BAHAGIAN REGULATORI FARMASI NEGARA (NPRA)
MINISTRY OF HEALTH MALAYSIA

GUIDANCE DOCUMENT FOR LOT RELEASE OF BIOLOGICAL PRODUCTS MANUFACTURED IN MALAYSIA

PREFACE

This document is intended as a general guidance for application of lot release of biological products (vaccine and plasma derived medicinal products) manufactured in Malaysia.

Although great care has been taken in compilation and preparation of this publication to ensure the accuracy, Bahagian Regulatori Farmasi Negara (NPRA) cannot in any circumstances accepts liability for any errors or omission in this document, or any action/decision taken or not taken as a result of using this document.

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ACRONYMS

The following acronyms are used in this document

LRC	Lot Release Certificate
NCL	National Control Laboratory
NNC	Notification of Non-Compliance
NPRA	National Pharmaceutical Regulatory Agency
NRA	National Regulatory Authority
OCABR	Official Control Authority Batch Release
PRH	Product Registration Holder(s)
TRS	Technical Report Series
WHO	World Health Organisation

GLOSSARY

Applicant/ Product Registration Holder (PRH):
The company or corporate or legal entity in the field of pharmaceuticals whose name the marketing authorization has been granted. This party is responsible to all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorized holder must be subjected to legislation in the country that issued the marketing authorization, which normally means being physically located in that country[1]

Combination Vaccine:
Vaccine with more than one antigen, combined in a single injection, e.g. DPT vaccine combining diphtheria, pertussis and tetanus antigens[2]

Diluent:
A liquid used to mix with a lyophilised (powder) vaccine in order to reconstitute the lyophilised vaccine and provide the final vaccine for administration[3]

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, characterised 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[4]

Lot release:
The process of NRA/ NCL evaluation of an individual lot of a licensed vaccine before giving approval for its releasing onto the market[4]

Monovalent Vaccine:
A monovalent vaccine contains a single strain of a single antigen, e.g. Measles vaccine[2]

Non-Compliance:
Failure or refusal to comply with a standard or a set of limits[4]

NRA/ NCL:
The National Regulatory Authority/ National Control Laboratory taking the responsibility for regulatory oversight of a product for the critical regulatory functions defined by WHO, including independent lot release. Usually it is the country of manufacture unless specific

agreements exist within defined territories such as in 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[4]

Plasma:
The liquid portion remaining after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure[5]

Plasma Derived Medicinal Products (PDMP):
Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units[1]

Polyvalent Vaccine:
A polyvalent vaccine contains two or more strains/serotypes of the same antigen, e.g. Polio Vaccine[2]

Reference Country:
The reference country for Malaysia is listed as per the latest version of Drug Registration Guidance Document by National Pharmaceutical Regulatory Agency (NPRA)[1]

Storage Temperature:
The temperature ranges for storage as stated by the manufacturer on the primary container label and the package insert and within the approved regulatory specification for the product[3]

Temperature Excursion:
An excursion event during which a product is exposed to temperatures outside the range prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer based on stability data[3]

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[1]

CONTENT

1. GENERAL OVERVIEW

As outlined in WHO guideline[4], National Regulatory Authority (NRA)/National Control Laboratory (NCL) are strongly advised to oversee the quality of biological products locally produced. The recommended quality assessment of the biological products includes:

a) Independent testing of biological products
b) Review of manufacturers' summary protocol.

When the quality of the product is proven to be consistent throughout lot release testing, NRA/NCL may consider conducting either full or selected lot release testing. This decision is made based on the nature of the product and the established experience.

2. IMPLEMENTATION OF LOT RELEASE FOR BIOLOGICAL PRODUCTS MANUFACTURED IN MALAYSIA

NPRA will implement the Lot Release for Biological Products manufactured in Malaysia in 3 phases as elaborated in Table 1 below:

Table 1: The implementation plan

Phase	Description	Lot Release Requirement
1	1. Facility and expertise to conduct tests are not fully established in NPRA 2. Applicable to biological products during disaster, registered through fast-track conditional registration	For each lot of biological product submitted for Lot Release, NPRA shall: 1. Review the lot summary protocol 2. Review the finished product test reports 3. Conduct physical tests on the finished product as follows: a) Physical appearance b) Solubility c) Particulate contamination (visible particles)
2	Facility and expertise to conduct tests are fully established in NPRA	For each lot of biological product submitted for Lot Release, NPRA shall: 1. Review the lot summary protocol 2. Conduct physical tests on the finished product as follows:

		a) Physical appearance b) Solubility c) Particulate contamination (visible particles) 3. Conduct other tests deemed necessary in accordance with recommendations by the World Health Organisation (WHO) or EU Official Control Authority Batch Release (OCABR), whichever is more stringent
3	Confirmation of the quality of the product through consistent test results for chosen parameters obtained from phase 2	For each lot of biological product submitted for Lot Release, NPRA shall: 1. Review the lot summary protocol 2. Conduct selected lot release tests from phase 2, based on a risk-based approach.

