

Annex 2

Guidelines for independent lot release of vaccines by regulatory authorities

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Recommendations published by WHO are intended to be scientific and advisory. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these recommendations may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these recommendations be made only on condition that the modifications ensure that the vaccine is at least as safe and efficacious as that prepared in accordance with the recommendations set out below. The parts of each section printed in small type are comments for additional guidance intended for manufacturers and NRAs, which may benefit from these details.

Abbreviations

AEFI	adverse events following immunization
BCG	bacille Calmette–Guérin
DTP	diphtheria–tetanus–pertussis vaccine
GMP	good manufacturing practices
HPV	human papilloma virus
MMR	measles, mumps and rubella vaccine
NCL	national control laboratory
NRA	national regulatory authority
OOS	out of specification
OPV	oral poliomyelitis vaccine
PMS	post-marketing surveillance
QMS	quality management system
SOP	standard operating procedure
USA	United States of America

1. Introduction

The lot release of vaccines by regulatory authorities is part of the regulation of vaccines and involves the independent assessment of each lot of a licensed vaccine before it is released on to 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) or national control laboratory (NCL) and, in some circumstances, by testing that is independent of the manufacturers' quality-control testing.

WHO provides support for lot release programmes through the provision of written standards and measurement standards, strengthening the lot release function of NRAs and providing training (1–4). However, a need for further guidance was identified at a WHO consultation held in Ottawa in 2007.

This document provides recommendations and strategies for the 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 bacille Calmette–Guérin (BCG), oral

poliomyelitis (OPV), measles, mumps and rubella (MMR), diphtheria–tetanus–pertussis (DTP), human papilloma virus (HPV) and rotavirus vaccines) (5–10).

Although it is difficult to provide a set of guidelines that apply 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 the criteria 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 incorrect decisions. These Guidelines also highlight the importance of networking and work sharing among NRAs/NCLs.

The Guidelines are intended to serve as a guide for national requirements for lot release. If an NRA wishes, the Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to the principles and technical specifications of the Guidelines should be made only if the modifications ensure that the risks of introducing vaccines for use in public health programmes are no greater than as outlined in the Guidelines.

1.1 Scope

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

The document is intended to provide guidance to the NRAs/NCLs and to vaccine manufacturers. It may also be relevant to public health authorities such as a national immunization programme.

2. Glossary

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

Deviation: departure from a standard, norm or 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 the quantity 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 period.

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

Marketing authorization: an official document issued by the competent NRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality.

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

Out of specification (OOS): an OOS result is generated when a vaccine is tested and fails to meet a predefined specification.

Responsible NRA/NCL: the NRA/NCL taking responsibility for regulatory oversight of a product with regard to the critical regulatory functions defined by WHO, including independent lot release. The responsible NRA/NCL is usually that of the country of manufacture, unless specific agreements exist within defined territories, such as in the European Union, where the “country” of manufacture is the European Union and the activity of the responsible NRA/NCL is designated from among the Member States.

Self-procured vaccine: a vaccine that is procured directly from a source outside the country without the intervention of WHO/United Nations procurement programmes.

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 called “lot summary protocol”) a document summarizing all manufacturing steps and test results for a lot of vaccine, which is certified and signed by the responsible person of the 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 and reasons for any recalls and corrective action taken, as well as other pertinent post-marketing information.

3. 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.

It is strongly recommended that NRAs/NCLs ensure that there is independent testing and 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 5.1), 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 provisions.

Lot release is part of the whole regulatory framework, which includes marketing authorization, good manufacturing practices (GMP) inspection and post-marketing surveillance (PMS). 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 certificates. The principles found in this document may assist in the development of these national guidelines.

3.1 **Considerations for establishing lot release procedures by the NRA/NCL**

Current approaches to conducting lot release of vaccines include review of the summary protocol only, review of the summary protocol with independent testing (full or selected testing), and 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 vaccine, taking into consideration the nature 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). 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” OOS results, which then require extensive investigation and 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 a country, either for domestic use or for export, the NRA of the country should take the responsibility for regulatory oversight of vaccine quality. The NRA/NCL should initially test the vaccine, 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 the case of a vaccine not licensed in the country of manufacture, the NRA that granted the marketing authorization should take full responsibility for 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 to be acceptable for assuring the safety and quality of these products. As a minimum, review of the summary protocol is essential. Independent tests may be useful, depending on the history of production, the nature of the product (see section 5.2.3) 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 from another competent NRA/NCL, should also be considered as an alternative (see section 7.1).

