

Training manual: licensing, lot release, laboratory access



DEPARTMENT OF VACCINES AND BIOLOGICALS



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Glossary

AD	auto-disable syringes
AEFI	Adverse events following immunization. Expected or unexpected signs or symptoms occurring in a person after receiving a vaccine. Serious or unexpected adverse events following immunization must be investigated to determine whether the vaccine has caused the reaction.
Batch record (23)	All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.
Batch certificate (18,23)	A document containing information as set out in Appendix 3 of the <i>Guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce</i> (18), normally issued for each batch by the manufacturer. This provides a warranty that a specific consignment of a product conforms to the documented specifications. Furthermore, a batch certificate may exceptionally be validated or issued by the competent authority of the exporting country, particularly for vaccines, sera or other biological products. The batch certificate accompanies each major consignment.
Batch or lot (23)	A defined quantity of starting material, packaging material, or product processed in a single process or series of process steps so that it can be expected to be homogeneous. In the case of continuous manufacture, a batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.
Batch or lot number (23)	A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, and the certificates of analysis, etc.

Biological drug	A medicine made from microorganisms, blood or other living tissues.
Certificate of a pharmaceutical product	A document containing information as set out in (18,23)Appendix 1 of the <i>Guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce</i> . It is validated and issued for a specific product by the competent authority of the exporting country and intended for use by the competent authority in the importing country. The product certificate should be requested by the importing authority primarily when it intends to issue or vary a product licence.
Competent authority (18)	The national authority as identified in the formal letter of acceptance in which each Member State informs WHO of its intention to participate in the Scheme. ... The competent authority can issue and receive certificates. WHO makes available on request a continuously updated list of addresses of competent authorities and, when applicable, the specific conditions for participation. A legally responsible government department or designated staff member or group for the regulation of medicines.
Drug regulatory authority (DRA) (18)	An authority appointed by the government to administer the granting of marketing authorizations for pharmaceuticals (and biologicals) in that country.
Drug master file (DMF) (40)	A master file that provides a full set of data on a product.
EMA	European Medicines Evaluation Agency: Agency for the centralized regulatory procedures for marketing authorizations in the European Union.
Establishment (50)	All locations including all buildings, utilities and support services, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.
Establishment licence (50)	The official document issued by a DRA or NRA authorizing an establishment to operate for the production of a drug(s) or biological product(s). The licence shall include the name and address of the manufacturer, the establishment and all locations of the establishment, the licence number, and the date of issuance.
EU	European Union

Expert committee on biological standardization	WHO committee responsible for establishing the WHO standard guidelines for biological products.
FDA	Food and Drug Administration (USA)
GCP	Good clinical practice
GLP	Good laboratory practice: a USA FDA term for quality and performance standards for non-clinical studies carried out to support the application for clinical studies in humans or for the application for a product licence.
GMP (23)	Good manufacturing practice: that part of pharmaceutical quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required by the marketing authorization.
GMP certificate	Official certificate issued by the NRA of the manufacturer's country indicating that the manufacturing establishment complies with national requirements for good manufacturing practice. The formats should follow that set out in the guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (18)
GMP inspection or audit	An official regulatory on-site review of the manufacturing and testing procedures and the facilities to determine compliance with good manufacturing practice. Licensing and maintenance of the licence is dependent on satisfactory compliance with GMP as determined by regular inspections by the NRA or its official designate(s).
ICH	International conference on harmonization: An international committee composed of the USA, the EU and Japan, mandated to prepare and to circulate, for discussion and comment, harmonized regulatory documents for human and animal medicines.
Licence	See marketing authorization
Licence holder (18)	An individual or corporate entity possessing a marketing authorization for a pharmaceutical (or biological) product.
Lot	See batch
Lot release	The process of NRA evaluation of an individual lot of a biological product before approving for release for use.

LQS (8)	Laboratory quality system: The full scope of activities, procedures and records that provide evidence that all laboratory operations are performed to a specified standard.
Marketing authorization (48)	An official document issued by the competent DRA or NRA for the purpose of the marketing of a product. It must set out, <i>inter alia</i> , the name of the product, the dosage form, the quantitative formula including excipients per unit dose, shelf life, storage conditions, and packaging characteristics. It also contains all the information approved for health professionals and the public, the sales category, name and address of the licence holder, and the period of validity of the licence.
Master file	See plant master file, drug master file, master validation file
Master formula (23)	A document or set of documents specifying the starting materials with their quantities and their packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.
Master validation file	A document explaining the policy and list of procedures performed by a manufacturing facility to ensure that the facility, equipment and procedures remain in compliance with GMP validation requirements.
NCL	National control laboratory
Notice of compliance (54)	Canadian term for the regulatory approval of a biological product for sale.
NRA	National regulatory authority (previously called NCA – national control authority)
PAHO	Pan American Health Organization. The international health organization in the Americas. Acts as the WHO Regional Office for the Americas (AMRO)
Plant master file (53)	The documents describing the manufacturing facility in detail including general data, the premises, equipment, personnel, sanitation, manufacturing control, quality control, packaging material testing, finished product testing, records, samples and stability.
PMS	Post marketing surveillance. The procedures involved in determining the safety, effectiveness and efficacy of vaccines after they have been approved and are in use.

Pre-qualification (Procedures for assessing the acceptability, in principle, of sale of vaccines for purchase by UN agencies) (7).	WHO assessment procedure for verifying that the vaccine (a) meets the specifications of the relevant UN agency and (b) the requirements recommended by WHO, including those for good manufacturing practices. The assessment includes an evaluation of vaccine production facilities and of the functions of the national regulatory authorities.
Product file (7)	The term for the documents submitted about a vaccine product to WHO for the pre-qualification process, or to a regulatory authority for marketing authorization.
Product licence	See marketing authorization
Registration	See marketing authorization
SOP (23)	Standard operating procedure: An authorized written procedure giving instruction for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling, inspections). Certain SOPs may be used to supplement product-specific master and batch production documentation.
Statement of licensing status (18)	A statement that attests only that a licence has been issued for a specific product or products for use in the exporting country.
Summary protocol	A document summarizing all manufacturing steps and test results for a lot of a vaccine, which is certified and signed by the responsible person of the manufacturing company.
TRS	Technical report series: a WHO publication dealing with technical information on various health issues.
UNICEF	United Nations Children's Fund
Validation (23)	The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.
Variation (48)	A change to any aspect of a pharmaceutical product including, but not limited to, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container or container labelling, and product information.

WHO (World Health Organization)

ATT (Access to Technologies)
GTN (Global Training Network)
EPI (Expanded Programme on Immunization)
VAB (Vaccines and Biologicals)
Previous names still on various documents
GPV (Global Programme for Vaccines and Immunization)
VSQ (Vaccine Supply and Quality)

WHO model certificates

Several models of the type of information that should be found in a licence for a biological product, for release certificates, or in the summary protocol for each lot of vaccine (see list in References section).

