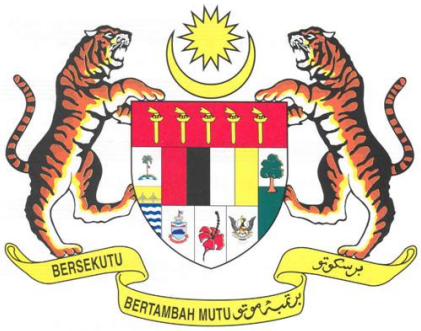

NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA)
MINISTRY OF HEALTH MALAYSIA

GUIDANCE DOCUMENT FOR BIOLOGICAL PRODUCTS LOT RELEASE IN MALAYSIA

PREFACE

This document is intended to provide general guidance. Although great care has been taken in compilation and preparation of this publication to ensure the accuracy, National Pharmaceutical Regulatory Agency (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.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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GUIDELINE HISTORY

No.	Guidelines	Description of amendment	Effective date
1.	a) Guideline for Vaccine Lot Release in Malaysia b) Guideline for Plasma Product Lot Release in Malaysia	Initial publication	a) 1Jul 2014 b) January 2016
2.	Guideline for Vaccine Lot Release in Malaysia	Revision of Guideline for Vaccine Lot Release, July 2014	1 April 2015
3.	Guidance Document for Vaccine Lot Release in Malaysia	Revision of Guideline for Vaccine Lot Release, April 2015	1 December 2016
4.	Guidance Document for Plasma Product Lot Release in Malaysia	Revision of Guideline for Plasma Product Lot Release, January 2016	1 December 2016
5.	Guidance Document for Biological Lot Release in Malaysia	1. Merging of (3) and (4) 2. Expansion of scope to: a) include vaccine for treatment b) include physical appearance test as part of Lot Release activity	December 2019

CONTENT

ACRONYMS

The following acronyms are used in this document

BCG	Bacille Calmette-Guerin Vaccine (BCG)
CQC	Centre for Quality Control
CDCR	Control of Drugs and Cosmetic Regulation 1984
DTaP-IPV	Diphtheria-Tetanus-Pertussis-Polio combination vaccine
DRGD	Drug Registration Guidance Documents
HepB	Hepatitis B
Hib	Haemophilus influenzae
LRC	Lot Release Certificate
NCL	National Control Laboratory
NNC	Notification of Non-Compliance
NPRA	National Pharmaceutical Regulatory Agency
NRA	National Regulatory Authority
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 authorisation has been granted. This party is responsible to all aspects of the product, including quality and compliance with the conditions of marketing authorisation. The authorised holder must be subjected to legislation in the country that issued the marketing authorisation, which normally means being physically located in that country[2]

Fractionation:
A (large scale) process by which plasma is separated into individual protein fractions that are further purified for medicinal use (variously referred to as plasma derivatives, fractionated plasma products or plasma-derived medicinal products). The term fractionation is used to describe a sequence of processes, including: plasma protein separation steps (typically precipitation and/or chromatography), purification steps (typically ion-exchange or affinity chromatography) and one or more steps for the inactivation or removal of blood-borne infectious agents (most specifically viruses and, possibly, prions)[8]

Cold Chain Monitors (CCM):
A single-use device used to monitor the temperature inside a shipping container. CCMs should be thrown away after being checked. CCMs are stored in a separate compartment of the shipping container[12]

Combination Vaccine:
Vaccine with more than one antigen, combined in a single injection, e.g. DPT vaccine combining diphtheria, pertussis and tetanus antigens[13]

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[14]

Electronic Data Logging Monitor (EDLM):
A small portable device used to measure and store temperature at pre-determined time intervals by means of an electronic sensor. It has programmable alarm capabilities, integrated displayed, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted database[15]

Freeze Indicator (FI):
An irreversible indicator used to indicate a product has been exposed to freezing temperature. It consists of a white backing card and a small vial of coloured liquid, all contained in a plastic casing. If the freeze indicator is exposed to temperatures below 0°C for more than 1 hour, the vial bursts and release the coloured liquid, staining the white backing card[16]

Licensed Importer:
A person to whom an import license has been issued under Regulation 12, CDCR 1984[1]

Licensed Wholesaler:
A person to whom a wholesaler's license has been issued Regulation 12, CDCR 1984[1]

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[6]

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[6]

Monovalent Vaccine:
A monovalent vaccine contains a single strain of a single antigen, e.g. Measles vaccine[13]

Non-Compliance:
Failure or refusal to comply with a standard or a set of limits[6]

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[6]

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[8]

