

2. General Considerations

Vaccines are biological products used in healthy populations. The impact of using sub-standard 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 could have a drastic impact should a large number of healthy individuals receive vaccines before the problem is recognized. For these reasons, a careful independent review of manufacturing and QC 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. Therefore it is essential to ensure the consistent quality of each lot before it is released to 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.

Finally, 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 results of tests using these preparations.

It is strongly recommended that NRAs/NCLs ensure there is independent lot release for vaccines used in their country either based on their own evaluation, using as a minimum a thorough review and approval of the manufacturers' summary protocol (for details see section 4.1) or through recognition of the decision of another regulatory authority.

All vaccine lots should be released by an NRA/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 considerations.

Lot release is part of the whole regulatory framework which includes marketing authorization, GMP (good manufacturing practices) inspection, and post marketing surveillance (PMS) etc. The relationship between the NRA and the NCL varies from country to country, but in all cases it is essential that the different branches of the regulatory structure interact and exchange information effectively.

Each country should establish the national guidelines for lot release that define all procedures, from the submission of the lot for release to the issue of lot release certificate. Principles found in this document may assist in the development of these national guidelines.

2.1 Consideration for Establishing Lot Release Procedures by NRA/NCL

There are currently different approaches to conducting lot release of vaccines including 1) review of summary protocol only, 2) review of summary protocol with independent testing (full or selected testing) and 3) recognition/acceptance of lot release certificates from the responsible NRA/NCL. These approaches are not mutually exclusive and different approaches may be used for different products in the same country.

It is the responsibility of the NRA/NCL to decide on an appropriate strategy for each particular vaccine taking into consideration the nature of the vaccine, the post-market experience including

production history and safety profile and the availability of other independent evidence of product quality (Details see section 4.2.3 establishment of testing policy). In some cases the same lot may be used to supply multiple countries. Multiple testing can be costly and time consuming. In addition many biological assays are highly variable and repetitive testing can result in 'false' out of specification results by chance which then require extensive investigation. This can delay vaccine supply. The decision to repeat tests on a lot that has already been tested by another competent authority should be carefully considered in light of all available information.

For vaccines produced and authorized in the country, either for use domestically or for export, the NRA of the country should take the responsibility for regulatory oversight of quality of the vaccine. Initially, the NRA/NCL should test the vaccine in addition to 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 the case a vaccine not licensed in the country of manufacture, the NRA who granted the marketing authorization should take the responsibility of regulatory oversight. However, cooperation with the NRA of the producing country is recommended.

For self-procured vaccines, the procuring NRA/NCL may consider alternative approaches as acceptable for assuring the safety and quality of these products. As a minimum, review of the summary protocol is essential. Independent tests might be useful depending on the history of production, nature of the product (details see section 4.2.3) and the capacity of the NCL. Recognition/acceptance of lot release certificates from the NRA/NCL of the country where the vaccine is manufactured or another competent NRA/NCL should also be considered as an alternative (see section 6.1).

For vaccines supplied through UN agencies, further release by the NRA/NCL of receiving countries is not recommended (see section 6.2), because they are prequalified by WHO and released by the responsible NRA/NCL.

2.2. Encouragement of Networking and Work-sharing

Regional laboratory networks can serve as a forum for sharing information, exchanging experience on technical issues and facilitating assistance between NRAs/NCLs. It is recommended that WHO Regional Offices take the lead in establishing regional laboratory networks in areas where this has not yet been developed. It would be useful to have a forum for sharing information on lots that were found to be out-of specification (OOS) in the regional network and this would also be beneficial on a global level.

Development of a network expands the capacity of individual NRAs/NCLs beyond their own limits through work-sharing and ideally avoids having the same lot tested a number of times unnecessarily by different NCLs by building confidence in the evaluation performed by other network members. It can contribute to reducing the number of animals used for testing through the sharing of test results and it could prevent samples being tested in laboratories which only perform given assays infrequently and as such may have problems maintaining technical competence. It can also allow development of more complex and specialized methods through repartition of tasks and it provides a support network for problem solving.