Introduction

It is the responsibility of each country to provide safe and effective medications including vaccines. Many small countries are now taking on the responsibility for procuring their own vaccines and their national regulatory authorities (NRAs) must quickly enter the realm of vaccine evaluation, licensing and lot release as recommended by the World Health Organization (WHO).

WHO's Global Training Network (GTN) was established in 1996 to provide training to national regulatory authorities and qualified manufacturers. There are now 14 training centres delivering courses and workshops in the network. Over 350 applicants from 57 countries have been trained in 9 GTN-certified curricula.

WHO has also developed an assessment tool for identifying the status of existing regulatory functions and training needs of national regulatory authorities. The system identifies the need for a legal system and six critical functions to provide quality vaccines. WHO's acronym for the six critical functions is "ASSURE":

- **A** published set of clear requirements for licensing (of products and manufacturers)
- **S**urveillance of vaccine performance in the field (safety and efficacy)
- **S**ystem of lot release
- **U**se of a laboratory when needed
- **R**egular inspections of manufacturers for good manufacturing practices (GMP) compliance
- **E**valuation of clinical performance through authorized clinical trial

Vaccines of "assured" quality are those meeting the following conditions:

- NRA independently controls the quality of the vaccine in accordance with the six specific functions defined by WHO;
- there are no unresolved reports of quality related problems (WHO/VSQ/96.02 Rev. 1)

WHO has prepared several documents and presentations for guidance of national regulatory authorities on the six critical functions (see References section). WHO has also published a document that: outlines the differences between the regulation of drugs and vaccines; and offers an effective mechanism for extending the functions of a Drug Regulatory Authority (DRA) in a vaccine-procuring country so that it also regulates vaccines (WHO/V&B/99.10). This document includes a list

of the six critical functions and a description of the indicators developed by WHO, in consultation with many regulatory authorities worldwide, that identify the activities to be performed for each function. First of all, however, the regulation of vaccines can be effective only if it is mandated by laws or regulations – a system to regulate vaccines. If national regulatory authorities are to have effective control of vaccines, they must have the power to do so.

These indicators have been prepared for two purposes: to enable assessment of NRA performance; and to aid countries in developing plans to access needed technical inputs such as training.

The fact that many non-producing countries procure their own vaccines has raised a need for training in the mechanics of procurement. Initially, short presentations on the regulatory aspects of ensuring the tendering and procurement of vaccines of assured quality were included in the procurement training workshops of WHO and the United Nations Children's Fund (UNICEF). Information about the NRA involvement in purchasing quality vaccines has also been included in recent procurement manuals prepared by WHO and UNICEF.

The GTN is now offering courses specifically for training on the four critical functions needed by an NRA of a vaccine-procuring country. This manual has been prepared as part of this effort. The four critical functions needed for effective control of imported vaccine are:

- licensing/registration;
- surveillance of vaccine performance in the field;
- approval and release of each lot before it is distributed in the country; and
- knowledge on when and how to access laboratory services.

This manual is divided into four modules: one for the system to regulate vaccines, and modules for licensing, lot release and laboratory access. A module on surveillance of vaccine performance will be developed separately.

Each module represents one of the critical functions and discusses the indicator for that function. For each indicator, there is a discussion section giving the background and a section on practical approaches that can be used by the trainers to design exercises for their classes. The manual was designed to be the basis of the training courses delivered by one or more training centres. Each of the modules is designed to be an independent teaching tool, cross-referencing the other modules where needed. The glossary of terms and abbreviations at the beginning of this document, and the list of references support all of the modules.

Each training centre can adapt the discussion and practical aspects to suit their course, and, depending on the course, one or more modules can be used. The manual can also be used by national regulatory authorities as a guide for implementing the functions, or for determining their training needs.

Module 1:

System to regulate vaccines

Introduction

National health authorities have the duty to ensure that pharmaceutical products used in their country, including biologicals, are of good quality, safe and efficacious (17, 15, 48).

To ensure the quality of pharmaceutical products, the manufacture and subsequent handling must take place under defined conditions and in conformance with prescribed standards. Legislative and administrative controls must reflect the special considerations to be applied to such products (20).

To accomplish this, the health authorities should establish and maintain a competent national regulatory authority that will be responsible for ensuring that the manufacturer complies with the accepted standards of good manufacturing practice and quality criteria specific to the product. Ensuring quality is particularly difficult for vaccines and other biologicals, because the quality of these products cannot be completely determined by tests on material in the final containers. (17, 15)

The primary responsibility for quality, safety and efficacy lies with the manufacturer, but the NRA of each country is responsible for establishing procedures for assuring that the products and manufacturers meet the required criteria. The procedures by which the NRA carries out these functions will depend on the resources available and whether the product is manufactured locally or imported (17, 15). These procedures must be backed by legislation and be legally enforced.

There are several aspects to a system to regulate vaccines. WHO has developed indicators for such a system, which are listed below (11). These indicators can be used to assess the existing system, to develop a new system or to expand the system for regulating drugs to include vaccines and biologicals. All of these indicators are essential for countries that manufacture vaccines. Some of them are for NRAs of countries that purchase their vaccines from manufacturers, importers or agents, and only a subset are relevant to countries whose vaccines are sourced through UN agencies.

The indicators in bold type are for countries that import their vaccines directly or through UNICEF. These indicators will be discussed in detail below.

Indicators: System to regulate vaccines

- **Statutory basis for establishment of vaccine regulatory system and enforcement power (all countries).**
- **Lines of authority which reflect the independence of regulatory authority from manufacturer (only for countries producing vaccines).**
- **If there is recognition of other regulatory authorities, criteria are established (all countries).**
- **Recall system (all countries).**
- **Mechanism to confirm the destruction of lots and system to document this has been done (all countries).**
- **Appropriate expertise of staff (all countries).**
- **Institutional development plan (all countries).**

Each of the indicators will be discussed with specific regard to the regulation of vaccines. This is followed by suggested approaches to implement the functions. Vaccines are part of the group of products known as immunobiologicals (vaccines, sera and toxins) and the discussions are applicable to these products as well.

1. **Statutory basis for establishment of vaccine regulatory system and enforcement power (all countries)**

A. *Discussion*

The objective of drug regulatory legislation is to provide a framework for drug regulation through the establishment of a national regulatory authority. The primary responsibility is to operate a system of administration and enforcement to ensure that all medicinal products subject to legislative control conform to specific standards (20). The terms of reference, functions, responsibilities, powers and composition of the authority must be clearly set out in the legislation (20).

The authority can be either independent or part of the ministry of health. The organizational structure of regulatory authorities in various countries differs. This may depend on the laws of the country, the size of the country, and the number of domestic manufacturers. In some countries, the licensing, facility inspections, clinical evaluation, surveillance of field performance, laboratory functions and lot release are under the same direction; in other countries they are separate departments reporting to a senior official of the ministry of health or other responsible ministry. There are also systems where the NRA and national control laboratory (NCL) functions are performed by external agencies reporting to the responsible ministry. Most are supported by expert committees (clinical committees, pharmaceutical committees, pharmacopoeial committees) advisory to the responsible ministry to provide specific expertise. As long as all the functions are effectively carried out, any of these organizational structures is appropriate.