Local manufacturers in Malaysia play important roles in assisting NPRA for the implementation of lot release for locally produced biological products. As outlined in WHO guideline[4], manufacturers are responsible to:

a) Collaborate with NPRA to develop product summary protocol template, by using relevant WHO product summary protocol template as an example
b) Assist NPRA in the technical transfer of test method. The method transfer between manufacturer from country of origin/ local manufacturer and NPRA should be done at an earlier stage of product registration to ensure reproducible test method for lot release
c) Provide reference standards, reagents, test kits or other necessary items in appropriate condition for testing
d) Submit samples in an appropriate condition, including packaging and label, upon NPRA's request

3. GENERAL PROCEDURES OF LOT RELEASE FOR BIOLOGICAL PRODUCTS MANUFACTURED IN MALAYSIA

3.1 Scope

The scope of this guideline includes the following registered biological products for human use:

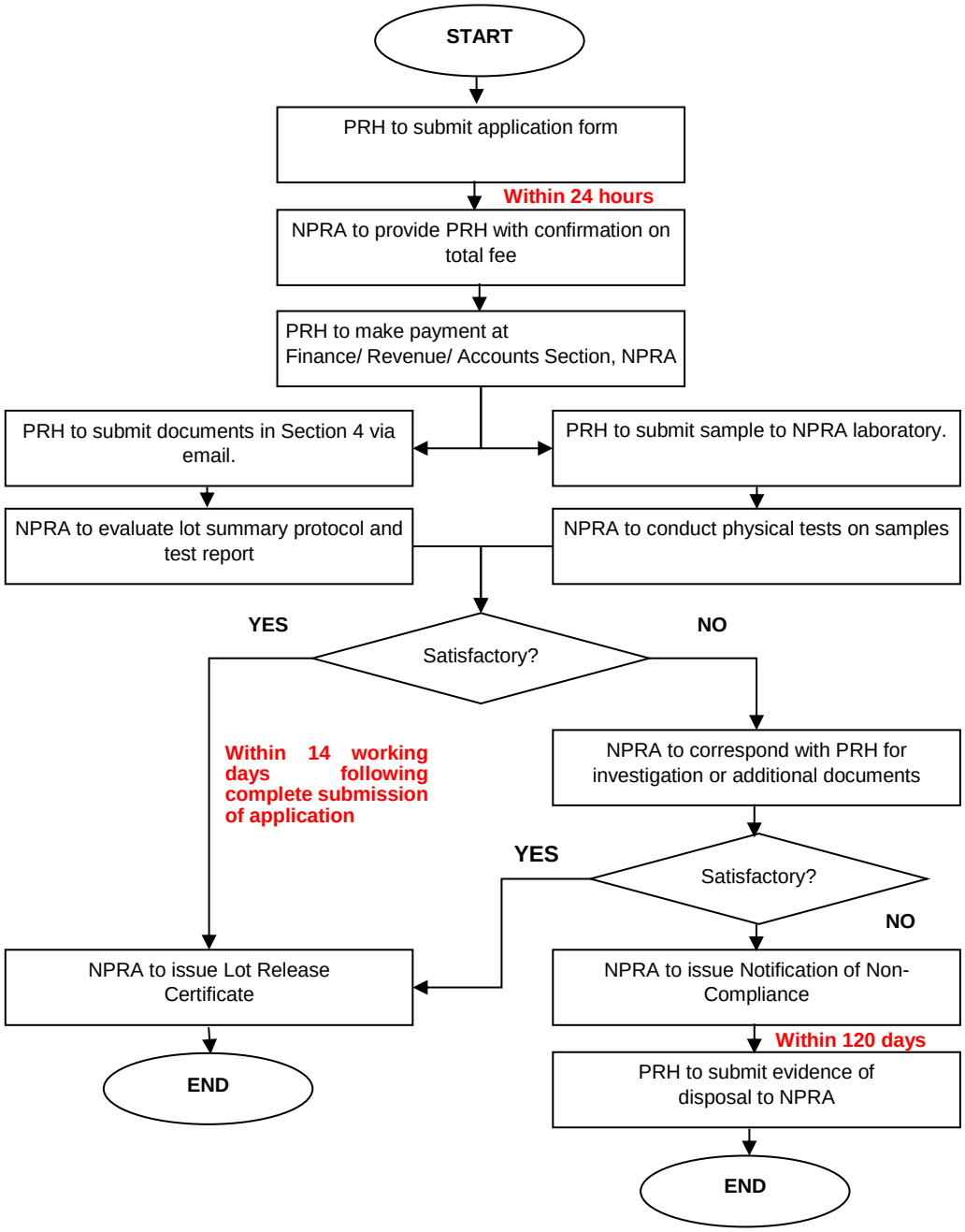
a) Vaccine (for prophylaxis and treatment)