Establishing these networks would be a part of the capacity building activities for the countries in a region. A fully functional regional laboratory network is a long-term goal, but cooperation can begin in the short term, through the sharing of scientific information and experiences with

methodologies regarding the evaluation and release of different products. Meetings to promote transparency and mutual confidence between the NRAs/NCLs should be organized periodically.

Although full mutual recognition of lot release certificates among NRAs/NCLs would be ideal, it is recognized that it is a complex issue with a number of difficulties in practice. Nevertheless an effective regional network can help build the foundations necessary for such a goal.

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

The quality, safety and efficacy of a medicinal product such as a vaccine are the responsibility of the manufacturer. The regulatory authority of the country is responsible for establishing procedures to ensure that this responsibility is met.

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

3.1 The Responsibility of the NRA/NCL in Lot Release

Marketing authorization for a vaccine should be granted by an NRA which should also be responsible for continued post authorization monitoring. In carrying out these activities, the NRA should have access to expert advice and laboratory facilities. The activities of the NRA should be backed by legislation which should include provisions for lot release.

An NRA/NCL that undertakes a lot release programme should have sufficient capacity and expertise to effectively evaluate lot release protocols. Timelines and responsibilities of the NRA/NCL for issuing the lot release certificate should be defined as part of the legal provision. The manufacturer and relevant health authorities should be informed in the event of a delay.

The NRA/NCL should have the authority to request appropriate samples from manufacturers when required. The samples should be properly identified and portions may be kept for future reference.

Where independent testing is required, they should be able to perform the appropriate tests on all relevant samples (which may include critical upstream components, bulk and finished products) or have access to a laboratory competent in the tests. This would require that the NRA/NCL have access to specialized facilities, equipment and expertise. The NCL should be independent of the manufacturer, and staff should not be shared. In particular there should be a clear separation of lot release activities in cases where the NCL and manufacturer share a site.

The NRA/NCL should ensure that the mechanism for the independent lot release procedure should be made public in a clear and transparent way regarding requirements, timelines etc so that the process is completed smoothly and in a timely manner.

NRAs/NCLs of producing/releasing countries have the responsibility to provide 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 should be established and the data submitted by manufacturers and other NCLs/NRAs should be kept as confidential unless agreed otherwise.

The NRA/NCL of a producing/releasing country 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.

3.2 The Responsibility of the Manufacturer in NRA/NCL Lot Release

The manufacturer has the following responsibilities in terms of NRA/NCL lot release: (a) collaborate with the responsible NRA/NCL to develop the product summary protocol template, when requested (the WHO summary protocol of each product could be used as the template); (b) submit each manufacturing and control summary protocol; (c) if requested, submit samples in an appropriate condition including packaging, leaflet and label; (d) assist the responsible NRA/NCL in technical transfer of testing methods; (e) submit the lot release certificate of the responsible NRA in the case of export products; (f) provide product specific reagents and working reference materials as needed; (g) participate in collaborative studies in establishment of a national standard; (h) work with NRA/NCL to resolve any discrepancy on test result; (i) take appropriate action on the issues related to any error/non compliance; (j) take appropriate action on any rejected lots according to GMP requirements (12); (k) provide any documents or other information regarding the quality of the vaccine, required by the NRA/NCL.

3.3 Establishment of Quality Management Systems for the NRA/NCL

A quality management system (QMS) should be in place to support lot release activities and should include the following key elements: trained and qualified personnel, management of records and documentation, identification and retention of samples (when applicable), use of validated test procedures, written procedures, internal and external audit systems and oversight procedures. Recommendation in the WHO Guidelines for national authorities on quality assurance for biological products should be applied (1).

4. Conducting Lot Release

The manufacturers' summary protocol should be reviewed by an NRA/NCL before release of a lot onto the market to ensure that specifications defined in the marketing authorization dossier are met. Product consistency should be assessed through trend analysis on successive lots (see section 5). Where NCLs 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 product report). Where appropriate, review of the summary protocol could be complemented by the independent testing. 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.

A need for independent testing should be carefully considered in the establishment of the lot release procedures. Assessment of vaccine lots by an NCL can add value to the information provided in the summary protocol, if the testing is performed by experienced, competent and skilled laboratory staff supported by a QMS and appropriate laboratory facilities.

