DRAFT GUIDELINE FOR LOT RELEASE OF HUMAN VACCINES, BLOOD PRODUCTS (PLASMA DERIVATIVES MEDICINAL PRODUCTS) AND ANTI-SERA.

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1. HISTORY

This is the Third edition (draft) of the guideline for the lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

2. APPLICATION-Guidance for Stakeholders and Regulators

This draft document is applicable for issuance of lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, based upon summary protocol review and/or quality control testing of samples to ensure safety, quality and efficacy of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

3. PURPOSE

This draft document is intended to provide general guidance. Although great care has been taken in compilation and preparation of this publication to ensure the accuracy, Drug Regulatory Authority of Pakistan (DRAP) cannot in any circumstances accepts liability for any errors or omissions in this document.

In the event of any contradiction between the contents of this document and any written Acts, Rules, Regulations and SROs etc., the latter should take precedence.

TABLE OF CONTENTS

4. INTRODUCTION TO LOT RELEASE

The lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera is a part of the regulation of biological products and involves the independent assessment of each lot of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera before it is released on to the market. The WHO provides recommendations and strategies for the lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera by the NRAs/NCLs of producing and procuring countries. The assessment is based, as a minimum, on the review of manufacturers' summary protocols. It may be supplemented by other documents such as the release certificate from the responsible national regulatory authority (NRA) or national control laboratory (NCL) and, in some circumstances, by testing that is independent of the manufacturers' quality control testing.

Vaccines are biological products used mainly in the prophylaxis. They are largely used in healthy populations. Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programs, thus potentially compromising public health strategies.

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 human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, proper storage conditions and efficient supply chain management must be ensured to preserve the sensitivity and limited shelf-life properties of these products. For the reasons stipulated above, a careful independent review of manufacturing and quality control data on every lot of products as stated is therefore necessary before use. Lot release program enables National Regulatory Authority (NRA) to ascertain the safety, quality and effectiveness of every lot of these products.

5. BACKGROUND

The principal function of NCLB is the certification of each lot of vaccine, anti-sera and blood products (plasma derivatives medicinal products) based on protocol review, and/or random laboratory and animal testing so as to ensure that the product complies with the requirements and specification established and approved by the DRAP during the registration and licensing procedure.

NCLB is mandated to issue Lot Release Certificate for each lot of vaccine, anti-sera and blood products (plasma derivatives medicinal products) whether imported or locally produced before its sale in the local market. The biological drug means any medicinal product produced by biological systems and which requires standardization by biological assays examined under authority vide DRAP Act, 2012 and in accordance with the Standard Operational Procedure for the Lot Release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

6. DEFINITIONS AND ACRONYMS

BCG	Bacillus Calmette-Guerin
The Act	the DRAP Act, 2012 (Act No.XXI OF 2012)
The Drugs Act	the Drugs Act, 1976 (Act No. XXXI of 1976)
DTaP-IPV	Diphtheria Tetanus Pertussis(acellular) -Inactivated Polio Vaccine
DRGD	Guidance Document for Submission of Application on FORM 5-F/ (CTD) For Registration of Pharmaceutical Drug Products for Human Use.
HepB	Hepatitis B
Hib	*Haemophilus influenza* Type B
LRC	Lot Release Certificate
NCLB	National Control Laboratory for Biologicals
NNC	Notification of Non-Compliance

DRAP	Drug Regulatory Authority of Pakistan
NRA	National Regulatory Authority
PRH	Product Registration Holder
MAH	Market Authorization Holder
TRS	Technical Report Series
WHO	World Health Organization
SAR	Sample and Application Receptionist

Applicant	A bio-pharmaceutical company or its authorized agent who submits information in support of an application.
Market Authorization Holder (MAH)/ Product Registration Holder (PRH)	Any person or legal entity that has received marketing authorization/ registration to manufacture and/or distribute a finished drug product.
Standard Operating Procedure (SOP)	A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.
Diluent	Diluent is an agent (a liquid) added to the product to reconstitute/ dilute to make it ready before final administration.
Electronic Data Logging Monitor (EDLM)	A small portable device is used to measure and record 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.
Freeze Indicator (FI)	An irreversible indicator used to indicate that the 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 releases the colored liquid, staining the white backing card. The freeze indicator is used to warn of freezing and is packed with vaccines that are sensitive to freezing temperatures: DTP, TT, DT, Td (freezing point of -6.5°C), hepatitis B (-0.5°C), liquid Hib and their combinations (DTP-HepB, and DTP-HepB+Hib vaccines) and JE.

Lot/Batch	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/batch into a number of sub-lots, which are later accumulated to form a final homogeneous lot/batch. In continuous manufacture, the lot/batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The lot/batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval
Lot Release	The process of evaluation of an individual lot of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera before giving approval for its releasing onto the market.
Marketing Authorization	An official document issued by the competent NRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality.
Out of Specification (OOS)	An OOS result is generated when a vaccine is tested and fails to meet a predefined specification.
Self-procured vaccine	A vaccine that is procured directly from a source outside the country without the intervention of WHO/United Nations procurement programs.
Source material/starting material	Any substance of a defined quality used in the production of a vaccine product, but excluding packaging materials.
Non-Compliance	Failure or refusal to comply with a standard or a set of limits.
NCLB	National control laboratory for biological (NCLB) is responsible for lot release or/and testing/ analysis of biological products.
Plasma Derived Medicinal Products (PDMP)	Any therapeutic product derived from plasma and produced by a manufacturing process.
Reference Regulatory Authority	The reference countries for Pakistan are the Stringent Regulatory Authorities of countries approved by the Policy Board of DRAP.
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.
Temperature Excursion	An excursion event during which a product is exposed to temperatures outside the range prescribed for storage and/or transport.