b) Plasma derived medicinal product (also known as plasma product)

3.2 General Procedures

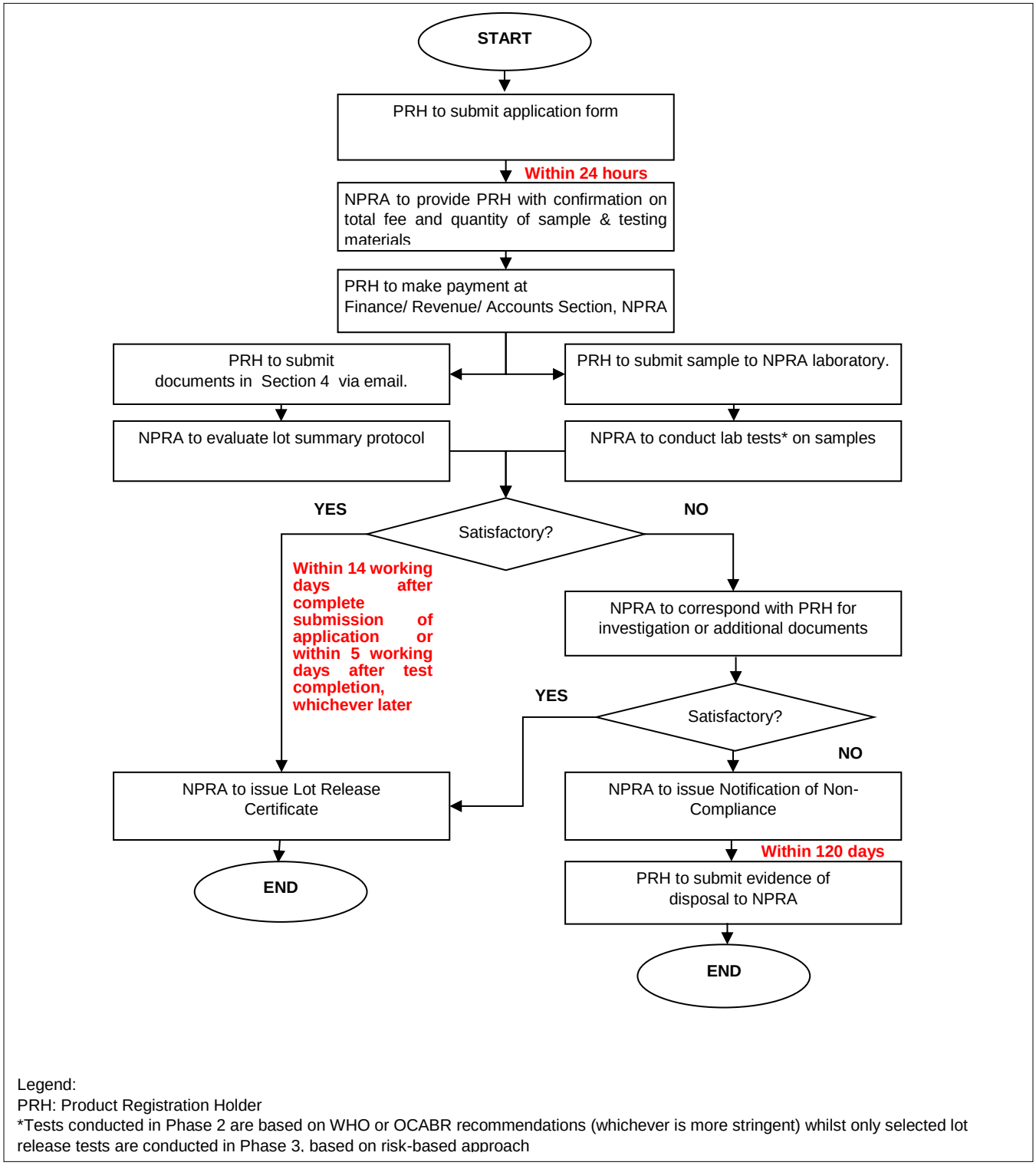
i. Product Registration Holder (PRH) submits application form (refer to Appendix 1) and documents via email to NPRA (vaccinecqc@npra.gov.my). Please refer to Section 4 of the guideline for further details on documents to be submitted.
ii. NPRA will respond to the email by providing confirmation on the amount of fee to be paid and number of samples and test items for testing to be sent to NPRA. Please refer to Section 9 of the guideline for further details on fees.
iii. Payment shall be made to NPRA **before** NPRA starts:
    a. Evaluation of lot summary protocol
    b. Evaluation of test report (only applicable to Phase 1)
    c. Conducting lot release testing
iv. PRH submits sample for testing to NPRA laboratory
v. NPRA officers evaluate lot summary protocol, test report (only applicable to Phase 1) and conduct lot release testing.
vi. NPRA will issue lot release certificates if all the requirements have been fulfilled. Please refer to Section 8 of the guideline for further details on timeline.
vii. Failure to comply with Lot Release requirements will lead to issuance of Notification of Non-Compliance (NNC) and the product will be rejected.
viii. In the event of non-compliance, it is the sole responsibility of the PRH to ensure proper and safe disposal of the product. A copy of disposal documentation shall be sent to NPRA within 120 days following issuance of NNC.