For vaccines supplied through United Nations agencies, further release by the NRA/NCL of receiving countries is not recommended (see section 7.2) because such products are prequalified by WHO and released by the responsible NRA/NCL.

3.2 **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 these have not yet been developed. It would be useful to have a forum in the regional network for sharing information on lots that were found to be OOS, 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, by building confidence in the evaluation performed by other network members, avoids the same lot being tested unnecessarily and repeatedly by different NCLs. 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.

Establishing networks would be part of the capacity-building activities for countries in a region. 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. Meetings should be organized periodically to promote transparency and mutual confidence between the NRAs/NCLs.

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

4. Responsibilities of the NRA/NCL and 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 for export.

4.1 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 evaluate lot release protocols effectively. Timelines and responsibilities of the NRA/NCL for issuing the lot release certificate should be defined as part of the legal provisions. 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, the NRA/NCL should have the capacity 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 that is competent in the tests. This would require that the NRA/NCL has 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 is made public in a clear and transparent way regarding requirements and timelines, 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 a product 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 confidential unless agreed otherwise.

The NRA/NCL of a producing/releasing country has the responsibility to ensure the production and release of vaccines of assured quality whether they are used within the country or exported. Vaccines for local use and those for export should have the same level of quality.

4.2 **Responsibility of the manufacturer in NRA/NCL lot release**

The manufacturer has a number of responsibilities in terms of NRA/NCL lot release. In this regard, the manufacturer should:

- 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);
- submit each manufacturing and control summary protocol;
- if requested, submit samples in an appropriate condition, including packaging, leaflet and label;
- assist the responsible NRA/NCL in technical transfer of testing methods;
- submit the lot release certificate of the responsible NRA in the case of export products;
- provide product-specific reagents and working reference materials, as needed;
- participate in collaborative studies in establishment of a national standard;

- work with NRA/NCL to resolve any discrepancy in test results;
- take appropriate action on any issues related to error or non-compliance;
- take appropriate action on any rejected lots according to GMP requirements (11);
- provide any documents or other information regarding the quality of the vaccine, as required by the NRA/NCL.

4.3 **Establishment of quality management systems for the NRA/NCL**

A quality management system (QMS) should be in place to support lot release activities. The QMS system 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. The recommendations in the WHO Guidelines for national authorities on quality assurance for biological products should be applied (1).

5. Conducting lot release

The manufacturer's summary protocol should be reviewed by an NRA/NCL, to ensure that specifications defined in the marketing authorization dossier are met before release of a lot on to the market. Product consistency should be assessed through trend analysis on successive lots (see section 6). Where NCLs do not receive consecutive lots, or receive only a small number of the production lots, interpretation of trend may require additional information (e.g. yearly biological product report). Where appropriate, review of the summary protocol can be complemented by independent testing. In the case of imported vaccines, any available lot release certificate issued by the responsible NRA/NCL, particularly 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.

5.1 **Protocol review**

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 should be approved by the person designated as responsible for quality assurance or quality control of the manufacturer. In general, the format and content of the protocol is finalized and approved by the NRA/NCL during the review of the licence application. The format of the protocol should be amended in response to changes in the approved production process and should be approved by the NRA/NCL.

5.1.1 Principles

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

An independent review of critical data from each lot of vaccines is essential, in order to:

- assure the consistency of quality of each manufactured lot;
- obtain confidence in the claimed strength of active components;
- assess the validity and accuracy of the tests performed.

This review 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.

5.1.2 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 developed carefully on the basis of 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 account specific requirements in the marketing authorization approved for the product. Any changes to the template due to changes in the manufacturing process or testing should be traceable. The template should be a controlled document and the manufacturer should not change it without the approval of the regulatory authority. It is important that NRA/NCL staff responsible for reviewing these documents ensure that the latest version of the licence 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 Table A2.1) that a summary protocol should cover.

