GUIDELINE FOR LOT RELEASE OF BIOLOGICAL DRUGS

Document Number: **NCLB/GL/LR/001**

Document History: **2nd Edition**

Effective Date: **20-09-2023**

Drug Regulatory Authority of Pakistan

Islamabad-Pakistan

1. HISTORY

This is the Second edition of the guideline for the lot release of biological products.

2. APPLICATION-Guidance for Stakeholders and Regulators

This document is applicable for issuance of lot release of human biological drugs based upon summary protocol review and/or quality control testing of samples to ensure safety, quality and efficacy of human biological products.

3. PURPOSE

This guidance document outlines the requirements for lot release of biological products to ensure that each lot meets approved specifications. It provides an overview of the lot release process how the procedure is established and what products are covered under the lot release system. The primary objective is to safeguard the public from substandard product batches. The National Control Laboratory for Biologicals (NCLB) accomplishes this task by reviewing the summary protocol and scrutinizing the manufacturer's protocol and analytical methods as well as performing analytical testing if required. This diligent process ensures that all product batches that reach the market adhere to the approved specifications at the time of registration and post registration changes/variations in approved specifications.

Please Note: It is important to acknowledge that these guidelines represent the best regulatory practices and recommendations from the current thinking perspective of NCLB, DRAP. However, if any contraindication arises between this guidance document and applicable Acts, Rules, Regulations, or SROs, it is advised that the latter be prioritized. Adhering to these guidelines is significant to ensure that products meet the necessary standards in quality, safety, and efficacy.

TABLE OF CONTENTS

4. INTRODUCTION TO LOT RELEASE

The lot release of biological products is a part of the regulation of biological products and involves the independent assessment of each lot of a licensed biological product before it is released on to the market. The WHO provides recommendations and strategies for the lot release of biological products 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 population. 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 biological products, proper storage condition and efficient supply chain management must be ensured to preserve the sensitivity and limited shelf life properties of these products. For the reasons as stipulated above, a careful independent review of manufacturing and quality control data on every lot of product as stated is therefore necessary before use. Lot release 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 on the basis of 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 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 Biological Products.

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 influenzae 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 in order to reconstitute/ dilute to make it ready before final administration.
Electronic Data Logging Monitor (EDLM)	A small portable device 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 coloured liquid, all contained in a plastic casing. If the freeze indicator is exposed to temperatures below 0°C for more than 1 hour, the vial bursts and release the coloured liquid, staining the white backing card. 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 biological drugs 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, Hib 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 biological 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 biological products by regulatory authority is part of the regulation of these products and involves independent assessment of each lot before it is released on to the market.

As per WHO guidelines, for self-procured biologicals, 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 the exporting country.

7.1. Scientific Guideline Applicable to Biological Products 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.

8. SCOPE OF LOT RELEASE

The scope of this 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
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 already registered Biological Drugs.

9.2. Authorized officer (Officer notified by DRAP (I&E) for clearance of the consignment of imported biological products) is responsible for ensuring that this procedure is being followed.

9.3. Federal Government Analyst, National Control Laboratory for Biologicals, is responsible to issue lot release certificate on the prescribed form.

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

10. PROCEDURE

Registration holders are fully responsible to ensure 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 DRAPs Post Registration Variation Guideline for further details (PE&R/GL/PV/01).

i. Guidance on the Submission of Application

This guideline outlines the essential documents to be submitted with lot release application. All the documents shall be written in English only. Each document must be clearly tagged (indexed and labelled). Documents to be submitted are:

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) Summary Protocol of the product lot applied for lot release.
f) 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.
g) Certificate of Analysis (CoA) for Finished Product and Diluent etc. if applicable.
h) Batch production record of locally manufactured biological drugs.
i) Samples in quantities (one unit commercial pack as per requirement of storage conditions of the applied product).
j) If the Federal Government Analyst decides for testing of the biological product 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.

Application with incomplete documents shall not be entertained. After scrutiny of necessary documents, the application/ sample Receiver enters the required information in Lot Release Entry Register. Similarly, data is also entered in computerized database and in the respective file of each importer/ local manufacturer's file index.

SAR/Authorized person also assigns a specific LR number to each application and the same number is also mentioned on the accompanied sample(s).