Summary protocol	(also called 'lot Summary protocol") a document summarizing all manufacturing steps and test results for a lot of vaccine which is certified and signed by the responsible person of the manufacturer.
Vaccine	A vaccine is a preparation of live attenuated, killed, fragmented microorganisms or toxoids etc. that is administered primarily to prevent disease. e.g. OPV, IPV, HBsAg and Tetanus toxoid etc.
Vaccine Vial Monitors (VVMs)	VVMs are small indicators adhered to vaccine vials and changes color as the vaccine is exposed to cumulative heat, letting health workers know whether the vaccine has exceeded a pre-set limit beyond which the vaccine should not be used.
Yearly human vaccines, blood products (plasma derivatives medicinal products) and anti-sera product report	A report submitted annually by manufacturers to the NRA/NCL, containing production information on both bulk and final lots, including test methods and results and reasons for any recalls and corrective action taken, as well as other pertinent post-marketing information.

7. GENERAL OVERVIEW OF LOT RELEASE

The lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera 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 TRS 1033-annex 10 (*Good Reliance Practices in the regulation of medical products: high level principles and considerations*) and DRAP' document QMSC/GL/RM/005: 2nd edition (Reliance Mechanism in Regulatory Processes "DRAP Approach on Good Reliance Practice), for self-procured human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, independent assessments may be based on review of manufacturer's summary protocol.

Currently, lot release for imported consignment is based on reliance in the form of summary protocol review along with lot release certificate of National regulatory authority of exporting country.

7.1. Scientific Guideline Applicable to Human Vaccines, Blood Products (Plasma Derivatives Medicinal Products) And Anti-Sera Lot Release

a) WHO, TRS-978, Annex-2, Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities,
b) WHO, TRS-822, Annex-2, 1992 Guidelines for national authorities on Quality Assurance for biological products.
c) WHO Report No. A75/40 dated 12 April 2022 on Availability, safety and quality of blood products.
d) WHO TRS 1033-annex 10, Good Reliance Practices in the regulation of medical products: high level principles and considerations.

8. SCOPE OF LOT RELEASE

The scope of this draft guideline includes the following registered biological products for human use as per Section 7 of Schedule 1 of DRAP Act 2012 (Amended vide SRO 219(I)/ 2022 dated: 14th February 2022).

a. Human vaccines
b. Blood products (Plasma Derivatives Medicinal Products)
c. Anti-sera

9. RESPONSIBILITIES:

9.1. It is the responsibility of the Importers and/or manufacturers to follow the procedure described in this guideline while submitting the request for lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

9.2. Authorized officer (Officer notified by DRAP (I&E) for clearance of the consignment of imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera) is responsible for ensuring that this procedure is being followed.

9.3. Federal Government Analyst, National Control Laboratory for Biologicals, is responsible for issue lot release certificate on the prescribed form (Annex-3).

9.4. Additional Director/ Director, NCLB will ensure the implementation of this guideline.

10. PROCEDURE

Registration holders are fully responsible for ensuring that the products comply with the product registration information. If there are any changes to the products,

MAHs/PRHs are expected to obtain approval for variation prior to submission of documents. Please refer to the DRAP's Post Registration Variation Guideline for further details (PE&R/GL/PV/01).

i. Guidance on the Submission of Application

This draft guidance outlines the essential documents submitted with the lot release application online through the URL: http:/edrap.dra.gov.pk/lotrelease. All documents are written in English only. Each document is clearly tagged (indexed and labelled). The following documents are submitted:

a) Lot Release Application on prescribed form (Appendix-I).
b) Prescribed Fee as per Appendix-II
c) Copy of registration letter/ import NOC from I&E Section of QA&LT Division of DRAP.
d) Copy of commercial invoice and Clearance certificate from DRAP.
e) Airway bill (if applicable)
f) Summary Protocol of the product lot applied for lot release.
g) Lot Release Certificate (For imported product in finished form, from the NRA/NCL of the country of origin) or Exemption Certificate if product is exempted from lot release in the exporting country.
h) Certificate of Analysis (CoA) for Finished Product and Diluent etc. (if applicable).
i) Batch production record of locally manufactured human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.
j) Samples in quantities (one-unit commercial pack as per requirement of storage conditions of the applied product).
k) If the Federal Government Analyst decides to test the human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, then the required quantity of samples is demanded from the applicant. On receipt, the same LR number already assigned to the lot release application is assigned to the samples.

Incomplete applications are not processed until all above-mentioned requirements/ documents are provided. Complete applications are submitted to the Additional Director/Director, NCLB, who assigns them to the Federal Government Analyst for review/ evaluation. The Federal Government Analyst evaluates the summary protocol and relevant NCLB test results (if tests are performed). If any deficiencies are identified during evaluation, a deficiency letter is issued to the applicant through the online portal. Upon receipt of the applicant's response and subject to the submission of all required information/documents, the Federal Government Analyst proceeds with the review and issues either a Lot Release Certificate (LRC) or a Rejection Certificate to the authorized company representative via the same portal. The status is

uploaded on the official DRAP website, and a printed copy of the Lot Release/Rejection Certificate is forwarded to the Archiving and Documentation Section of NCLB, in accordance with the SOP for Lot Release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

ii. Risk based classification of Lot Release Applications

Based upon origin of the human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, lot release applications are classified in following categories: -

Risk Classification	Description	Requirements/ Assessment
Low Risk	Imported from Stringent Regulatory Authorities (SRAs)/ RRAs* countries/ WHO ML-4	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.
Low-to-Mild Risk	Imported from WHO Prequalified (PQ) facilities/products.	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Verification of WHO-PQ status. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.
Mild Risk	Imported from NRAs/NCLs with WHO Maturity Level 3 (ML-3)	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.
Moderate Risk	Imported from non-SRA countries/ non-WHO-PQ facilities/ WHO ML-1/2	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration

		ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin. iii. Testing based on trend analysis**.
High Risk	Locally manufactured	i. Review of manufacturer's summary protocol based on product dossier, which has been approved by DRAP during product registration ii. Testing of the products as per available capacity / facility.

* RRAs countries as approved by the Registration Board, DRAP in its 275th meeting held on October 25–27, 2017, and subsequently by the Authority (as time to time), are listed in Appendix V.