Table A2.1

Information to be included in the summary protocol for review

Items	Essential information to cover	Critical parameters to review
Identity of manufacturer	Name of manufacturer	Traceability and identity
Licence number	Unique licence 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	For each critical starting material (e.g. seed lots, cell banks, starting materials of animal origin etc.), intermediate, final bulk and final product	Compared against noted expiry dates etc., to calculate and confirm values
Flowchart	Flowchart for traceability of the 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 the NRA on the marketing authorization and/or recommended by WHO (e.g. OPV) (6)

Table A2.1 *continued*

Items	Essential information to cover	Critical parameters to review
Manufacturing process	Each production process (such as cultivation, purification, inactivation), the methods of quality-control tests as well as their release specifications and the results obtained; the lot number of intermediates and their size/volume, storage conditions	Confirm they are the same as the approved ones; yields of critical production processes are within the acceptable range
Formulation	Amount of active components in the final formulations, with the lot numbers and volumes of bulk concentrates; storage conditions	Verify calculated and actual values based on information provided
Quality-control tests	Actual results of tests on critical starting materials, intermediates, final bulk and final product and the specification; include the individual tests and the mean value; provide the starting date of the test, method, and a list of reference preparations, standards, critical reagents and their qualification status, plus the performance of relevant reference preparations, standards and internal controls, such as results of assay validity criteria (e.g. slope, intercept, linearity, 50% end-points, results of internal controls, challenge doses); provide statistical results, such as mean, geometric mean, standard deviation, 95% confidence intervals, etc., if applicable; include results of failed tests or note invalid tests if a test has been repeated	Demonstrate that the identity, purity, safety, potency (strength) and thermostability of the product are in compliance with the approved specifications; monitor the performance of reference material/test

5.1.3 Checklist for protocol review

The use of checklists in the review of protocols is highly recommended to ensure a complete and thorough review. A checklist should be developed for each section of the protocol, 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 the 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 to a registered product and/or a test, in accordance with both the 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).

5.1.4 Protocol review process

The value of the protocol review process depends 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 of laboratory control methods. A summary protocol for a product can be reviewed by one person, or by a team of experts, depending on the complexity of the product and the structure of the NRA/NCL. Validated software, with adequate access controls and traceability for tracking and trending of the data submitted, may be useful for performing a meaningful review of protocols.

The lot release process starts with receipt of the manufacturer's 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 individuals within the NRA/NCL who have already been identified on the basis of 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, these should already be in place before starting the review process. Databases on lot size, results of tests, performance of reference standards and controls, and so on are useful for tracking and trending of information. The results of tests and performance characteristics of reference standards and controls and specification limits, including appropriate confidence intervals of typical results for a period of time, should be shown. In all cases, databases should be secured to avoid unauthorized addition, revision or deletion of information, and a back-up system should be provided. A separate procedure should be developed for tracking

and trending of manufacturers' results and the 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 Table A2.1 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, this is not done in other countries, since diluents are not considered on their own to be biologicals.

5.1.5 Handling discrepancies and OOS results in summary protocols

Any discrepancies, errors or OOS results found in the summary protocol submitted should be documented and verified before they are communicated to the manufacturer. A procedure to communicate these issues should be developed by the NRA/NCL. This may include formal notification by memo or letter, an e-mail or minutes of telephone discussions. Manufacturers' responses should be reviewed and documented in making the decision on the lot. This can include submission by the manufacturer of the corrected page/version of the summary protocol, which then should be traced by the 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 of the issues, including steps for 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 may be required. Such information exchange can help to judge the corrective and preventive actions introduced by the manufacturer.

5.2 Independent testing

Independent testing enables the NCL to monitor key product parameters and the consistency of production on the basis of its own data. The development of NCL technical expertise also enables other issues regarding quality control of products to be independently assessed when they arise.

If quality testing is performed by a laboratory other than the 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 interest. 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.

5.2.1 Purpose of independent testing

A lot release testing programme allows NCLs to verify the test results of manufacturers. 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 drifts in these parameters that are unaccounted for. This can serve as feedback to the 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 important for the overall competence of an NCL in effectively monitoring the product.

5.2.2 Prerequisites for setting up independent testing for lot release

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

A good QMS is essential when setting up a testing policy. The QMS should include a quality assurance system that is appropriate for testing laboratories, that is based on internationally recognized quality standards, and that undergoes regular internal and external review (see WHO guidelines (1)).

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

Relevant test methods should be validated following quality assurance 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 regard to 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 element in 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 process, to allow for transfer and qualification/validation of the methodology prior to application to the first lot for lot release testing. Since specifications

for some biological assays (e.g. potency, purity) 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.