After thorough summary protocol review and relevant tests results of NCLB if test performed, the Federal Government Analyst issues the Lot Release Certificate or the Rejection Certificate in duplicate, as the case may be, and status is uploaded on official website of DRAP and hands over the application along with the Lot Release /Rejection Certificate to the Archiving and documentation record section of the NCLB as per SOP for Lot Release of Biological Products. One copy of Lot Release /Rejection Certificate is attached with the application and filed in the respective file cabinet. The other copy is entered in Lot Release Dispatch Register/logbook and is handed over to authorized company representative.

In case of the rejection of a lot, a copy of lot rejection certificate will also be forwarded to the Division of Quality Assurance & Lab Testing, DRAP for initiating regulatory actions as applicable.

ii. Risk based classification of Lot Release Applications

Based upon origin of the biological products, lot release applications are classified in following categories,

Risk Classification	**Description**	**Requirements/ Assessment**
Low Risk	Imported from Stringent Regulatory Authorities and WHO pre-qualified sources.	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Review of recognized LRC from National Regulatory Authority/Agency (NRA) of the Country of Origin.
Moderate Risk	Imported from other than Stringent Regulatory Authorities and WHO pre-qualified sources.	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Review of recognized LRC from National Regulatory Authority/Agency (NRA) of the Country of Origin. iii. Testing of the products.
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.

iii. Criteria for Lot Release of Human Biologicals:

Based on origin and WHO guidelines, following mechanism will be followed for lot release of biological products:

Sr. No.	Description of Source of Origin of Product	Recommended requirements for lot release.
1.	Imported products.	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Review of recognized LRC from National Regulatory Authority/Agency (NRA) of the Country of Origin. iii. Testing of the products.
2.	Locally manufactured products.	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.

11. IMPORTED BIOLOGICAL DRUGS

11.1. Upon arrival of the shipment/consignment of imported biological products 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 period not exceeding two working days, with the direction to obtain lot release certificate from National Control Laboratory for Biologicals before release/ supply/ sale/ use of the biological drug.

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.i (a to i) addressed to the Director/FGA, NCLB.

11.3. Upon receiving the request for issuance of lot release certificate, the Federal Government Analyst, NCLB shall apply the prescribed procedure applicable to each biological drug and issue a certificate on prescribed form, if application found satisfactory in all aspects and lot rejection certificate if application not found satisfactory, 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 working days.
b)	Lot Release based upon Summary Protocol Review and Testing/ Analysis.	Within 60 working days.

c)	In case of emergency/ shortage/ Pandemic, declared by Federal Government/ Provincial Government or the DRAP Authority.	Within 2 working days.

11.4. Upon receiving the lot release certificate from National Control Laboratory for Biologicals the importer submits it to the authorized officer of DRAP (I&E) to get permission for the release/ supply/ sale/ use of the biological drug 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 BIOLOGICAL PRODUCTS:

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.i (a to i) addressed to the Director/FGA, NCLB of each lot/batch, within a week, directly to National Control Laboratory for Biologicals to obtain lot release.

12.2. Upon receiving the request for issuance of lot release certificate, after thorough review of summary protocol and/or testing of the applied biological product, the National Control Laboratory for Biologicals issues a certificate on prescribed form (Attachment-3/4) as per SOP for Lot Release of biological products.

12.3. As per schedule I of the DRAP Act 2012, the companies are to clearly specify in the BPRs which type of biological drugs they are manufacturing.

13. TESTING POLICY:

13.1. For local and imported products

13.1.1. The biological products for which the NCLB has the testing facility shall be subjected to the laboratory testing as and when necessary and shall be subject to the condition whether the product under question is a locally manufactured

or an imported product. Based on origin and WHO guidelines, following mechanism is followed for lot release of biological products:

Sr. No.	Description of Source of Origin of Product	Recommended requirements for lot release.
1.	Imported products.	i. Review of manufacturer's summary protocol based on product dossier which has been approved by DRAP during product registration ii. Review of recognized LRC from National Regulatory Authority (NRA) of the Country of Origin. iii. Testing of the products.
2.	Locally manufactured products.	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.

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

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

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

c) 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.

13.1.3. 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 biological drugs manufactured as per section 13.1.2.c).

13.1.4. In terms of summary protocol review of such locally produced biological drugs, the local summary protocol shall start onward from the last procedure conducted by the original manufacturer of the product.

13.1.5. 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.

13.1.6. 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.

13.1.7. For reference of requirements each biological product 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.

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

13.1.9. 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.