Plasma Derived Medicinal Products (PDMP):
Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units[2]

Polyvalent Vaccine:
A polyvalent vaccine contains two or more strains/serotypes of the same antigen, e.g. Polio Vaccine[13]

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)[2]

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[14]

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[14]

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[2]

Vaccine Vial Monitors (VVM):
Chemical-indicator labels placed on vaccine vials, ampoules, tubes or other types of primary containers by the vaccine manufacturer. A vaccine vial monitor shows the cumulative heat exposure that an individual container of vaccine has received through a gradual and irreversible colour change[14]

Viral Inactivation:
A process of enhancing viral safety in which the virus is intentionally killed[8]

Viral Removal:
A process of enhancing viral safety by removing or separating the virus from the protein(s) of interest[8]

1. INTRODUCTION

Vaccines are biological products used mainly in the prophylaxis and in some instances, treatment of disease. They are largely used in healthy population including healthy babies and young children. Because of their inherently complex and variable nature, major consequences may arise due to deleterious effect such as reversion to virulence/toxicity or loss of immunogenicity. Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programmes, thus potentially compromising public health strategies[6].

Plasma-Derived Medicinal Products (PDMPs) are prepared from human plasma and include products such as albumin, coagulation factors and immunoglobulins, which are life-saving for several chronic and acute life-threatening diseases. They are complex in nature and their quality and safety rely heavily on source materials as well as subsequent manufacturing processes including infectious marker testing and viral removal and inactivation.

In addition to manufacturing complexity inherent to biological products, proper storage condition and efficient supply chain management must 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 product as stated is therefore necessary before use. Lot release programme will enable National Regulatory Authority (NRA) to ascertain the safety and effectiveness of every lot of these products.

1.1 General Overview of Lot Release

The lot release of biological products by regulatory authority is part of the regulation of these products and involves independent assessment of each lot before it is released on to the market.

As per WHO guidelines[6], for self-procured biologicals, independent assessments may be based on:

a) as a minimum, review of manufacturers' summary protocols

Supplemented with the followings:

b) recognition/acceptance of release certificate from responsible NRA or national control laboratory (NCL)
c) 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.

1.2 Scientific Guideline Applicable to Biological Products Lot Release

Guidelines for implementation of lot release on biological products are as follows:

a) Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities and Technical Report Series (TRS), available at WHO website: https://www.who.int/biologicals/vaccines/en/
b) Guidelines on Quality Assurance and Safety: Blood Product and Related Biologicals, available at WHO website: https://www.who.int/bloodproducts/en/

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

2.1 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

This document is intended to provide guidance to PRHs, importers and wholesalers of the above products.

The content of this guideline will be reviewed and amended accordingly in the future for locally produced products.

2.2 Lot Release in Malaysia

This guideline is largely based on the recommendation outlined in the Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities[6] and Assessment Criteria for National Blood Regulatory Systems[7]. The lot release approaches for registered imported vaccines and plasma derived medicinal products in Malaysia will include all the following: -

a) Review of manufacturer's summary protocol based on product dossier which has been approved by NPRA during product registration
b) Review of recognised LRC from National Regulatory Agency (NRA) of Country of Origin
c) Inspection upon arrival in the warehouses
d) Test conducted on the products (refer to section 5)

