Vaccines' Lot Release Guideline in Bangladesh

National Control Laboratory (NCL)

Directorate General of Drug Administration (DGDA)

Ministry of Health & Family Welfare (MOH&FW)

Govt. of the People's Republic of Bangladesh

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This Guideline adapted from "Guidelines for independent lot release of vaccines by regulatory authorities" (TRS_978_Annex_2) by WHO

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List of Abbreviations:

AEFI: Adverse Event Following Immunization
CoA: Certificate of Analysis
DTP: Diphtheria, Tetanus and Pertussis
EPI: Expanded Program on Immunization
EU: European Union
GMP: Good Manufacturing Practice
HPV: Human Papillomavirus
IS: International Standard
IU: International Unit
LR: Lot Release
MA: Marketing Authorization
MOH&FW: Ministry of Health & Family Welfare
MMR: Measles, Mumps and Rubella
NCL: National Control Laboratory
NNB: National Control Laboratory Network for Biologicals
NRA: National Regulatory Authority
OOS: Out of Specification
OPV: Oral Polio Vaccine
PMS: Post Marketing Surveillance
QA: Quality Assurance
QC: Quality Control
QMS: Quality Management System
SD: Standard Deviation
SOP: Standard Operating Procedure
TRS: Technical Report Series
UN: United Nation
WHO: World Health Organization
3 Rs: Replacement, Reduction and Refinement

1. Introduction

Vaccine lot release conducted by the regulatory authorities is part of the regulation of vaccines and involves the independent assessment of each individual lot of a licensed vaccine before it is released onto the market. This 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)/National Control Laboratory (NCL) and in some circumstances, by independent testing which is independent of the manufacturers' quality control (QC) testing.

WHO provides support for lot release programs through provision of written and measurement standards, strengthening lot release function of the NRAs and providing training. However, a need for further guidance was identified at WHO consultation held in Ottawa in 2007.

This document provides recommendations and strategies for lot release of vaccines by the NRAs/NCLs of producing and procuring countries. It should be read in conjunction with the recommendations/guidelines for specific products (e.g., recommendations for BCG, OPV, MMR, DTP, HPV, and rotavirus vaccines etc.).

Though it is difficult to provide a set of guidelines applicable to all national situations, an attempt has been made to cover a range of acceptable possibilities. Independent lot release involves the confirmation that each lot meets the specifications in the approved marketing authorization for the product. Under defined circumstances, laboratory testing by an NCL can provide added value to this confirmation. The need for testing should however be justified according to criteria as specified in this document and the laboratory should operate under an appropriate quality assurance system. When independent laboratory testing is undertaken, NCLs should ensure that it is conducted according to the principles defined in this document. Testing under inappropriate conditions may generate inaccurate data and lead to misleading decisions. This guideline also highlights the importance of networking and work sharing among NRAs/NCLs.

The guideline is intended to serve as a guide for national requirements for lot release. Accordingly, modification were made to the WHO-TRS (987, Annexure-2) considering that risks outways the benefit & it complies with national, International regulatory & legal standards.

2. Scope:

This document focuses on vaccines for human use. However, the main principles can also be applied to other biologicals.

This document provides guidance to DGDA, NCL and local vaccine manufacturers and importers. It may also be relevant to public health authorities such as Expanded Program on Immunization (EPI).

3. Glossary:

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

3.1 Deviation: Departure from a standard or norm or from set of limits.

3.2 Lot/sub-lot: A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a lot into a number of sub-lots, which are later brought together to form a final homogeneous lot. In continuous manufacture, the lot must correspond to a defined fraction of the production, characterized by its intended homogeneity. The lot size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

3.3 Lot Release: The process of NRA/NCL evaluation of an individual lot of a licensed vaccine before giving approval for its release onto the market.

3.4 Marketing Authorization: An official document issued by the competent national drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality.

3.5 Non-compliance: Failure or refusal to comply with a standard or a set of limits.

3.6 OOS: Out of Specification. An OOS result is generated when a vaccine is tested and fails to meet a pre-defined specification.

3.7 Responsible NRA/NCL: The NRA/NCL taking the responsibility for regulatory oversight of a product for the critical regulatory functions defined by WHO, including independent lot release. Usually it is the country of manufacture unless specific agreements exist within defined territories such as in the European Union where the 'country' of manufacture is the EU and the

activity of the responsible NRA/NCL is designated from among the Member States.

3.8 Self-procured vaccine: A vaccine that is procured directly from a source outside the country without intervention of WHO/UN procurement programs.

3.9 Source Material/Starting material: Any substance of a defined quality used in the production of a vaccine product, but excluding packaging materials.

3.10 Summary Protocol: (Also named as '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 manufacturing company.

3.11 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, reasons for any recalls and corrective action taken, as well as other pertinent post- market information.

4. General Considerations:

Vaccines are biological products used in healthy populations. The impact of using substandard lots may not be known for a very long time (years). Similarly, safety issues with a particular lot may not be known immediately (within a few hours) after administration, and there could be a drastic impact if a large number of healthy persons receive a vaccine before a problem is recognized. For these reasons, a careful independent review of manufacturing and quality-control data on every lot is necessary before it is marketed. Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programmes, thus potentially compromising public health strategies. Consequently, it is essential to assure the consistent quality of each lot before it is released onto the market.

Furthermore, vaccines and many of the tests applied to them are of a biological and complex nature, and have an inherent potential for variability. Therefore, an independent review of critical data from each lot of vaccines is essential to assure the consistent quality of each manufactured lot.

Reference standards used in the testing of vaccines are also biological in nature and prone to the same issues of complexity and stability as the vaccines themselves. For new products, national or international standards or reference preparations are not always available and there may be limited data on the stability of in-house or working standards used. Independent review of data is necessary in order to gain confidence in the results of tests using these preparations.