4.1 Protocol Review

The manufacturers' summary protocols summarize information taken from the production and test records according to GMP requirements to ensure that the lot meets the specifications in the market authorization. In addition, summary protocols submitted to the NRA/NCL have to be approved by the appropriate quality assurance (QA) or QC responsible person of the manufacturer. Generally, the format and content of the protocol is finalized and approved by the NRA/NCL during the review of the license application and the format of the protocol should be amended in response to changes in the approved production process and approved by the NRA/NCL.

4.1.1 Principles

Protocol review is conducted by qualified NRA/NCL staff. As far as possible, the same format of the summary protocol should be used for the same product in different markets. However, the format of summary protocol can vary with respect to additional information required by the NRA of importing country.

An independent review of critical data from each lot of vaccines is essential in order to a) assure the consistency of quality of each manufactured lot; b) obtain confidence in the strength of active components claimed, and c) assess the validity and accuracy of the tests performed.

This encompasses the traceability of critical source materials, active and critical components used in the manufacture of the product, 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.

4.1.2 Summary Protocol Template

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

Each summary protocol is product-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 protocol for review

Items	Essential information to cover	Critical parameters to review
Identity of manufacturer	Name of the manufacturer	Traceability and identity
Licence 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 numbers of the final products, 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 within allowed parameters
Expiry dates	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

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	Compared 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
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 NRAs on marketing authorization and/or recommended by WHO (e.g. OPV)(6);
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 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 condition.	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 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	To demonstrate identity, purity, safety, potency (strength) and thermostability of the product are in compliance with the approved specifications. Monitor the performance of reference material/test

4.1.3 Checklist for Protocol Review

Use of a checklist in the review of protocols is highly recommended to ensure a complete and thorough review. A checklist for each section of the protocol should be developed to ensure a complete review of the information. Checklists are usually 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 specific for a registered product and/or a test, in accordance with both marketing authorization dossier and WHO Recommendations 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.).

4.1.4 Protocol Review Process

The value of the protocol review process is highly dependent on the quality of the information provided by the manufacturer in the summary protocols. Reviewing summary protocols requires a good understanding of the product and laboratory control methods. A summary protocol for a product can be reviewed by a single individual or a team of experts depending upon the complexity of the product and the structure of the NRA/NCL. A validated software with adequate access controls and traceability for trending and tracking of the data submitted may be useful to perform a meaningful review of protocols.

The lot release process starts with the receipt of manufacturers' protocol and test samples if required and/or examples of the final label. After initial verification of the label information for the test sample and on the protocol, the protocols are logged into a database or otherwise recorded. At receipt, the first step in protocol review should be to confirm that the manufacturer has used the approved template for the given vaccine. Then the protocols are routed to the various individuals within the NRAs/NCLs that had already been determined based on their expertise. This should be traceable according to QA management procedures.

If databases are used to capture information for a particular test or section of the protocol, they should already be set-up before starting the review process. Databases on lot size, results of tests, performance of reference standards and controls, etc. are useful for tracking and trending of information. 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. should be shown. In all cases databases should 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 4.1.2 have been compared against the characteristics approved in the marketing authorization and have been found to be compliant.

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

4.1.5 Handling Discrepancies and OOS Results in Summary Protocols

Any discrepancies, errors or OOS found in the summary protocol submitted should be documented and verified before communicating these to the manufacturer. A procedure to communicate these issues should be developed at the NRA/NCL. 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.

4.2 Independent Testing

Independent testing enables the NCL to monitor key product parameters and consistency of production based on their own data. The development of NCL technical expertise also enables independent assessment of other issues regarding quality control of products when they arise.

If quality testing is performed by a laboratory other than NCL, the laboratory should be contracted, information exchange should be handled in a confidential manner and there should be a system to ensure that there is no conflict of interests. The qualification of the laboratory should be assessed and the performance of the laboratory testing should be evaluated by the NRA/NCL according to WHO recommendations (2). The final decision on the test results lies with the responsible NRA/NCL.

4.2.1 Purpose of Independent Testing

A lot release testing program allows NCLs to verify the test results of manufacturer. When testing is performed in a systematic way by a qualified NCL, it can help to 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 NCLs 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.