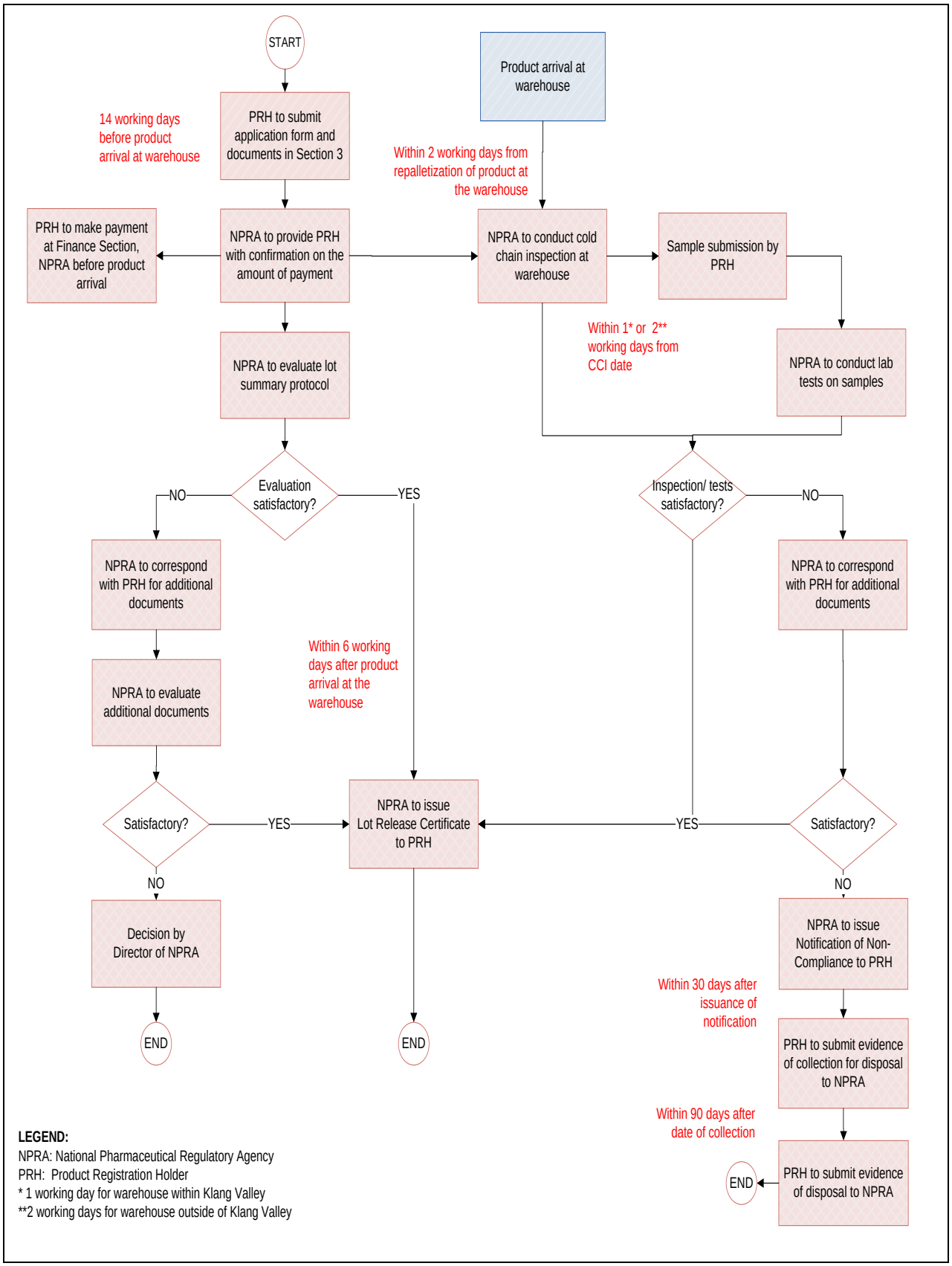
PRHs are fully responsible to ensure the products comply with the product registration information. If there are any changes to the products, PRHs are expected to obtain approval for variation prior to submission of documents. Please refer to the Malaysian Variation Guideline for Biologics (MVGB) for further details.

2.3 General Procedures of Lot Release in Malaysia

The Process Flow 1 diagram (below) illustrates the process of lot release involving the following parties:

a) Product Registration Holder (PRH)
b) National Pharmaceutical Regulatory Agency (NPRA)
c) Importers
d) Wholesalers

Process Flow 1: LOT RELEASE PROCESS



General Procedures:

i. PRH submits application form (refer to Appendix 1) and documents (refer to section 3) via email to NPRA (vaccinecqc@npra.gov.my)
ii. NPRA will respond to the email by providing confirmation on the amount of fee to be paid. Please refer to section 10 of the guidelines for further details on fees.
iii. Before product arrival, applicant makes payment to NPRA.
iv. NPRA officers evaluate summary protocol.
v. Within 2 working days after re-palletization of product at warehouses, NPRA officers will conduct cold chain inspection.
vi. For warehouses within Klang Valley, PRH are expected to send samples to NPRA for lab testing within 1 working day after cold chain inspection. Whilst warehouses located out of Klang Valley, the samples are expected to be sent within 2 working days.
vii. NPRA will issue lot release certificates if all the requirements have been fulfilled, within 6 working days after product arrival at warehouse.
viii. If one of the requirements is not met, NPRA will issue notification of non-compliance to reject the product.
ix. 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 collection for disposal documentation shall be sent to NPRA within 30 days after issuance of rejection and a copy of disposal documentation shall be sent to NPRA within 90 days after the collection date.
x. The product with the same lot number which has been previously imported, will not be repeated in evaluation and testing
xi. For cases stated in (x), PRH will only submit the application form, import packing list, air waybill and make payment for cold chain inspection.