3.3 Process flow 1: Lot Release procedures for Phase 1



Legend:
PRH: Product Registration Holder

3.4 Process flow 2: Lot Release procedures for Phase 2 and Phase 3



Legend:
PRH: Product Registration Holder
*Tests conducted in Phase 2 are based on WHO or OCABR recommendations (whichever is more stringent) whilst only selected lot release tests are conducted in Phase 3, based on risk-based approach

4. THE SUBMISSION OF DOCUMENTS

This guidance outlines the necessary documents to be submitted for lot release application. All the documents shall be written in *Bahasa Malaysia* or English only. Each document must be clearly tagged (indexed and labelled). Documents to be submitted are:

a) Application form
b) Lot summary protocol
c) Plasma Pool Certificate (For Plasma Derived Medicinal Products only)(If applicable)
d) Certificate of Analysis (CoA) for finished product and diluent (if applicable)
e) Finished product test report with raw data (only applicable to Phase 1)

Incomplete submission of documents may result in rejection of the application.

4.1 Application Form

a) Application form is available on NPRA official website (refer to Appendix 1) and PRH shall use the same form without any amendments
b) The lot number (in final packaging) stated on the application form must be identical to the lot number on the lot summary protocol and certificate of analysis.
c) The application form shall be submitted to NPRA via email: vaccinecqc@npra.gov.my
d) Incomplete form will not be processed.

4.2 Lot Summary Protocol (LSP)

As defined by WHO Guidelines[4], lot summary protocol is a document summarising all manufacturing steps and test results for each lot produced 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.

The evaluation of the LSP will be based on product dossier which has been evaluated and approved by NPRA during product registration and variation submission.

4.3 Plasma Pool Certificate (For Plasma Derived Medicinal Products only)

Plasma pool certificate provided should be issued by the NRA from the country of origin. In the event where the NRA does not provide a plasma pool certificate, plasma pool certificate from any of the NPRA's eight (8) reference countries (United Kingdom,

Sweden, France, United States of America, Australia, Canada, Japan and Switzerland) will be accepted.