5.2.3 Establishment of a testing policy

Implementation of a lot release testing policy should be considered by the NCL only if the prerequisites noted in section 5.2.2 have been addressed. Testing under inappropriate conditions may generate inaccurate or misleading data and cause unnecessary delay or rejection of lots that meet specifications.

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

A testing policy should be established for each product and should consider four main questions:

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 testing be done on every lot or on a reduced percentage of lots?
4. Are testing results available from another NCL?

Information influencing the decisions includes the nature of the final product (live or 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 quality control methods. An important factor is the manufacturer's production history, which can be obtained from the summary protocol and/or yearly biological product reports, which, in some circumstances (see below), contain production and testing information. Other information to be considered includes the GMP inspection report, adverse events following immunization (AEFI) report, product complaints and other PMS safety and quality information. The testing policy for the same product at other NCLs may also be taken into consideration in establishing 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 for such a risk analysis is given in Appendix 1.

An annual review of the important parameters, based on data provided in the lot release protocol to the 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, particularly 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 biological product reports are requested from the manufacturer for each vaccine (12). This information is used to assess product consistency. It is particularly helpful in markets where a limited number of lots is released, as it provides more comprehensive information on which to base the decision on whether to test, or the testing frequency and the type of testing required for each vaccine.

5.2.4 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 the 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 in 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 to new manufacturers) for which there is little accumulated experience, and to sophisticated combined vaccines for which testing and interpretation of results may be complicated.

The development and adoption of more effective test methods should be encouraged and should be approved by the NRA. If a different test method is used by the NCL, then – in case of data discrepancies between the manufacturer and the NCL – the approved test method defined in the marketing authorization should be used to solve the 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

a planned programme and 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 is 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 of which lots will undergo testing.

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

Development of testing methodology and capability should begin as soon as possible for both the responsible NRA/NCL and the manufacturer, possibly at the stage of clinical trials. However, while testing of samples by an NCL for clinical trial approval is recommended in WHO guidelines (13), 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.

5.2.5 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 on the decision-making process.

Control charts of critical parameters of reference preparations should be kept, to monitor performance over time. This allows an overview of the performance of both the reference preparation 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 or 50% end-point – that may indicate problems with the stability of the reference standard or changes in other assay systems (e.g. animals, cells, critical reagents). Other examples of the utility of trend analysis are assay validity criteria based on 95% confidence intervals. If the assay validity criteria on any attribute of reference standard, slope, intercept or potency of control are based on 95% confidence intervals, and the actual data do 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 also be used 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 multicomponent 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 International Units, against an International Standard where one exists.

5.2.6 Standards

The intention of the WHO International Standards is to serve as a basis for calibration of secondary standards (e.g. regional and national standards) (14). Generally, the International Standards are not used directly in the assays as a working standard. The regional or national standard is calibrated against the International Standard, 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 regional level, and a suitable concept for development, establishment, distribution and use of regional reference preparations should be put in place.

5.2.7 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 should not place undue stress on the supply of the materials, as stocks of these are often limited.

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 and benefit of parallel testing, taking into account the frequency of rejection of lots 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 favoured wherever possible. However, the type of testing should be driven by the scientific need for valid relevant data. Moreover, in the spirit of minimizing animal testing worldwide, agreements should be sought with the NCL of the exporting country or with other NCLs, in a mutual recognition or collaborative agreement, in order to utilize the results of animal testing already performed by another NCL.

5.2.8 Release specifications

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

Since these specifications 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 licence specifications. Ideally, the responsible NCL staff should be involved in assessing the test methods, validity criteria and product specifications in the decision-making process for marketing authorization.

5.2.9 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 taken into account in the specifications. To be in compliance with the marketing authorization, the test results 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 its retest policy and determine how, if applicable, the combination of results is carried out 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 for dealing with results that do not comply with the specifications. This should include confirmation that the results reflect the actual quality of the lot tested and are not due to analytical error by the NCL, or to 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 feedback mechanism from the NCL to the NRA and/or the GMP inspectorate is highly advisable, in order to coordinate and optimize regulatory actions (e.g. urging licence variation or refinement of product specification based on trend analysis).