3. GUIDANCE ON THE SUBMISSION OF DOCUMENTS

This guidance outlines the essential 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) Lot Release Certificate
d) Plasma Pool Certificate (For Plasma Derived Medicinal Products only)
e) Certificate of Analysis (CoA) for Finished Product and Diluent
f) Importing Packing List*
g) Air Waybill*

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

*may be submitted 2 working days before product arrival.

3.1 Application Form

a) Application form is available through the 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, lot release certificate 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.

3.2 Lot Summary Protocol (LSP)

As defined by WHO Guidelines[6], lot summary protocol is a document summarising 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.

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.

3.3 Lot Release Certificate (LRC)

Lot release certificate provided should be issued by the NRA from the country of origin.

In the event where the NRA does not provide a release certificate, lot release certificate from any of the NPRA's 8 reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland) will be accepted.

3.4 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 8 reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland) will be accepted.

3.5 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 in the application form)
d) Date of expiry
e) Date of manufacture
f) List of tests
g) Specification of tests
h) Result of tests
i) Approval from responsible person

3.6 Importing Packing List

PRH shall provide the details of importing packing such as:

a) Product name
b) Lot number
c) Numbers and types of package
d) Quantity

The importing packing list must be submitted to NPRA 2 working days prior to product arrival.

3.7 Air Waybill (AWB)

For products transported via air route, PRH shall provide the details of AWB such as:

a) Air waybill number
b) Airport of departure
c) Airport of destination
d) Flight number
e) Shipper's name and address
f) Consignee's name and address

The air waybill must be submitted to NPRA 2 working days before the product arrival.

4.0 GUIDANCE ON TEMPERATURE MONITORING

Deviation of temperature or incorrect storage condition may affect the quality, efficacy and subsequently the safety of the product. Hence, it is recommended that all products are always transported and stored in their respective recommended condition with continuous monitoring. Transportation of these products can be done by either active or passive packaging systems

4.1 Types of Packaging Systems

(a) Active System
Actively powered systems employ electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation[3]. An active packaging system can range from parcel size to full trailer load. The larger systems resemble transportable refrigerators and feature cooling and heating units that circulate air around the product space.

(b) Passive System
Passive systems on the other hand maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant such as frozen gel packs, phase change materials or dry ice[3]. These systems comprise the product surrounded by thermal media, which is prepared to specific temperatures and encapsulated within an insulation material.

The choice of packaging system for the international shipment of temperature-sensitive products is at the discretion of the manufacturer and product registration holder.

4.2 Temperature Monitoring Devices

Temperature indicators such as electronic data logging monitor (EDLM) and vaccine vial monitors (VVM) serve as a quick reference to help recipient countries determine whether the shipment has been exposed to temperatures outside the recommended range[9]. EDLM records data digitally over time or in relation to location either with a build-in or external instrument or sensor[9]. EDLM is the preferred temperature indicators as they provide the most reliable and accurate record of temperature conditions for active and passive packaging systems. It is mandatory to have at least one EDLM in each and every international shipping carton or pallet[3-5].

EDLM used for monitoring temperature should have the following functions:
1) A “start” function to activate the device at the time the carton is being loaded[9]
2) A “stop” function to allow the recipient to stop the recording when the product arrives at its destination[9]

Manufacturers shall only include WHO Prequalified Temperature Monitoring Devices for transportation and shipping of their products. Kindly refer to the following link for more information on these devices:
http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue

The use of cold chain monitor cards (CCM), vaccine vial monitors (VVM) and/or freeze indicators (FI) solely or together for international shipments are no longer recommended[9]. They may be used to supplement EDLM included in the shipment. However, in the event of a discrepancy in temperature data recorded by EDLM and CCM/ VVM/ FI, the temperature recorded by the electronic device is the one referred to[9]. Assessment of temperature data recorded by EDLM shall be done to confirm that the temperature throughout transportation of the products does not exceed the requirements as stated in the following guidelines:

a) WHO Guidelines on the International Packaging and Shipping of Vaccines, December 2005 (WHO/IVB/05.23)
b) WHO Temperature Sensitivity of Vaccines, August 2006 (WHO/IVB/06.10)
c) WHO Guidelines on Proper Handling of Diluent, October 2015 (WHO/IVB/15.08)

Batteries for electronic devices do not perform under extremely cold temperatures, such as when products are transported with dry ice. All manufacturers are encouraged to validate their Class A and B packaging with frozen ice packs in order to phase out the use of dry ice. In exceptional cases – where dry ice continues to be used – WHO recommends the inclusion of one cold chain monitor card per shipping carton instead of an electronic device[9].

