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PHARMACY AND POISONS BOARD

GUIDANCE FOR REGULATORY LOT RELEASE OF BIOLOGICAL PRODUCTS

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Abbreviations and Acronyms

The following abbreviations and acronyms are used in this guidance document:

BCG	Bacilli Calmette-Guerin Vaccine (BCG)
CQC	Centre for Quality Control
DTaP-IPV	Diphtheria-Tetanus-Pertussis-Polio combination vaccine
DRGD	Drug Registration Guidance Documents
HepB	Hepatitis B
Hib	Hemophilus influenzae
LRC	Lot Release Certificate
MAH	Marketing Authorization Holder
NCL	National Control Laboratory
NCN	Non-Compliance Notification
NNC	Notification of Non-Compliance
NQCL	National Quality Control Laboratory
NRA	National Regulatory Authority
OCABR	Official Control Authority Batch Release
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PPB	Pharmacy and Poisons Board
TRS	Technical Report Series
WHO	World Health Organization

FORWARD

This document is intended as a general guidance for application for regulalory lot release of biological products (vaccine and plasma derived medicinal products) marketed in Kenya whether manufactured in Kenya or imported.

The document has been developed in reference to WHO Guidelines for independent lot release of vaccines by regulatory authorities, accessible on (https://www.who.int/biologicals/WHO_ECBS/en/ and http://apps.who.int/medicinedocs/en . The Board shall reference the WHO guidelines in updating and implementing this guidance document in keeping with regulatory best practices.

Through the implementation of these guidance document in regulatory Lot release oversight, the Board shall achieve its function of ensuring that all vaccines and Plasma Derived Medicinal Products manufactured in, imported into or exported from Kenya conform to prescribed standards of quality safety and efficacy.

Applicants including manufacturers, Marketing authorization holders and importers are encouraged to acquaint themselves with this guidance and refer to the WHO guidelines when in doubt.

Thank you.

DR. F.M SIYOI

Chief Executive Officer, Pharmacy and Poisons Board

GLOSSARY OF TERMS

Applicant/ Marketing Authorization Holder (MAH): The company or corporate or legal entity whose name the marketing authorization has been granted. This MAH is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The party must be subjected to legislation in the country that issued the marketing authorization, which normally means being physically located in that country.

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.

Diluent: A liquid used to mix with a Lyophilized (powder) vaccine in order to reconstitute the Lyophilized vaccine and provide the final vaccine for administration.

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 analyzed via proprietary hardware, software, desktop application or through hosted database.

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)
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 colored 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 colored liquid, staining the white backing card.
Licensed Importer:	A person to whom an import license has been issued under Cap 244.
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, characterized by its intended homogeneity. The lot size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.
Lot release:	The process of NRA/ NCL evaluation of an individual lot of a licensed vaccine before giving approval for its releasing onto the market
Monovalent Vaccine:	A monovalent vaccine contains a single strain of a single antigen, e.g., Measles vaccine
Non-Compliance:	Failure or refusal to comply with a standard or a set of limits
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.
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.
Plasma Derived Medicinal Products (PDMP):	Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units.
Polyvalent Vaccine:	A polyvalent vaccine contains two or more strains/serotypes of the same antigen, e.g. Polio Vaccine.
Reference Country:	The reference country for Kenya is listed as per the latest version of Drug Registration Guidance Document by the Board
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.
Stringent Regulatory Authority:	A Medicines Regulatory Authority in a country which is: a) A member of the International Conference on Harmonization (ICH) as at 23rd October 2015 (European Union (EU) in including United Kingdom, Japan and the United States of America); or

b) An ICH Observer as at 23rd Oct 2015, being the European Free Trade Association (EFTA) as represented by Swiss Medic and Health Canada; or

c) A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

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.

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.

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

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

Acknowledgements

1. Introduction

1.1 General information

1.1.1 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.

1.1.2 Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programme, thus potentially compromising public health strategies.

1.1.3 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.

1.1.4 In addition to manufacturing complexity inherent to biological products, proper storage condition and efficient supply chain management must be ensured to preserve these products' sensitivity and limited shelf-life properties.

1.1.5 A careful independent review of manufacturing and quality control data on every lot of products is therefore necessary before use. Lot release programme form imported products will enable the Board to ascertain the safety and effectiveness of every lot of these products.

1.1.6 Regulatory Lot release of biological products by the Board is part of the regulation of these products and involves independent assessment of each lot before it is released on to the market.

1.1.7 Self-procured biologicals shall be subjected to independent assessments like locally manufactured products based on risk. As a minimum, review of manufacturers' summary protocols shall be undertaken.

1.1.8 Recognition/acceptance of release certificate from responsible NRA or national control laboratory (NCL) and/or independent Lot testing may be undertaken in addition to Lot Summary Protocol assessment.

1.1.9 Depending on the product, the Board has adopted product-specific Lot release approaches taking into consideration aspects such as nature of the product and post-marketing experience including production history and safety profile.

1.1.10 Vaccines distributed through United Nations agencies are prequalified by WHO, to ensure that the products comply with the quality and safety standards established by the Organization. therefore Lot release in shall not be undertaken for vaccines supplied through United Nations agencies,

1.1.11 However, on justifiable grounds, the Board may issue a certificate of release for vaccines on the basis of, as a minimum, a review of the lot summary protocol for the relevant lot.

1.2 Legal mandate

1.2.1 Under the Laws of Kenya (Cap 244) the Pharmacy and Poisons Board is legally mandated to exercise regulatory oversight over biological products including vaccines. To regulatory oversight, the Board as National Regulatory Authority (NRA) implements and enforces regulatory lot release" (also called official authority batch release) for biological products marketed in Kenya whether locally produced or imported.

1.2.2 Through independent lot release, the Pharmacy and Poisons Board, like for all Health Products and Technologies, will oversee the quality of biological products and to ensure the quality, safety, and efficacy/effectiveness on a lot-by-lot basis. Regulatory Lot release takes into account the nature and inherent variability of biological products.

1.2.3 The Board takes the responsibility for regulatory oversight of vaccine quality produced and authorized in Kenya, either for domestic use or for export.

1.3 Scope

1.3.1 This guidance covers regulatory Lot release of biological products encompassing Vaccines and Plasma Derived Medical Products (PDMP) manufactured and marketed in Kenya.

1.3.2 It also covers imported vaccines whether under the Kenya Expanded Programme on Immunization and vaccines that fall under non-expanded program/private importation.

1.3.3 This guidance will apply to locally manufactured biological products including vaccines under the expanded and non-expanded programs.

1.4 RLR Strategy in view Capacity consideration

1.4.1 Currently, Kenya exclusively utilizes imported vaccines for its use. This however is likely to change in the future once local manufacturing commences.

1.4.2 The Board oversights RLR of vaccines and PDMP in Kenya. In the oversight, the implementation of necessary policies, guidelines, procedures, and forms in line with the World Health Organization and major international guidelines is necessary. This oversight entails the following different approaches that have been adopted in conducting Regulatory Lot Releases.

a) review of the summary protocols only,

b) review of the summary protocols combined with Independent Lot Testing (i.e., either full or selected testing), and

c) recognition and acceptance of Lot Release Certificates (LRC) from the responsible NRA or National Control Laboratory (NCL).