13.1.10. For the imported biological products for which the NCLB does not have the testing facilities at present shall be evaluated on the basis of 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.

13.1.11. For the imported biologicals 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.

13.1.12. 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.

14. HANDLING OF SAMPLE

14.1. Sample room in-charge is responsible for entering the sample information into the log books 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 in to the log book.

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 OF SAMPLES

15.1. Analyst/Manager Laboratory Operations performs the specified tests as per testing policy detailed as under; (as per testing policy described in SOP for lot release of biological products, SOP No. NCL/LR/SOP/006/11).

15.1.1 The imported products received are released on the basis of summary protocol review and LRC/ Exemption certificate from the country of origin.

15.1.2 The locally manufactured products are released on the basis of summary protocol review or/and testing.

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 on the basis of the marketing authorization dossier approved by the DRAP. WHO templates are available for some vaccines, but the agreed protocol should also take into account 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 are 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 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	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

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 461 (I) / 2013 dated 30-05-2013 and appendix-II of the guideline.

17.2.2. For the imported biologicals 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 have a mechanism for fast track release of the biological products 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 que 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 imported 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 lots 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 have been accumulated. The alert or warning limits and action limits of consistency trends should be defined on statistical grounds. In general, when data are distributed normally, ±2 and ±3 standard deviations of the mean are set for the alert or 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 condition may affect the quality, efficacy and subsequently the safety of the product. Hence, it is recommended that all

products should always be 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. For more information DRAP's Guidelines for Good Cold Chain Management Practices for Time and Temperature Sensitive Drug Products could be consulted i.e. readily available on DRAP's official website.

21. TYPES OF PACKAGING SYSTEMS

21.1. Active System

Actively powered systems employ electricity or other fuel source 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 build-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 and every 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 frozen ice packs in order to phase out the use of dry ice. In exceptional cases – where dry ice continues to be used – WHO recommends the inclusion of one cold chain monitor card per shipping carton instead of an electronic device.

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.

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

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

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 the case where stability data is lacking. Stability data is crucial and contribute 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 the 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 in order 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 includes appearance, identity, potency, safety and for some products, thermo-stability (e.g.

OPV). Type of tests conducted depends on the dosage form of the finished products but not limited to these tests:-

a) Solution/ liquid:

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

b) Freeze dried/ lyophilized:

i. pH test
ii. Appearance test
iii. Solubility test
iv. Osmolality (if required)
v. Bacterial endotoxin testing (BET) (if required)
vi. Particulate contamination test (visible & sub-visible particles) on reconstituted finished products.
vii. 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

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

a) Decision by the FGA, NCLB 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 of lot release/lot rejection are clearly stated in the lot release/lot rejection certificate, as the case may be 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 lot 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 situation, 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 biological drug, the aggrieved party may file an appeal against the decision of the 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

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)

CONTACT INFORMATION

NATIONAL CONTROL LABORATORY FOR BIOLOGICALS

Address: Prime Minister's National Health Park, Chak Shahzad, Park Road,
Islamabad Pakistan
Email: director@nclb.dra.gov.pk
Phone:92-51-9255263
Website:www.nclb.dra.gov.pk

****

APPENDIX-I

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

Lot Release Application Form

The Director/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 biological product 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 _____

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 _____ Received By (sig) _____
Application accepted □ Yes Name _____
If rejected (reason) _____ Designation _____

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

_____
Director/Federal Government Analyst

APPENDIX-II

SCHEDULE OF LOT RELEASE FEE

For Imported Vaccines, Sera and other Biological Products etc:

The lot release fee for all the imported biologicals including vaccines, sera and other biological products as provided in section 7 of Schedule-I of the DRAP Act, 2012 etc. is Rs. 20,000.00 per lot.

For Locally Manufactured Vaccines, Sera and other Biological Products etc:

The lot release fee for locally manufactured products is given below:

Product	Fee per lot/sample (in rupees)
Tetanus Toxoid.	30,000.00
Anti Tetanus Sera.	30,000.00
Oral Polio Vaccine.	20,000.00
Measles Vaccine.	20,000.00
Rabies Vaccine.	30,000.00
Hepatitis-B Vaccine.	20,000.00
Snake Venom Anti Sera.	30,000.00
Interferon	20,000.00
Any other biological locally manufactured	20,000.00

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 product.
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.
Branch: Civic Centre G-6, Islamabad, Pakistan
Branch code: 0117