4.2.2 Prerequisites for Setting Up Independent Testing for Lot Release

A defined strategy for testing needs to be established as part of overall lot release policy. Knowledge of the marketing authorization dossier is essential to identify and assess the critical parameters for testing. Ideally the NCL staff should be involved in the marketing authorization evaluation process (for pharmaceutical quality information at least).

When setting up testing policy a good QMS is essential. The QMS should 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 (1)).

This would include aspects related to technical staff training, maintenance of equipment, standard operating procedures (SOP) for techniques, daily running of the system and dealing with OOS results. The NCL should have sufficiently skilled, trained and qualified personnel with the appropriate technical and scientific expertise, and appropriate equipment/infrastructure should be available.

Relevant test methods should be validated following QA standards (including equipment qualification) if independent testing has to be performed. It is also necessary to establish documented and approved procedures and guidelines both for internal use and for transparency with any partners including other NCLs and the manufacturer of the product.

While not necessarily a prerequisite, good communication with the manufacturer of the product is an important aspect for developing an effective system. NCLs should discuss with the manufacturer the transfer of assays if required. This should begin as early as possible in the marketing authorization procedure to allow transfer and qualification/validation of the methodology prior to apply to the first lot for lot release testing. Since specifications for some biological assays (i.e. potency, purity etc) are dependent on the analytical technique used, comparison of testing results between the NCL and the manufacturer is important to avoid potential discrepancies that may be related to the methodology used and not to the quality of the product.

4.2.3 Establishment of Testing Policy

Implementation of a lot release testing policy should only be considered by the NCL if the prerequisites noted in section 4.2.2 above have been addressed. Testing under inappropriate conditions may generate inaccurate or misleading data and cause unnecessary delay or rejection of lots which meet the specifications.

The decision to conduct independent testing at the NCL should take into account the capacity of the NCL and the information available from other NRAs/NCLs who may also release the same product.

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

1. Should the vaccine be tested by an independent authority?
2. If testing is required, what critical parameters should be tested by the NCL?
3. Should it be done on every lot or on some reduced percentage of lots? and
4. Are testing results available from another NCL?

Information influencing the considerations includes the 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. An important factor is the manufacturers' production history which could be obtained from summary protocol and/or yearly biologic product reports, in some circumstances, (see below) which contains production and testing information. Other information to be considered includes 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.

A risk based analysis for a particular product can help to determine if testing is required and if so at what frequency. A model procedure of such risk analysis is given in the appendix.

An annual review of the important parameters based on data provided in the lot release protocol to NRA/NCL can be used to support the evaluation of consistency for each product. Other information based on marketing authorization or inspection issues is also relevant but is not always available to the NCL, in particular when the NCL and the NRA are separate institutions, or when intergovernmental mutual recognition agreements for GMP inspections are not in place for imported products.

In some countries, yearly biologic product reports are requested from the manufacturer for each vaccine (13). This information is used to assess product consistency. It is particularly helpful in markets where a more limited number of lots are released, as it provides more comprehensive information on which to base the decision on whether to test, or to decide testing frequency and the type of testing required for each vaccine.

4.2.4 Criteria for Selection of Tests for Lot Release and Percentage of Lots to Be Tested

Once the decision to perform testing is taken, the NCL should concentrate on a 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 should 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 NRA. 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 should 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 should be clearly defined 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, the choice of lots to be tested should be in the hands of the NCL and the manufacturer should not be aware in advance as to which lots will undergo testing.

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 NRA/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 (11), 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.

4.2.5 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 standardisation 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 exists.

4.2.6 Standards

The intention of the WHO International Standards (IS) is to serve as a basis for calibration of secondary standards (e.g. regional and national standards) (14). Generally the ISs are not used directly in the assays as a working standard. The regional or national standard is calibrated against IS to make a common working standard available to NCLs and manufacturers.

The regional or national standards should be established by a collaborative study which should include the manufacturers. Practical aspects of secondary standard preparation need to be considered at the regional level and a suitable concept for development, establishment, distribution and use of regional reference preparations should be put in place.