1.4.3 At the minimum, RLR of locally manufactured biological products will entail a review of Lot Summary Protocols.

1.4.4 In the case of a vaccine manufactured in Kenya but not licensed and marketed in Kenya, the NRA that grants the marketing authorization shall take full responsibility for regulatory oversight. However, cooperation with the Kenya Pharmacy and Poisons Board is recommended.

1.4.5 Despite Regulatory Lot Release overseen by the Board, the quality, safety, and efficacy of a medicinal vaccine and PDMP shall remain the responsibility of the manufacturer. Manufacturers are expected to undertake full tests and take responsibility for the quality of the vaccines they manufacture and market in Kenya as specified by WHO and as prescribed in the applicable PPB procedures.

1.4.6 In addition to mandatorily carrying out a critical review of the Product Summary Protocols (PSP), Regulatory Lot Release (RLR) will require that the initial Lots of biological products manufactured locally by a new manufacturer will be tested in addition to, and independent from, manufacturer lot release testing.

1.4.7 For independent testing of routine batches, the Board may request the National Quality Control Laboratory or any other Laboratory designated for this purpose based on the level of establishment of the facility and expertise and capacity to conduct tests as described by the SOP for use of outsourced testing laboratories.

1.4.8 The Independent Testing for initial Lots for a new product or new manufacturer will be undertaken in Kenya from a suitable Laboratory with requisite capacity (the National Quality Control Laboratory or where there is no full capacity, any other suitable local Laboratory designated for ILT).

1.4.9 However, where there exists an inadequate local capacity for ILT, the samples may be tested in a laboratory outside Kenya that has been duly evaluated and formally designated for this purpose.

1.4.10 Upon confirmation of the consistency of the quality of the products through Independent Lot Testing (ILT) of the chosen parameters, regulatory lot release (RLR) of further lots may exclude ILT. Where justified, full or selected testing or no testing may be applied in RLR depending on the nature of the product and established experience.

1.4.11 Where justified and there exist capacity, the Board will undertake tests of product Lots (in part or whole) using its lab or using the National Quality Control laboratory or any other laboratory in the country or outside the country designated for this purpose.

1.4.12 The testing strategy proposed under this guide will be reviewed once local manufacturing commences and will in addition undergo regular reviews to reevaluate the need and appropriateness in the prevailing situation. Additional tests may be included, or existing tests deleted, as required.

1.4.13 Informal testing outside a planned program and without sufficient preparation unless adequately justified is discouraged, as this can generate non-relevant or misleading test results.

1.4.14 As guided by the WHO[1] the Board has the responsibility to decide on an appropriate strategy for each vaccine and PDMP subject to regulatory lot release. The decision taken by the Board will take into consideration the nature of the vaccine and PDMP, the post-marketing experience for each

[1] WHO Technical Report Series, No.978. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Geneva, World Health Organization, 2013

product (including production history and safety profile), and the availability of other independent evidence of product quality

1.4.15 When the quality of the product is proven to be consistent throughout lot release testing, PPB 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.

1.4.16 Vaccines manufactured in Kenya for domestic use and those for export are subjected to the same regulatory oversight requirements.

1.5 Communication in Regulatory Lot Release

1.5.1 There is established a clear communication between all entities involved in RLR ranging from the Pharmacy and Poisons Board, the National Quality Control Laboratory and other Quality Control Laboratories engaged by the Board based on established criteria, manufacturers and Marketing authorization holders, the Kenya Expanded program (KEPI) and other procurement agencies as well as importers.

1.5.2 The Board has established a lot release portal and an official email through which all communications (information/feedback/questions/answers/coordination) to stakeholders and entities involved in the lot release shall happen.

1.5.3 In keeping with good regulatory practices including transparency, the Board shall fully open this channel to ensure that different entities of the regulatory structure interact and exchange information effectively.

PART ONE

Regulatory Lot Release of Biological Products Manufactured in Kenya

2. Lot Release of locally Manufactured Biological

2.1 Successful implementation of regulatory Lot release oversight entails a coordinated approach involving key critical parties that play a critical role. They include the Board as the NRA and, the National Quality Control Laboratory and any other designated laboratories, the Local manufacturers in Kenya, and, for imported products, the Marketing Authorization Holders or the importers as the case may be.

2.2 Good coordination and communication are needed between the Board and the NQCL/other Laboratories designated for this purpose. Similarly, adequate interaction and effective exchange of information between Board departments are critical in Regulatory Lot Release oversight. They include marketing authorization (MA), good manufacturing practices (GMP) inspection, and postmarketing surveillance.

2.3 Any manufacturer of vaccines in Kenya shall be compliant with GMP, have the vaccines authorized to be marketed in Kenya, and meet all the post-marketing requirements including vaccine quality, safety, and efficacy.

2.4 As recommended by the WHO (Guidelines for national authorities on quality assurance for biological products should be applied), a domestic manufacturer is expected to develop a quality management system (QMS) to support lot release activities covering:

a) trained and qualified personnel,

b) management of records and documentation,

c) identification and retention of samples (when applicable),

d) use of validated test procedures,

e) written procedures,

f) internal and external audit systems, and

g) oversight procedures.

Roles of local manufacturers/MAHs

2.5 Local manufacturers play important roles in the implementation of regulatory lot release for locally produced biological products. As outlined in WHO guideline, local manufacturers are, among others, responsible for:

a) Collaborating with PPB in developing Product Summary Protocol template based on WHO product summary protocol template.

b) Assisting the Board in the technical transfer of test methods. They ensure that method transfer between manufacturer and PPB is undertaken during the product registration process to ensure a reproducible test method for regulatory lot release.

c) Providing reference standards, reagents, test kits or other necessary items in appropriate condition for regulatory lot release testing

d) Submitting sample lots in an appropriate condition, including packaging and labels and in the recommended quantities, upon PPB's request.

2.6 The Pharmacy and Poisons Board will implement regulatory Lot Release for Biological Products manufactured in Kenya in phases. For the moment, three (3)-phased Lot release approach is described below:

Table 1: The implementation pla

Prevailing condition	**Lot release Requirement**
Phase 1	
Phase 1 Lot release is applicable in any one of the following conditions: **1.** Facility and expertise to conduct tests are not fully established in the Board or in National Quality Control Laboratory/other formerly Laboratories designated for this purpose. **2.** For biological products granted emergency use marketing authorization (during a disaster)	For each lot of biological products submitted for RLR meting phase I conditions, the application shall be accompanied by a Lot of Summary Protocol and Finished Product Test Report. Upon receipt of Lot samples, the Board shall: **1.** Review the Lot Summary Protocol, **2.** Review the finished Product Test Reports, **3.** Conduct the following physical tests on the finished product: **a)** Physical appearance **b)** Solubility **c)** Particulate contamination (visible particles) **4.** Conduct other tests deemed necessary in accordance with recommendations by the World Health Organization for new vaccines wholly manufactured in Kenya using Laboratories outside Kenya.