The NRA should have a defined organizational structure with the responsibilities, relationships, coordination and legal status of employees specified according to their role in a clearly defined decision-making process. The decision-making responsibilities for vaccines and biologicals within the authority should be delegated to departments with the necessary competence in the field of biologicals.

B. Practical approaches

- Review the existing national legislation for drugs and biologicals to determine if the present laws effectively cover the regulation of vaccines according to the WHO recommendations for the critical functions of the NRA of a vaccine-importing country: licensing, post-marketing surveillance, lot release and access to suitable laboratories when needed.
- If not, draft appropriate amendments in conjunction with the legal department of the ministry of health, or other responsible ministry, to ensure that vaccines are covered by the national drug regulations.
- If an overall drug policy is not effectively in place, WHO has developed guidelines to assist countries with newly developing and small regulatory authorities and limited resources to plan and implement drug regulation. Several guidance documents have been published by WHO on developing national drug policies (11,12,14,20). The most recent (20) provides an example of a legislative scheme for regulating medicinal products.

2. If there is recognition of other regulatory authorities, criteria are established (all countries)

A. Discussion

New small regulatory authorities in the development stages of pharmaceutical regulation often do not have the resources or expertise to implement the full range of functions/expertise. In this situation, reliance on other well-established regulatory authorities can be a great asset. It is of paramount importance that the legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries.

To be assured that vaccines are of good quality, NRAs can identify and officially recognize regulatory authorities of countries that sell vaccine to UN agencies, knowing that WHO has made an evaluation of the regulatory functions and found them to be fully satisfactory. For the list of NRAs, please refer to the web site address: http://www.who.int/vaccines-access/Restructuring/Vaccines/Vaccine_Quality/NRAs/NRAs.html. WHO publishes the list of vaccines and manufacturers that are pre-qualified (http://www.who.int/vaccines-access/Restructuring/Vaccines/Vaccine_Quality/UN_Prequalified/UN_Prequalified_producers.htm). Major industrialized countries and the European Union countries have well established and internationally recognized regulatory authorities working under laws or directives, regulations and guidelines that ensure the quality safety and efficacy of local manufacturers for licensing. These manufacturers are routinely assessed for compliance with good manufacturing practices during regular GMP inspections.

New regulatory authorities can rely on expertise of other NRAs by, for example, requiring that licences are granted to vaccines that are licensed in the country of origin and distributed on that local market (although there may be exceptions).

They can also request from the manufacturer the full list of countries where the product is licensed and distributed, which gives additional assurance that the product has been reviewed and found acceptable by several regulatory authorities.

By joining the WHO certifications scheme on the quality of pharmaceutical products moving in international commerce (13, 18), a country importing vaccines can obtain information from the NRAs of other participating Member States on the status of license of a vaccine and for batch certificates for each lot of vaccine to be imported. The importing country, by joining the scheme, can require the manufacturer to include these certificates with the documentation for licensing or lot release. By reviewing certificates issued by responsible authorities of the country of manufacture, the importing country can be assured that products listed are licensed in the country of origin and have been inspected for GMP compliance. Member States have been urged to adopt and apply internationally recognized and respected standards of GMP as recommended by WHO (22-24, 26).

The following is a brief summary of the certification scheme (13,18):

- A pharmaceutical product is a medicinal product for human use or a veterinary product administered to food producing animals that is subject to legislative control in the exporting Member State and importing Member State. Member States that do not manufacture or export products can apply as importing nations only, and be eligible to receive the certificates from the exporting country.
- Under this scheme, at the request of an interested party, the exporting Member State would issue certificates and send them to the competent authority in the importing Member State. The latter would decide to grant or refuse authorization for sale or distribution, or it would request supplemental information. Three documents can be requested within the scope of the scheme (19).
 - 1) “Certificate of a pharmaceutical product”. The competent authority of the exporting Member State certifies on the form that the product is:
 - authorized for sale or distribution in the exporting country; and
 - the manufacturing plant is subject to inspections at scheduled intervals and meets GMP and quality control (QC) as recommended by WHO.
 - 2) “Statement of licensing status”. This document from the competent authority attests only that a licence has been issued for a specific product or products for use in the exporting country. It is expected to be used by importing agents in considering bids for international tender, only for facilitating screening and preparation of information for the conditions of bidding. The above-mentioned “Certificate of a Pharmaceutical Product” should be the basis for licensing and importation.

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- 3) “Batch certificate of a pharmaceutical product” is a vital instrument of drug procurement. The certificate is intended to accompany and attest to the quality and expiry date of a batch of product that is already licensed in the importing country. This certificate is normally issued by the manufacturer and is usually mandatory in tender and procurement documents. For vaccines and other biologicals, an additional batch certification for individual batches may be undertaken by the competent authority stating that the records of the manufacturing procedures and the quality control tests for the batch meet specifications. The requirements for the submission of the specific information included in the certificate would be a condition of the licence issued by the NRA of the importing Member State.
- Member States apply to participate in the scheme by notifying the Director-General of WHO in writing (18) providing the name and address of their competent authority and any significant reservations to their participation.
 - Exporting Member States shall ensure that:
 - authorization for sale is subject to appropriate testing for quality and stability by the competent authority and adequate laboratory facilities are available for this purpose;
 - the pharmaceutical industry is obliged to follow the requirements for GMP;
 - the competent authority is empowered to conduct investigations to ensure manufacturers conform to GMP (e.g. examination of records, taking of samples); and
 - GMP inspectors have appropriate qualifications and experience.
 - Upon request of the competent authority of the importing Member State, the competent authority of the exporting Member State should provide:
 - information on implementation of GMP (may require manufacturer’s consent);
 - information on controls on the product by the competent authority;
 - names and functions of the persons designated to sign certificates for products to be exported;
 - copies of all information and labelling (packaging materials, leaflets) supplied with the product as approved by the competent authority of the exporting country, including the dates they were approved; and
 - other information such as quality control data could also be supplied with the consent of the manufacturer.

National regulatory authorities should also forge links with other NRAs for the exchange of information on safety and other issues within legal and confidentiality limits. Exchange of information on adverse events, complaints, recalls, and other vaccine-related events that may affect public health should be communicated between NRAs where the product is licensed. Exchange of information on manufacturers’ proprietary technical information should take place only with the permission of the manufacturer.

It is a major responsibility of an NRA and its staff to maintain confidentiality of all proprietary information received from manufacturers and/or other NRAs. Nor should they divulge the status of the evaluation of a licensing file to anyone other than the manufacturer or manufacturer's agent. It is also important to have provisions to ensure that NRA staff members have no real or perceived conflict of interest in any product subject to the country's regulations.

