及び検定試験の実施について、最終的な判断は各国の規制当局にあるべきとの主張がされた。その他の部分については、軽微な修正が行われた。その他 ECBS 2009 で議論された事項について、資料４に整理した。

D. 考察

ロットリリースは、製造販売承認後に市場に出荷される前にロット毎に製造所規制当局により独立に実施される評価及び承認の過程であり、最低限、製造所から提出されるＳＬＰ（製造及びすべての QC 工程）の評価に基づき実施されることが国際的にも WHO ガイドライン案においても求められている。ロットリリースには、検定試験も含まれるが各国でその程度は異なる。

ワクチンにロットリリースが要求される理由としては、ワクチンが国民（社会）の健康を守る重要な手段であること、多くの健常人に用いられること、品質（安全性あるいは有効性）の不良が接種後すぐに明らかとならないことが多いこと、生物学的製剤が本質的にバラツキの避けられない原材料から製造されること、試験法や標準品等もまた本質的にバラツキが避けられないこと、発生する問題の多くがロットに関連していること等が挙げられる。

我が国ではワクチンのロットリリースは事実上、薬事法に基づき NIID で実施される国家検定（検定試験）の合格をもって行われている。ＳＬＰ（製造及びすべての QC 工程）評価に関しては、薬事等施行規則第 197 条第２項により、検定の申請書には、自家試験の記録を記載した書類を添えなければならないことになっており、本項によって自家試験の記載内容も国家検定の判定材料となるといった解釈もあるが、自家試験記録に記載された内容は国家検定合否判定においては絶対的なものではなく、参考資料として捉えるべきとの解釈もある。また、現在 NIID に提出される自家試験記録には製造記録が必ずしも含まれていない。ワクチンの品質保証システムの向上、国際調和の観点からロットリリースにおけるＳＬＰ評価は、今後我が国に導入し、発展させていくことが望まれる。そのためには、関連する法令等を整備するとともに、NIID の製造販売承認申請書類へのアクセス、承認審査への関与、GMP 調査との連携が体系的に実施され、NRA である厚生労働省、承認審査・GMP 調査・PMS などを担当する（独）医薬品医療機器総合機構との連携を充実させていく必要がある。

検定試験の実施は、製造所の試験結果を確認するセーフティネットとな

っている。WHO ガイドライン案では、ＳＬＰ評価を実施することで検定試験の実施が不必要になるとの考えではなく、同一ロットに対して試験を輸入国毎に繰り返し実施することは非効率であるため避けるべきとの考えであると理解できる。製造国の規制当局が試験を実施することは妥当と考えられる。各国の規制当局には、自国で使用するワクチンの品質を保証する体制・手順を整備する責任があり、最終的な判断は各国の規制当局に委ねられている。

E. 結論

ロットリリースにおけるＳＬＰ評価は、ワクチンの品質保証システムの向上、国際調和の観点から今後我が国に導入し、発展させていくことが望まれる。そのためには、関連する法令等を整備するとともに、NCL である NIID の製造販売承認申請書類へのアクセス、承認審査への関与、GMP 調査との連携が体系的に実施され、NRA である厚生労働省、承認審査・GMP 調査・PMS 等を担当する医薬品医療機器総合機構との連携を充実させていく必要がある。

F. 健康危険情報

なし

G. 研究発表

１．論文発表

なし

２．学会発表

1. Yuen, C., Horiuchi, Y., Asokanathan, C., Cook, S., Douglas-Barsley, A., Ochiai, M., Corbel, M. and Xing, D. 2009. An *in vitro* biochemical assay system alternative to the *in vivo* Histamine sensitisation test for pertussis vaccines. (7th World Congress on Alternatives & Animal Use in the Life Sciences, Rome, 2009年8-9月)
2. 落合雅樹、山本明彦、片岡紀代、堀内善信、荒川宜親、2009. Development of alternative assays to the mouse histamine sensitization test for acellular pertussis vaccines. (第13回日本ワクチン学会学術集会、札幌、2009年9月)

H. 知的財産権の出願・登録状況

なし

World Health Organization

WHO/BS/09.2109
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 19 to 23 October 2009

Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). **The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Comments proposing modifications to this text MUST be received by 9 October 2009** and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Dr Dianliang Lei at email: leid@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

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1. Introduction

Vaccine lot release conducted by the regulatory authorities is part of the regulation of biological products and involves the independent assessment of each individual lot of a licensed vaccine before it is released onto the market. This assessment is based, as a minimum, on the review of manufacturer's protocols. It may be supplemented by other documents such as the release certificate from another National Regulatory Authority (NRA)/National Control Laboratory (NCL) and by independent testing as required and is independent of the manufacturer's quality control (QC) testing and release.