** Key Factors in Trend Analysis:

- **Consistency of manufacturing processes**: as reviewed the tests results obtained by manufacturers or NCLB's including out-of-trend and non-conformity lead to insufficient lot-to-lot consistency in accordance with Out-of-Trend (OOT) SOP no. NCL/QA/SOP/048.
- **Post-Marketing Surveillance (PMS) experience**: Information related to Adverse Drug Reaction/ AEFI reports, product complaints, product recalls, and withdrawals contribute to the post-market safety profile of the drug product.

iii. Criteria for Lot Release of Human Vaccines, Blood Products (Plasma Derivatives Medicinal Products) And Anti-Sera:

Based on origin and WHO guidelines, following mechanism will be followed for lot release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera:

Risk Classification	Description	Requirements/ Assessment
Low Risk	Imported from Stringent Regulatory Authorities (SRAs)/ RRAs countries/ WHO ML-4	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.

Low-to-Mild Risk	Imported from WHO Prequalified (PQ) facilities/products.	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Verification of WHO-PQ status ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.
Mild Risk	Imported from NRAs/NCLs with WHO Maturity Level 3 (ML-3)	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin.
Moderate Risk	Imported from non-SRA countries/ non-WHO-PQ facilities/ WHO ML-1/2	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin ii. Testing based on trend analysis.
High Risk	Locally manufactured	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Testing of the products as per available capacity / facility.

11. IMPORTED HUMAN VACCINES, BLOOD PRODUCTS (PLASMA DERIVATIVES MEDICINAL PRODUCTS) AND ANTI-SERA

11.1. Upon arrival of the shipment/consignment of imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, the importer applies for the grant of permission to the authorized officer of DRAP (I&E) for custom clearance of the consignment. The authorized officer grants provisional release of the consignment i.e. to take the consignment from port

to the importer's warehouse cold room for proper storage, within a time not exceeding two working days, with the direction to obtain lot release certificate from National Control Laboratory for human vaccines, blood products (plasma derivatives medicinal products) and anti-sera before release/ supply/ sale/ use of the above-mentioned products.

11.2. Upon receiving the consignment, the importer applies for the lot release of each lot / batch separately on prescribed form (Appendix-I) as per requirements mentioned in section 10.1 (a to j).

11.3. Upon receiving the application for issuance of lot release certificate, the Additional Director/ Director, NCLB, assigns to the Federal Government Analyst for review. The Federal Government Analyst reviews the summary protocol and relevant NCLB test results (if applicable) and issues a certificate on prescribed form (appendix-III) and lot rejection certificate if application is not found satisfactory (appendix-IV), within a time frame depending upon the assessment applicable, as per WHO recommendations summarized in following table:-

Sr. No.	Description	Review Time
a)	Lot Release based upon Summary Protocol Review only	Within 7 days
b)	Lot Release based upon Summary Protocol Review and Testing/ Analysis	Within 60 days.
c)	In case of emergency/ shortage/ Pandemic, declared by Federal Government/ Provincial Government or the DRAP Authority.	Within 2 days.

11.4. Upon receiving the lot release certificate from National Control Laboratory for human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, the importer submits it to the authorized officer of DRAP (I&E) to get permission for the release/ supply/ sale/ use of the human vaccines, blood products (plasma derivatives medicinal products) and anti-sera accordingly.

11.5. The authorized officer of DRAP (I&E) will grant permission to the importer, within two working days of receipt of lot release certificate, to place the product on the market.

11.6. If any requirement is not met, the Federal Government Analyst will issue lot rejection certificate. A copy shall also be sent to the Director, QA&LT/ BE&R (DRAP) for further necessary actions as per prescribed procedures.

11.7. In the event of non-compliance, it is the responsibility of the product registration holder and area FID to ensure proper and safe disposal of the product. The record of the disposal/destruction documentation shall be sent to NCLB within 90 days after issuance of rejection certificate.

12. LOCALLY MANUFACTURED HUMAN VACCINES, BLOOD PRODUCTS (PLASMA DERIVATIVES MEDICINAL PRODUCTS) AND ANTI-SERA:

12.1. Upon completion of manufacturing process and quality control testing and quality assurance review of each lot, the manufacturer applies for the lot release on prescribed application form as per requirements mentioned in section 10.1 (a to j).

12.2. Upon receiving the application for issuance of lot release certificate, the Additional Director/ Director, NCLB, assigns to the Federal Government Analyst for review. The Federal Government Analyst reviews the summary protocol and relevant NCLB test results (if applicable) and issues a certificate on prescribed form (appendix-III) and lot rejection certificate if application is not found satisfactory (appendix-IV), within a time frame depending upon the assessment applicable, as per WHO recommendations summarized in above table.

12.3. As per schedule I of the DRAP Act 2012, the companies are to clearly specify in the BPRs about human vaccines, blood products (plasma derivatives medicinal products) and anti-sera) they are manufacturing.

13. TESTING POLICY:

13.1. For local and imported products

Based on the country of origin and in line with WHO guidelines, the following mechanism is applied for testing human vaccines, blood products (plasma derivatives medicinal products) and anti-sera samples submitted with Lot Release applications: -

Risk Classification	Description	Requirements/ Assessment
Low Risk	Imported from Stringent Regulatory Authorities (SRAs)/ RRAs countries/ WHO ML-4	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin. ii. Reliance is applied.

Low-to-Mild Risk	Imported from WHO Prequalified (PQ) facilities/products.	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Verification of WHO-PQ status. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin. v. Reliance is applied.
Mild Risk	Imported from NRAs/NCLs with WHO Maturity Level 3 (ML-3)	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin. ii. Reliance is applied
Moderate Risk	Imported from non-SRA countries/ non-WHO-PQ facilities/ WHO ML-1/2	i. Review of manufacturer's summary protocol of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, which has been approved by DRAP during product registration. ii. Review of recognized LRC from National Regulatory Agency (NRA) of Country of Origin ii. Testing based on trend analysis.
High Risk	Locally manufactured	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Testing of the products as per available capacity / facility.