6. Data monitoring

All critical quantitative data from quality-control 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 have been accumulated. The alert or warning limits and action limits of consistency trends should be defined on statistical grounds. In general, when data are distributed normally, ± 2 and ± 3 standard deviations of the mean are set for the alert or warning limits and action limits respectively. The variability and precision of the test should be considered when defining the limits. Care should be taken in interpreting such limits when they are based on small datasets. Trend analysis of key parameters may be requested from manufacturers or from 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 1 year) should be analysed statistically, compared to data of the previous period, in order to detect any significant differences or shift in trends.

An SOP should be developed to describe this tracking and trending of manufacturers' and, where available, the NCL's results. This procedure will describe parameters to be tracked and trended, the frequency of periodic reviews, criteria for judgement, and actions to be taken in the case of outlier results, etc.

6.1 Trend analysis including data from the NCL

In cases where independent testing of lots is performed at the NCL, all data from these tests, including performance of reference standards and controls, should also be trended and analysed. It should be kept in mind that not all countries test all consecutive lots from a manufacturer. In such cases, the trends should be interpreted with caution and additional information from the manufacturer may be required, either directly or through contact with the relevant national inspectorate.

6.2 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 manufacturer's release, so this should be taken into consideration when the NCL makes the comparison.

7. Evaluation of the lot and the decision-making process

7.1 Establishment of decision-making procedures

The authority responsible for issuing a release certificate may differ between countries. Therefore, it is critical that the roles and responsibilities of both the NRA and the NCL are clearly defined, particularly when they are separate entities. When all elements are available for final evaluation, a formal decision-making process should be in place to decide whether the lot can be released. An SOP should be in place to describe clearly the process and required elements for the final decision. Good coordination and communication are needed, especially when different bodies are involved in this process.

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

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

1. An SOP for summary protocol review should describe 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 manufacturer's correction, review of corrected pages, investigation, conclusion).

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

2. An SOP should describe the acceptance criteria for NCL test results and record 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 in accordance with general quality assurance principles, in order 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). 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 quality assurance, 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 should be available that describes the acceptance criteria for release of vaccines in exceptional cases, which deviate from the normal procedure. Examples include release for an emergency/crisis situation, urgent need due to a critical supply shortage, when information is pending regarding correction of the summary protocol, or in the event of discrepancies between the test results of the NCL and the manufacturer. The procedure should be developed on the basis of a risk–benefit analysis that takes into account all available information. This should be applied only 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 steps in the decision-making process should be documented.

7.2 Recognition of, and 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 on the basis of the existing release certificate. Processes for doing this may range from a list of countries that are acceptable to the importing country, through to mutual recognition agreements. Examples are described below.

Establishment of mutual recognition agreements is a legal approach. Many NRAs/NCLs use such agreements to: enhance international regulatory cooperation in order to maintain high standards of product safety and quality; reduce the regulatory burden for NRAs/NCLs and manufacturers; and improve the free flow of goods and increase the accessibility of medicinal products

globally. Reciprocal mutual recognition of release certificates involves a number of legal aspects that should be addressed; however, the 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.

Examples of agreements range from accepting the test results provided by another NCL, thus avoiding repeat testing and facilitating harmonization without compromising the safety and quality of the product, to full mutual recognition of the lot release certificate. The test results provided by another NCL can thus be used in addition to the protocol review by the local NRA/NCL, when they lot release the product.

Situations may exist where a two-way recognition of certificates or test results is not possible, owing to technical or other limitations. However, even in cases where reciprocity is not attainable, an NRA/NCL may still wish to recognize 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 recognize the certificate or test results.

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

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

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

7.3 **Release certificate issued by the NRA/NCL of a producing/ releasing country for United Nations procurement**

The responsible NRAs/NCLs are required to issue a certificate of release for vaccines that are distributed through United Nations agencies (16). Vaccines distributed through United Nations agencies are prequalified by WHO, to ensure that the products comply with the quality and safety standards established by the Organization. This release certificate is issued on the basis of, as a minimum, a review of the lot summary protocol for the relevant 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 regulatory oversight, assessing and approving changes to manufacturing processes – including testing and specifications, compliance with GMP – and PMS of AEFI. The release certificate issued by the responsible NRA/NCL should be forwarded by the United Nations 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, in order to strengthen the NCLs' capacity and obtain information on the quality of the product at the receiving site. If a deficient result is detected, the responsible NRA/NCL should be consulted.