WHO have provided support for setting up lot release programs including provision of written and measurement standards, strengthening lot release function of the NRAs and providing training (1, 2, 3, 4). However, a need for further guidance was identified at WHO consultations held in Ottawa in 2007.

This guideline should be read in conjunction with the recommendations/guidelines for specific products (e.g., recommendations for BCG, OPV, MMR, DTP, HPV, and rotavirus vaccines etc.) (5, 6, 7, 8, 9,10). The document is intended to serve as a guide for setting up national requirements for lot release and for this purpose it could be adopted as a whole or partially.

1.1 Scope

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

This document is intended to provide guidance to the National Regulatory Authority and/or National Control Laboratory, and to vaccine manufacturers. It may also be relevant to public health authorities, such as the National Immunization Programme.

2. General Considerations

National requirements for lot release should define all procedures, from the submission of the lot for release to the issue of lot release certificate.

Vaccines are biological medicines 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 potency and safety data on every lot is necessary before it is marketed. Problems regarding vaccine quality have a direct impact on the public acceptance of immunization programs, thus potentially compromising public health strategies.

Furthermore vaccines and the tests applied to them being of a biological and complex nature, 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 that there is independent lot release for vaccines used in their country either based on their own evaluation, as a minimum a thorough review and approval of a summary protocol including manufacturing and testing activities, or that of another regulatory authority. If the vaccine is produced in the country of use or is self procured, the NRA/NCL should play an active part in its release. Where vaccines are provided by UN agencies and therefore prequalified by WHO they will be released by the producing country and could be exempt from release by the receiving country.

While ideally all vaccine lots should be released by an NRA/NCL, 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.

3. Responsibility of 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 relationship between the NRA and the NCL varies from country to country but in all cases the different branches of the regulatory structure (marketing authorization, GMP (good manufacturing practices) inspection, lot release and post marketing surveillance (PMS)) must interact and exchange information effectively.

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

3.1 Responsibility of the NRA/NCL in Lot Release

Marketing approval for a biological product should be granted by an NRA which should also be responsible for continued post-licensing 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 performing lot release 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 shall 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 shall 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 bulk and finished products) or access to a competent laboratory for 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.

Development of testing methodology and capability should begin as soon as possible for both 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.

The NRA/NCL should ensure that the mechanism for the independent lot release procedure is communicated clearly to the involved manufacturers 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 regarding confidentiality of information should be established and the data submitted by manufacturers and other NCLs/NRAs shall be kept as confidential unless agreed otherwise.

The NRA/NCL of a producing country has the responsibility to ensure the production and release of good quality vaccines whether they are used in the country or exported. The criteria for local used vaccine and those for export should be the same.

3.2 Responsibility of Manufacturer in NRA/NCL Lot Release

The manufacturer has the following responsibilities in terms of NRA/NCL lot release: (a) collaborate with the 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 NCL in technical transfer of testing methods; (e) submit an NRA/NCL lot release certificate of the producing/releasing country 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 required by the NRA/NCL.

3.3 Establishment of Quality Management Systems for the NRA/NCL

A quality management system (QMS) shall 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), written procedures, internal and external audit systems and oversight procedures.

4. Conducting Lot Release

The manufacturer's summary protocol should be reviewed by a competent authority 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. Where appropriate, review of the summary protocol could be complemented by the independent testing. In all cases, any available lot release certificate issued by another NRA/NCL, in particular the one from the producing/releasing 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 the 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. If this is not the case it may give misleading information, causing unnecessary delay in releasing vaccine onto the market and rejection of vaccine that meets specifications.

4.1 Protocol Review

The manufacturer's 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 protocol submitted to the NRA/NCL has to be approved by the appropriate quality assurance (QA) or QC responsible person. 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.