DGDA has independent laboratory i.e., NCL for testing of vaccines and independent unit for lot release of vaccines. Lot release is done based on minimum a thorough review and approval of the manufacturers' summary lot protocol with or without laboratory testing (for details see section 5.1), or through recognition of the decision of another regulatory authority.

All vaccine lots should be released by DGDA/NCL; however, in defined exceptional circumstances such as a public health emergency, exemption could be allowed. The permitted circumstances and the procedures to be followed to ensure quality in the absence of lot release should be covered by legal provisions.

Lot release is part of the whole regulatory framework, which includes Marketing Authorization, Regulatory Inspection (RI), Licensing Premises (LI), Laboratory Access & Testing (LT) and Post-Marketing Surveillance & Control (MC). DGDA and NCL maintains an effective mechanism for interaction between each department and exchange of information among them.

This is a national guideline for lot release of vaccine in Bangladesh. It explains total procedures from the submission of the lot for release to the issue of lot release certificates.

4.1 Consideration for Establishing Lot Release Procedures by NRA/NCL:

NCL, DGDA will follow the following approach for conducting lot release of locally produced, self-procured and vaccines procured through United Nation's (UN) agencies:

4.1.1 review of the summary protocol only

4.1.2 review of the summary protocol with independent testing (partial/ selected testing)

4.1.3 review of the summary protocol with independent testing (full testing) and

4.1.4 recognition/acceptance of lot release certificates from the responsible NRA/NCL of vaccine.

NCL, DGDA will decide appropriate strategy taking into consideration the type of the vaccine, the post-marketing experience (including production history and safety profile), and the availability of other independent evidence of product quality (see section 5.2). Considering the highly variable nature of biological products including vaccine and the complexity of the test method, any further (repeat) testing will be carefully justified to avoid "false" OOS results, which then require extensive investigation and delay vaccine supply.

For vaccines produced and authorized either for domestic use or for export, NCL/DGDA will take the responsibility for regulatory oversight of vaccine quality. The NCL/DGDA will initially perform test on selective consecutive batches of the vaccine until ensuring the quality of vaccines and development of confidence of NCL, in addition to carrying out a critical review of the summary protocols. After confirmation of the consistency of the quality through testing the chosen parameters, release of further lots should include full or selected testing or no testing, depending on the nature of the product and established experience.

In case, any of the manufacturer decide for toll manufacturing of a vaccine in any other country where it is not licensed, DGDA/NCL will take full responsibility for regulatory oversight. However, there should be a procedure to ensure good cooperation between the NRA of the country of manufacture and DGDA/NCL that granted the marketing authorization.

4.2 Encouragement of Networking and Work-sharing:

DGDA of Bangladesh is a member of WHO National Control Laboratory Network for Biologicals (WHO-NNB) and WHO Rapid Alert system. DGDA will share OOS and any other information/issues that will be useful for other countries in the network. This will also help limiting/ eliminating unnecessary or repeat testing/evaluation which is already done by other countries.

The sharing of test results can contribute to reducing the number of animals used for testing and can prevent samples being tested in laboratories that perform certain assays only infrequently, and so may have problems in maintaining technical competence. Work-sharing also enables the development of more complex and specialized methods through repetition of tasks and it provides a support network for problem solving.

NCL/DGDA will take part of the capacity-building activities for countries in a regional laboratory network. A fully functional regional laboratory network is a long-term goal, but cooperation can begin in the short term, with sharing of scientific information and experiences with methodologies regarding the evaluation and release of different products. NCL/DGDA will actively participate in the meetings organized by WHO to promote transparency and mutual confidence between the NRAs/NCLs.

5. The Responsibility of the NRA/NCL and the Manufacturer in Lot Release:

The quality, safety and efficacy of a medicinal product such as vaccines are the responsibility of the manufacturer. DGDA/NCL will ensure that the quality, safety and efficacy of a medicinal product such as vaccines are met.

The same requirements of regulatory oversight should apply to the production of vaccines whether they are intended for domestic use or export.

5.1 The Responsibility of the DGDA/NCL in Lot Release:

DGDA will grant/ issue the Marketing Authorization for vaccine and will be responsible for continued post authorization monitoring. To carry out this monitoring, DGDA has established NCL for vaccine testing and lot release committee comprising of experts on lot release activities. These activities are specifically mentioned in proposed Drug Act 2022; however, for the interim period such activities are performed by the executive order from Ministry of Health & Family Welfare (MOH&FW).

Responsibilities of the DGDA/NCL for issuing the lot release certificate has been mentioned in legal provision. Timelines and other details will be defined in in-house procedure. The manufacturer and relevant health authorities should be informed in the event of a delay.

The DGDA/NCL have the procedure to request adequate samples required for lot release from manufacturers, when required. The procedure also describes lot identification and retention for future reference.

NCL also has access to external qualified laboratory with specialized facilities, equipment and expertise.

NCL is independent of the manufacturer and any other laboratory. NCL does not share any staff or resource which can create conflict.

The DGDA/NCL post and regularly update mechanism for the independent lot release procedure in DGDA website in a clear and transparent way regarding requirements, timelines etc. so that the process is completed smoothly and in a timely manner.

DGDA/NCL will be responsible for providing information concerning the quality of the lot of product in question to the NRA/NCL of an importing country upon request. Rules and procedures regarding confidentiality of information is maintained and the data submitted by manufacturers and other NCLs/NRAs is kept as

confidential unless agreed otherwise as per the defined procedure of NCL/DGDA. The DGDA/NCL has the responsibility to ensure the production and release of assured quality vaccines whether they are used in the country or exported. The vaccines for local use and those for export should have the same level of quality.