13.1.1. Locally manufactured products fall into the following three categories:

13.1.2. Manufactured from imported Ready-to-Fill Bulk (RTFB).

13.1.3. Manufactured from imported Bulk Concentrate, that is formulated and filled.

13.1.4. Manufactured from locally produced concentrate by way of Basic Manufacture either from Seed Cells, Seed Viruses, Seed Bacteria and/or

rDNA vector expressed in relevant host(s) or from Hyper immune sera raised in equine etc.

13.1.5. For such locally produced drugs consistency of lot-to-lot production is of paramount importance and this consistency should be established for initial lots produced, by the manufacturer at least for the two critical tests that is Potency and Sterility. An additional safety test is to be incorporated for human vaccines, blood products (plasma derivatives medicinal products) and anti-sera manufactured as per section 13.1.4.

13.1.6. In terms of summary protocol review of such locally produced human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, the local summary protocol shall start onward from the last procedure conducted by the original manufacturer of the product.

13.1.7. In case of RTF bulk import, the local manufacturer shall provide data of the processing/distribution of the RTFB into small aliquots, the history of its storage and quality control tests performed if redistributed into containers suitable for single lot filling.

13.1.8. In case of Bulk Concentrate (BC) import, the local manufacturer shall provide data of the processing/ distribution of the BC into small aliquots, the history of its storage and quality control tests performed if redistributed into containers suitable for single lot filling.

13.1.9. For reference of requirements, each human vaccines, blood products (plasma derivatives medicinal products) and anti-sera has predefined WHO TRS requirements and/or approved specifications by DRAP at the time of Registration or renewal of registration, the manufacturer shall consult the relevant TRS and mention it on their summary protocol. The manufacturer is supposed to certify that the product under review is the same that they have registered with the DRAP/ MoH and that the change in their composition has been duly notified, validated and incorporated in the approved product dossier. Any change in the product profile shall necessitate a revalidation of initial three to five lots.

13.1.10. A significant change in the processes of production, i.e., from RTF to BC or from BC to RTF or by way of basic manufacturing shall have to be revalidated.

13.1.11. The above-mentioned requirements are as per DRAP Act, 2012/ Drugs Act 1976 and National cGMP requirements which clearly require validation and documentation for every change in the approved procedure of manufacture.

13.1.12. For the imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera for which the NCLB does not have the testing facilities at present shall be evaluated based on lot summary protocol till the development of the testing facility. This is under the pretext that the manufacturer's country NCA or NRA is fulfilling the necessary requirements of lot release.

13.1.13. For imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera originating from other countries because of a pandemic or in response to an emergency such as epidemic or disaster as defined in WHO Document for Disaster Management, sampling and testing shall not be applicable at the import stage.

13.1.14. In situations of exigency like earthquakes, floods, natural disasters, pandemics, major epidemics and war etc. in the public interest, a provision for exemption from lot release had been provided through SRO 779(I)/2000, dated 5th November 2001.

14. HANDLING OF SAMPLE

14.1. Sample room in-charge is responsible for entering the sample information into the logbooks and stores the samples as per Receiving, Handling, Storage and distribution of Biological Product Samples SOP No. NCL/QA/SOP/034/09.

14.2. Sample room in-charge ensures that samples are stored at appropriate and prescribed storage temperature throughout the storage period.

14.3. He issues the sample on the direction of FGA, NCLB, to analyst for performing test/ analysis and record the entry of the same into the logbook.

14.4. Sample room in-charge ensures that samples are stored at appropriate and prescribed storage temperature throughout the storage period.

14.5. Sample room in-charge also segregates expired samples and maintains record as per SOP: *Procedure for disposal/destruction of expired laboratory samples* (SOP No. NCL/QA/SOP/056/05).

14.6. Sample room in-charge is also responsible for intimating the Manager Laboratory Operations/ FGA, NCLB for destruction of the expired samples as per SOP: *Procedure for disposal/destruction of expired laboratory samples* (SOP No. NCL/QA/SOP/056/05).

15. TESTING SAMPLES

15.1. The Analyst/ Manager, Laboratory Operations, performs the test/analysis in accordance with the testing policy described in Section 13.1 of this Guideline and in the SOP for Lot Release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera (SOP No. NCL/LR/SOP/006/10).

15.2. Manager Laboratories Operations also supervises testing being performed by the analyst.

15.3. In case the quantity of samples is insufficient, sample demand notice duly signed by FGA, NCLB is issued to the applicant.

15.4. Upon receipt of the samples, procedure for sample receiving, handling and storage as per SOP for Receipt, Handling and Storage of Test items SOP No. NCL/QA/SOP/034/09 is followed for samples.

15.5. Analyst submits the report to the Manager Laboratory Operations who checks reports of the test/ analysis results and sends the reports to Manager QA for review.

15.6. Manager QA reviews the test/analysis report and ensures that proper procedure is adopted, and all the parameters meet the requirements of testing.

15.7. Manager QA forwards the report to Federal Government Analyst, NCLB.

15.8. Federal Government Analyst, based upon test/analysis report(s) and review of summary protocol and other allied documents, approves and issues lot release/ rejection certificate(s) to the applicants.

16. SUMMARY PROTOCOL TEMPLATE

16.1. Since protocol review is an essential component of the lot release process, it is crucial that the template of the summary protocol is developed carefully based on the marketing authorization dossier approved by DRAP. WHO templates are available for some vaccines, but the agreed protocol should also consider the specific requirements in the marketing authorization approved for the product. Any changes to the template due to changes in the manufacturing process or testing should be traceable. The template should be a controlled document, and the manufacturer should not change it without the approval of the DRAP. It is important that NCLB staff responsible for reviewing these documents ensure that the updated version of the documents and registration status is reflected in the summary protocol submitted by the manufacturer.

16.2. Each summary protocol is product specific, but there is a number of general information narrated below, that a summary protocol should cover.