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.

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

This encompasses the traceability of 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 shall 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
Lot number	Lot numbers of the final products 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, intermediates, final bulk, and final product.	Expiry date of each component fits the shelf life of the final product
Dates of manufacturing	Of each starting material, 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 licensing 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 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	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

	doses). Provided with statistical results, such as, mean, geometric mean, standard deviation, 95% confidence intervals, etc, if applicable. Include results of failed or invalid tests if a test has been repeated	

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, which would be product specific, 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.).

If there is a well designed protocol and a database to capture the information, the use of checklists may not be needed (see 4.1.4).

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 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 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, 95% 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.

For freeze-dried vaccines, the protocol or Certificate of Analysis of the particular lot of diluent should be reviewed

4.1.5 Handling Discrepancies and Out of Specification (OOS) Results in Summary Protocols

Any discrepancies, errors or OOS found in the information 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. Manufacturer's 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. Testing requirements for each specific product should be reviewed periodically to ensure that the appropriate level of scrutiny is applied, in line with the history of the product, consistency of production or the development of new or improved tests approved for marketed products.

The decision to conduct independent testing should be evaluated for each particular vaccine. The NRA/NCL from vaccine producing country should give special attention to vaccines produced locally where regulatory oversight is important.

4.2.1 Purpose of Independent Testing

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. A lot release testing program also allows NCLs to maintain independent expertise on test methods. 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. This is an important aspect for overall competence of an NCL in its ability to effectively monitor these products. In addition to the utility at the national level it can also help when providing ad hoc expertise to third parties if needed.

4.2.2 Prerequisites for Setting Up Independent Testing for Lot Release

A defined strategy for testing needs to be established as part of global lot release policy based on a product specific approach. Knowledge of the marketing authorization dossier is essential to identify and assess the critical parameters for testing. Ideally there should be involvement of the NCL staff in the marketing authorization evaluation (for pharmaceutical quality information at least).

When setting up testing program 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 ISO 17025).

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 method 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 manufacturers.

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 licensing procedure to allow transfer and qualification/validation of the methodology prior to supply of the first batch. 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 pre-requisites noted in section 4.2.2 above have been addressed. Testing under inappropriate conditions may provide misleading or inaccurate data and cause unnecessary delays or rejection of batches which meet the specifications.

The establishment of a testing policy should consider three main aspects. First should the vaccine be tested by an independent authority, second if testing is required what critical parameters should be tested by the NCL and third should it be done on every lot or on some reduced percentage of lots.

The decision to conduct independent testing at the NCL should consider the capacity of the NCL and the information available from other NRAs/NCLs who may also release the same products. It should be based on an analysis of whether testing would help evaluation of product manufacturing and testing consistency, adverse reaction reports and inspections' observations. The decision should be reviewed in the light of experience with the product.

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, as well as the testing results from other NCL where available. An important factor is the manufacturers' production history which could be obtained from yearly biologic product reports (see below) which contains production and testing information including trend of critical test parameters. Other information to be considered includes on site GMP inspection reports, adverse event following immunization (AEFI) report, production complaints and other post marketing surveillance safety and quality information. The awareness of testing programs for the product at other NCLs may also be taken into consideration in the final analysis.

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

If the decision to perform testing is taken, the NCL should concentrate on a selection of critical elements to be tested, determined on a product specific basis and not attempt to repeat all tests in the marketing authorization dossier. Key elements of focus where tests may be considered necessary include appearance, identity, potency, safety and thermostability. Systematic testing of simple physical-chemical parameters (e.g. pH, osmolarity) will 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). The added value of testing any of these parameters at the NCL should be carefully considered after coordination with relevant surveillance bodies.

Testing is generally focused on the final bulk or final product; however 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 adjuvants in the final product prevents immunochemical analyses).

As noted above, the rationale of the testing scheme should also consider the life-cycle of the product and past experience. Specific attention should be paid to new vaccines, for which there is little accumulated experience and sophisticated combined vaccines for which testing and interpretation of results can be complicated. If necessary, NCLs should be encouraged to develop and adopt more effective test methods, if a different test method is used by the NCL, in case of discrepant data between the manufacturer and the NCL, then the approved method test method defined in marketing authorization shall be used to solve the test issue.