B. Practical approaches

- Obtain the list of WHO pre-qualified vaccines/manufacturers and keep it updated ([http://www.who.int/vaccines-access/Restructuring/Vaccines/Vaccine_Quality/UN_Prequalified/ UN_Prequalified_producers.htm](http://www.who.int/vaccines-access/Restructuring/Vaccines/Vaccine_Quality/UN_Prequalified/UN_Prequalified_producers.htm)).
- Join the WHO certification scheme and inform manufacturers of the requirement for supplying scheme certificates.
- Obtain addresses of other NRAs and the contact names of those responsible for vaccines and biologicals.
- Send staff to regional or international regulatory meetings to make personal contacts with regulatory staff of other countries.
- Instruct staff in their responsibilities regarding maintaining confidentiality and guarding against conflict of interest (see References).

3. Recall system (all countries) (11, 15, 17, 20)

A. Discussion

Provisions must exist for the recall and destruction of unsafe, defective or inappropriately labelled medicinal products so they cannot re-enter the market (20). This complements the pre-market regulatory role of the NRA to ensure that only safe effective products are available to the public.

National regulatory authorities should have a system for enforcing the recall of batches, for communicating the decisions to users, and for notifying the NRAs of other countries importing the product (15, 17).

Whenever there is a need to remove a product from the market, the NRA must be able to do so or ensure it is done quickly and efficiently. They must provide information to manufacturers, importers and agents as well as the users of vaccines on the type of situation or conditions that would require notification of the NRA to consider the necessity of a recall. The reasons for recall could include:

- a quality problem, product problem, storage problem, label problem or such complaint;
- an adverse event linked to the product;
- a product reaches its expiry date.

However, the decision as to the need for recall must be made on a case-by-case basis.

B. Practical approaches

- The NRA must require, in the conditions of the licence, that manufacturers, importers, or agents maintain an inventory of the distribution of all products. This must be made immediately available to the NRA on request. If the NRA is to perform the recall, a regularly updated distribution list should be submitted, to be maintained by the NRA.
- Prepare instructions for purchasers (such as immunization programmes that distribute vaccines) of their responsibility to maintain and make available the distribution lists in case of a recall.
- There should be a set procedure and report form for notifying the parties involved within a specific timeframe of any problem that could result in a recall.
- The NRA should prepare a list of conditions and events and inform the manufacturers, importers and immunization programme of their responsibilities in this regard. The manufacturers should also report any recalls of product that have occurred in other countries to the NRAs where the product in question is licensed.
- The manufacturers' recall procedure should be evaluated and approved at the time of licensure. (See module on licensing.)
- Prepare instructions and a report form for the end users of vaccine to document the return of a product. Special labels should be supplied to identify recalled shipments. Typical information to be recorded is:
 - request for recall made by
 - date request received
 - reason for return
 - product name
 - unit size and number of doses per unit
 - manufacturer
 - lot number
 - expiry date
 - purchase date
 - source: name and address
 - number of units received
 - number of units used
 - number discarded (if any, include the reason)
 - number of units remaining for return
 - shipped to
 - date of shipment
 - number of boxes
 - confirmation of use of "recall label"
 - signature of authorized individual.
- Set up communications with other NRAs in countries for the exchange of information on recalls.

4. Mechanism to confirm the destruction of lots and system to document that this has been done (all countries) (20)

A. Discussion

In the case of a recall, or when lots of product have reached expiry while still in storage, there must be a mechanism whereby the NRA is assured that the lots have been destroyed and records kept for confirmation of the procedure. The NRA should develop report forms with the information required and circulate it to all manufacturers, importers and immunization programmes. End users, such as clinics and hospitals, should be informed that expired product should be returned to the source for destruction.

B. Practical approaches

- Prepare an internal NRA document listing the requirements for destruction and notification of destruction.
- Prepare instructions and report forms for the end users to document the destruction and submit to the NRA.
- Typical information to be recorded is:
 - product name
 - unit size and number of doses per unit
 - manufacturer
 - lot number
 - expiry date
 - purchase date
 - source: name and address
 - number of units received
 - number of units used
 - number discarded (if any including reason)
 - number remaining destruction
 - date time and method of destruction or labelling, address, and shipping date if returned for destruction
 - signature of authorized individual
 - confirmation signature for destruction if performed on site.

5. Appropriate expertise of staff (all countries)

A. Discussion

The structure of a national regulatory authority for biological products will require personnel qualified and experienced in the control of biological products and experts in appropriate disciplines such as biochemistry, biology, pharmacy, microbiology and infectious disease. The qualifications and experience of the staff should be appropriate to the functions and activities to be carried out and the range of products to be controlled.

Qualified independent experts and advisory committees are indispensable as a source of specific technical and clinical advice and expertise when needed. In addition, access to suitable laboratory testing facilities may be required by the NRA (see modules on licensing and laboratory access). The type of input needed from experts and advisers will depend on the expertise in-house and the range of products considered for regulatory action.

Besides the technical responsibilities, there are administrative responsibilities for the management of the regulatory activities. Staff will be needed for preparation of guidelines for manufacturers and users (e.g. format and content of the licensing files), dissemination of information, management of incoming documents, writing of internal procedures, tracking of submissions and correspondence, issuing of licenses, renewals, maintaining a suitable reference library, organizing training, etc.

The administrative activities will be a major responsibility of a newly developing NRA. It is not expected that a small regulatory authority would have the technical expertise in-house to fulfil all the review functions, but could rely on products licensed (and therefore evaluated) in the country of origin with a known effective NRA, and appropriate advisers and experts. Well-planned and responsible performance of the administrative regulatory functions by suitably qualified staff and well-chosen experts will result in an efficient and credible NRA.

Staff capabilities in other languages should also be considered. Documents for licensing and lot release from other countries will not necessarily be translated into the local language, and expertise at least in reading several major languages will be needed by the administrative and the technical staff, advisory committees and experts. The NRA may require that some parts of the licensing files for submission be translated into the local language; however, this will not be possible for information coming from other NRAs.

All of the above can be effectively implemented if there is an existing drug regulatory authority with experience in the administrative aspects which can be built on for the regulation of vaccines (11).

B. Practical approaches

- Assess the potential for extending the drug regulatory authority functions to regulate vaccines (refer to task force example in reference 11).
- Make an evaluation of the staff and their qualifications and experience.
- Assign existing staff to specific positions.
- Identify the expertise available in the existing drug advisory committees.
- Prepare a list of expertise needed for a vaccine licensing evaluation, which will be needed to complement the NRA staff expertise.
- Contact NRAs of other countries to identify those that can offer assistance with certain regulatory matters.

6. Institutional development plan (all countries)

A. Discussion

The staff of newly developing regulatory authorities for vaccines and other biologicals will require instruction in the processes of administration and management of submissions, technical and clinical evaluation for licensing, as well as post-licensing responsibilities. In some cases staff will have had experience as part of a drug regulatory authority. However, each staff member of the authority should undergo suitable training and attend hands-on training courses for the administrative and technical aspects of licensing and control procedures they perform for vaccines and biologicals.

Regulatory requirements and responsibilities evolve with time because of technological advances, development of new products, with continuing upgrading of good manufacturing practice guidelines, good clinical practice (GCP) guidelines, good laboratory practice (GLP) guidelines, and manufacturing and testing methods of existing products. Ongoing training will be essential for the NRA to keep up to date with all these advances to effectively carry out their functions.