Phase 2	
Phase 2 lot release is applicable in cases where: **1.** The facility and expertise to conduct tests are fully established in the Board or **2.** in the National Quality Control Laboratory/ other Laboratory designated for this purpose.	For each lot of biological products submitted for Regulatory Lot Release meeting Phase II conditions, the application shall be accompanied by the lot summary protocol. Upon receipt of Lot samples, the Board shall: **1.** Review the Lot Summary Protocol **2.** Conduct the following physical tests on the finished product: **a)** Physical appearance **b)** Solubility **c)** Particulate contamination (visible particles) **3.** Conduct other tests deemed necessary in accordance with recommendations by the World Health Organization (WHO)
Phase 3	
Phase 3 lot release is applicable in cases where: confirmation of the quality of the product through consistent test results for chosen parameters obtained from phase 2 lot release is considered adequate in providing assurance of product quality.	For each lot of biological products submitted for Lot Release under phase 3 conditions, the application shall be accompanied by the lot summary protocol. Upon receipt of samples, the Board shall: **1.** Review the lot summary protocol **2.** Conduct selected lot release tests from phase 2, based on a risk-based approach and in accordance with procedures for lot release.

2.7 The Board recognizes that regulatory lot release testing of biological products under inappropriate conditions may generate inaccurate data and lead to incorrect decisions. This is because, like many biological assays, vaccines and PDMP are highly variable, and repetitive testing can result in "false" OOS results, which then require extensive investigation and delay vaccine supply.

2.8 Therefore, the decision to repeat tests on a lot that has already been tested by another competent authority will be considered only in exceptional cases and will be carefully considered in light of all available information.

2.9 In this regard, where applicable, Regulatory Lot Release will leverage reliance in different relevant forms including acceptance and recognition,

networking and work-sharing with other NRAs/NCLs while ensuring that independent laboratory testing when conducted, is in accordance with the principles defined by the WHO. *(Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No.978).*

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3. General RLR procedures for locally manufactured Biological Products.

1.1 Scope

1.1.1 These procedures RLR of vaccines and Plasma Derived Medicinal Products for human use that will be manufactured and marketed in Kenya

1.1.2 Vaccines will include all vaccines under the Expanded Programme on Immunization and non- Expanded Programme on Immunization vaccines as well as imported and domestically-produced vaccines.

1.2 Responsibility and authority

1.2.1 The Chief Executive Officer is the authorized officer with overall authority to declare recognition and acceptance of lot release certificates from the recognised responsible NRA or National Control Laboratory (NCL) and for Signing and issuing the regulatory lot release certificates. The duty of signing certificates of lot release may be delegated but not the authority.

1.2.2 The Director Medical Products and Health Technologies is responsible for:

a) the review/coordinating the review of Lot summary protocols and/or designating an individual identified to possess product understanding to review the Lot summary protocol.

b) inspecting/coordinating the inspection for compliance with Good Manufacturing Practices of vaccine manufacturing facilities

c) ensuring/coordinating an effective post-marketing surveillance activity regarding lots of vaccines in circulation: continued post-authorization monitoring

1.2.3 The Director Quality Control or his designate is responsible for:

a) coordinating the independent testing (full or partial testing),

b) determining what type of test to be performed (if any) and,

c) designating an individual identified to possess an understanding of laboratory control methods to evaluate the Lot summary report and the Lot test report (for phase 1 only),

d) Signing and issuing the regulatory lot release certificates.

1.2.4 A Designated PPB QC analyst is responsible for screening an application to confirm completeness and compliance with requirements and,

forwarding the application to the directorate of Medical products and Health Technologies for LSP review upon compliance screening requirements.

1.3 General procedures

1.3.1 Upon payment of the application fee, the Marketing Authorization Holder (MAH) submits an application in the PPB RLR portal (https://lotrelease.pharmacyboardkenya.org) and attaches applicable documents.

1.3.2 Any questions or clarification regarding and responses on applications are forwarded via email to the Pharmacy and Poisons Board (lotrelease@pharmacyboardkenya.org). Please refer to Section 4 of this guidance for further details on documents to be submitted.

1.3.3 An autogenerated email shall be sent confirming receipt of a successful application and, where applicable, the number of samples and test items for testing to be sent to the Board.

1.3.4 Upon successful application, the Board shall perform an evaluation of the Lot Summary Protocol and, for Phase 1 only, conduct an evaluation of Lot Test Report for which regulatory lot release is being sought.

1.3.5 The MAH submits sample for testing to PPB laboratory as may be requested accompanied by a duly filled test request form downloadable from the portal (https://lotrelease.pharmacyboardkenya.org)

1.3.6 Where applicable, the Board will conduct or coordinate an independent lot testing of the samples from the designated laboratories with established capacities (testing facility and expertise) in accordance to Lot release LAB/QCL/PCL/SOP/034 (refer to implementation plan under approach to lot release in Kenya section).

1.3.7 Upon fulfillment of all requirements and confirmation that the lot meets all requirements, the Board will issue Lot Release Certificates. Please refer to Section 8 of the guideline for further details on the timeline.

1.3.8 Failure to comply with Lot Release requirements will lead to the issuance of Non-Compliance Notification (NCN) and the product will be rejected.

1.3.9 In the event of non-compliance, it is the sole responsibility of the MAH to ensure proper and safe disposal of the product. A copy of disposal documentation shall be sent to the Board within 120 days following issuance of NNC.

4. Requirements for Regulatory Lot release documentation for locally manufactured

4.1 General considerations

4.1.1 The following constitute the necessary documents to be submitted for independent/regulatory lot release application in Kenya.

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)

f) Lot release certificate for vaccines from responsible NRA in the case of imported bulk vaccines for manufacturing in Kenya.

4.1.2 All the documents shall be written in English or in Swahili only and where applicable must be clearly tagged (indexed and labeled).

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

4.1.4 Applications including documentation submitted shall comply with good documentation practices.

4.2 Application Form

4.2.1 An online application form is adopted for all applications for Lot release. The form is available on PPB official website (refer to Annex 1 for form format). All applications shall be made only through the portal (https://lotrelease.pharmacyboardkenya.org)

4.2.2 Incomplete forms and/or applications shall not be processed.

4.2.3 The Lot number (as it appears in final packaging) stated on the application form must be identical to the lot number on the lot summary protocol and certificate of analysis.

4.3 Lot Summary Protocol (LSP)

4.3.1 As defined by WHO Guidelines, lot summary protocol is a document summarizing all manufacturing steps and test results for each lot produced and which is certified and released by the responsible person of the manufacturing company.

4.3.2 The test results included in the lot summary protocol shall include the test specifications and date the test was conducted.

4.3.3 The evaluation of the Lot Summary Protocol will be based on the product dossier which was evaluated and approved by the Board during product registration and variation submission.

4.4 Plasma Pool Certificate (For Plasma Derived Medicinal Products)

4.4.1 Plasma pool certificate submitted towards lot release application should be a lot release certificate issued by the responsible NRA/NCL from the country of origin.

4.4.2 In cases where the NRA of the country of origin does not provide a plasma pool certificate, plasma pool certificates from any one of the Stringent Regulatory Authorities will be accepted.