4.3 Packaging and Shipping Validation

Before a product is transported to Malaysia or if changes are introduced either in the current packaging or shipment procedures, manufacturer is required to submit packaging and shipping validation documents to NPRA. The validation data submitted must be sufficient to prove that the product remains stable at the recommended storage condition.

'Validation' is the confirmation that temperatures inside the shipping containers of every temperature-sensitive product shipment remains within the defined temperature range for a period of 48 hours[9]. Validation should be performed under highly controlled-conditions to demonstrate that processes, methods and systems consistently produced results meeting predetermined criteria[3]. Manufacturers must document the validation of their packaging. Validation data should be produced for 3 successful consecutive tests at the defined ambient temperatures minimum 48 hours[9]. If changes are introduced either in the packaging or the shipment procedures, the shipment must be validated again[9].

Documents to be submitted to NPRA for assessment are as listed below:

1) Cover letter stating the mode of transportation.
2) The validation report should include:
    a) Standard operating procedure or test protocol used for validation of packaging
    b) The start date, end date and time of at least 3 consecutive validation runs
    c) Detailed information of the mode of transportation, i.e. external and internal dimensions of the insulated container, packaging materials, weight empty and weight fully loaded (total weight)
    d) Detailed temperature history for all tests in tabular format (for all internal and external ambient channels)
    e) Validation report has to be embossed with the company's official seal in order to showcase certification and be signed by authorised personnel who prepared and

approved the document. Signature indicates agreement with content and its accuracy and its alignment with applicable guidelines, policies and procedures governing qualification and Good Distribution Practices (GDPs).

3) All the documents shall be written in *Bahasa Malaysia* or English only. If validation documents are prepared in a foreign language, the report must be translated to English and stamped with company's official seal to signify authentication.

As guidance, manufacturer may also refer to WHO Guidelines on the International Packaging and Shipping of Vaccines, December 2005 (WHO/IVB/05.23).

4.4 Transport of Diluent

Diluent is a diluting agent (e.g. a liquid) added to reconstitute lyophilised product before administration. Some diluents may be sensitive to heat or freezing, and may require transportation and storage in the cold chain.

There are different types of diluent, and each is specific to the product that it accompanies. The most comment diluent is pharmacologically inactive aqueous solution (Sodium Chloride; NaCl) or water for injection; this type of diluent is used to reconstitute a lyophilised product such as BCG vaccine (BCG), or Human Coagulation Factor (II, IX, VIII) which is administered by injection. It is also used to make up an oral vaccine such as Cholera vaccine.

On other hand, some liquid diluents are pharmacologically active that contain live vaccine and thus must be kept in the refrigerator[16]. These include liquid vaccines that are used to reconstitute a lyophilised component of a polyvalent vaccine (such as liquid DTaP-IPV) vaccine that is used to reconstitute a lyophilised Hib vaccine). Thus, manufacturer's guidance for specific temperature requirements shall be followed to ensure diluent is transported and handled in recommended storage condition.

All diluents shall not be frozen, not even during transport. Diluent that has been frozen should not be used because of the risk of crack in the vial/ampoule that may cause contamination. In addition, if diluent contains an active ingredient, the diluent may be damaged by freezing[14]. If diluents are found to be frozen, an appropriate action should be taken to isolate and dispose the vials according to decision by NPRA.

4.5 Handling of Temperature Excursion

Any temperature reading outside the ranges specified by the manufacturers is considered a temperature excursion.

Manufacturer as well as the PRH should clearly understand what the consequences of temperature excursions are during products storage and transport from manufacturing site to Malaysia. It is the responsibility of manufacturer and PRH to assess if the available stability data are sufficient to address the potential temperature excursions. Additional studies shall be considered in the case where stability data is lacking. Stability data is crucial and contribute to support the release decision in case of temperature excursions.

5. GUIDANCE ON PRODUCT TESTING

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, assessment of appearance, solubility and particulate contamination in products will be conducted as part of independent testing by NPRA. This assessment will be carried out according to relevant guidance documents and pharmacopeia.

Test conducted on the product should comply with the latest approved product specification provided by PRH.

5.1 Guidance on sample submission

PRH shall provide an appropriate number of finished products with diluents (if applicable), not less than 3 containers/ vials/ ampoules/ pre-filled syringes and complete sample submission application form (please refer to Appendix 2) to NPRA. All products shall be submitted within 1 working day (warehouse within Klang Valley) or within 2 working days (warehouse out of Klang Valley) from the date of cold chain inspection. Products can be delivered by hand by PRH or via courier service.