5.2 The Responsibility of the Manufacturer/Importer in DGDA/NCL Lot Release:

The manufacturer has the following responsibilities in terms of DGDA/NCL lot release:

5.2.1 Collaborate with the DGDA/NCL to develop the product summary protocol template, when requested (the WHO summary protocol of each product could be used as the template);

5.2.2 Submit each manufacturing and control summary protocol

5.2.3 If requested, submit samples in an appropriate condition including packaging, leaflet and label

5.2.4 Assist DGDA/NCL in technical transfer of testing methods including training, wherever required

5.2.5 Submit the lot release certificate of the responsible NRA in the case of vaccines from outside Bangladesh

5.2.6 Provide product specific reagents and working reference materials with certificate, as needed

5.2.7 Participate in collaborative studies in establishment of a national standard

5.2.8 Work with DGDA/NCL to resolve any discrepancy on test result

5.2.9 Take appropriate action on the issues related to any error/ noncompliance

5.2.10 Take appropriate action on any rejected lots according to GMP requirements

5.2.11 Provide any documents, data (paper and electronic) or other information regarding the quality of the vaccine, required by the DGDA/NCL

5.2.12 Provide justification of any variation of test method used, for example for In-vivo test in place of In-vitro test.

5.3 Establishment of Quality Management Systems for the DGDA/NCL:

DGDA/NCL established a quality management system (QMS) to support lot release activities which include the following key elements:

5.3.1 Trained and qualified personnel

5.3.2 Adequate and calibrated equipment

5.3.3 Management of records and documentation

5.3.4 Identification and retention of samples (when applicable)

5.3.5 Use of validated test procedures, written procedures

5.3.6 Internal and external audit systems and oversight procedures

5.3.7 Health, Safety and Environmental compliance

5.3.8 Maintain appropriate storage system

5.3.9 Ensure data integrity

NCL follows WHO Guidelines for national authorities on quality assurance and other quality-related documents

6. Conducting Lot Release:

6.1 While conducting lot release:

6.1.1 The manufacturers' summary lot protocol is reviewed by DGDA/NCL before release of a lot onto the market to ensure that specifications defined in the marketing authorization dossier are met.

6.1.2 Where appropriate, review of the summary lot protocol could be complemented by the independent testing (partial/ complete testing).

6.1.3 Product consistency will be assessed through trend analysis on successive lots (see section 7). When NCL do not receive consecutive lots or receive only a small number of the production lots, interpretation of trend may require addition information (e.g. yearly biological/vaccine product report) from manufacturer.

6.1.4 In case of imported vaccines, any available lot release certificate issued by the responsible NRA/NCL, in particular the one from the producing country, should be considered in the overall assessment of a vaccine lot. If the lot release certificate is not provided together with the summary protocol, the NRA/NCL should have the authority to request it.

6.1.5 In case of public health emergency expedited lot release may be

performed based on 'reliance' mechanism. In such case lot release may be considered based on the lot release certificate provided by the NRA of country of origin and or any other responsible NRA.

6.1.6 In case of serious public health emergency/outbreak of disease lot release can be waived; however, lot release certificate must be taken when the situation will be under control.

6.1.7 Parallel testing may be performed where a quicker lot release is required.

NCL maintain appropriate laboratory facilities with experienced, competent and skilled laboratory staff along with established QMS for performing independent testing, when required.

6.2 Protocol Review:

The manufacturers send the summary lot protocols which contain summarized information taken from the production and test records according to GMP requirements to ensure that the lot meets the specifications in the market authorization. Summary lot protocol of manufacturer will be approved by the appropriate quality assurance (QA) or QC responsible person and submit to DGDA/NCL.

The format and content of the protocol is finalized and approved by the DGDA/NCL during the review of the license application and the format of the protocol will be amended in response to changes in the approved production process and approved by the DGDA/NCL.

6.2.1 Principles:

Protocol review is conducted by lot release committee of DGDA/NCL. The same format of the summary protocol will be used for the same product in different markets. In case, vaccines are to be exported to outside Bangladesh protocol format may be adjusted depending on the information required.

Independent review of critical data from each lot of vaccines is essential in order to:

6.2.1.1 assure the consistency of quality of every lot of each vaccine;

6.2.1.2 obtain confidence in the strength of active components claimed, and

6.2.1.3 assess the validity and accuracy of the tests performed.

DGDA/NCL review the traceability of critical source materials, active and

critical components used in the manufacture of the product, used reference standard/ working standard and the results from tests performed by the manufacturer at various stages of production, including tests performed on critical components, intermediates, final bulk and final product. However, lot release certificate will be issued based on the careful reviewed of the information on final product.

6.2.2 Summary Protocol Template:

Format of summary lot protocol is approved by DGDA/NCL which is developed as per WHO templates and the information and specific requirements from approved marketing authorization dossier.

The summary protocol template is a controlled document. If any changes to the template due to changes in manufacturing process or testing should be traceable. Lot release committee is responsible for reviewing these documents and ensure that the latest version of the license is reflected in the summary lot protocol submitted by the manufacturer.

Each summary lot protocol is vaccine specific, but there are a number of general items (see the following table) that a summary protocol should cover.