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

4.5.1 All release tests and its specification shall be based on product dossier as evaluated and approved by the Board during product registration.

4.5.2 Certificate of analysis for finished product and diluent shall contain at least 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 performed

g) Test specification

h) Test results

i) Declaration whether the Lot complies or not

j) Approval from responsible person & the date

4.5.3 Any other information the company wishes to include shall have to be approved by the Board.

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

4.6.1 Test report with raw data shall be in a scanned copy of the original document attached together with the application form or shared in a link which would allow the Board to access the document.

4.6.2 The finished product test report with raw data 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 the 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 the responsible person

5. Product Testing

5.1 Testing of biological products shall be conducted in accordance with WHO Technical Report Series, No.978. *Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities. Geneva, World Health Organization, 2013*

5.2 Assessment of vaccine lots will be undertaken when this can add value to the information provided in the summary protocol if the testing is performed by experienced, competent, and skilled laboratory staff supported by a QMS and when there exist appropriate laboratory facilities.

5.3 Whether the tests are performed by PPB laboratory or by the National Quality Control Laboratory or by any of the contracted laboratories, the final decision on the test results lies with the Pharmacy and Poisons Board.

5.4 Implementation of a lot release testing policy in Kenya will be considered by the Board once the prerequisites noted in section 5.2.2 of the WHO guidelines,[2] have been addressed. Testing under inappropriate conditions may generate inaccurate or misleading data and cause unnecessary delay or rejection of lots that meet specifications.

5.5 In its RLR oversight of new manufacturers, the Board adopted independent lot testing, with the objective of monitoring key product parameters, ensure the consistency of production, and verify the manufacturer's test results.

5.6 In Phase 1 (and where justified, in Phase 2 and 3), the following physical test shall be conducted by PPB on the finished product:

a) Physical appearance

b) Solubility

c) Particulate contamination (visible particles)

5.7 For Phase 2 and Phase 3, the following tests may be conducted by PPB on the finished product:

[2] Guidelines for national authorities on quality assurance for biological products. In: WHO Expert Committee on Biological Standardization. Forty-second report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822), Annex 2.

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)

5.8 Under justifiable circumstances, the Board may accordingly design Independent Lot release tests to ensure the safety profile of the biological product.

5.9 Under these exceptional circumstances, the Board:

a) may receive samples before manufacturers have completed their product testing for the purpose of parallel testing.

b) the selection of lot release tests will be established based on recommendations published by World Health Organization (WHO).

6. Sample Submission

6.1 General considerations.

6.1.1 Products shall be submitted within 1 or 2 working days following successful submission of application.

6.1.2 while handling and transporting the biological products, the applicant (manufacturer/MAH) shall be responsible for ensuring that samples submitted for testing adhere to the approved storage temperature of the respective product.

6.1.3 Samples delivered to the Board from the applicant shall be accompanied by an appropriate temperature monitoring device or indicator such as temperature data loggers for the purpose of recording and monitoring the temperature throughout the entire transportation journey.

6.1.4 Considering the conditions of delivered samples, the Board reserves the right to reject any samples. Delivered samples that do not comply with the latest approved storage temperature conditions will not be received.

6.1.5 When a delivered sample is not received, the board may request for additional samples to conduct independent lot release testing if deemed necessary.

6.2 Sample Submission

6.2.1 The number of samples to be submitted for lot release testing depends on the profile of each type of the product.

6.2.2 Applicants (manufacturer/MAH) shall provide the quantities of finished products with diluents (if applicable) requested in the autogenerated application receipt mail.

6.2.3 For the purpose of independent lot release, not less than three (3) containers/vials/ampoules/pre-filled syringes shall be submitted to the Board upon submission of an online application.

6.2.4 Products can be delivered by hand or via courier service.

6.2.5 Upon delivery, the applicant (manufacturer/MAH) or representative submitting the lot samples shall fill and sign on the test request form or in the case of courier delivered, a duly filled test request form by the MAH/ applicant shall accompany the samples.

6.2.6 A copy of the test request form shall be retained by the laboratory.

6.2.7 The type of screening tests to be conducted will depend on the dosage form of the finished products as described belo

Solution/ liquid:	a) Appearance test b) Particulate contamination (visible particles) test
Freeze dried/ Lyophilized & frozen solution:	c) Appearance test d) Solubility test e) Particulate contamination (visible particles) test on reconstituted finished product

7. Non-Compliance

7.1 Lot Rejection Criteria of locally manufactured Biological Products

7.1.1 Biological products considered to be non-compliant following independent regulatory lot release shall be rejected.

7.1.2 Rejection shall be based on one or more of the following conditions:

a) testing fails to meet specification

b) forgery in test reports submitted (for Phase 1)

c) failure to provide testing reagents, reference standards, reagents, test kits, or other necessary items for testing (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 the product (including quarantined products) without approval from the Board

h) testing specification and test method are not updated accordingly or updated without the Board's approval

- *approval for product variation by the Board shall be received before the submission of lot release application*

i) the product information leaflet and label are not updated accordingly or updated without PPB's approval

- *approval for product variation by the Board shall be received before the submission of the lot release application*

j) the decision from the Chief Executive Officer of PPB based on the supporting document, comments from another NRA (if available), and summary from the evaluator

7.2 Decision making

7.2.1 Whenever a lot of biological products have been considered non-compliant, a decision shall be made to reject the Lot and the non-compliance notification (NCN) issued.

7.2.2 The reasons for non-compliance will be clearly stated in the non-compliance notification.

7.3 Decision review and appeal

7.3.1 If an applicant/manufacturer/MAH feels aggrieved by the decision of the Board to reject a Lot, he can appeal against the decision requesting a review of the decision.

7.3.2 An appeal for review shall be submitted to the Chief executive officer.

7.3.3 Upon decision by the CEO sustaining rejection of the Lot, the applicant may appeal to the Board.

7.3.4 All decisions made by the Board shall be final and no further appeal shall be allowed in any circumstances.

7.3.5 In the interest of the public and, in the quest to fully implement transparency and accountability aspects of good regulatory practice the Board will publish the list of product batches that passed or failed NRA lot release

7.4 The fate of non-compliant products

7.4.1 In the event of non-compliant products, the Board shall ensure the supply of the product for local use will not be affected.

7.4.2 The Board shall ensure that non-compliant products are not released onto the market and will be disposed of in Kenya.

7.4.3 The Board shall provide appropriate proof of disposal within 120 days after issuance of non-compliance notification.

7.4.4 The current performance indicators for national lot release activities

7.4.5 The mechanism for the independent lot release procedure is public, clear, and transparent regarding requirements and timelines so that the process is completed smoothly and in a timely manner. The Board has established and implemented performance indicators along the entire national lot release activity chain to include:

a) percentage of nonconforming results attributable to the lab and/or human error discrepancy obtained for the annual lots.

b) Compliance with timelines in the service charter, this guideline and shred publicly in the websites.

7.4.6 Analyses of the measured indicators along with the investigations done to identify trends or abnormalities shall be maintained.

7.4.7 Documentation for follow-up of any observed abnormalities, including justifications for any identified abnormalities as well as any process optimizations introduced to avoid recurrence shall be maintained.