There should be an institutional training plan to establish the training needs, goals and timetables, to identify potential courses, and to ensure that individual staff members who receive training will pass on the information to the remaining staff. Teaching other staff is a good training exercise. It is very effective for the staff member presenting the information and extends the training to all staff.

B. Practical approaches

- Identify training courses on regulatory topics.
 - conferences
 - specific courses held at other NRAs
 - WHO Global Training Network courses (GTN) (see WHO web site in References section)
 - other WHO training (21)
- Invite experts from another NRA to visit.
- Identify countries that will accept visiting NRA staff for several months to give in-depth training in regulatory functions to one or two individuals.
- Identify consultants with expertise in various aspects of regulatory procedures who can also be contracted to provide short-term or longer-term training on site.
- Incorporate the above possibilities into a training plan.
- The training plan form prepared by GTN as part of its application process provides guidance for developing a training plan:
 - What is the source of vaccines used in the country: [] UN agency [] bought directly [] local producer;
 - What are the essential control functions being performed for vaccines used in the country:

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- a) written criteria for licensing of vaccines
 - b) post-marketing surveillance for vaccine-related adverse events and efficacy
 - c) lot-by-lot release of vaccines
 - d) accredited laboratory testing facility for final product tests
 - e) regular inspections for compliance with GMP
 - f) use of clinical data in licensing decisions

Draw up a flow-chart indicating how each of the essential control functions is being done at the institution, using performance against indicators (11);

- Identify the aspects of the current national regulatory system that are lacking;
 - What current *issues* at your institution will be remedied through participation in training;
 - Make an overall plan on how to address these issues and what they involve;
 - What are some of the *strengths* of the institution that might be further reinforced by additional training;
 - List the specific areas of training needs. What courses or training sessions are proposed? What advice is needed? Are more staff needed? What qualifications and expertise are needed?
 - What positions and individuals are identified for training? What course(s)? How does the training relate to their position?
 - Make plans for training sessions at the institution upon the return of staff sent for training;
 - Identify the resources and support from management needed;
 - Describe plans for ongoing training by internal seminars, journal reviews, attendance at international meetings, new employee training, etc.
- Obtain support and approval of management. Adequate funding and resources will be necessary.
 - Set up a record system for all training activities.
 - If the country has a functioning drug regulatory authority and needs to add the capabilities for licensing and control of vaccines and other biologicals, the WHO model in the publication *Regulation of vaccines: building on an existing Drug Regulatory Authority* (11) can be consulted to develop a training plan. This model proposes the establishment of a task force to consider the requirements and to plan the implementation of control of vaccines to supplement the system already existing for drugs.

Module 2: Licensing

Introduction

Licensing (also referred to as marketing authorization or registration) is a mechanism for pre-qualifying a vaccine and the facility(ies) where it is manufactured before it is used in the country issuing the licence. This procedure is carried out by the national regulatory authority of the country granting the licence or its official agency.

The objectives can be effectively achieved only if: there is a mandatory system to license/authorize all products and manufacturing facilities; all stages of manufacture are supervised by qualified personnel; licensing is complemented by an efficient system of inspection; and the legislation is enforceable (20).

Therefore, the NRA must have the power to:

- issue, vary and revoke licences for biological products on the grounds of quality, safety and efficacy;
- secure subsequent safe and effective use by controlling, under the terms of the product licence, the content of all labelling (including package leaflets), and the channels through which the product can be supplied;
- inspect and license all manufacturer premises and importing agents (and other distributors where applicable) to ensure they comply with the relevant regulations (17).

Each vaccine from every manufacturer must be evaluated to determine: (i) that the manufacturing facility complies with good manufacturing practices; (ii) that the details of the production and controls demonstrating the quality of the raw materials, intermediates, and final product are sufficient; (iii) that the preclinical and clinical studies and marketing and adverse events history show that the product is safe and effective for the use claimed in the population indicated; and (iv) that the labelling and package leaflet meet country requirements. The licence granted is a legal document specifying that all the requirements have been satisfactorily met, and it gives details of the conditions under which the product can be marketed. Licence holders do not have to be the respective manufacturer, but could also be the local agent for a manufacturer, or an importing agent. There must be an affidavit that the person applying for the licence can legally act for the manufacturer.

The following indicators cover the regulatory activities and procedures considered essential to the critical function of licensing of vaccines. All of the indicators apply to vaccine-manufacturing countries, some apply to vaccine-procuring countries, and only a subset apply to countries that use vaccines pre-qualified for supply to

UN agencies. These indicators can be used to self-assess the activities of the NRA's licensing procedures and to determine the training needs of NRA staff. WHO uses these indicators: when assessing the NRA of a manufacturing country during the pre-qualification assessment for vaccines proposed for purchase by UN agencies; and when performing external assessments of an NRA at country request.

The discussion of each of the indicators is from WHO guidance documents. Some are for pharmaceutical products in general, since many aspects of licensing are common to chemical drugs and biological drugs. Some of the references are specific to biologicals.

Indicators: licensing process

- **Evaluation of both facilities and products for licensing** (all countries);
- **Single standard of evaluation for imported and locally produced vaccines** (countries producing vaccines);
- **Written guidelines for submission of the file** (all countries);
- **Written guidelines for GMP assessment** (all countries);
- **Established procedure for review of licence application** (all countries);
- **Criteria for departures from the normal review process** (all countries);
- **Written guidelines for variance to licence** (all countries);
- **Criteria for the selection and use of expert committees** (all countries);
- **Appropriate consultation between manufacturers and NRA prior to submission** (countries producing vaccines);
- **List of licensed products and manufacturers** (all countries).

This module will present a discussion of each indicator for the licensing process needed for countries that import vaccine (bold in the list above).

1. Evaluation of both facilities and products for licensing (all countries)

A. Discussion

It is very important that both the manufacturing facilities and the production and quality control processes be evaluated for the licensing of a vaccine. A vaccine against a particular disease organism can be manufactured by different methods, using different strains of the organism, under different conditions, at different production scales, and using different equipment. The quality of the facilities in which the product is manufactured, the location and configuration of production areas, the quality and maintenance of the equipment used, the control of air and humidity, the flow of the production operations, the number of staff working in production areas, the proximity to other manufacturing operations, operation on campaign system (producing different vaccines in the same area on rotation), and transportation of intermediate products between plants, can all affect vaccine quality. Since biological systems of production have inherent variability even in the same production procedure, it is essential to evaluate the full manufacturing process, not just the final product. It is also necessary that each vaccine from an established manufacturing

process has been shown to be safe, immunogenic and effective in controlled clinical studies or field trials. A vaccine made by another manufacturer or by a different method, even with the same laboratory testing specifications and results, cannot be automatically assumed to give the same safety, immunogenicity and efficacy profile in the clinical situation.