Table. Information to be included in the summary lot protocol for review

Items	Essential information to cover	Critical parameters to review
Identity of manufacturer	Name of the manufacturer	License validity check, Latest inspection report
License number	Unique license number	License number
Site(s) of manufacturing	Site of manufacturing for each bulk, final bulk and final product	Name and address of each bulk, final bulk and finished product manufacturing site
Name of the product	Trade name & International/ common name	Approved Trade name & International/ common name according to MA dossier
Name and lot number	Name and lot numbers of the final products, bulk, final bulk and the diluent, if applicable.	Final lot name and lot number, Each bulk lot number (if applicable), Final bulk lot number & Diluent lot number (if applicable)
Lot size	Volume, number of doses and type of container	Batch/lot volume, final production batch size, number of doses, container details

Expiry dates	For each starting material (if applicable), intermediates, final bulk, and final product.	Expiry date of each starting material (if applicable), intermediates, final bulk and final product
Dates of manufacturing	Of each critical starting material (e.g. seed lots, cell banks, starting materials of animal origin etc.), intermediate, final bulk and final product	Check and compare against noted expiry dates etc; to calculate and confirm values
Flow chart	Flow chart for the traceability of manufacturing process for major components including lot numbers	Identity and logic flow for starting materials, intermediates, final bulk and final product confirmed with room environmental details (wherever required)
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 DGDA on marketing authorization and/or recommended by WHO (e.g. OPV);
Manufacturing process	Each production processes (such as cultivation, purification, inactivation, etc.), the methods of QC tests as well as their release specifications and the results obtained. Lot number of intermediates and their size/volume, storage conditions.	Confirm they are the same as per approved dossier by MA. Confirm the yields of critical production processes are within the acceptable range.
Formulation	Date of formulation. Amount of active components in the final formulations, with the lot numbers and volumes of bulk concentrates. Storage condition.	Date of formulation. Verify calculated and actual values based on information provided as per product specific annexure

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. Testing method should be Validated/verified. Provide the starting date of test, method, and a list of reference preparations, standards, critical reagents and their qualification status, performance of relevant reference preparations, standards and internal controls, such as results of assay validity criteria, (for example, slope, intercept, linearity, 50% end points, results of internal controls, challenge doses). Provided with 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	Date of QC tests for identity, purity, safety, potency (strength) and thermostability of the product are in compliance with the approved specifications. Check traceability of validated/ verified method, reference material, test parameters and result.
Details on final lot	Filling & sealing information, Physical checking and labelling, Packaging details	Check details of Filling & sealing information, Physical checking and labelling, Packaging details with environmental condition of the room
Storage condition of finished product	Detail information of storage condition (temperature, humidity)	Check data of storage condition
Batch release certificate from manufacturer	Name of the product with batch number and quantity. Method reference	Check the batch release certificate and method reference

6.2.3 Checklist for Summary Lot Protocol Review:

NCL has vaccine specific checklist in the review of summary lot protocols for thorough review. A checklist for each section of the protocol should be developed to ensure a complete review of the information. Checklists has been developed according to the critical parameters in the production and control

processes, such as strain and acceptable passage level of seed, acceptable passage level of cell substrate, purification method, methods and release specifications of quality control tests and shelf life of intermediates. Checklists are vaccine specific for a registered product and/or a test, in accordance with both Marketing Authorization dossier and WHO TRS and may be a copy of the protocol template with the specific required manufacturing information included for reference (e.g. name of the cell line, origin, testing methods and specifications for starting materials, intermediates, final bulk and final product etc.).

6.2.4 Protocol Review Process:

Summary lot protocol review process is highly dependent on the quality of the information provided by the manufacturer. Reviewing summary lot protocols requires a good understanding of the product and laboratory control methods. After receiving the document from manufacturer for lot release of a product, documents are reviewed by one person or lot release committee and approved by DGDA/NCL. A validated database with adequate access controls and traceability for trending and tracking of the data submitted is maintained by NCL.

DGDA/NCL starts lot release process with the receipt of manufacturers' documents including packaging and labelling insert and required number of test samples. After initial verification of the label information for the test sample and on the summary lot protocol, the protocols are documented into a database or otherwise recorded. At receipt, the first step in protocol review should be confirmed that the manufacturer has used the approved template for the given vaccine. Then the protocols are routed to the lot release committee within the DGDA/NCL that had already been formed based on their expertise. This should be traceable according to QA management procedures.

NCL maintains database for capturing information on lot size, results of tests, information of reference standards and controls, etc. are useful for tracking and trending of information for a particular test or section of the protocol. The results of tests and performance characteristics of reference standards and controls, specification limits, including appropriate confidence intervals of typical results for a period of time, etc. will be shown. In all cases, databases will be secured to avoid unauthorized addition, revision or deletion of

information and a backup system should be provided. A separate procedure should be developed for tracking and trending of manufacturers' results and information describing parameters to be tracked and trended, frequency of periodic reviews, actions to be taken in case of out of normal trends, etc.

In general, a particular lot of the product is satisfactory if the protocol review shows that all of the elements described in the table in section 6.2.2 have been compared against the characteristics approved in the marketing authorization and have been found to be compliant.

For freeze-dried/thawed vaccines, the protocol or Certificate of Analysis of the particular lot of diluent is also reviewed.

6.2.5 Handling of Discrepancies and OOS Results in Summary Protocols:

In the submitted summary lot protocol if any discrepancies, errors or OOS found will be documented and verified before communicating these to the manufacturer. NCL/DGDA has procedure to communicate this issue to the manufacturers or NRA of the vaccine producing country and other related activities to resolve this issue with appropriate traceability. This may include formal notification by memo or letter, an email or minutes of telephone discussions. Manufacturers' responses should be reviewed and documented in making the decision on the lot. This can include submission by manufacturer of the corrected page/version of the summary protocol which then should be traced by NRA/NCL. Depending upon the nature and severity of the discrepancies or errors, the manufacturer may be asked to perform an investigation to determine the root cause for the discrepancies, including steps for the corrective and preventive actions to avoid similar problems in the future. For imported lots, communication with the NRA of the producing/releasing country may be required. For producing/releasing countries, communication with the country inspectorate could be required. Such information exchange can help to judge the corrective and preventive actions introduced by the manufacturer.