8. Timeline

Phase 1

8.1 Upon successful application for Lot release and payment of prescribed fees, the Board will:

8.1.1 send an acknowledgment note/email within one (1) hour.

8.1.2 Screen the application within 24 working hours of application

8.2 Upon screening of the application and in the view of the Board:

8.2.1 the application is incomplete or, there are queries, inconsistencies, or clarification regarding the application an email to the applicant will be sent within 24 hours of screening clearly stating the matter

8.2.2 The applicant/MAH is unable to provide the needed clarification or the application shall be rejected an email to the applicant will be sent within 24 hours clearly stating the reason for rejection.

8.2.3 The application is complete, the application will be approved for an evaluation immediately without further communication to the applicant/MAH. However, the application status will change to "approved for evaluation".

8.3 Once a complete application (comprising the documents, samples, and fees specified above) has been received, screened, and approved for evaluation, the Board will evaluate the documents and the sample within 14 calendar days.

8.4 Upon successful evaluation of application and sample, and has determined that all the Lot Release requirements have been fulfilled a Lot release certificate shall be issued within 24 hours of the determination.

8.5 An email shall be sent within 24 hours at any stage of the review of application documents if, in the view of the Board, the documents are determined not to be accurate[3].

8.6 Upon determination that a Lot of a biological product is non-compliant and a decision made to reject the Lot, non-compliance notification (NCN) will be issued within 24 hours.

[3] The Board considers the term "accurate" to means that the data are correct, truthful, complete, valid and reliable.

8.7 Evidence of disposal of a Lot considered non-compliant and for which NCN had been issued shall be issued to the Board within 90 days of the NCN issue.

Consider table below for timelines:

Table 2 : Timelines

SN	Description of Activity	Timeline
1.	Acknowledgment of successful application	Within 1 hour
2.	Screening	Within 24 hours of successful application
3.	Notification about a) incomplete or, b) queries or, c) inconsistencies or, d) clarification regarding the	Within 24 hours of screening.
4.	Notification of rejection of application when an applicant/MAH is unable to provide the needed clarification	Within 24 hours
5.	Submission of samples	Within 24 hours of submission of application
6.	Evaluation of a screened application and submitted samples	Within 14 calendar days
7.	Issue of Lot release upon successful evaluation of application and submitted sample and having confirmed that all the Lot Release requirements have been fulfilled	Within 24 hours.
8.	Notification of rejection at any stage of the review of application and submitted sample under evaluation upon determination that the documents are not accurate	Within 24 hours of determination
9.	Issue of a non-compliance notification (NCN) upon determination that a Lot of a biological products is non-compliant and a decision has been made to reject the Lot	within 24 hours.
10.	Submission of evidence of disposal of a Lot considered non-compliant and for which NCN had been issued	within 90 days of the NCN issue.

9. Fees

9.1 Every application for independent regulatory Lot release shall be accompanied by a prescribed fee.

9.2 Payment made shall NOT be REFUNDABLE once the application has been submitted and a payment notice has been issued.

9.3 Applications without the correct fees paid will not be processed.

9.4 The fees levied for regulatory Lot release shall be updated on the PPB website.

9.5 The fees imposed for Phase 2 and Phase 3 are product-specific and shall be updated on the PPB website to include the fees for each type of product and test.

9.6 The fees shall automatically be levied once the applicant selects the product at the time of application.

9.7 The processing fee and any other charges shall be paid in the form of a banker's cheque made payable to the Pharmacy and Poisons Board.

PART TWO

Guidance Document for Lot Release of imported Biological Products

10. Introduction

10.1 General information

10.1.1 Regulatory Lot release of imported biological products by the Board is part of the regulation of these products and involves an independent assessment of each lot before it is released on to the market.

10.1.2 Self-procured biologicals shall be subjected to independent assessments like locally manufactured products based on risk. As a minimum, a review of manufacturers' summary protocols shall be undertaken.

10.1.3 Recognition/acceptance of release certificate from responsible NRA or national control laboratory (NCL) and/or independent Lot testing may be undertaken in addition to Lot Summary Protocol assessment.

10.1.4 Depending on the product, the Board has adopted product-specific Lot release approaches taking into consideration aspects such as the nature of the product and post-marketing experience including production history and safety profile.

10.1.5 Lot release in Kenya shall not be undertaken for vaccines supplied through United Nations agencies, because such products are prequalified by WHO and released by the responsible NRA/NCL. PPB will recognize the release by the responsible NRA/NCL.

10.2 Legal mandate

10.2.1 Under the Laws of Kenya (Cap 244 Sec (3B) (2b)), the Pharmacy and Poisons Board is legally mandated to implement and enforce lot release (also called official authority batch release) for biological products marketed in Kenya whether locally produced or imported.

10.2.2 Through independent lot release, the Pharmacy and Poisons Board, like for all Health Products and Technologies, can oversee the quality of biological products and ensure the quality, safety, and efficacy/effectiveness on a lot-by-lot basis. Independent/Regulatory Lot

10.3 Scope

10.3.1 This guidance document is designed to assist MAH, Importers, and distributors of imported Vaccines and plasma-derived medicinal products in Kenya when applying for regulatory lot release for imported vaccines and PDMP.

11. Strategy and Capacity consideration

11.1 The Board has developed and implemented the necessary policies, guidance documents, procedures, and forms in line with World Health Organization and major international guidelines. In the case of vaccines and blood products (plasma-derived medicinal products (PDMPs) and related in-vitro diagnostics (IVDs)), different approaches are currently used for conducting lot release.

11.2 Regulatory release of imported biological products (vaccines and PDMPs) has been designed to comprise:

a) Review of manufacturer's summary protocol based on product dossier which as assessed and approved by the Board during product registration

b) Review of Lot Release Certificate (LRC) from responsible National Regulatory Agency (NRA) or National Control Laboratory (NCL) of Country of Origin recognized by the Board.

c) Inspection upon arrival in the warehouses

d) Test conducted on the products (refer to section 15)

11.3 To ensure compliance and avoid rejection of applications, MAHs are expected to ensure the products comply with Marketing authorization and all the product registration information. If there are any changes to the products, MAHs are expected to obtain approval for variation before submission of documents.

11.4 For independent Lot release testing, the Board may request the National Quality Control Laboratory or any other Laboratory designated for this purpose based on the level of establishment of the facility and expertise to conduct tests as described by the LAB/QCL/PCL/SOP/034 for use of outsourced testing laboratories.

11.5 As guided by the WHO[4], PPB has the responsibility to decide on an appropriate strategy for each vaccine and PDMP subject to regulatory lot release. The decision should take into consideration the nature of the vaccine, PDMP, and blood products related

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

12 General procedures

12.1 Upon payment of the applicable fee, the Marketing Authorization Holder (MAH) submits an application in the PPB portal (https://lotrelease.pharmacyboardkenya.org) and attaches applicable documents. Please refer to Section 20 of the guideline for further details on fees.

12.1.1 Any questions or clarification regarding and responses on applications are forwarded via email to the Pharmacy and Poisons Board (lotrelease@pharmacyboardkenya.org). Please refer to Section 13 of the guideline for further details on documents to be submitted.