4.4 Certificate of Analysis (CoA) for Finished Product and Diluent

All release tests and its specification shall be based on product dossier which has been evaluated and approved by NPRA during product registration. Certificate of analysis for finished product and diluent may contain the following information:

a) Name of manufacturer
b) Product name, dosage form and strength
c) Lot number (must be identical to the lot number on the application form)
d) Date of expiry
e) Date of manufacture
f) List of tests
g) Test specification
h) Test results
i) Approval from responsible person & the date

4.5 Finished product test report with raw data (only applicable to Phase 1)

Test report with raw data shall be in scanned copy of the original document and sent through email together with application form or shared in a link which allows NPRA to access the document. Test report may contain the following information:

a) Product name, dosage form and strength
b) Lot number (must be identical to the lot number on the application form)
c) Name of test
d) Instrument ID
e) Test method (include preparation of each solution)
f) Printed weight, pH and raw data which is generated by instrument
g) Lot Number & Date of expiry for kits and reference standards (if applicable)
h) Purity of reference standards (if applicable)
i) Calculation of test (if applicable)
j) Test specification
k) Test results
l) Date of analysis
m) Name of analyst
n) Date of approval
o) Approval from responsible person

5. PRODUCT TESTING

WHO recommended NRA to conduct independent testing to monitor key products parameters, consistency of production and to verify manufacturer's test results.

For Phase 1, physical test conducted by NPRA on the finished product are as follows:

a) Physical appearance
b) Solubility
c) Particulate contamination (visible particles)

For Phase 2 and Phase 3, test conducted by NPRA on the finished product are stated in WHO guidelines[4] or EU OCABR guidelines as follows:

a) Physical test (physical appearance, solubility and particulate contamination (visible particles)
b) Identity
c) Potency
d) Specific safety (e.g. bacteria endotoxin)
e) Thermostability (if applicable)

Lot release tests are not limited to the afore-mentioned tests and should be tailored accordingly to ensure the safety profile of the biological product. The selection of lot release tests will be established based on recommendation published in World Health Organisation (WHO) Technical Report Series (TRS) or EU OCABR guidelines, whichever is more stringent**.**

Under certain circumstances, NPRA may consider to receive samples before manufacturers have completed their product testing for the purpose of parallel testing[4].

6. SAMPLE SUBMISSION

All products shall be submitted within 1 or 2 working days following submission of application. PRH is responsible to ensure that samples submitted for testing adhere to the approved storage temperature of the respective product. Samples delivered to NPRA from manufacturer shall be accompanied by an appropriate temperature monitoring device or indicator for the purpose of recording the temperature throughout the entire transportation journey. NPRA reserves the right to reject any samples not compliant with the latest approved storage temperature conditions and request for additional samples to conduct testing if deemed necessary.

6.1 Sample Submission for Phase 1

PRH shall provide an appropriate number of finished products with diluents (if applicable), not less than three (3) containers/ vials/ ampoules/ pre-filled syringes and complete sample submission form to NPRA. Products can be delivered by hand or via courier service.

Type of testing conducted depends on the dosage form of the finished products.

a) Solution/ liquid:
   - Appearance test
   - Particulate contamination (visible particles) test

b) Freeze dried/ lyophilised & frozen solution:
   - Appearance test
   - Solubility test
   - Particulate contamination (visible particles) test on reconstituted finished product

6.2 Sample Submission for Phase 2 and Phase 3

The number of samples to be submitted for lot release testing depends on the profile of each type of the product. NPRA's officer shall issue an official letter within 24 hours after submission of application to inform applicant on the amount of samples and test items.

7. NON-COMPLIANCE

7.1 Rejection Criteria for Lot Release of Biological Products manufactured in Malaysia

Product shall be rejected under conditions including but not limited to:

a) testing fails to meet specification
b) forgery in test reports provided (applicable for Phase 1)
c) failure to provide testing reagents, reference standards, reagents, test kits or other necessary items for testing (applicable for Phase 2 and 3)
d) failure to provide additional data requested
e) failure of the manufacturer to comply with Good Manufacturing Practice (GMP) requirement
f) failure to include temperature monitoring device for sample submission
g) release of product (including quarantined products) without approval from NPRA
h) testing specification and test method are not updated accordingly or updated without NPRA's approval (approval for product variation by NPRA shall be received before the submission of lot release application)
i) the product information leaflet and label are not updated accordingly or updated without NPRA's approval (approval for product variation by NPRA shall be received before the submission of lot release application)
j) decision from Director of NPRA based on the supporting document, comments from another NRA (if available) and summary from evaluator

7.2 Decision making

The reasons of non-compliance will be clearly stated in the non-compliance notification. However, an appeal against the decision may be submitted to the Senior Director of Pharmaceutical Services. All decisions made henceforth by Senior Director of Pharmaceutical Services are final and no further appeal shall be allowed in any circumstances.