When a licensing system is being introduced by a country, there will be products already being used in the public and/or private markets. A procedure must be put in place to avoid interruptions in the supply of vaccines during the establishment of the licensing system, as well as to bring existing vaccines and biologicals under regulatory control by issuing provisional licences (see section 5 below).

Every NRA must be clearly aware that an assessment of the product and the manufacturer must be made as the basis for issuing a licence. (Just entering a product on a registration list is not considered by WHO to be a sufficient evaluation for licensing.)

B. Practical approaches

- Prepare and publish the requirements for licensing including the evaluation of both the manufacturing facility and products(s) (see section 2).
- Prepare a list of the products presently on the market that will need to be licensed.
- Identify those permitted to be licence-holders and, if not the manufacturer, specify their relationship to the manufacturer and responsibilities for the product.
- Design the licence form to identify the licence-holder, manufacturer (if different), product, each formulation and presentation, and manufacturing facility(ies). Separate licences for each product and facility are not mandatory, but it must be clear that both the product in all its forms and the facilities where it is manufactured are evaluated.
- Design the guides for manufacturers to indicate that the evaluation of a vaccine product for licensing will be based on the review of the product file (see section 4 below) and will require licensing approvals by the NRA of the country of manufacture.
- Design the guides for manufacturers to indicate that the evaluation of the manufacturing facility will be based on both facility information in the documents submitted and on the results of a GMP inspection. The inspection may be on-site inspection by the NRA of the importing country, where feasible, and/or specific recognition of the GMP guidelines and GMP certificates/reports from the NRA of the country of origin.
- Include conditions in the licence to ensure that updates to both the facilities and product are provided to keep the information up to date and in compliance with the terms of the licence.
- Establish and publish the procedures and implementation dates for the introduction of the licensing system; set the procedure for provisional licences for products existing on the market (see section 5 below).
- Define the timeframes for the review and licensing procedure.

2. Written guidelines for submission of the file (all countries)

A. Discussion

In countries where vaccines are manufactured, licensing requires a full evaluation and approval by the NRA. If importing countries need products that have not been evaluated or licensed by the NRA of the country of origin, or the quality of review is uncertain, the importing country NRA must also make a full evaluation of the facilities and product before granting a licence. This involves a detailed review by the NRA or expert committees of:

- the technical file on chemistry and manufacturing and control by the manufacturer;
- the GMP assessments including inspection of the manufacturing facilities;
- the animal studies and the human studies showing safety and efficacy;
- the labels, packaging, leaflet contents and any administrative requirements.

It may also include testing or evaluation of samples of vaccine lots.

Manufacturers of vaccines must produce their products in compliance with their national regulations as well as with various international guidelines in force in countries they export their products to. They depend on published regulations and guidelines to develop and establish their production and control procedures, design and/or operate their production facilities, perform the appropriate supporting studies, and submit documents with the required format and contents. The national regulatory authorities of vaccine-producing countries and WHO have published regulations and guidelines for manufacturers, defining exactly what information and what detail is required in the submission, with regard to manufacturing, quality control, pre-clinical (animal and in-vitro studies) and clinical studies, as well as for labelling. Information provided by these regulatory authorities can provide general guidelines for all drugs and biological products, and some for vaccines in general. WHO provides vaccine-specific manufacturing and control requirements in the WHO technical report series (TRS) (31-44). Other publications for industry cover good manufacturing practice guidelines for manufacturers (22-26). Small countries which have yet to introduce their licensing guidelines can draw from a diversity of national and international licensing systems in determining their own requirements (49-60).

Legal licence requirements will indicate the timing and schedule of GMP inspections that will be required for licensing and renewals (see section 3) and the requirements for updating the licence if changes are made (see section 6).

These instructions for manufacturers for preparing and submitting an application for a biological product are issued as various documents: requirements, regulations, guidelines, and points to consider. Many of these are available for reference (Australia, Canada, European Union – EU – USA, 50-52,54,58-60) and many can be downloaded from web sites (see web sites in References section).

The standards adopted by the importing country should be in written form and should be both general and product specific for each biological product to be imported.

They should be based on up-to-date standards, such as those available from WHO, and be harmonized as much as possible with those of other countries (17).

The general guidelines for submitting applications give a detailed outline of the format and contents of the documents to be submitted. Specific guidelines describe the technical requirements for individual products (vaccines, products made by biotechnology, combined vaccine products, etc.) or for various aspects of manufacturing processes (sterile filling, sterilization processes), facilities (air and water systems, cleaning processes) and other GMP topics, and pre-clinical/clinical requirements. Many countries have their own requirements and others have adopted the requirements of the European Union. WHO guidelines and technical report series requirements have been prepared for countries to reference, adopt or use as a model (21-44). WHO also prepares model certificates for licences as a guide for countries initiating (or upgrading) their licensing procedures (15,18).

The document submitted when applying for permission to sell a new medicinal product is known by different names in different countries. This depends on the definition of terms used in the laws and regulations that govern the product or type of product in each individual country. For example, in the USA, the document submission for a biological product is a biologics licence application (BLA); in the European Union and Australia it is an application for marketing authorization; in Canada it is a new drug submission (NDS). Each jurisdiction has specific requirements of what technical, pre-clinical and clinical data should be submitted in the file, the format, the language, and whether it can or must be in paper and/or electronic form. The information and data required are essentially the same for Australia, Canada, the European Union, and the USA (50-52,54,58-60). These documents can be consulted when the written guidelines for licence applications are being prepared.

The information recommended by WHO to be included in the submission for a biological product licence is summarized as follows (17):

- Information on the manufacturing establishment (can be called a plant master file):
 - personnel: qualifications, experience, organization, reporting relationships, training schedules and records;
 - location and construction of the building(s) used for manufacture and control;
 - flow of raw materials, personnel, manufactured product through the facility;
 - animal facilities;
 - air, water, steam, power supply;
 - drainage and waste;
 - segregation of operations;
 - list of major equipment;
 - maintenance schedules for equipment and building services;
 - cleaning procedures, schedule and control measures;
 - quality assurance and quality control procedures;
 - storage and quarantine facilities, and procedures for raw materials, packaging materials, in-process and bulk materials, and final product;

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- validation procedures;
 - documentation and record keeping systems;
 - labelling and packaging facilities and procedures;
 - recall and retrieval procedures;
 - assurance by a GMP certificate (13,18) or report from the country of origin that the manufacturer has been inspected and found to satisfactorily comply with GMP (if not done, or no report is available, an inspection must be performed before the licence is issued).
- Information on the product:
 - information on source materials (e.g. microorganisms, cells, etc.), including their specifications and the test used to demonstrate compliance with specifications;
 - description of the cold chain procedures employed;
 - information on the raw materials and packaging materials, including specifications and tests used to demonstrate compliance;
 - information on the methods of manufacture including a description of the seed lot and cell substrate systems used, together with in-process, bulk and final product specifications and tests used to demonstrate compliance;
 - demonstration of the consistency of manufacture, for which the results of tests on a minimum of three satisfactory and consecutive production batches, ideally of different bulk lots, of a size contemplated for routine production are normally required;
 - any proposal for the reprocessing of the product;
 - results of stability studies justifying the proposed validity period of the product under the indicated storage conditions;
 - labels and package inserts;
 - documentation used in the manufacturing and control procedures including standard operating procedures (SOPs) and protocols containing details of production and quality control testing;
 - reports of pre-clinical studies;
 - clinical trial data;
 - list of countries in which the product is approved for use.