Items	**Essential Information**	**Critical Parameter to review**
Identity of Manufacturer	Name of Manufacturer	Traceability and identity
License Number	Unique License Number	Traceability and identity
Site(s) of Manufacturing	Site of manufacturing for each bulk, final bulk and final product	Traceability and identity
Name and Lot Number	Name and lot number of the final product, bulk, final bulk and the diluent if applicable	Unique, systematic, traceability and identity
Lot size	Volume, number of doses and type of container	Listed information should fit with allowed parameters

Expiry date	For each starting material (if applicable), intermediates, final bulk and final product	Expiry date of each component fits the shelf life of the final product.
Date of manufacturing	For each critical starting material (e.g. seed lots, cell banks, starting materials of animal origin etc.) intermediate, final bulk and final product	Compared against noted expiry dates etc. to calculate and confirm values.
Flow chart	Flow charts for traceability of the manufacturing process for major components, including lot number	Identity and logic flow for starting material, intermediates, final bulk and final product confirmed.
Strains and cell substrates	Name, seed lot number, passage number	Strain of production seed and type of cell substrate, lot/bank number, passage number of master and/or working lot/ bank are the same as the one approved by the NRA on the marketing authorization and/ or recommended by WHO (e.g. OPV) (6)
Manufacturing process	Each production process (such as cultivation, purification, inactivation), the methods of quality-control tests as well as their release specifications and the results obtained; the lot number of intermediates and their size/volume, storage conditions	Confirm they are the same as the approved ones, yields of critical production processes are within the acceptable range.
Formulation	Amount of active components in the final formulations, with the lot numbers and volumes of bulk concentrates; storage conditions	Verify calculated and actual values based on information provided.
Quality-control tests	Actual results of tests on critical starting materials, intermediates, final bulk and final product and the specification; include the individual tests and the mean value; provide the starting date of the test, method, and a list of reference preparations, standards, critical reagents and their qualification status, plus the performance of relevant reference preparations, standards and internal controls, such as results of assay validity criteria (e.g. slope, intercept, linearity, 50% end-points, results of internal controls, challenge doses); provide statistical	Demonstrate that the identity, purity, safety, potency (strength) and thermostability of the product are in compliance with the approved specifications; monitor the performance of reference material/test

	results, such as mean, geometric mean, standard deviation, 95% confidence intervals, etc., if applicable; include results of failed tests or note invalid tests if a test has been repeated	

17. CLARIFICATION FOR APPLICANTS

17.1. Lot release is applicable to every batch/lot in a shipment which means if there are one or more batches/lots, lot release will be applicable to each and every batch separately, for which separate fee shall be deposited.

17.2. If same batch is imported again in a different shipment, again the lot release will be applied, and lot release fee will be deposited.

17.2.1. Fee Schedule will be according to SRO 496 (I) / 2023 dated 17-04-2023 (appendix II of this guideline) and annex. 4 of the SOP.

17.2.2. For the imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera originating from other countries as a result of a pandemic or in response to an emergency such as epidemic or disaster as defined in WHO Document for Disaster Management, sampling and testing shall not be applicable at the import stage.

17.2.3. In the situations of exigency like earthquakes, floods, natural disasters, pandemics, major epidemics and war etc. in the public interest, a provision for exemption from lot release had been provided through SRO 779(I)/2000, dated 5th November 2001.

17.2.4. NCLB also has a mechanism for fast-track release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera in cases of an emergency such as Earthquakes, floods, natural disasters, pandemics, major epidemics and war etc., in the larger public interest. In these cases, products are released out of queue on top priority basis. However, the manufacturers/importers are bound to fulfill the requirements mentioned earlier in the guideline.

18. RESPONSIBILITY OF THE MANUFACTURER IN NCLB LOT RELEASE

In this regard, the manufacturer should:

(a) Submit each manufacturing and control summary protocol.
(b) If requested, submit samples in an appropriate condition.
(c) Submit the lot release certificate of the responsible NRA in the case of import products.
(d) Provide product-specific reagents and working reference materials, as needed.
(e) Take appropriate action on any issues related to error or non-compliance.
(f) Take appropriate action on any rejected lot(s) according to GMP requirements.
(g) Provide any documents or other information regarding the quality of the vaccine, as required by the NCLB.

19. DATA MONITORING

All critical quantitative data from quality-control results, and especially potency, from the manufacturer or other sources, will be used for trend analysis as an essential part of lot release. Statistical analysis will be conducted once sufficient data has been accumulated. The alert or warning limits and action limits of consistency trends should be defined on statistical grounds. There are following scenarios:

(a) when data are normally distributed, ±2 and ±3 standard deviations from the mean are applied as the alert (warning) limits and action limits, respectively, when both upper and lower specifications are defined for human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.
(b) When only a lower specification is defined (e.g., Tetanus toxoid vaccine), ±3 and ±4 standard deviations from the mean are applied as the alert (warning) limits and action limits, respectively.

The variability and precision of the test should be considered when defining the limits. Care should be taken in interpreting such limits when they are based on small datasets. NCLB may request manufacturers or importers for key parameters for trend analysis. More complex specific trend analysis statistical methods can be used when sufficient data and expertise are available, particularly when data are not normally distributed. In addition, a set of data from a certain period (e.g. 6 months or 1 year)

should be analyzed statistically, compared to previous data, in order to detect any shifts/ drifts in trends.

19.1. Trend analysis including data from the NCLB

In cases where independent testing of lots is performed at the NCLB all data from the tests performed at NCLB, including performance of reference standards and controls should also be trended and analyzed.

19.2. Comparison of Results of the Manufacturer with Those of the NCLB

Results from the NCLB should be compared with those of the manufacturer. Any systematic differences should be documented. Any differences in trends should be investigated and resolved, in collaboration with the manufacturer/importer. Trend analysis is performed in accordance with SOP for Trend Analysis.

20. GUIDANCE ON TEMPERATURE MONITORING

Deviation of temperature or incorrect storage conditions 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 conditions with continuous monitoring. Transportation of these products can be done by either active or passive packaging systems.