6.3 Independent Testing:

NCL developed technical expertise that enables independent testing to monitor and assess the key product quality control parameters and consistency of product as well as other issues when they arise.

NCL/DGDA has subcontracting procedure to carry out the quality testing to be performed by another laboratory other than NCL that laboratory already pre-assessed

by NCL according to WHO recommendations. All information exchange will be handled in a confidential manner and there will be a system to ensure that there is no conflict of interests. The final decision on the test results lies with the responsibility of DGDA/NCL.

6.3.1 Purpose of Independent Testing:

NCL verifies the test results of manufacturer during lot release. All testing is performed in a systematic way by qualified NCL personnel and monitor the continuing suitability of the methods and reference materials and allow detection of possible unaccounted-for drifts in these parameters. This can help for feedback to marketing authorization, in case, a need is identified to revise the specification in the marketing authorization dossier and the expertise can be used to aid GMP inspectors in a coordinated approach. Testing by NCL also maintains independent expertise in the test methods. This is an important aspect for overall competence of an NCL in its ability to effectively monitor the product.

6.3.2 Prerequisites for Setting Up Independent Testing for Lot Release:

A defined procedure is established for testing as part of overall lot release activities. NCL staff are involved in the marketing authorization evaluation process (for pharmaceutical quality information at least), should have knowledge of the marketing authorization dossier and able to identify and assess the critical parameters for testing.

NCL has Quality Management system (QMS) for setting up testing policy of lot release procedure. The QMS include a quality assurance system appropriate for testing laboratories which is based on internationally recognized quality standards and that undergoes regular internal and external review (e.g. as WHO Guidelines)

QMS ensure technical staff training, maintenance of equipment, standard operating procedures (SOP) for techniques, daily running of the system and dealing with OOS results. The NCL have sufficiently skilled, trained and qualified personnel with the appropriate technical and scientific expertise, and appropriate equipment/infrastructure also available.

Vaccine specific test methods are validated following QA standards (including equipment qualification), before independent testing are performed. NCL has

established documented and approved procedures and guidelines both for internal use and for transparency with any partners including other NCL and the manufacturer of the product.

NCL has good communication system with the manufacturer. NCL will discuss with the manufacturer and MA department for the transfer of assays, if required to allow transfer and qualification/validation of the methodology prior to apply to the first lot for lot release testing. Comparison of testing results between the NCL and the manufacturer is important and done by trend analysis, since specifications for some biological assays (i.e. potency and or antigen content, identity, preservative content etc.) are dependent on the analytical technique used, to avoid potential discrepancies that may be related to the methodology used and not to the quality of the product.

6.3.3 Establishment of Testing Policy:

NCL implements lot release testing policy by addressing the pre- requisites noted in section 6.3.2.

To conduct independent testing, NCL will estimate the own laboratory capacity and will take the information available from other NRAs/NCLs who can also release the same product.

The establishment of a testing policy should be made separately for each product and should consider four main aspects:

6.3.3.1 Should the vaccine be tested by an independent authority?

6.3.3.2 If testing is required, what critical parameters should be tested by the NCL?

6.3.3.3 Should it be done on every lot or on some reduced percentage of lots? and

6.3.3.4 Are testing results available from another NCL?

Following points need to consider which may influence the testing policy:

- Nature of the final product (live, inactivated),
- The biological nature and complexity of source material,
- The complexity, robustness and level of control of the manufacturing process and
- The nature and complexity of the QC methods.

Manufacturers' production history and other information required for deciding testing

policy will be obtained from summary lot protocol and/or yearly biologic product reports, in some circumstances, which contains production and testing information. Other information may be obtained from GMP inspection report, adverse event following immunization (AEFI) report, product complaint and other post marketing surveillance safety and quality information. The testing policy for the same product at other NCLs may also be taken into consideration in establishment of the testing policy.

Risk-based approach for analysis will be applied while deciding testing policy. In order to decide risk-based approach consistency of the product will be evaluated. Consistency will be assessed based on-

- Previous testing report in NCL
- Manufacturer's yearly test report
- From DGDA GMP inspection report
- From trend analysis data of NCL and manufacturer

Based on the information, frequency and parameters of testing will be decided.

6.3.4 Criteria for Selection of Tests for Lot Release and Percentage of Lots to be Tested:

Once the decision to perform independent testing is taken, the NCL will concentrate on selection of critical elements from the marketing authorization requirements to be tested and the percentage of lots to be tested.

Key elements of focus where tests may be considered necessary include appearance, identity, potency, specific safety and for some products thermostability (e.g. OPV). Systematic testing of simple physical-chemical parameters may not be the highest priority when considering the best use of resources. Some parameters are better monitored through other tools such as GMP compliance (e.g. sterility testing by aseptic process validation and environmental monitoring by the manufacturer). In all cases the added value of the independent results for the tests chosen should be carefully considered in the context of the overall evaluation of the lot.

Testing is generally focused on the final product. The formulated final bulk may be tested in some cases (e.g. in the case of combination vaccines). Nevertheless, a complete evaluation of the properties under question may require assessment of

upstream components (e.g. monovalent bulks). This may also be necessary if test procedures cannot be applied to final products (e.g. if the presence of adjuvant in the final product prevents immunochemical analyses).

Specific attention will be paid to new vaccines as well as new manufacturers, for which there is little accumulated experience and sophisticated combined vaccines for which testing and interpretation of results can be complicated.

It should be encouraged to develop and adopt more effective test methods which should be approved by DGDA. If a different test method is used by the NCL, in case of discrepant data between the manufacturer and the NCL, then the approved test method defined in marketing authorization should be used to solve the test issue.