12.1.2 An autogenerated email shall be sent confirming receipt of a successful application and, where applicable, the number of samples and test items for testing to be sent to the Board.

12.1.3 Upon successful application, the Board shall perform an evaluation of lot summary protocol of the lot for which regulatory lot release is being sought

12.1.4 Within 3 days of receipt of the product Lot in the MAH/Importer/wholesaler warehouse, designated PPB staff shall conduct a cold chain inspection.

12.1.5 The MAH submits samples for testing to PPB laboratory as may be requested. MAHs/importers/wholesalers are expected to send samples to PPB for lab testing within 2 working days after cold chain inspection.

12.1.6 Where applicable, the Board will conduct or coordinate the independent lot testing of the samples from the designated laboratories with established capacities (testing facility and expertise) in accordance with Lot release SOP.

12.1.7 Upon fulfillment of all requirements and confirmation that the lot meets all requirements, the Board will issue lot release certificates. Please refer to Section 19 of the guideline for further details on the timeline.

12.1.8 The product with the same lot number which has been previously imported, will not be subjected to repeated evaluation and testing in which case MAHs/importers will only submit the application form, import packing list, air waybill, and make payment for cold chain inspection.

12.1.9 Failure to comply with Lot Release requirements will lead to the issuance of Non-Compliance Notification (NCN) and the product will be rejected.

12.1.10 In the event of non-compliance, it is the sole responsibility of the MAH to ensure proper and safe disposal of the product. A copy of disposal documentation shall be sent to the Board within 120 days following issuance of NNC.

13 Documentation Requirements for Lot release of imported biological products

13.1 General considerations

13.1.1 The following constitute the necessary documents to be submitted for independent/regulatory lot release application in Kenya.

a) Application form (filled online)

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 (maybe submitted 2 working days before product arrival)

g) Air Waybill (may be submitted 2 working days before product arrival).

13.1.2 All the documents shall be written in English or Swahili only and must be tagged (indexed and labeled).

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

13.1.4 Applications including documentation submitted shall comply with good documentation practices.

13.2 Application Form

13.2.1 An online application form is adopted for all applications for Lot release. The form is available on PPB official website (refer to Annex 2 for form and format). All applications shall be made only through the portal (https://lotrelease.pharmacyboardkenya.org)

13.2.2 Incomplete forms will not be processed and/or applications shall not be processed.

13.2.3 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.

13.3 Lot Summary Protocol (LSP)

13.3.1 As defined by WHO Guidelines, lot summary protocol is a document summarizing all manufacturing steps and test results for each lot produced, certified, and released by the responsible person of a manufacturing company.

13.3.2 The test results included in the lot summary protocol shall include the test specification and date the test was conducted.

13.3.3 The evaluation of the Lot Summary Protocol will be based on the product dossier which has been evaluated and approved by the Board during product registration and variation submission.

13.3.4 Critical data shall be reviewed from each lot of vaccines to assure the consistency of quality of each manufactured lot, obtain confidence in the claimed strength of active components; and assess the validity and accuracy of the tests performed.

13.4 Lot Release Certificate (LRC)

13.4.1 The Lot release certificate submitted towards the lot release application should be a lot release certificate issued by the responsible NRA/NCL from the country of origin.

13.4.2 In exceptional cases where the responsible NRA/NCL does not provide a Lot release certificate, a Lot release certificate issued by any of them from any one of the Stringent Regulatory Authorities will be accepted.

13.5 Plasma Pool Certificate (For Plasma Derived Medicinal Products)

13.5.1 Plasma pool certificate submitted towards lot release application should be a lot release certificate issued by the responsible NRA/NCL from the country of origin.

13.5.2 In exceptional cases where the responsible NRA/NCL of the country of origin does not provide a plasma pool certificate, plasma pool certificates from any one of the Stringent Regulatory Authorities will be accepted.

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

13.6.1 All release tests and its specification shall be based on product dossier which has been evaluated and approved by the Board during product registration.

13.6.2 Certificate of analysis for finished product and diluent shall 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 performed

g) Test specification

h) Test results

i) Declaration whether the Lot complies or not

j) Approval from responsible person & the date

13.7 Importing Packing List

13.7.1 MAHs/importers shall provide the details of importing packing including:

a) Product name

b) Lot number

c) Numbers and types of package

d) Quantity

13.7.2 The importing packing list must be submitted to the Board working days prior to product arrival.

13.8 Air Waybill (AWB)

13.8.1 MAHs/Importers shall provide air waybill details for vaccines and PDMPs transported via air route including:

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

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

14 Guidance On Temperature Monitoring

14.1 General guidance

14.1.1 Biological products should always be transported and stored in their respective recommended condition with continuous monitoring since a deviation of temperature or incorrect storage condition may affect the quality, efficacy/effectiveness, and subsequently the safety of the product.

14.1.2 Products should be transported in either active or passive packaging systems.

14.1.3 Although the choice of a packaging system for the international shipment of temperature-sensitive products is at the discretion of the manufacturer MAH, the risk profile of the product should be used to determine the nature of the packaging chosen.

Types of Packaging Systems

Active System:	Actively powered systems employ electricity or another fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation. 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.
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. These systems comprise the product surrounded by thermal media, which is prepared to specific temperatures and encapsulated within an insulation material.

14.2 Temperature monitoring devices

14.2.1 Temperature indicators such as electronic data logging monitor (EDLM) and vaccine vial monitors (VVM) will serve as a quick reference to help determine whether the shipment has been exposed to temperatures outside the recommended range.

EDLM:	Records data digitally over time or in relation to location either with a build-in or external instrument or sensor. Is the preferred temperature indicators as it provides the most reliable and accurate record of temperature conditions for active and passive packaging systems.
CCM, VVM & FI:	There sole or combined use for international shipments are no longer recommended. They may be used to supplement EDLM included in the shipment.

14.2.2 A shipment of biological products imported into Kenya should have at least one EDLM in each and every international shipping carton or pallet.

14.2.3 EDLM used for monitoring temperature of imported biological products should have the a “start” function to activate the device at the time the carton is being loaded and a “stop” function to allow the recipient to stop the recording when the product arrives at its destination

14.2.4 Be it as it may, manufacturers/MAHs/importers should 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

14.2.5 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. They may be used to supplement EDLM included in the shipment.

14.2.6 Whenever CCMs, VVM and FI are used to augment EDLMs, the temperature recorded by the EDLMs shall be referred in the event of a

discrepancy in temperature data recorded by the different temperature monitoring devices.

14.2.7 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)

14.2.8 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.

14.2.9 In exceptional cases where dry ice continues to be used, one cold chain monitor card per shipping carton instead of an electronic device should be included in line with WHO recommendations.

14.3 Packaging and shipping validation

14.3.1 The manufacturer/MAH is required to submit packaging and shipping validation documents to PPB:

a) before a product is transported to Kenya or

b) in cases where changes are introduced either in the current/registered packaging or,

c) in cases where there are changes in shipment procedures.

Packaging & shipping 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 hours9.
Conditions of validation	Validation should be performed under highly controlled-conditions to demonstrate that

processes, methods and systems consistently produced results meeting predetermined criteria.