21. TYPES OF PACKAGING SYSTEMS

21.1. Active System

Actively powered systems employ electricity or other fuel sources to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulations. 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.

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

21.3. 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 to determine whether the shipment has been exposed to temperatures outside the recommended ranges. EDLM records data digitally over time or in relation to location either with a built-in or external instrument or sensor. EDLM is the preferred temperature indicators as they provide the most reliable and accurate record of temperature conditions for active and passive packaging systems. At least one EDLM be added in each international shipping carton or pallet.

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.
2. A “stop” function to allow the recipient to stop the recording when the product arrives at its destination.

Manufacturers shall preferably include WHO Prequalified Temperature Monitoring Devices for transportation and shipping of their products.

The use of cold chain monitor cards (CCM), vaccine vial monitors (VVMs) and/or freeze indicators (FI) solely or together for international shipments is also recommended but not mandatory. 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. 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 active and passive packaging systems with ice packs 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.

21.4. Transport of Diluent

Some diluents may be sensitive to heat or freezing and may require transportation and storage in the cold chain. There are different types of diluents, 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 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.

Not all diluents shall 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. If diluents are found to be frozen, appropriate action should be taken to isolate and dispose of the vials according to decision by NCLB.

In some countries, for freeze-dried vaccines, the protocol or certificate of analysis of the lot of diluent is reviewed. However, this is not done in other countries, since diluents are not considered on their own to be biological.

21.5. 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 product's storage and transport from manufacturing site to Pakistan. 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 cases where stability data is lacking. Stability data is crucial and contributes to support the release decision in case of temperature excursions.

22. SAMPLE SUBMISSION

Product registration holder shall provide an appropriate number of finished products with diluents (if applicable), vials/ ampoules/ pre-filled syringes etc. Products can be delivered by self at the sample receiving area of NCLB or through courier services by the applicant / product registration holder.

MAH/ Applicants shall make sure that products submitted to NCLB adhere to the approved storage temperature requirements. Appropriate temperature monitoring devices or indicators shall be attached together with the products to monitor temperature during transportation. NCLB has the absolute right not to accept any product that does not comply with the latest approved storage temperature.

Key elements of focus where tests may be considered necessary include appearance, identity, potency, safety and for some products, thermo-stability (e.g. OPV). Type of test conducted depends on the dosage form of the finished products but not limited to these tests: -

a) Solution/ liquid:

i. Identification
ii. pH test
iii. Bacterial endotoxin testing (BET) (if required)
iv. Sterility test
v. Appearance test
vi. Potency
vii. Osmolality (if required)
viii. Particulate contamination test (visible & sub-visible particles)

b) Freeze dried/ lyophilized:

i. pH test
ii. Appearance test

iii. Solubility test
iv. Identification
v. Potency
vi. Osmolality (if required)
vii. Bacterial endotoxin testing (BET) (if required)
viii. Particulate contamination test (visible & sub-visible particles) on reconstituted finished products.
ix. Sterility test
x. Moisture content/Loss on Drying (LOD)

23. CRITERIA FOR REQUESTING ADDITIONAL DATA

NCLB shall request additional data from MAH / PRH under conditions including but not limited to:

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

24. REJECTION CRITERIA FOR A LOT/BATCH

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

a) Decision by the FGA NLCB based on the supporting documents, comments from another NRA (if available) and recommendations/summary from evaluator.
b) Failure to include temperature monitoring device/indicators.
c) Failure of the temperature monitoring device to monitor the temperature during transportation.
d) No supporting data for temperature excursion.
e) Failure to meet the approved specifications.
f) Failure to provide additional data requested.
g) The product information leaflet and label are not updated accordingly or updated without DRAP's approval (approval for product variation by DRAP shall be provided before/ along-with the submission of lot release application).

25. ESTABLISHMENT OF DECISION-MAKING PROCEDURE

The reasons for lot release/lot rejection are clearly stated in the lot release/lot rejection certificate, and all steps in the decision-making process should be documented.

i. A formal decision-making process should be in place to decide whether the lot can be released or rejected. An SOP is in place to describe clearly the process and required elements for the final decision.

ii. A general release process chart is in place, outlining the lot approval process and the persons responsible for each activity.

iii. Procedures should cover the options used: release upon review of summary protocol only and/or release upon review of summary protocol plus independent testing by the NCLB.

iv. The NCLB should produce conclusion regarding the summary protocol review.

v. An SOP should describe the acceptance criteria for NCLB test results and record all the individual test results in certificate(s) of analysis.

vi. An SOP should be available that describes the acceptance criteria for release of vaccines in exceptional cases, which deviate from the normal procedure. Examples include release for an emergency/crisis, urgent need due to a critical supply shortage, when information is pending regarding correction of the summary protocol, or in the event of discrepancies between the test results of the NCL and the manufacturer.

vii. Release of vaccine lots in emergency situations such as a vaccine shortage due to a disease outbreak, natural disaster, manufacturing problems (e.g. OOS) or other unforeseen circumstances.

viii. Periodic evaluation of the frequency of independent testing (to consider modification, suspension or continuation of the current strategy);

ix. Periodic evaluation of tests performed for lot release of a particular product (to consider deletion, inclusion or modification of given tests).

26. APPEALS AGAINST DECISION OF NCLB

There is no appellate laboratory for biological products established or notified by the Federal Government against the decision of NCLB. In case of the rejection of a

request for release of a lot of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, the aggrieved party may file an appeal against the decision of National Control Laboratory for Biologicals to the Drug Registration Board of DRAP. All decisions made henceforth by the appellant authority are final and no further appeal shall be allowed in any circumstances.

27. NON-COMPLIANT PRODUCTS

In the event of non-compliant products, the MAH/PRH shall ensure the sufficient supply of the compliant product for use in people of Pakistan. The product registration holder shall ensure that non-compliant products are not released onto the market and shall be disposed of as per prescribed procedures.