There will be a regular review of the testing policy in order to re-evaluate the need and appropriateness in the current situation. Additional tests may be included or existing tests deleted as required. Informal testing outside of a planned programme without sufficient preparation should be avoided as this can generate non-relevant or misleading test results.

The percentage of lots of a given product to be covered by the testing programme which will be described in the internal procedure in advance. If a reduced percentage of lots are tested the lots should be representative of the total production (e.g. selected number of bulks covering a maximum of final lots or selection of filled lots issued from the same bulk). If less than 100% of lots are tested, decision to which lot will be tested will be controlled by NCL and manufacturer will not be aware about it.

The percentage of lots tested should be monitored and revised if necessary, based on the experience with the product and data from the yearly biological product report (e.g. good consistency over a significant period may lead to reduce the percentage of lots covered, while observance of an undue number of failing results and/or specific testing issues may result in increased percentage of lots to be tested).

Development of testing methodology and capability should begin as soon as possible for both responsible DGDA/NCL and manufacturer, possibly at the clinical trial stage. However, while testing of samples by an NCL for clinical trial approval stage is recommended in WHO guidelines, this is not considered lot release per se. Although additional guidance in this area is needed this document

focuses only on the lot release procedure for licensed products.

6.3.5 Importance of Reference Preparations for Lot Release:

Appropriate use of reference preparations in independent testing is of critical importance for the interpretation of the results. This has a particular impact on the ability to make relevant comparisons between test results from different laboratories (e.g. manufacturer and NCL) and the decision making process.

Control charts of critical parameters of reference preparations should be kept to monitor performance over time. This allows overview of both the reference preparation activity and the method. For example, it could show if there has been a trend or a shift in the reference standard attributes, such as slope, intercept, 50% end point that may indicate problems with stability of the reference standard or changes in other assay systems, for example, animals, cells, critical reagents, etc. Another example of the utility of trend analysis is the assay validity criteria based on 95% confidence intervals. If the assay validity criteria on any attribute of reference standard, slope, intercept, etc or potency of control is based on 95% confidence intervals and the actual data does not show approximately 95% acceptance of the assay based on that particular attribute, there may be problems with setting the limits or performance of that attribute.

The observations from this exercise can be important for feedback to marketing authorization authorities and/or bodies involved in biological standardization activities and can be used also to evaluate the appropriateness of the reference materials used and/or the need for new ones.

Reference reagents are developed to improve standardization of assays. They are becoming increasingly important in the context of new vaccines such as multi-component vaccines. In many cases the reference reagents are established and prepared by the manufacturer as they are often product specific. These reference reagents should be calibrated in IU against an international standard, when it is exist.

6.3.6 Standards:

NCL will procure working standard and reference standard/ secondary standard for test analysis of vaccine and biologicals.

Until NCL able to procure Working Standard (WS) will use WHO International

standard (IS) as a basis for calibration of secondary standards

6.3.7 Practical Considerations:

The number of samples of the final lot or upstream components requested by NCL should be appropriate for the testing required and the sampling procedures will ensure the representativeness of the lot in question. A system will be in place for recording, tracking and appropriate storage of all samples upon receipt from the manufacturer.

It may be necessary to obtain product specific reference materials or reagents from the manufacturer. The amount requested should be relevant to the amount of testing to be performed and not place undue stress on the supply of the material as it is often available in limited stocks.

The time required for testing is an important issue as it can greatly influence the supply chain and can have a significant impact when products have short shelf lives. This can be of particular concern when in vivo tests, which can take several weeks to complete, are involved. Under certain circumstances, the DGDA/NCL may agree to receive samples from manufacturers before they have completed their own test procedures so that testing by the NCL is done in parallel. In such cases, the lot cannot be released by the NCL until all the test results from the manufacturer have been received (including the completed and signed final summary protocol with their test results). The NCL will evaluate the risk-benefit of parallel testing, mainly considering the frequency of lots rejected by either the manufacturer or the NCL.

When animals are used for testing, the NCL should be aware of the potential variability of the source, housing and handling of animals. NCL will apply the 3R principles (reduction, replacement, refinement) to minimize the use of animals for ethical reasons. Validated In-vitro alternatives should be favored wherever possible. However, the type of testing should be driven by the scientific need for valid relevant data. Moreover, agreements will be sought with NCL from the exporting country or other NCLs in a mutual recognition or collaborative agreement, to utilize results of animal testing already performed by another NCL in the spirit of minimizing animal testing worldwide.

6.3.8 Release Specifications:

DGDA/NCL lot release will only pertain to products that have a valid marketing authorization in which specifications have been approved by DGDA.
Usually NCL experts are involved in assessing test method, validity criteria and product specification prior to MA approval. There is also procedure to let NCL be aware of any variations of the approved license specifications happened.

6.3.9 Evaluation of NCL Results:

The NCL test results should be assessed against the specifications approved in the marketing authorization dossier. It is understood that the variability expected in the results for a given test method for a given product should already be accounted for in the specifications. To be in compliance with the marketing authorization, the test result should fall within the defined acceptance criteria, which are based on the validated methodology used by the NCL and the specifications approved in the marketing authorization.
The NCL will define and follow on it's own re-test policy, if applicable, combination of their results is performed and how these results are evaluated. The acceptance criteria should also be predefined and laid down in relevant SOPs.
The NCL has a predefined standard procedure to deal with results that do not comply with the specifications. This include a confirmation that the results reflect the actual quality of the lot tested and is not due to analytical error by the NCL or the influence of variables unrelated to the product.
The manufacturer will be notified when an OOS result is confirmed and exchanges should ensue to try to identify the cause of the discrepancy.
A test report, including the results and outcome of all of the testing will be prepared for final evaluation of the lot and the decision making process.
A feedback mechanism from NCL to DGDA exist in order to coordinate and optimize regulatory actions (e.g. urging license variation, refinement of product specification based on trend analysis etc.).