14.3.2 The validation data submitted must be sufficient to demonstrate that the product remains stable at the recommended storage condition.

14.3.3 Packaging and shipping 'Validation' is the confirmation that temperatures inside the shipping containers of every temperature-sensitive product shipment remain within the defined temperature range for a period of 48 hours9.

14.3.4 Validation should be performed under highly controlled conditions to demonstrate that processes, methods, and systems consistently produced results meeting predetermined criteria.

14.3.5 Manufacturers/MAHs must document the validation of their packaging. Validation data should be produced for 3 successful consecutive tests at the defined ambient temperatures minimum of 48 hours.

14.3.6 Any changes introduced either in the packaging or the shipment procedures after packaging and shipping validation has been performed, the shipment must be re-validated.

14.3.7 The shipment validation documents to be submitted shall include the report of validation and a cover letter stating the mode of transportation. 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)

14.3.8 The validation report has to be embossed with the company's official seal to showcase certification and be signed by authorized 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).

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

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

14.4 Transport of Diluent

14.4.1 Thus, the manufacturer's guidance for specific temperature requirements shall be followed to ensure diluent is transported and handled in recommended storage conditions.

14.4.2 All diluents shall not be frozen, not even during transport. Diluent that has been frozen should not be used because of the risk of a crack in the vial/ampoule that may cause contamination.

14.4.3 If diluent contains an active ingredient, the diluent may be damaged by freezing. If diluents are found to be frozen, appropriate action should be taken to isolate and dispose of the vials according to a decision by Pharmacy and Poisons Board.

14.4.4 Some diluents may be sensitive to heat or freezing and may require transportation and storage in the cold chain.

14.4.5 There are different types of diluents, and each is specific to the product that it accompanies.

Pharmacologically inactive	The most common diluent is pharmacologically inactive aqueous solution (Sodium Chloride; NaCl) or water for injection; this type of diluent is used to reconstitute a lyophilized 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.

Pharmacologically active

On other hand, some liquid diluents are pharmacologically active that contain live vaccine and thus must be kept in the refrigerator16. These include liquid vaccines that are used to reconstitute a lyophilized component of a polyvalent vaccine (such as liquid DTaP-IPV) vaccine that is used to reconstitute a Lyophilized Hib vaccine).

14.5 Handling of Temperature Excursion

14.5.1 It is the responsibility of manufacturer/MAH to assess if the available stability data are sufficient to address the potential temperature excursions.

14.5.2 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.

Temp excursion

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

14.5.3 Manufacturer/MAHs should clearly understand what the consequences of temperature excursions are during products storage and transport from manufacturing site to Kenya.

15 Guidance on Product Testing

15.1 General guidance

15.1.1 The Board is responsible for regulatory Lot release. It oversees the conduct of independent Lot testing to monitor key products parameters, consistency of production and to verify test results of the manufacturer.

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

15.1.3 Test conducted on the product should comply with the latest approved product specification approved by the Board.

15.2 Guidance on sample submission

15.2.1 For the purpose of independent regulatory Lot release, the manufacturer/MAHs shall provide not less than 3 finished product containers/ vials/ ampoules/ pre-filled syringes with diluents (if applicable) alongside a duly completed sample submission form to the Board. The form is downloadable on ppblotrelease@pharmacyboardkenya.org in the format attached herewith as annex xxx

15.2.2 All products shall be submitted within 2 working day from the date of cold chain inspection.

15.2.3 manufacturers/MAHs shall submit samples of finished products and diluents (where appropriate) by hand or via courier service.

15.2.4 Manufacturers/MAHs ensure that products submitted for testing adhere to the manufacturer-specified and PPB-approved storage temperature requirements.

15.2.5 Appropriate temperature monitoring devices or indicators shall be attached together with the products in order to monitor temperature during transportation.

15.2.6 The board reserves the right to reject any product that does not comply with the latest approved storage temperature.

15.2.7 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.

7.1.1 Type of testing conducted depends on the dosage form of the finished products:

Solution/ liquid:	a) Appearance test b) Particulate contamination (visible particles) test
Freeze dried/ lyophilised:	a) Appearance test, b) Solubility test c) Particulate contamination (visible particles) test on reconstituted finished product

16 Criteria for Requesting Additional Data

16.1 The Board may request additional data from manufacturers/MAHs under specific conditions including:

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

16.2 Applicants are duty bound to provide any additional information requests

17 Exceptional provisions and guidance during public health emergencies

17.1 General

17.1.1 Public health emergencies shall be construed to include pandemics, epidemics, a shortage of products on the market, or an urgent need for biological products due to changes in national health policy recommendations or life-threatening situations.

17.1.2 These exceptions shall not be applicable as an alternative plan to support improper supply planning and handling of stockouts by manufacturers/MAHs or for all other cases requiring prompt Lot release.

17.1.3 Requests for immediate Lot release of biological products will be handled on a case-to-case basis.

17.1.4 Under this exceptional case, application shall be supported by related documents.

17.2 General Procedure for Exceptional Case:

17.2.1 Manufacturer/MAHs shall make an application to the Board requesting for exemption from the routine procedure with sufficient justification and attaching any documents supporting the request via PPB portal Lot release portal (http://ppblotrelease@pharmacyboardkenya.org).

17.2.2 Payment of application fee indicated in the portal shall be paid at the application stage before the arrival of the Lot

17.2.3 An auto-generated email will be sent confirming receipt of the application and confirming the fee to be paid.

17.2.4 The Board shall conduct a review of the application and all documents submitted as justification in view of the prevailing emergency situation or public health concerns on a priority basis.

17.2.5 Upon the arrival of biological products at the warehouse, manufacturer/MAH/importer shall conduct cold chain inspection and send the samples to the Board Lot release testing (physical appearance, solubility, and particulate contamination tests)

17.2.6 Upon convincing itself that the application for exemption from Lot release routine procedure in the interest of justifiable public health

concerns, and upon completion of tests and confirming that the product complies with all test requirements, the Board will issue lot release certificates immediately.

17.2.7 If one or all of the requirements is not met, the product will be rejected and a notification of non-compliance issued.

17.2.8 Upon receipt of NCN, the manufacturer/MAH/importer shall institute appropriate measures to safely dispose of the non-complying product. It is the sole responsibility of the manufacturer/MAH/importer to ensure proper and safe disposal of a non-complying product.

17.2.9 A copy of disposal documentation comprising collection for disposal and destruction documentation shall be sent to the Board within 90 days after issuance of NCN.

17.3 General Procedure for Exceptional Case:

17.3.1 The biological product with the same Lot number previously imported, will not be repeated in evaluation and testing.