It shall be the responsibility of the Marketing Authorization Holder/PRH and area FID to ensure proper and safe disposal/destruction of the product. The record of the disposal/destruction documentation shall be sent to NCLB within 90 days after issuance of rejection certificate.

27.1. Non-compliant product importers/ manufacturers

Failure of importers/ manufacturers to meet the requirement of Good Manufacturing Practice or Good Distribution Practice, as the case may be, may result in regulatory actions against them. In such cases, the MAH/PRH shall have a contingency plan to ensure the regular supply of the compliant product for use in Pakistani population.

28. APPENDIX

Appendix I: Lot Release Application Form
Appendix II: Schedule of Lot Release Fee
Appendix III: Lot Release Certificate (LRC)
Appendix IV: Lot Rejection Certificate
Appendix V: Reference Regulatory Authorities (RRAs)

29. REFERENCES

i) The DRAP Act, 2012

ii) The Drugs Act, 1976

iii) The Drugs Licensing, Registration & Advertisement Rules, 1976

iv) WHO TRS 978, Annex II. Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities.

v) WHO. Assessment Criteria for National Blood Regulatory Systems. Geneva, World Health Organization, 2012

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

vii) WHO. Guidelines on the International Packaging and Shipping of Vaccines. Geneva, World Health Organization, December 2005 (WHO/IVB/05.23).

viii) WHO. WHO Guidance Note: Vaccine Diluents. The Proper Handling and Use of Vaccine Diluents. Geneva, World Health Organization, 2015 (WHO/IVB/15.08)

ix) WHO Temperature Sensitivity of Vaccines. Geneva, World Health Organization, August 2006 (WHO/IVB/06.10)

x) WHO. How to Use Passive Containers and Coolant – Packs for Vaccine Transport and Outreach Operations. In: WHO Vaccine Management Handbook, Module VMH-E7-02.1. Geneva, World Health Organization, 2015. (WHO/IVB/15.03)

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

xii) WHO. Expanded Program on Immunization of the Department of Immunization, Vaccines and Biologicals. Training for Mid-Level Managers (MLM). Module 1: Cold Chain, Vaccines and Safe-Injection Equipment Management. Geneva, World Health Organization, 2008 (WHO/IVB/08.01)

xiii) WHO TRS 1033-annex 10, Good Reliance Practices in the regulation of medical products: high level principles and considerations.

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CONTACT INFORMATION

NATIONAL CONTROL LABORATORY FOR BIOLOGICAL
Address: Prime Minister's National Health Park, Chak Shahzad, Park Road, Islamabad Pakistan
Email: director@nclb.dra.gov.pk
Phone:92-51-9255632
Website:www.nclb.dra.gov.pk

APPENDIX-I

(For Official use only)	
L.R No.	
Date of Receipt	

Lot Release Application Form

The Federal Government Analyst,
National Control Laboratory for Biologicals,
Drug Regulatory Authority of Pakistan,
Ministry of National Health Services, Regulations and Coordination,
Prime Minister's National Health Complex,
Park Road, Chak Shahzad,
Islamabad.

Reference No. _____
Dated: _____

Please issue the lot release certificate in respect of the human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, as detailed below. All the required documents are enclosed along with one unit commercial pack as per requirement of storage conditions of the applied product. The sample of the product for testing will be provided, if required:-

Importer/ Manufacturer Details

Name and address of the Importer/manufacturer _____
Commercial Invoice No. _____
Invoice Date _____
Date of Receipt of Shipment _____
Date of Endorsement of Invoice _____
Mode of Shipment _____
Port of Receipt of Shipment _____
Name and Address of the Indent Holder (if applicable) _____

Product details

Name of Product _____
Generic Name of Product _____
Registration No. _____
Lot No. _____
Manufacturing Date (dd/mm/yyyy) _____
Expiry Date (dd/mm/yyyy) _____
Storage Temp _____
Transportation Temp. _____
Name and address of Manufacturer _____
Pharmaceutical form _____
Type of Container _____
Number of Doses per container _____
Volume per container _____
Strength _____
Transportation/Storage data evidence _____

Total Quantity applied for Lot Release

Solvent/ Diluent Details (in case of Freeze Dried Product)

Solvent/ Diluent Name
Lot No.
Type of container
Volume per container
Registration No.
Mfg. Date
Exp. Date
Name & address of Manufacturer

Details of Fee Deposited

Bank Name
Bank Code
Deposit Date
Deposit Slip No.
Amount Deposited
Endorsement from DRAP □ Yes

Lot Release Requested By Authorized Person

Name
Designation
Signature
Date
Telephone No.
Cell No.
Name of Firm/ Pharmaceutical Company
Complete Address
Official Stamp

For Official Use only:

1. Summary Protocol Received □ Yes
2. Lot release certificate from NRA of exporting country received (in case of imported products) □ Yes □ Exemption Certificate
3. Batch Production Record received (for locally manufactured products). □ Yes □ No
4. Copy of the Registration Letter received. □ Yes
5. Copy of the paid bank challan received. □ Yes
6. Copy of Invoice/Clearance certificate received. □ Yes

Date of Receipt
Application accepted □ Yes
If rejected (reason)
Received By (sig)
Name
Designation

Assessment required □ Summary protocol review □ Laboratory Access
Assigned reviewer
Deadline for assessment

Federal Government Analyst

APPENDIX-II

*SCHEDULE OF LOT RELEASE FEE

Locally Manufactured & Imported Human Vaccines, Blood Products (Plasma Derivatives Medicinal Products) And Anti-Sera.