8. 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. The release certificate is the official document authorizing the manufacturer to release the lot on to the market. The certificate may include the following information:

- name and address of the manufacturer;
- site(s) of manufacturing;
- trade name and/or common name of product;
- marketing authorization number;
- lot number(s) (including sub-lot numbers and 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 the agent authorized to issue the certificate;
- the date of issue of the certificate;
- the 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, stating, 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 the basis for the release decision (e.g. evaluation of the summary protocol, independent laboratory testing, specific procedures laid down in defined document, as appropriate).

For lots that fail to comply with the provisions, a different form should be issued, ideally with a different colour from the approval certificate, which clearly states that the lot is non-compliant.

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

Authors and acknowledgements

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of Public Health, Brussels, Belgium; Mr A. Mhenni, National Agency for Sanitary and Environmental Control of Products, Tunis, Tunisia; Dr C. Milne, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France; Dr P. Minor, National Institute for Biological Standards and Control, Potters Bar, England; Dr T.O. Owolabi, Central Drug and Vaccine Laboratory, Lagos, Nigeria; Mr J. Peart, Health Canada, Ottawa, Canada; Dr M. Pfeleiderer, Paul-Ehrlich-Institute, Langen, Germany; Dr D.M. Pascual, Centro para el Control Estatal de la Calidad de los Medicamentos, Havana, Cuba; Dr P. Richardson, European Medicines Agency, London, England; Dr A. Rinfret, Health Canada, Ottawa, Canada; Dr A. Sabouraud, Sanofi Pasteur, Marcy L'Etoile, France; Dr L. Set, Health Sciences Authority, Singapore, Singapore; Dr S. Siti Namtini, National Agency of Drug and Food Control, Jakarta, Indonesia; Mr J-M. Spieser, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France; Dr A. Sturgess, Merck & Co., Inc., Whitehouse Station, NJ, USA; Dr H. Rode, Health Canada, Ottawa, Canada; Dr D. Wood, World Health Organization, Geneva, Switzerland; and Ms L.M. Yong, Centre for Analytical Science, Health Sciences Authority, Singapore, Singapore.

The first draft of this Guideline was prepared by a drafting group whose members were: Dr I. Knezevic, World Health Organization, Geneva, Switzerland; Dr D. Lei, World Health Organization, Geneva, Switzerland; Dr F. Fuchs, Agence Française de Sécurité Sanitaire de Produits de Santé, Lyons, France; Dr M. Baca-Estrada, Health Canada, Ottawa, Canada; Dr C. Milne, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France; Mrs T. Jivapaisarnpong, Ministry of Public Health, Bangkok, Thailand; Dr R. Gupta, Food and Drug Administration, Rockville, MD, USA; Dr E. Chaves Leal, Instituto Nacional de Controle de Qualidade em Saúde, Rio de Janeiro, Brazil; Dr J. Wang, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China; and Dr D. Xing, National Institute for Biological Standards and Control, Potters Bar, England.

The second draft of the Guideline was prepared by the drafting group at a meeting held in Cairo in March 2008. The third draft of the guideline was prepared by the group, taking into account comments on the second draft from national vaccine regulatory authorities and the vaccine industry.

The fourth draft was prepared Dr M. Baca-Estrada, Health Canada, Ottawa, Canada; Dr R. Gupta, Food and Drug Administration, Rockville, MD, USA; Mrs T. Jivapaisarnpong, Ministry of Public Health, Bangkok, Thailand; Dr I. Knezevic, World Health Organization, Geneva, Switzerland; Dr D. Lei, World Health Organization, Geneva, Switzerland; Dr C. Milne, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France; and Dr D. Xing, National Institute for Biological Standards and Control, Potters Bar, England, following a WHO informal consultation held in Thailand in November 2008 with the following participants: Dr M. Baca-Estrada, Health Canada, Ottawa, Canada;