7. Data Monitoring:

All critical quantitative data from QC results and especially potency from the manufacturer or other sources NCL 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 will be defined on statistical grounds. Generally, ± 2SD and ± 3SD of mean are set for the alert or warning limits and action limits, respectively, when data are normally distributed. In general, the variability and precision of the test will be considered when defining the limits. Care will be taken in interpreting such limits when based on small data sets. Trend analysis of key parameters may be requested from manufacturers or the responsible NRA/NCL. 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 one year) will be analyzed statistically compared to that of the previous period in order to detect any significant differences or shift in trends.

NCL has the established procedure describing this tracking and trending of manufacturers' and where available the NCL results, will be developed. This procedure will describe parameters to be tracked and trended, frequency of periodic reviews, criteria for judgment, actions to be taken in case of out of trends, etc.

7.1 Trend Analysis Including the Data from the NCL:

NCL will perform independent testing of lots. All data from the tests, including performance of reference standards and controls will also be trended and analyzed. It should be kept in mind that not all countries test all consecutive lot from a manufacturer. For these cases the interpretation of 'trends' will be made with caution and may require additional information from the manufacturer either directly or through contact with the relevant national inspectorate.

7.2 Comparison of Results of the Manufacturer with Those of the NCL:

Results from the NCL will be compared with those of the manufacturer. Any systematic differences will be documented. Any differences in trends will be investigated and resolved, in collaboration with the manufacturer. Testing by the NCL may, however, occur months after the manufacturers' release, so this should be taken into consideration when the NCL makes the comparison.

8. Evaluation of the Lot and Decision Making Process:

8.1 Establishment of Decision Making Procedures:

Head of NCL is responsible for issuing lot release certificate. Once all respective batch/lot documents are available for final evaluation, a formal decision making process is in place to decide whether or not the given lot can be released. An established procedure will be in place to clearly describe the lot release process and required documents for the final decision. Good coordination and communication is needed especially when different bodies i.e., DGDA/NCL/Manufacturer/Importers etc., are involved in this process.

In order to provide continuity and develop expertise on each particular product, it is desirable that product specialists are assigned with the responsibility of managing the relevant information for each product. A general lot release process chart will be in place outlining the lot approval process and the persons responsible for each activity.

The approach to independent lot release by LR committee will be appropriately described in NCL lot release flow charts. Procedures will cover the relevant options used: release upon review of summary protocol only and/or release upon review of summary protocol plus independent testing (partial/full testing) by NCL. The respective flow chart will define the initial step of receiving application to final decision is taken based on the formal written conclusions. SOPs or documents are necessary to cover the following essential elements:

8.1.1 An SOP for summary protocol review describing all reviewing steps up to and including the final conclusion on the summary protocol (e.g. need for manufactures' correction, review of corrected pages, investigation, conclusion etc.).

8.1.2 The DGDA/NCL has established a formal vaccine specific checklist regarding the summary protocol review and this checklist will be filled up to ensure compliance with approved specifications and will be signed by the responsible person.

8.1.3 An SOP is available for describing acceptance criteria for each parameters of individual vaccine as per MA Dossier and recording all the individual test results in Certificate of Analysis (CoA).

8.1.4 After analysis of vaccine in NCL, a formal report will be developed by responsible analyst to capture the test results and final CoA will be signed by the responsible person of NCL.

8.1.5 A retest policy is developed following general QA principles, to define the policy for retesting and handling of OOS results. In addition, an SOP also in place to give guidance on retest policy according to product-specific recommendations (e.g. combination of results, calculation method etc.). If any non-compliance occurs, a full traceability investigation will be conducted on test reports and the manufacturer will be contacted for further investigation and record the communication. As part of the QA, in the event of derogation, an SOP exists to outline the decision making process including documentation and written criteria to support the decision made.

8.1.6 An SOP describing the acceptance criteria for lot release of vaccines in exceptional cases when deviation from the normal procedure is necessary. Examples include, release for an emergency/crisis situation, urgent need due to a critical supply shortage, when information is pending regarding correction for summary protocol, or in the event of discrepancies between NCL and manufacturer's test results. The procedure will be developed, based on a risk/benefit analysis taking into account all available information. This will only be applied by the Head of NCL for signing the release certificate with approval from Director General of DGDA. Documentation supporting compliance with approved specifications (summary protocol review and test reports, if applicable), will be included.

8.1.7 All the steps in the decision-making process will be documented.

8.2 Recognition of/Confidence in Lot Release by Other NRAs/NCLs:

In cases where a lot has already been released by another NRA/NCL, it may be possible to accept that lot for release based on the existing release certificate. DGDA/NCL has mechanism for recognition of test result and lot release by another NRA/NCL through to Mutual approach. NCL has list of NRAs/NCLs who it recognizes. NCL maintains strong collaboration and communication between the different NRAs/NCLs and a good level of transparency.

Agreements covering specific products could enable DGDA/NCL to accept the test results provided by another NCL, thus avoiding repeat testing and facilitating harmonization without compromising the safety and quality of the product or extending the agreement to full mutual recognition of all lot release. The test results

provided by another NCL could thus be used, in addition to the protocol evaluation by DGDA/NCL when they evaluate the lot for release.

These types of approaches provide the advantage of limiting repeated evaluation and testing and they serve to streamline the release procedure.

Other benefits of the confidence building required for such approaches may be training and capacity building for review and product assessment.

NCL will always ensure the integrity of confidentiality of the stakeholders including manufacturer/ procuring agencies.