The lot release fee, in accordance with SRO 496(I)/2023 dated: 17th April 2023, for locally manufactured and imported human vaccines, blood products (plasma derivatives medicinal products) and anti-sera, as specified in Section 7 of Schedule-I of the DRAP Act, 2012, is provided below: -

Product	Fee per lot/sample (in PKR)
Tetanus Toxoid.	30,000.00
Anti Tetanus Sera.	30,000.00
Oral Polio Vaccine.	20,000.00
Measles Vaccine.	20,000.00
Rabies Vaccines.	30,000.00
Hepatitis-B Vaccine.	20,000.00
Snake Venom Anti Sera.	30,000.00
Interferon	20,000.00
Any other imported vaccines, sera and interferon	20,000.00

***** The applicable fee is subject to revision, as amended from time to time and as notified by DRAP.

PROCESSING FEES

a. Lot release application fee will be charged for every product of the consignment.
b. Fee will be charged for each lot/batch of products.
c. Payment made once shall not be transferable/ refundable after submission of application.
d. Applications without the prescribed fee shall not be entertained.

Mode of payment

The lot release fee shall be paid in any branch of Allied Bank on the prescribed deposit slip available online on official website of DRAP www.dra.gov.pk and deposited in the branches of Allied Bank in favor of head of account as given below:

Title of Account: Drug Regulatory Authority of Pakistan.
Account No: **0010008463700018**
Bank: Allied Bank Limited.

APPENDIX-III

Government of Pakistan
Ministry of National Health Services, Regulations and Coordination

DRUG REGULATORY AUTHORITY OF PAKISTAN NATIONAL CONTROL LABORATORY FOR BIOLOGICALS

LOT RELEASE CERTIFICATE

(For Imported Biological Drug- Plasma-derived product in finished form)

Examined under authority vide DRAP Act, 2012 (Act XXI of 2012) dated Nov 13, 2012 and in accordance with the Standard Operational Procedure for the Lot Release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

Certificate Reference Number			
Date of Receipt of release application			
Date of Issue			
Trade Name			
International non-proprietary Name/common name			
Pakistan Registration number			
Dosage form			
Type of container			
Strength Details	**Group**	**Strength**	**Unit**
Invoice number and date			
Name and address of the Registration number holder			
Name and Address of the Authorized Person			
Storage temperature			

It is certified that this release of the batch is based on Summary Protocol Review (SPR) and lot mentioned below complies with the relevant specifications in the marketing authorization and provisions for the release of biological products and has been approved for release.

Batch No.	Manf. Date	Exp. Date	Total Qty Released

Federal Government Analyst, NCLB

APPENDIX-IV

Government of Pakistan
Ministry of National Health Services, Regulations and Coordination

DRUG REGULATORY AUTHORITY OF PAKISTAN NATIONAL CONTROL LABORATORY FOR BIOLOGICALS

LOT REJECTION CERTIFICATE

(For Imported Biological Drug- Plasma-derived product in finished form)

Examined under authority vide DRAP Act, 2012 (Act XXI of 2012) dated Nov 13, 2012 and in accordance with the Standard Operational Procedure for the Lot Release of human vaccines, blood products (plasma derivatives medicinal products) and anti-sera.

Certificate Reference Number			
Date of Receipt of release application			
Date of Issue			
Trade Name			
International non-proprietary Name/common name			
Pakistan Registration number			
Dosage form			
Type of container			
Strength Details	**Group**	**Strength**	**Unit**
Invoice number and date			
Name and address of the Registration number holder			
Name and Address of the Authorized Person			
Storage temperature			

It is certified that this rejection of the batch is based on Summary Protocol Review (SPR) and lot mentioned below complies with the relevant specifications in the marketing authorization and provisions for the release of

biological products and has been rejected.

Batch No.	Manf. Date	Exp. Date	Total Qty Released

Federal Government Analyst, NCLB

APPENDIX-V

Reference Regulatory Authorities (RRAs)

Sr. No	Country Regulatory authority	Country Regulatory authority	Link for database
01	**USA**	Food & Drug Administration (FDA)	https://www.accessdata.fda.gov/scripts/cder/daf/
02	**Canada**	Health Canada	https://health-products.canada.ca/dpdbdpp/index-eng.jsp
03	**Australia**	Therapeutic Goods Administration (TGA)	http://tgasearch.clients.funnelback.com/s/search.html?query=&collection=tga-artg
04	**Japan**	Pharmaceuticals and Medical Devices Agency (PMDA)	http://www.pmda.go.jp/PmdaSearch/iyakuSearch/
05	**UK**	Medicines and Healthcare Regulatory Agency (MHRA)	http://www.mhra.gov.uk/spc-pil/
06	**France**	National Agency for the Safety of Medicine and Health Products (ANSM)	http://agenceprd.ansm.sante.fr/php/ecodex/
07	**Germany**	Federal Institute for Drugs and Medical Devices	http://www.dimdi.de/static/de/db/dbinfo/aj29.htm
08	**Netherland**	Medicines Evaluation Board	http://www.geneesmiddeleninformatiebank.nl/nl
09	**Switzerland**	Swissmedic	http://www.swissmedicinfo.ch/Accept.aspx?ReturnUrl=%2f
10	**Austria**	Austrian Agency for Health and Food Safety	https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx?_afrLoop=5355900 7139362908&_afrWindowMode=0&_adf.ctrl-state=11ajcl0qd9_4
11	**Denmark**	Danish Medicines Agency	http://www.produktresume.dk/docushare/dsweb/View/Collection-256
12	**Sweden**	Medical Products Agency	https://lakemedelsverket.se/english/product/Medicinal-products/

13	**Norway**	Norwegian Medicines Agency	https://www.legemiddelsok.no/
14	**Europe**	European Medicines Agency (EMA)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=
15	**Belgium**	Federal Agency for Medicines and Health Products	http://bijsluiters.faggafmps.be/?localeValue=nl
16	**Finland**	Finnish Medicine Agency	http://www.fimea.fi/web/en/databases_and_registeries/spcs/human_medicinal_products
17	**Italy**	Italian Medicine Agency (AIFA)	https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/
18	**Ireland**	Health Products Regulatory Authority (HPRA)	http://www.hpra.ie/
19	**Iceland**	Icelandic Medicine Agency	https://www.serlyfjaskra.is/
20	**Spain**	Spanish Agency for Medicines and Health Products	https://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm
21	**WHO**	World Health Organization	https://extranet.who.int/prequal/content/prequalified-lists/medicines