17.3.2 In the event that part Lot importation is involved (as provided in 9.3.1), the manufacturer/MAH/importer will only fill the application form online, attach the import packing list, air waybill and make payment for cold chain inspection

18 Guidance on Non-Compliance of imported biological products.

18.1 Rejection Criteria for Lot Release

18.1.1 The Board shall, upon review of an application and documentation submitted for Lot release of an imported biological product, reject the Lot and issue NCN under conditions including but not limited to:

a) Supporting documentation that is considered not to be accurate.[5]

b) Comments/advisory/decision/ from another NRA (if available)

c) Failure to include a temperature monitoring device

d) Failure to use a prequalified temperature monitoring device

e) Failure of the temperature monitoring device to monitor the temperature of the whole journey

f) No supporting data for temperature excursion

g) Release of the product (including quarantined products) without approval from the board

h) Testing fails to meet specification

i) Failure or refusal to provide additional data requested

j) The product information leaflet and label are not updated accordingly or updated without PPB's approval (approval for product variation by PPB shall be received before the submission of lot release)

18.1.2 The Board shall clearly state a reason for non-compliance/rejection of a Lot releases application and/or Lot whose Lot release is sought in the non-compliance notification.

18.2 Decision making

18.2.1 The decision to reject a Lot release application/product will be made in a transparent manner and in such a way that the applicant can access to both the process and the criteria of regulatory decision.

[5] The term "accurate" means submitted data are correct, truthful, complete, valid and reliable.

18.2.2 If an applicant/manufacturer/MAH/importer feels aggrieved by the decision of the Board to reject a Lot, he can appeal against the decision requesting for a review of the decision.

18.2.3 An appeal for review shall be submitted to the Chief executive officer, Pharmacy and Poisons Board.

18.2.4 Upon decision by the CEO sustaining rejection of the Lot, the applicant may appeal to the Board.

18.2.5 All decisions made by the Board shall be final and no further appeal shall be allowed in any circumstances.

18.3 Non-compliant products

18.3.1 No matter the outcome of an application, the applicant/manufacturer/MAH/importer shall ensure the supply of the product for local use will not be affected.

18.3.2 The applicant/manufacturer/MAH/importer shall ensure that non-compliant products are not released onto the market and will be disposed of in Kenya. He shall provide appropriate proof of collection and of appropriate disposal within 90 days after issuance of non-compliance notification.

18.4 Importer and wholesaler considered non-compliant

18.4.1 Failure of importer or wholesaler to meet the requirement of Good Distribution Practice may result in a revocation of import or wholesale licence.

18.4.2 In such cases, the MAH shall have a contingency plan to ensure that the supply of the product for local use will not be jeopardized.

19 Timelines

SN	Description of Activity	Timeline
	Phase 2 & 3	
1.	Acknowledgment of successful application	Within 1 hour
2.	Screening	Within 24 hours of successful application
3.	Notification about e) incomplete or, f) queries or, g) inconsistencies or, h) clarification regarding the application and attached documents including packing list and airway bill	Within 24 hours of screening.
4.	Notification of rejection of application when an applicant/MAH is unable to provide the needed clarification	Within 24 hours
5.	Inspection of the Lot at the applicant's warehouse	Within 2 working days after receipt of products at warehouse
6.	Submission of samples and testing materials	Within 24 hours of submission of application
7.	Evaluation of a screened application and submitted samples and test materials	Within 14 working calendar days or within 5 working days following test completion, whichever is later.[6]
8.	Issue of Lot release upon successful evaluation of application and submitted sample and having confirmed that all the Lot Release requirements have been fulfilled	Within 24 hours.
9.	Notification of rejection at any stage of the review of application and submitted sample under evaluation upon determination that the documents are not accurate	Within 24 hours of determination
10.	Issue of a non-compliance notification (NCN) upon determination that a Lot of a biological products is non-compliant and a decision has been made to reject the Lot	within 24 hours.
11.	Submission of evidence of disposal of a Lot considered non-compliant and for which NCN had been issued	within 90 days of the NCN issue.

[6] The timeline is product specific; each biological product differs in testing procedures and test duration.

20 Fees for lot release of imported biological product

20.1 Every application for independent regulatory Lot release shall be accompanied by a prescribed fee

20.2 Payment made shall NOT be REFUNDABLE once the application has been submitted and payment notice has been issued

20.3 Applications without the correct fees paid will not be processed.

20.4 The fees levied for regulatory Lot release shall be updated on PPB website.

20.5 The fees imposed are product specific and shall be updated on PPB website to include the fees for each type of product and test.

20.6 The fees shall automatically be levied once the applicant selects the product at the time of application.

20.7 The processing fee and any other charges shall be paid in the form of banker's cheque made payable to the Pharmacy and Poisons Board

Applicants may get more information and answers by contacting the Pharmacy and Poisons Board;

Department	Quality Control Pharmacy and Poisons Board of Kenya
Telephone Number	+254 720 608 811
Email	qc@pharmacyboardkenya.co.ke
Postal Address	27663
Postal Code	00506

21 References

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Revision history

Authors/contributers

ANNEXES

Annex 1: Online application form for Regulatory Lot Release of vaccines and PDMP manufactured in Kenya

Applicant information	
Name & Address of the MAH	
Contact person	
Contact number	
Product information	
Category	Vaccine, plasma derived product
Name of the product as registered	
Ingredient and strength	
Name of manufacturer	
Address of manufacturer	
MAL number	
Lot number	
Date of manufacture	
Date of expiry	
Storage conditions	
Type of final container for the product	Vial, ampoule, prefilled syringe, others (specify)
Diluent information	
Name of diluent	
Lot number	
Date of manufacture	
Date of expiry	
Storage conditions	
Type of final container for the product	Vial, ampoule, prefilled syringe, others (specify)
Quantity manufactured	
Total final containers manufactured	
Total dose of production	
Documentation	
Documents submitted	Lot Summary Protocol, Plasma Pool Certificate (if applicable), Certificate of Analysis of Finished Product, Finished product test report (with raw data)
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	

Annex 2: Online application form for Regulatory Lot Release of vaccines and PDMP imported into Ken

Applicant information	
Name & Address of the MAH	
Name & Address of Importer	
Name & Adress of Warehouse	
Contact Person	
Contact number	
Product information	
Category	Vaccine, plasma derived product
Name of the product as registered	
Ingredient and strength	
Name of manufacturer	
Name of the other manufacturer (if any)	
MAL number	
Lot number	
Date of manufacture	
Date of expiry	
Storage conditions	
Type of final container for the product	Vial, ampoule, prefilled syringe, others (specify)
Diluent information	
Name of diluent	
Lot number	
Date of manufacture	
Date of expiry	
Storage conditions	
Type of final container for the product	Vial, ampoule, prefilled syringe, others (specify)
Quantity imported	
Quantity in primary packaging	
Quantity of secondary packaging	
Total number of units per shipment (specify number of doses for vaccines)	
Transportation	
Arrival date	
Transit point (if any)	
Route of transportation	Air, ocean
Mode of transport	Active mode, passive mode
Documentation	
Documents submitted	Lot Summary Protocol, Lot Summary Certificate, Plasma Pool Certificate (if applicable), Certificate of Analysis of Finished Product, Importing packing list, Airway bill/seaway bill
Redressing, repackaging, relabeling information (only available for MAL NO. without suffix-R)	
Does this product require redressing/repackaging/relabeling?	Yes No
Yes; if yes, have you obtained approval	Yes

to conduct ANY redressing/repackaging for the product from the Board?	No
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	

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