PRH shall make sure that products submitted for testing adhere to the approved storage temperature requirements. Appropriate temperature monitoring devices or indicators shall be attached together with the products in order to monitor temperature during transportation. NPRA has the absolute right to reject any product that does not comply with the latest approved storage temperature.

Testing will be conducted for the first shipment of the same lot of products. However, if temperature excursion is detected during cold chain inspection for the same lot which has passed the testing previously, testing will be carried out again.

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:
   - Appearance test
   - Solubility test
   - Particulate contamination (visible particles) test on reconstituted finished product

6. CRITERIA FOR REQUESTING ADDITIONAL DATA

NPRA shall request additional data from PRH under conditions including but not limited to:

a) Insufficient information
b) Deviation of information from the approved product specification
c) Deviation of information from the approved product label
d) Unreliable data
e) Out of trend during trend analysis

7. GUIDANCE ON EXCEPTIONAL CASE

This guidance shall only apply to the emergence of crisis such as a pandemic, an epidemic, a shortage of product on the market or an urgent need e.g. due to changes in national health policy recommendations, life-threatening situations. Exceptional case application shall be supported by related documents. It is not applicable as an alternative plan to support improper supply planning and handling of stock by PRH.

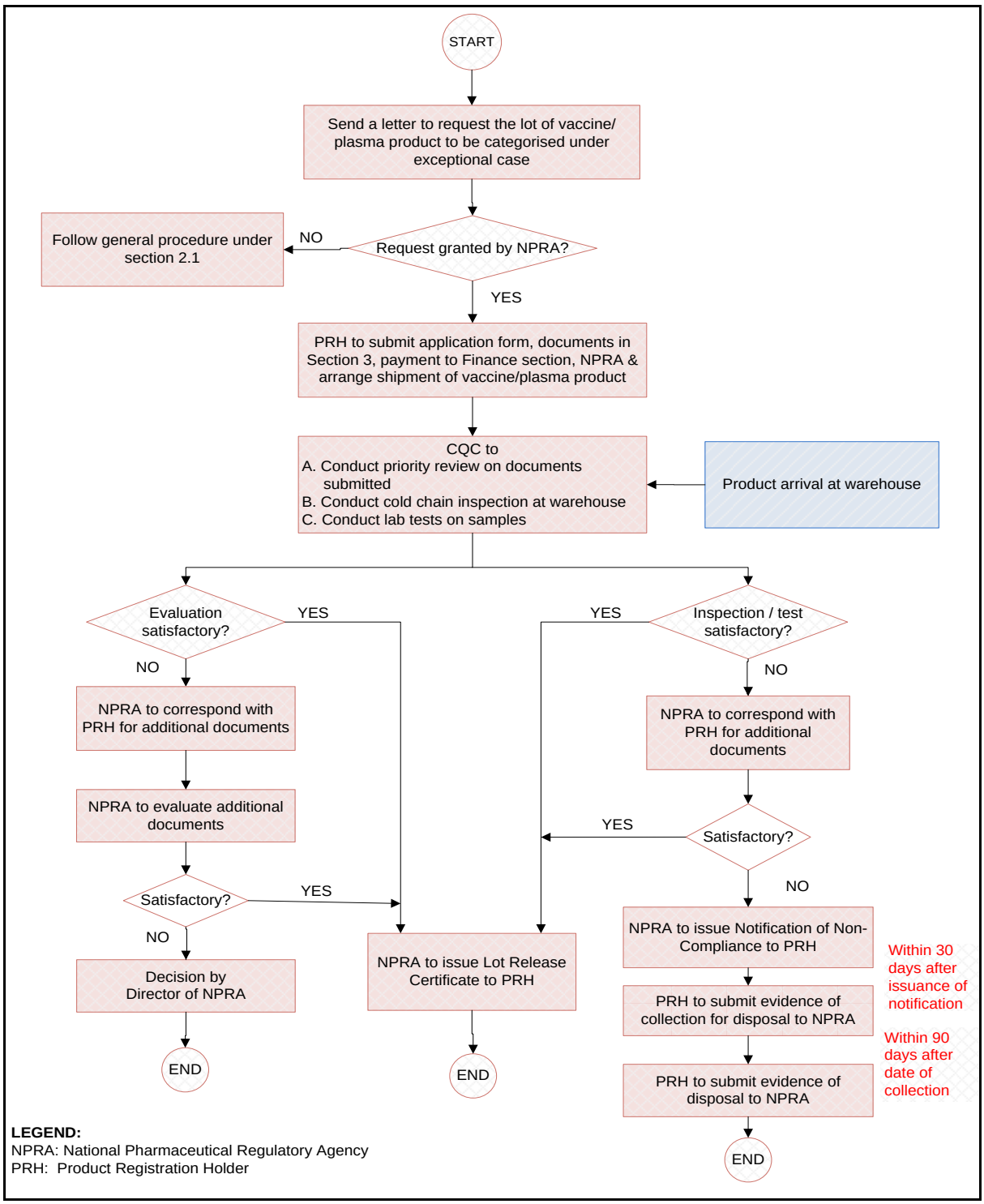
For other situations in which product need to be released immediately, it will be handled on a case-to-case basis.