4.2.7 Practical Considerations

The number of samples of the final lot or upstream components requested by NCLs should be appropriate for the testing required and the sampling procedures should ensure the representativeness of the lot in question. A system should 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 NRA/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 should 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. It is desirable to 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 should 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.

4.2.8 Release Specifications

NRA/NCL lot release should only pertain to products that have a valid marketing authorization in which specifications have been approved by the competent NRA of the country using the vaccine.

As it is these specifications which are used to judge the test results it is important to have a mechanism in place to allow the testing NCL to be aware of the latest version of the approved license specifications. Ideally, the responsible NCL staff should be involved in assessing the test methods, validity criteria and the product specifications in the decision making process for authorization.

4.2.9 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 (15).

The NCL should clearly define their re-test policy and determine how, 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 should have a predefined standard procedure to deal with results that do not comply with the specifications. This should 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 should 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 should be prepared for final evaluation of the lot and the decision making process.

A feed back mechanism from NCL to NRA and/or the GMP inspectorate is highly advisable in order to coordinate and optimize regulatory actions (e.g. urging license variation, refinement of product specification based on trend analysis etc.).

5. Data Monitoring

All critical quantitative data from QC results and especially potency from the manufacturer or other sources should be used for trend analysis as an essential part of lot release. Statistical analysis should be conducted once sufficient data has been accumulated. The alert or warning limits and action limits of consistency trends should be defined on statistical grounds. Generally, $\pm 2SD$ and $\pm 3SD$ 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 should be considered when defining the limits. Care should 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) should be analyzed statistically compared to that of the previous period in order to detect any significant differences or shift in trends.

An SOP describing this tracking and trending of manufacturers' and where available the NCL results, should 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.

5.1 Trend Analysis Including the Data from the NCL

In cases where independent testing of lots is performed at the NCL all data from the tests performed at NCL, including performance of reference standards and controls should 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' should be made with caution and may require additional information from the manufacturer either directly or through contact with the relevant national inspectorate.

5.2 Comparison of Results of the Manufacturer with Those of the NCL

Results from the NCL 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. 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.

6. Evaluation of the Lot and Decision Making Process

6.1 Establishment of decision making procedures

The Authority responsible for issuing a release certificate may vary between countries. Therefore, it is critical that the roles and responsibilities, of both NRA and NCL, are clearly defined, in particular when they are separate entities. Once all elements are available for final evaluation, a formal decision making process should be in place to decide whether or not the given lot can be released. An SOP should be in place to clearly describe the process and required elements for the final decision. Good coordination and communication is needed especially when different bodies 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 should be in place outlining the lot approval process and the persons responsible for each activity.

The approach to independent lot release by the competent authority should be appropriately described in NRA/NCL process charts. Procedures should cover the relevant options used: release upon review of summary protocol only and/or release upon review of summary protocol plus independent testing by NCL. They should also define how and by whom the final decision is taken based on the formal written conclusions of the defined options used. SOPs or documents are necessary to cover the following essential elements:

1. An SOP for summary protocol review describing acceptance criteria for the completeness of the summary protocol and 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.).

The NRA/NCL should produce a formal written conclusion regarding the summary protocol review. A summary decision form should be filled to ensure compliance with approved specifications and should be signed by the responsible staff.

2. An SOP describing the acceptance criteria for NCL test results and recording all the individual test results in certificate(s) of analysis.

For the lot release following independent testing by the NRA/NCL, a formal written conclusion form containing the outcome of test results should be developed. A summary decision form should be used to capture the test results and ensure compliance with approved specifications and should be signed by the responsible staff.

A retest policy should be developed following general QA principles, to define the policy for retesting and handling of OOS results. In addition, an SOP should be in place to give guidance on retest policy according to product-specific recommendations (e.g. combination of results, calculation method etc). In the event of non compliance, a full traceability

investigation should be conducted on test reports and the manufacturer should be contacted for further investigation. As part of the QA, in the event of derogation, an SOP should outline the decision making process including documentation and written criteria to support the decision made.

3. An SOP describing the acceptance criteria for 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 should be developed, based on a risk/benefit analysis taking into account all available information. This should only be applied by the staff officially responsible for signing the release certificate. Documentation supporting compliance with approved specifications (summary protocol review and test reports, if applicable), should be included.