If the licence issued by the importing country NRA requires as a condition that a vaccine eligible for importation must already be licensed in the country of origin, then the manufacturer will have prepared and submitted the application document in the format required in that country. The importing country must decide if the national requirements for licence documents must conform to a national format and be officially translated into the local language, or whether they will accept submissions in other specified format(s) and language(s). The capabilities of the staff and experts to evaluate documentation in other languages, and the likelihood that manufacturers will prepare complex documentation in multiple languages must be considered when making these decisions.

WHO has a published procedure to assess the acceptability in principle of vaccines for purchase; “Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies” (7). A successful outcome of the evaluation process leads to the inclusion of the candidate vaccine on a public list of pre-qualified vaccines.

- The evaluation process requires:
 - i) Submission of a product summary file. The requirements for the product file are:
 - composition of the vaccine;
 - layout of the production facilities;
 - organizational chart of the company;
 - copy of the relevant national requirements for production;
 - staffing of production, quality control and quality assurance units, plus information on the staff’s professional qualifications;
 - copy of the original regulatory approval by the NRA of the country of origin;
 - list of countries where the product is registered and is currently distributed by the applicant or any other authorized entity;
 - clinical data showing the safety and efficacy of the vaccine in the target population, at the dosage and schedules intended to be used in national immunization programmes;
 - additional data on reactogenicity or lack of efficacy detected through post-marketing surveillance;
 - flow-chart of the production process with a detailed description of the relevant steps involved. For recombinant vaccines, an adequate description of the construction of the recombinant vector should be provided;
 - detailed description of the quality control methods used (a) during the production and (b) applied to the final product: this should include adequate characterization of starting materials and gene products if applicable;
 - quality specifications set at different stages of the production process and for the final product.

The information that WHO requires in the file could be used as the basis of documentation required for licensing in individual countries buying vaccines through UNICEF or other UN agencies. If different documentation is to be submitted for licensing a vaccine, depending on its source (e.g. UN agency), the written guidelines for licensing must clearly indicate the conditions.

- ii) Testing consistency of final product characteristics:

Another general requirement for licensing and for WHO pre-qualification is the submission of samples together with the summary lot protocols for 3–5 batches of product to show consistency of manufacture. For single component vaccine, the requirement is usually for final lots produced from consecutive bulk lots. This approach includes vaccines where many final lots are made from large volume bulks.

If the vaccine is lyophilized, then the requirement could be for several lyophilized lots from several different bulk lots. For combined vaccines, the batches to be submitted should be specified: usually the requirement is for final product with consecutive bulks, but it will depend on the product and the components. In all cases, the manufacturing process will determine how best to choose samples to demonstrate the consistency of manufacture.

NRAs of manufacturing countries with laboratory facilities review the records and may test these lots as part of the product evaluation for licensure. Small regulatory authorities of countries importing through UN agencies will be assured of the consistency of manufacture, because tests are carried out by WHO-designated laboratories during the pre-qualification procedure. For products licensed and lot released in the country of origin and not being supplied through UN agencies, the adequacy of the consistency testing can be evaluated by the importing country NRA from the data submitted in the licensing document. If testing is required to be performed by the importing country, access to suitable laboratory facilities will be needed (see module 4 on laboratory access).

Although the technical and clinical content of an application are the basis of the licensing evaluation for quality, safety and efficacy, there may be other necessary documentation required such as application forms, certification letters or forms attesting to the accuracy and completeness of the data and reports submitted, required submission format and language, submission summary forms, and expert reports. Application forms are issued by the regulatory authorities outlining the information required to accompany the technical and clinical data. A responsible person is identified on the application form as the contact person at the manufacturer, importer or agent.

Regulations, requirements and guidelines published by major manufacturing countries reflect systems that have been in place for many years, supported by the legal system, long-term national regulatory authorities and laboratories, manufacturers with well developed regulatory affairs departments, professional regulatory affairs associations, and private companies that offer regulatory services. It is different and difficult for newly developing authorities to begin the licensing process. Manufacturers and agents must be informed, well in advance of the impending process, of the dates and administrative mechanisms with which they will need to comply. The guidelines and administrative functions of the NRA must be in place before initiating the licensing procedures. Other government offices such as legal departments, vaccine procurement departments, advisory committees, immunization programmes, customs department, etc. must be involved in the development and implementation of the licensing system.

When a licensing system is first being introduced, conditions for the issuing of provisional licences to existing products on the market are required to ensure there is no disruption in the supply of needed vaccines. Written guidelines must be prepared to guide manufacturers, importers and agents through the requirements for the provisional licences and on the timeframe for complying with the new licensing procedures.

B. *Practical approaches*

- Obtain copies of the instructions for manufacturers from WHO and other countries for reference: Australia (57-58), Canada (53-55), EU (59-60), and USA (49-52). It will be useful to review the various procedures and format from countries that supply the vaccines proposed for licensing; the NRA should be familiar with the types of submission format or may wish to evaluate them to decide on a specific format for their submissions. The WHO pre-qualification document (7) and the WHO document listing the suggested information about the product and the facility to be included in a product file (15) are also good references regarding the information required for the licence file for products procured through UN agencies.
- Adopt or develop the specific country requirements for information to be submitted that meets WHO licensing recommendations and the laws of the country, and harmonize with other major manufacturing countries.
- Obtain copies of the administrative procedures from WHO documents and from other countries, to aid in the planning or updating of forms, records, inventory system, and correspondence for the management of submissions (see References).
- Plan the national administrative procedures and prepare guidelines in writing.
- Prepare internal correspondence forms and report forms covering all the expected correspondence with manufacturers, importers or agents:
 - licence forms
 - form for rejection of licence
 - licence-renewal forms
 - acknowledgement letter for receipt of applications
 - request form for additional information
 - summary forms for the review of the technical and clinical parts of the submission
 - report forms for review by advisory committees and experts.
- Determine any specific conditions for licensing, such as:
 - requiring vaccines to be licensed in the country of origin,
 - labelling and packaging requirements,
 - the required documentation and samples to be submitted for the licence, and
 - the conditions of the licence regarding lot release and procurement.
- Obtain UNICEF and WHO requirements for information on the vaccine labels and package inserts (instruction leaflets) in order to develop national requirements.
- Prepare guidelines for provisional licences and gradual entry of existing products into the new licensing system.

