHPRA Service desk. SAHPRA /SANCLBP will be able to access all the documents uploaded.

NOTE: Any variation should obtain prior approval from SAHPRA before including it in the summary protocol. If the applicant submit documentation for Lot release that does not correspond to SAHPRA's approved registration records, this lot release request will be rejected.

It is the responsibility of the HCR to inform SAHPRA who should be a user of the Service Desk system. Should you require credentials as user for the SAHPRA Service desk system please send a request to servicedesk@sahpra.org.za with subject line "SAHPRA Service desk system application form" and copy the email Lotrelease@sahpra.org.za. If there is a request on any other issues related to Lot Release and SSDS, please send an email to Lotrelease@sahpra.org.za .

Upon application submission the applicant particulars must conform with the systems requirements e.g where the system requires product name only record product name. i.e., it is not acceptable to record product name and batch number at the same time.



4.2.1 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.
- Under exceptional circumstances and with good motivation, final labelled containers without

packaging may be accepted;

- Provisionally labelled containers will be accepted, provided that this is pre-arranged with SAHPRA. A lot release certificate will only be issued once proof of final packaging and labelling has been provided.

4.2.2 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.

4.3 Documentation submission

- All lot release documentation must be uploaded to the SSDS. Document names should include the type of vaccine, the corresponding batch no. and a short description without special characters. All supporting documents that are large must be zipped and submitted as zip file.
- Documents required during submission among others are application form, proof of payment, lot summary protocol and proof of cold chain data
- If additional information is requested from the applicant and is not received within 3 working days, the application will be rejected. The applicant will be required to re-apply and relevant fees will be applicable

4.3.1 Lot summary release protocol submission

- Lot summary protocols (not Certificates of Analysis) must be uploaded when creating a task on the SSDS

- 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 application and the samples has been accepted,

4.3.2 Proof of cold chain integrity

A VAR must be provided 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 SSDS

4.3.3 Proof of payment of the lot release

- Upon submission of the application the system will generate an invoice with the reference to use while making payments, please make use of the reference the system will generate.

- Proof of payment must be uploaded onto the SSDS;

- No release certificate will be issued without proof of payment.

4.4 Acknowledgement of the receipt

- The SANCLBP will acknowledge receipt of samples and or documentation confirming that they are for a first or further release via the SSDS;

- HCR will receive the notification of acknowledgement of receipt, if samples are in good order no action will be required from the HCR. If the samples are damaged the SSDS email will request the HCR to re-submit another set of samples.

- The HCR is advised to follow up with SAHPRA at lotrelease@sahpra.org.za and copy biological unit manager if acknowledgement of receipt has not been received within two (2) working days.

4.5 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 VAR and proof of secondary packaging is required;

- A copy of the lot summary protocol as detailed in section 4.3.1 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);

4.6 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 HCR by 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 registration (Appendix I). The lead time countdown will start once the lot release task has been accepted and samples sent.

- It remains the HCR’s responsibility to keep a record of all samples and information submitted to the SANCLBP. The VAR 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 3.8.

5. REFERENCES

5.1. Medicines and related substances Act no 101 of 1965

5.2. 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)

6. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces guideline for Lot Release of Human Vaccine, document no.: SAHPGL-PEM-BIO-01_v4. It will be reviewed on this timeframe or as and when required.

7. APPENDICES

7.1 Appendix I: Product-specific lead times for Lot Release

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