8.3 Release Certificate Issued by the NRA/NCL of a Producing/Releasing Country for UN Procurement:

If DGDA/NCL performs lot release of UN procured vaccine, such lot release will be done on as a minimum, reviewing of the lot summary protocol only because vaccines distributed through the UN Agencies are prequalified by the WHO, to ensure that the product complies with the quality and safety standards established by the WHO.

The release certificate issued by NRA/NCL should be forwarded by the UN Agencies to the DGDA/NCL and the summary protocol will be provided upon request.

DGDA/NCL may consider review of summary lot protocol and/or testing to develop competency, confidence in their activity and also to have an overview of the quality of vaccine. However, if any deficient result is detected responsible NRA/NCL of the producing country should be consulted.

9. Lot Release Certificate:

A release certificate for each vaccine lot will be issued by the NCL, DGDA and sent to the manufacturer (and procuring agencies/distributors/local agents/organizations, where applicable) confirming that the particular lot meets the approved specifications and related provisions. This release certificate is the official document that authorizes the manufacturer (and procuring agencies/distributors/local agents/organizations, where applicable) to release the specific lot onto the market. The certificate may include the following information, but not limited to:

9.1 Name and address of manufacturer;

9.2 Site(s) of manufacturing;

9.3 Trade name and/common name of product

9.4 Marketing authorization number

9.5 Lot number(s) (including sub-lot numbers, packaging lot numbers, if necessary)

9.6 Type of container

9.7 Number of doses per container

9.8 Number of containers/lot size

9.9 Date of start of period of validity (e.g. manufacturing date) and/or expiry date

9.10 Storage condition

9.11 Signature and function of the authorized person and authorized agent to issue the certificate

9.12 Date of issue of certificate

9.13 Certificate number

Other details, such as dosage form, strength of the product, registration code (NRA/NCL code for lot release) may also be included in the certificate according to the requirements of different countries.

The conclusion should be included clearly in the certificate, for example: "the lot mentioned above complies with the relevant specification in the marketing authorization and provisions for the release of biological products and has been approved for release". The statement should also give an indication of what the release decision was based on e.g. evaluation of summary protocol, independent laboratory testing, specific procedures laid down in defined document etc. as appropriate.

For those lots failing to comply with the provisions, a different form will be issued which clearly states that the lot is non-compliant, ideally with a different color from the approval certificate.

The language on the lot release certificate is in English language.

10. Reference Documents:

10.1 Guidelines for National Authorities on Quality Assurance for Biological Products. In: WHO Expert Committee on Biological Standardization. Forty-second Report. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 822).

10.2 Regulation of vaccines: Building on existing drug regulatory authorities. Geneva, World Health Organization, 1999 (WHO/V&B/99.01).

10.3 WHO NRA assessment tools/indicators. Geneva, World Health Organization, 2008.

Available at:
(http://www.who.int/immunization_standards/national_regulatory_authorities%20/vaccine_indic ators/en/index.html/).

10.4 Training manual: licensing, lot release, laboratory access. Geneva, World Health Organization, 2001 (WHO/V&B/01.16).

10.5 Requirements for dried BCG vaccines. In: WHO Experts Committee on Biological Standardization. Thirty-six Report. Geneva, World Health Organization, 1987, Annex 2 (WHO Technical Report Series, No. 745).

10.6 Recommendations for the production and control of poliomyelitis vaccine (oral). In: WHO Expert Committee on Biological Standardization. Fifty Report. Geneva, World Health Organization, 1999, Annex 1 (WHO Technical Report Series, No. 904).

10.7 Requirements for measles, mumps and rubella vaccines and Combined vaccines (Live). In:WHO Expert Committee on Biological Standardization. Forty-third Report. Geneva, World Health Organization, 1994, Annex 3 (WHO Technical Report Series, No. 840).

10.8 Requirements for Diphtheria, Tetanus, Pertussis and Combined vaccines. In: WHO Expert Committee on Biological Standardization. Fortieth Report. Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 800).

10.9 Guidelines to Assure the Quality, safety, and efficacy of recombinant human papillomavirus virus-like particle vaccine. In: WHO Expert Committee on Biological Standardization. Fifty seventh Report. Geneva, World Health Organization, 2006, (WHO Technical Report Series, in press).

10.10 Guidelines to assure the quality, safety and efficacy of live attenuated

rotavirus vaccines (oral). In: WHO Expert Committee on Biological Standardization. Fifty -sixth Report. Geneva, World Health Organization, 2005, Annex 3 (WHO Technical Report Series, No. 941).

10.11 Guidelines on clinical evaluation of vaccines: regulatory expectations. In: WHO Expert Committee on Biological Standardization. Fifty-fifth report. Geneva, World Health Organization, 2004. Annex 1 (WHO Technical Report Series, No. 932).

10.12 Good Manufacturing Practices for pharmaceutical products: main principles. In: WHO Expert Committee on Biological Standardization. Geneva, World Health Organization 2003. Annex 4 (WHO Technical Report Series, No. 908).

10.13 Yearly Biologic Product Reports for Lot Release. Health Canada, 2008. Available at: (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/lot/index eng.php).

10.14 Recommendations for the preparation, characterization and establishment of international and other biological reference standards. In: WHO Expert Committee on Biological Standardization Fifty-fifth report. Geneva, World Health Organization, 2004. Annex 2 (WHO Technical Report Series, No. 932).

10.15 M. Cuervo and A. Yanes. Comparison between in vitro potency tests for Cuban Hepatitis B vaccine: contribution to the standardization process. Biologicals, 2004, 32:171-176.

10.16 Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. Geneva, World Health Organization, 1997 (WHO/VSQ/97.06).

10.17 Proposed Drug Act 2022.

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