All the steps in the decision making process should be documented.

6.2 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. Acceptable processes may range from a list of countries acceptable to the importing country, through to Mutual Recognition Agreements, and examples are detailed below.

Establishment of mutual recognition agreements is a legal approach. Many NRAs/NCLs establish the practice with the aims of 1) enhancing international regulatory cooperation to maintain high standards of product safety and quality; 2) facilitating the reduction of the regulatory burden for NRAs/NCLs and manufacturers; 3) improving the free flow of goods and accessibility to medicinal products globally. Reciprocal mutual recognition of release certificates involves a number of legal aspects that should be addressed; however the real key to successful mutual recognition is the building of mutual confidence between the interested parties. This requires strong collaboration and communication between the different NRAs/NCLs and a good level of transparency.

Agreements covering specific products could enable NRAs/NCLs 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 the local NRA/NCL when they evaluate the lot for release.

Situations may exist where a two-way recognition of certificates or test results is not possible due to technical or other limitations. However even in cases where reciprocity is not attainable an NRA/NCL may still wish to recognise a release certificate from another NRA/NCL. This should be possible provided the releasing NRA/NCL has clearly established procedures that are transparent and relevant to the NRA/NCL wishing to recognise the certificate/test results.

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.

It is important to note that the product manufacturers should be involved in the establishment of the agreement to share product information since there are issues of confidentiality which need to be addressed.

When these types of arrangements are foreseen, specific SOPs, should also be developed to clearly establish what information is necessary and how it should be received and processed before final release onto the local market is accepted.

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

The responsible NRAs/NCLs are required to issue a certificate of release for vaccines that are distributed through the UN Agencies (16). 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. This release certificate is issued based, as a minimum, on reviewing of the lot summary protocol for the particular lot.

The responsible NRA/NCL plays a key role in ensuring that products meet the specifications outlined in the marketing authorization and WHO recommendations. This is achieved by maintaining the regulatory oversight assessing and approving changes to manufacturing process including testing and specifications, compliance with GMP and post-market surveillance of vaccine adverse reactions. The release certificate issued by the responsible NRA/NCL of a should be forwarded by the UN Agencies to the NRA/NCL of the receiving country and the summary protocol will be provided upon request.

The receiving country may wish to review the summary protocol to develop its competency and have an overview of the vaccine quality.

In some countries, testing is undertaken on the product received by a competent laboratory for the purpose of strengthening the NCLs' capacity and obtaining information on the quality of the product at the receiving site. If a deficient result is detected the responsible NRA/NCL should be consulted.

7. Lot Release Certificate

A release certificate for each vaccine lot should be issued by the NRA/NCL and sent to the manufacturer confirming that the particular lot meets the approved specifications and related provisions. This release certificate is the official document that authorizes the manufacturer to release the specific lot onto the market. The certificate may include the following information:

- Name and address of manufacturer;
- Site(s) of manufacturing;
- Trade name and/common name of product
- Marketing authorization number
- Lot number(s) (including sub-lot numbers, packaging lot numbers if necessary)
- Type of container

- Number of doses per container
- Number of containers/lot size
- Date of start of period of validity (e.g. manufacturing date) and/or expiry date
- Storage condition
- Signature and function of the authorized person and authorized agent to issue the certificate
- Date of issue of certificate
- 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 should be issued which clearly states that the lot is non-compliant, ideally with a different color from the approval certificate.

It is advisable that the language on the lot release certificate is the national language plus an English translation of the information.

8. Glossary

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

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

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.

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

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.

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

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

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.

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

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

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.

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.

9. Abbreviations:

AEFI: Adverse Event Following Immunization

DTP: Diphtheria, Tetanus and Pertussis vaccine

GMP: Good Manufacturing Practices

HPV: Human Papillomavirus Vaccine

IS: International Standard

MMR: Measles, Mumps and Rubella vaccine

NCL: National Control Laboratory

NRA: National Regulatory Authority.

OPV: Oral Polio Vaccine

PMS: Post Marketing Surveillance

QA: Quality Assurance

QC: Quality Control

QMS: Quality Management System

SOP: Standard Operating Procedures

UN: United Nations

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