7.3 Non-compliant products

In the event of non-compliant products, the PRH shall ensure the supply of the product for the local use will not be affected. The PRH shall ensure that non-compliant products are not released onto the market and will be disposed in Malaysia. PRH shall provide appropriate proof of disposal within 120 days after issuance of non-compliance notification

8. TIMELINE

NPRA will issue lot release certificates if all the Lot Release requirements have been fulfilled. Table 2 and 3 below show the timeline for each activity according to the implementation phases.

Activity	**Timeline**
Processing of application form, confirmation on total fee	Within 24 hours
Issuance of lot release certificate upon complete submission of application, which includes a. documents in Section 4 b. sample AND c. payment	Within 14 working days
Submission of evidence of disposal in the event of non-compliance	Within 120 days following issuance of Notification of Non-Compliance

Table 2: Timeline for Lot Release of Biological Product Manufactured in Malaysia in Phase 1

Activity	**Duration**
Processing of application form, confirmation on total fee, quantity of sample and testing materials	Within 24 hours
Issuance of lot release certificate upon complete submission of application, which includes a. documents in Section 4 b. sample c. testing materials AND d. payment	Within 14 working days following complete submission of application, or within five (5) working days after test completion, whichever later The timeline is product specific; each biological product differs in testing procedures and test duration.
Submission of evidence of disposal in the event of non-compliance	Within 120 days following issuance of Notification of Non-Compliance

Table 3: Timeline for Lot Release of Biological Product Manufactured in Malaysia in Phase 2 and Phase 3

9. PROCESSING FEES

a) Every application for lot release shall be charged
b) Payment made shall NOT be REFUNDABLE once the application has been submitted and payment notice has been issued
c) Applications without the correct fees paid will not be processed.

9.1 Types of processing fees

9.1.1 Fee for Phase 1

The fees imposed for Phase 1 shall be updated on NPRA website.

9.1.2 Fees for Phase 2 and Phase 3

The fees imposed for Phase 2 and Phase 3 are product specific and shall be updated on NPRA website to include the fees for each type of product. NPRA's officer shall advise applicant upon receiving lot release application.

9.2 Mode of payment

The processing fee and any other charges shall be paid in the form of credit card/ bank draft/banker's cheque/ money order/ postal order made payable to "Biro Pengawalan Farmaseutikal Kebangsaan".

10. REFERENCES

1. MALAYSIA. Drug Registration Guidance Document 2nd edition. National Pharmaceutical Regulatory Agency (NPRA), 2019. Available from http://www.npra.gov.my

2. WHO. Types of Vaccine and Adverse Reaction. In: WHO Vaccine Safety Basics Learning Manual. Geneva, World Health Organization, 2013.

3. WHO. How to Monitor Temperatures in the Vaccine Supply Chain. In: WHO Vaccine Management Handbook, Module VMH-E2. Geneva, World Health Organization, 2015. (WHO/IVB/15.04)

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

5. WHO. Recommendations for the Production, Control and Regulation of Human Plasma for Fractionation. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 941)

11. APPENDIX

Appendix 1: Application Form for Lot Release

Appendix 2: Application Form for Sample Submission

Appendix 1: Application Form for Lot Release

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Ministry of Health Malaysia
Lot 36, Jalan Profesor Diraja Ungku Aziz (Jalan Universiti), 46200 Petaling Jaya, Selangor
Tel: 03-7883 5400
Fax: 03-7956 7075
Email: vaccinecqc@npra.gov.my

LOT RELEASE APPLICATION FORM FOR BIOLOGICAL PRODUCTS MANUFACTURED IN MALAYSIA

1. APPLICANT INFORMATION	
1.1 Name & Address of Product Registration Holder	
1.2 Contact Person	
1.3 Contact no.	

2. PRODUCT INFORMATION		
2.1 Category	☐ Vaccine ☐ Plasma product	
2.2 Name of product as registered in Quest3+		
2.3 Ingredients & strength		
2.4 Name of manufacturer		
2.5 Address of manufacturer		
2.6 MAL no.		2.7 Lot no. of product
2.8 Date of manufacture		2.9 Expiry date
2.10 Storage condition		2.11 Type of final container for product ☐ Vial ☐ Ampoule ☐ Prefilled syringe ☐ Others; please specify _____