Mr L. Belgharbi, World Health Organization, Geneva, Switzerland; Dr E. Chaves Leal, Instituto Nacional de Controle de Qualidade em Saúde, Rio de Janeiro, Brazil; Mr W. Effiok, Central Drug and Vaccine Laboratory, and Secretary, National Vaccine Advisory Committee, Lagos, Nigeria; Dr S. Fakhrzadeh, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; Dr S. Jadhav, Serum Institute of India Ltd., Pune, India; Mrs T. Jivapaisarnpong, Ministry of Public Health, Bangkok, Thailand; Dr D. Khokal, Therapeutic Health Products Regulation Group, Singapore, Singapore; Dr I. Knezevic, World Health Organization, Geneva, Switzerland; Dr H. Langer, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; Dr D. Lei, World Health Organization, Geneva, Switzerland; Dr A. Maes, Scientific Institute of Public Health, Brussels, Belgium; Ms D. Messaoud, National Agency for Sanitary and Environmental Control of Products, Tunis, Tunisia; Dr P. Minor, National Institute for Biological Standards and Control, Potters Bar, England; Dr S. Morgeaux, Agence Française de Sécurité Sanitaire de Produits de Santé, Lyons, France; Dr S.S. Namtini, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr D.M. Pascual, Centro para el Control Estatal de la Calidad de los Medicamentos, Havana, Cuba; Dr M. Pfeleiderer, Paul-Ehrlich-Institute, Langen, Germany; Dr C. Ponsar, GlaxoSmithKline Biologicals, Rixensart, Belgium; Dr C. Rolls, Therapeutic Goods Administration, Canberra, Australia; Dr A. Sabouraud, Sanofi Pasteur, Marcy l'Etoile, France; Ms J. Tresnabudi, Bio Farma, West Java, Indonesia; Dr J. Wang, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China; Dr D. Wood, World Health Organization, Geneva, Switzerland; Dr D. Xing, National Institute for Biological Standards and Control, Potters Bar, England.

The fifth draft was prepared by Dr D. Lei, World Health Organization, Geneva, Switzerland; Dr P. Minor, National Institute for Biological Standards and Control, Potters Bar, England; and Dr C. Milne, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France, on the basis of comments from national regulators, the vaccine industry and the general public.

The sixth draft was prepared by Dr D. Lei, World Health Organization, Geneva, Switzerland, and the drafting group, on the basis of comments from the Expert Committee on Biological Standardization and the participants in the Committee meeting of 2009 and comments from the public consultation.

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Appendix 1

A model procedure to document the decision-making process in lot release

This Appendix is intended to assist NCLs in documentation of the information and the process used in the evaluation of specific issues in vaccine lot release. Examples include:

- release of vaccine lots in emergency situations such as a vaccine shortage due to a disease outbreak, natural disaster, manufacturing problems (e.g. OOS) or other unforeseen circumstances;
- periodic evaluation of the frequency of independent testing (to consider modification, suspension or continuation of the current strategy);
- periodic evaluation of tests performed for lot release of a particular product (to consider deletion, inclusion or modification of given tests).

Since each situation is specific, it is expected that modifications to the structure and content of this template may be required in order for it to be applicable to different issues.

1. Issue

Define the problem/issue to be analysed.

2. Purpose/objective

Outline the purpose and/or objectives of this analysis (for instance, to evaluate the consistency of production of a vaccine) and explore whether changes to the frequency of independent testing or elimination of a specific test are justified on the basis of the consistency of production.

3. Background

Give a brief history of the problem/issue and identify critical information.

4. Issue analysis

List all key components of the issue to be analysed, taking into account relevant information from the NCL/NRA and manufacturers. Justify the results/conclusions with regulatory and scientific data, including published and unpublished information.

5. Options analysis

- List all the options considered to address the issue/problem, including the status quo.
- List and discuss the positive and negative aspects of each option.
- Outline the proposed solution or accepted alternative and why it was selected.
- If relevant, discuss the benefits and costs of the proposed solution compared to the benefits and costs of the other solutions.

6. Considerations

Identify any additional relevant information. For instance, discuss with other NCLs that are responsible for releasing this vaccine in other countries, in order to share information regarding production and quality control of this vaccine.

7. Recommendations

Indicate what the recommendation is and who is responsible for its approval.

8. Implementation and evaluation plan

Show how the proposed changes will be implemented in terms of timing, organizational and personnel changes and resource allocation.

Indicate when and how the proposed changes will be evaluated and against what benchmarks.

9. References and attachments

Include any references, reports and relevant information used in the risk analysis, such as GMP inspection report, regulatory post-marketing unit report, quality-control product report from the NCL, and/or a summary of decisions regarding variations submitted for regulatory approval.

I approve the recommendation proposed in this analysis,

Dr [insert name]

Director of National Control Laboratory