General Procedure for Exceptional Case:

i. PRH sends a requisition to Director of NPRA with accompanying justification for exemption.
ii. If the request is accepted, PRH submits application form (refer to Appendix 1) and documents (refer to section 3) via email to NPRA (vaccinecqc@npra.gov.my)
iii. NPRA will respond to the email by providing confirmation on the amount of fee to be paid. Please refer to section 10 of the guidelines for further details on fees.
iv. Before product arrival, PRH makes payment to NPRA.
v. Priority review on all the documents submitted will be conducted.
vi. Upon the arrival of products at warehouse, NPRA shall conduct cold chain inspection.
vii. Soon after arrival of products at warehouse, PRH are expected to send the samples to NPRA for testing (physical appearance, solubility and particulate contamination tests)
viii. NPRA will issue lot release certificates immediately after test completed, if all the requirements have been fulfilled
ix. If one of the requirements is not met, NPRA will issue notification of non-compliance to reject the product.
x. 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 collection for disposal documentation shall be sent to NPRA within 30 days after issuance of rejection and a copy of disposal documentation shall be sent to NPRA within 90 days after the collection date.
xi. The product with the same lot number which has been previously imported, will not be repeated in evaluation and testing
xii. For cases stated in (xi), PRH will only submit the application form, import packing list, air waybill and make payment for cold chain inspection

The Process Flow 2 diagram (below) illustrates the process of lot release under exceptional case.

Process Flow 2: LOT RELEASE PROCESS FOR EXCEPTIONAL CASE



8. GUIDANCE ON NON-COMPLIANCE

8.1 Rejection Criteria for Lot Release

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

a) decision from Director of NPRA based on the supporting document, comments from another NRA (if available) and summary from evaluator
b) failure to include temperature monitoring device
c) failure to use a WHO prequalified temperature monitoring device
d) failure of the temperature monitoring device to monitor the temperature of whole journey
e) no supporting data for temperature excursion
f) release of product (including quarantined products) without approval from NPRA
g) testing fails to meet specification
h) failure to provide additional data requested
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)

8.2 Decision making

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

8.3 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 collection for disposal within 30 days after issuance of non-compliance notification and proof of disposal within 90 days after the date of collection.

8.4 Non-compliant product importer or wholesaler

Failure of importer or wholesaler to meet the requirement of Good Distribution Practice may result in a revocation of import or wholesale licence. In such cases, the PRH shall have a contingency plan to ensure that the supply of the product for the local use will not be jeopardised.

9. TIMELINE

Table 1 below shows the timeline for each activity in the lot release process.

Table 1: Activity timeline in the lot release process

Activity	Duration
Submission of application form and documents in section 2.2.1 - 2.2.5	14 working days before product arrival at warehouse
Payment for lot release	Within 14 working days before product arrival at warehouse
Submission of import packing list and airway bill (Section 2.2.6 and 2.2.7)	2 working days before product arrival
Conduct inspection	Within 2 working days after product re-palletization at warehouse
Submission of samples of lots inspected to NPRA for testing	Within 1 working day from cold chain inspection for warehouses within Klang Valley, 2 working days for outside of Klang Valley
Issuance of lot release certificate	Within 6 working days after product arrival at warehouse
Submission of evidence of collection for disposal in the event of non-compliance	Within 30 days from issuance of notification of non-compliance
Submission of evidence of disposal in the event of non-compliance	Within 90 days from date of collection for disposal

10. 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 will not be processed.

10.1 Types of Fees

The fees imposed for vaccine and plasma product lot release are shown in Table 2, Table 3 and Table 4. The evaluation fee will be waived if the same lot arrives at different times.