3. DILUENT INFORMATION (IF ANY)	
3.1 Name of diluent	3.2 Lot no. of diluent

3.3 Date of manufacture	3.4 Expiry date
3.5 Storage condition(s)	3.6 Types of final container for diluent ☐ Ampoule ☐ Prefilled syringe ☐ Vial

4. QUANTITY MANUFACTURED

4.1 Total final containers manufactured	4.2 Total dose of production

5. DOCUMENTATION

5.1 Documents submitted	☐ Lot Summary Protocol ☐ Plasma Pool Certificate (if applicable) ☐ Certificate of Analysis of Finished Product ☐ Finished product test report (with raw data)

6. APPLICANT DECLARATION

I hereby certify that the above information given are true and correct as to the best of my knowledge.
I understand that if any of the above information is found to be false or untrue or misleading or misrepresenting, I am aware that I may be held liable for it, this application will be rejected and any payments made will not be refunded.

Remarks

Name	Signature	Date

FOR OFFICE USE ONLY

Application number:	LR documents complete? ☐Yes ☐No.	Received by, date & signature
Product under: ☐Phase 1 ☐Phase 2 ☐Phase 3	List of pending documents: ☐Lot summary protocol ☐COA ☐ Plasma Pool Certificate (if applicable) ☐Finished product test report	
SAB reference no.: NPRA.600-2/6/1 Jld. (3) Bil.( )	Date of issuance:	Issued by, date & signature
Date of payment received:	Receipt no.:	Received by, date & signature

Appendix 2: Application Form for Sample Submission

BAHAGIAN REGULATORI FARMASI NEGARA (NPRA)
Lot 36, Jalan Profesor Diraja Ungku Aziz (Jalan Universiti), 46200 Petaling Jaya, Selangor
Tel: 03-7883 5400
Fax: 03-7956 7075
Phase 1 Email: vaccinecqc@npra.gov.my
Phase 2 & 3 Email: biotesting@npra.gov.my

SAMPLE SUBMISSION FORM FOR BIOLOGICAL PRODUCTS MANUFACTURED IN MALAYSIA

1. APPLICANT INFORMATION

1.1 Name & Address of Product Registration Holder	
1.2 Contact Person	
1.3 Contact no.	

2. PRODUCT INFORMATION

2.1 Category	☐ Vaccine ☐ Plasma product
2.2 Name of product as registered in Quest3+	
2.3 Ingredients & strength	
2.4 Name of manufacturer	
2.5 Address of manufacturer	

2.6 MAL no.	2.7 Lot no. of product
2.8 Date of manufacture	2.9 Expiry date
2.10 Storage condition	2.11 Type of final container for product ☐ Vial ☐ Ampoule ☐ Prefilled syringe ☐ Others; please specify _____

3. DILUENT INFORMATION (IF ANY)

3.1 Name of diluent	3.2 Lot no. of diluent
3.3 Date of manufacture	3.4 Expiry date
3.5 Storage condition(s)	3.6 Types of final container for diluent ☐ Ampoule ☐ Prefilled syringe ☐ Vial

4. QUANTITY, SIZE AND DOSAGE FORM (SAMPLE AND DILUENT) SUBMITTED

4.1. Sample

4.1.1 Quantity	4.1.2 Size (mL) per container	4.1.3 Dosage form ☐ Liquid/Solution ☐ Freeze Dried/Lyophilized ☐ Others: _____

4.2 Diluent

4.2.1 Quantity	4.2.2 Size (mL) per container

4.3 Testing material (To list down the reagents, standards, etc submitted for testing purpose)

No.	Item	Expiry Date	Storage Condition	Quantity

*Kindly attach a second copy if the space is insufficient

5. APPLICANT DECLARATION

I hereby certify that the above information given are true and correct as to the best of my knowledge.
I understand that if any of the above information is found to be false or untrue or misleading or misrepresenting, I am aware that I may be held liable for it, this application will be rejected.

Remarks

Name	Signature	Date

FOR OFFICE USE ONLY	
Samples received by:	Date and time:

Application number:

Adherence to recommended storage temperature:
- ☐ Comply
- ☐ Not comply, remarks _____

Serial number (data logger/indicator for temperature sensitive items):

Mode of sample submission:
- ☐ Hand delivered
- ☐ Courier service (delivery provider and tracking number)

Sample submission status:
☐Accept
☐Reject