There should be a regular review of the testing strategy in order to re-evaluate needs and appropriateness in the current context. Additional tests may be included or existing tests deleted as required.

The percentage of lots of a given product to be covered by the testing program 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 should be in the hands of the NCL and the manufacturer should not be aware in advance as to which lots will undergo testing. Spot testing by the NCL should be avoided as this could generate non relevant or misleading test results.

The percentage of lots tested should be monitored and revised if necessary based on the experience with the product (e.g. good consistency over a significant period may mean reducing 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).

Testing conducted by others NCLs with continuous extensive monitoring of the given product may be considered as an element in determining the testing policy.

4.2.5 Importance of Reference Preparations for Lot Release

Appropriate use of reference preparations in independent testing as part of lot release 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 licensing 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 can also be calibrated in IU against international standard, when it is appropriate.

4.2.6 Standards and Reference Reagents

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). It may not be appropriate to use

ISs 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.

In some cases IS do not exist for a given purpose. Therefore, regional or national standards may be developed to provide a common reference. Development of these standards should as far as possible be a collaborative effort and would ideally also 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 (e.g. monovalent bulks) requested should be appropriate for the testing required and the sampling procedures should ensure a representative look at the lot in question. A system should be in place for the 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. It is possible 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 final NCL release cannot be given until all the elements from the manufacturer have been received (including the completed and signed final protocol with their test results).

When use of animals is necessary for test procedures, the NCL should be aware of the potential variability depending on their source and issues regarding housing and handling. 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. Ultimately, the involvement of testing NCL staff in assessing test methods, validity criteria and the NRA product specifications decision making process is paramount.

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 must 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, averaging 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 condition of the lot that is 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 discrepant situation.

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.

The NCL should perform trend analysis on its own results for a given product as well as compare the trend in their results with those of the manufacturer.

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 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, ± 2SD and ± 3SD of mean are set for the alert or warning limits and action limits, respectively, when data are normally distributed. 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 NRA/NCL of the producing/releasing country. 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' results and information 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.

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.

6. Evaluation of the Lot and Decision Making Process

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. A written guidance/procedure 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 interact 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 lot 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. Written acceptance criteria for summary protocol and all the intermediate reviewing steps leading to the final conclusion on the protocol (e.g. need for correction, submission of revised pages, investigation, etc.).

   As part of the lot release process the NRA/NCL should produce a formal written conclusion as regards the summary protocol review. A summary decision form should be in place to ensure compliance with approved license specifications (e.g. comparison of approved and lot specifications) and should be signed by the responsible scientist.

2. A written procedure describing the acceptance criteria for NCL test results and recording all the individual test results in certificate(s) of analysis.
   As part of the lot release process the NRA/NCL should produce a formal written conclusion form containing the outcome of test results.
   For lot release following independent testing by the NCL, a summary decision form should be used to capture the test results and ensure compliance with approved specifications. 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 (e.g. as recommended by ISO17025).

3. A written procedure that describes 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 be only applied by the individual 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 shall be documented. An example of assessment of product specific lot release issue and documentation is provided in the appendix.

6.1 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 that many NRAs/NCLs establish with the aim of enhancing international regulatory cooperation to maintain high standards of product safety and quality, while facilitating the reduction of the regulatory burden for NRAs/NCLs and manufacturers and 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 must 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 make their evaluation of 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.

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

The NRAs/NCLs from producing/releasing countries 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 examination of the lot summary protocol for the particular lot.

The NRA/NCL of the producing/releasing country plays a key role in ensuring that products meet the specifications outlined in the Marketing Authorization. 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 NRA/NCL of a producing/releasing country should be forwarded by the UN Agencies to the NRA/NCL of the receiving country and the summary protocol will be provided upon request.

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/or international non proprietary name/ 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/batch 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 testing) may also be included in the certificate according to the requirements of different countries.

The conclusion shall be included clearly in the certificate, for example: "the lot mentioned above complies with the 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. 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 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 avoiding having the same lot tested a number of times unnecessarily by different NCLs. It contributes to reducing the number of animals used for testing through the sharing of test results. 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.

9. Glossary

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