Table 2: Fee for vaccine lot release (West Malaysia)

Type of Vaccine	Cold Chain Inspection and Evaluation of LSP	Cold Chain Inspection only (LSP has been evaluated)
Monovalent vaccine	RM 300/vaccine lot	RM 200/vaccine lot
Polyvalent vaccine	RM 500/vaccine lot	
Combination vaccine	RM 1000/vaccine lot	

Table 3: Fee for vaccine lot release (East Malaysia)

Type of Vaccine	Cold Chain Inspection and Evaluation of LSP	Cold Chain Inspection only (LSP has been evaluated)
Monovalent vaccine	RM 600/vaccine lot	RM 500/vaccine lot
Polyvalent vaccine	RM 800/vaccine lot	
Combination vaccine	RM 1300/vaccine lot	

Table 4: Fee for plasma product lot release

Type of Plasma Product	Cold Chain Inspection and Evaluation of LSP	Cold Chain Inspection only (LSP has been evaluated)
Single	RM 500/plasma product lot	RM 200/plasma product lot
Complex	RM 800/plasma product lot	

10.2 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".

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12. APPENDIX

Appendix 1: Application Form for Lot Release

Appendix 2: Application Form for Sample Submission

NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor
Tel: 03-7883 5400
Fax: 03-7956 7075
Email: vaccinecqc@npra.gov.my

LOT RELEASE APPLICATION FORM

1. APPLICANT INFORMATION

1.1 Name & Address of Product Registration Holder	
1.2 Name & Address of Importer	
1.3 Name & Adress of Warehouse	
1.4 Contact Person	
1.5 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 Name of other manufacturer (If any)	

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 IMPORTED

4.1 Quantity in primary packaging	**4.2 Quantity in secondary packaging**	**4.3 Total no. of units per shipment** *(Specify no. of doses for vaccines)*

5. TRANSPORTATION

5.1 Arrival date	**5.2 Transit point (if any)**
5.3 Route of transportation ☐ **Air** ☐ **Ocean**	**5.4 Mode of transportation** ☐ **Active system** ☐ **Passive system**

6. DOCUMENTATION

6.1 Documents submitted	☐ **Lot Summary Protocol** ☐ **Lot Release Certificate** ☐ **Plasma Pool Certificate (if applicable)** ☐ **Certificate of Analysis of Finished Product** ☐ **Importing Packing List** ☐ **Air Way Bill / Sea Way Bill**

7. REDRESSING / REPACKING/RELABELLING INFORMATION (ONLY APPLICABLE FOR MAL NO. WITHOUT SUFFIX -R)

7.1 Does this product require redressing/repacking/ relabelling? ☐ **Yes. Refer to 7.2** ☐ **No**	**7.2 Have you obtained approval to conduct ANY redressing/repacking for the product from NPRA?** ☐ **Yes. Approval date:_____** ☐ **No**

8. 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

LR documents complete?	☐ **YES**	**Received by, date & signature**
	☐ **NO. List of pending documents:** ☐ **LRC** ☐ **COA** ☐ **AWB/SWB** ☐ **Importing Packing List** ☐ **Plasma Pool Certificate**	
SAB reference no.: **NPRA.600-2/6/1 Bil.( )**	**Amount:** ☐ **RM200 (CCI Only)** ☐ **RM300 (Monovalent V)**	**Issued by, date & signature**

Date of issuance:	☐ **RM500 (Polyvalent V/Single PP)** ☐ **RM800 (Complex PP)** ☐ **RM1000 (Combination V)** ☐ **Other: _____**	
Date of payment received:	**Receipt no.:**	**Received by, date & signature**

NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor
Tel: 03-7883 5400
Fax: 03-7956 7075
Email: uab@npra.gov.my

SAMPLE SUBMISSION APPLICATION FORM

1. APPLICANT INFORMATION

1.1 Name & Address of Product Registration Holder	
1.2 Name & Address of Importer	
1.3 Name & Address of Warehouse	
1.4 Contact Person	
1.5 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 and address of manufacturer	
2.5 MAL no.	**2.6 Lot no. of product**
2.7 Date of manufacture	**2.8 Expiry date**

2.9 Storage condition	**2.10 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**
4.2 Diluent	**4.2.1 Quantity** **4.2.2 Size (mL) per container**

5. TRANSPORTATION AND COLD CHAIN INSPECTION (CCI)

5.1 Arrival date (at warehouse)	**5.2 Date of CCI**

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.

Remarks		
Name	**Signature**	**Date**

FOR OFFICE USE ONLY

Samples received by:	**Date and time:**
Adherence to registered storage temperature: ☐ **Comply** ☐ **Not comply, remarks** _____ **Serial number (data logger/indicator):** **Mode of sample submission:** ☐ **Hand delivered** ☐ **Courier service (delivery provider and tracking number)**	