3. Written guidelines for GMP assessment (all countries)

A. Discussion

The NRA of every country, whether it is a vaccine manufacturer or vaccine importer, should require that all vaccines (and other drugs and biologicals) be manufactured in compliance with good manufacturing practices. Manufacturers of drugs, vaccines and other biologicals are regulated in most countries by national GMP regulations or guidelines, or by international GMP guidelines that have been adopted by the country. WHO has published a general GMP guideline for all pharmaceuticals (23) and a supplementary GMP guideline specific to biologicals (22). In addition, WHO has also published a guide to inspections of biologicals manufacturers (4) based on these guidelines. The GMP regulations or guidelines from major countries (e.g. Australia, Canada, the EU, and the USA) are essentially equivalent, but do differ in some details and emphasis.

GMP is a set of conditions under which drugs and biologicals for human use must be manufactured in order to ensure that the product is made by a validated reproducible process, in a specified controlled environment by trained operators. It thus ensures a consistent product, meeting predetermined specifications, and that each batch is fit for the intended use. WHO defines GMP as “that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization” (23).

The guiding principle of GMP is that quality is built into a product, not just tested at the end. GMP is critical for vaccines because they are biological products made from microorganisms or other living tissues that have a high degree of variability. Manufacturing must be rigidly controlled at all stages of manufacture and testing.

The full scope of GMP includes:

- Organization and personnel:
 - qualifications, experience, work habits, training, clothing, personal hygiene.
- Premises:
 - design, construction, air handling, water and plumbing, maintenance, sanitation.
- Equipment:
 - design, location, qualification, calibration, written procedures, cleaning and maintenance.
- Production and in-process controls:
 - written procedures, identification of equipment, adequate starting materials, details of production methods, sampling and testing intermediates, recording and assessment of deviations, sterilization and depyrogenation, contamination control, records on pre-approved forms.

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- Quality control:
 - independent from production, raw material controls, reference reagents and standards, intermediate and final product testing, quarantine storage, stability testing and expiry dating, release for distribution, validated methods.
 - Documentation of processing and distribution:
 - maintenance of records, dating and signing of records, batch records and review, equipment logs, traceability.
 - Animals:
 - procurement procedures, animal care, allocation to use, facilities.
 - Quality assurance:
 - records of suppliers contractors and consultants, document approval and control, validation and calibration of equipment, investigation of deviations, environmental monitoring, internal inspections, training.
 - Labelling, packaging and distribution:
 - materials, operations, storage, distribution.
 - Containment practices:
 - procedures to be followed if pathogens or dangerous materials are used in manufacture.
 - Sanitation and cleaning:
 - waste control, pest control, storage of cleaning agents, validation of cleaning procedures.

In the country of origin, the NRA makes inspections to ensure that the manufacturing and control operations are in compliance with GMP. For a vaccine-importing country, although there may be experience in inspections for drug manufacture, experience in GMP inspections for vaccines is generally not available. This is because there may be no local manufacturers, and the opportunity to be trained sufficiently and travel to manufacturers to perform inspections is often lacking. However, if the licensing process requires the inclusion of the GMP certificate (or other written evidence of compliance with GMP) from the country of origin, this ensures that a functioning NRA has made this determination.

Countries that import their vaccines may have national GMP regulations for drugs that cover pharmaceuticals and biologicals. Those without requirements can officially adopt the WHO or other international or regional GMP requirements (e.g. ASEAN, EU, or USA requirements). Or they can officially accept the GMP requirements in effect in the country of origin for each of the vaccines imported. The WHO regulations and other internationally accepted GMP regulations can also be used to develop or update national GMP guidelines.

The importing NRA can officially accept GMP inspections performed by the NRAs of major manufacturing countries by identifying the form of written evidence that will be accepted as verification of compliance with GMP by the vaccine facility (GMP certificate, or satisfactory inspection report from the NRA of the manufacturing country). The WHO certification scheme for quality of pharmaceuticals moving in international commerce provides a mechanism for

accepting the GMP inspections of other countries. Member States that export pharmaceuticals (including vaccines and biologicals) in this scheme have declared that their requirements and inspections for GMP follow the WHO guidelines. As this is a voluntary declaration by the Member State, it may be necessary for the regulatory authority of the importing country to contact other countries licensing the product to verify or confirm that GMP requirements in some countries are equivalent to those in WHO guidelines.

The type of evidence of GMP compliance to be included in the licensing submission must be described in the requirements for submission of the file. Conditions of the licence should include the requirement that all regular inspection certificates or reports be submitted to the NRA in the importing country. This provides evidence of the continuing satisfactory operations of the manufacturer. These documents should include reports of any serious non-compliance problems found by the manufacturer's NRA that would compromise or suspend production operations.

In addition to general guidelines on GMP, there are many specific guidelines on various aspects of GMP (sterility, validations, etc.) that can aid vaccine-importing countries to understand and evaluate these aspects in the submitted licensing documents. Many documents are now available by fax or email or on the Internet at the web sites of NRAs (see web sites in References).

Although the major evaluation of a vaccine manufacturing facility is done by a GMP inspection during an official on-site inspection, there are many aspects of GMP that can be reviewed during the evaluation of the licensing file. Sufficient information about the facility in the licensing document on organization, personnel, descriptions of processes, documentation and validation, will permit an independent review of certain aspects of GMP, and will provide information on the facility and its operations for the NRA files.

Some GMP inspection procedures will be necessary in countries that import vaccine. The receipt and storage of vaccines arriving at importers' or agents' warehouses in the country, if applicable, needs to be assessed for compliance with temperature conditions, record keeping, and segregation of quarantine and released product. This is especially true for vaccines that have specific temperature requirements and are subject to quarantine storage until released by the NRA of the importing country on a lot-by-lot basis.

B. Practical approaches

- Join the WHO certification scheme to obtain access to information on GMP assessments by other member NRAs.
- For reference, obtain copies of blank GMP certificates or other official documents used as evidence of GMP compliance from each of the NRAs of the countries of vaccines licensed (or to be licensed) in your country.
- Obtain copies of the most recent version of GMP guidelines from the ASEAN, Canada, the EU, the USA, WHO and others, as applicable for reference.
- Include the GMP requirements, guidelines and other regulations that are adopted into the written guidelines for manufacturers for submission of the file.

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- Ensure that the licensing conditions include a requirement for updates from the manufacturer on GMP inspections by the NRA of the country of origin including any incidents of non-compliance.
 - Ensure that information requested about the manufacturing facility for the licence submission has sufficient GMP data for the file.

4. Established procedure for review of licence application (all countries)

A. Discussion

Not only are explicit written guidelines needed for manufacturers, so that the full information will be submitted, but clear instructions are also needed to describe the review and evaluation procedures performed by the NRA. These procedures should include consistently applied administrative handling of incoming applications and documents, proper tracking and filing, and maintaining confidentiality of the information received.

The evaluation of the information and data submitted by an applicant for a licence occurs in three stages.

- The first stage is the administrative handling of the incoming documents and initial review (screening) of the submitted documents to make sure the all the required information has been provided according to the published requirements available to the manufacturer.
- The second stage is the assignment of various parts of the file to appropriate experts for in-depth evaluation.
- The third stage is a summary review by the NRA of all of the evaluations and a critical assessment as to whether the claims made for the vaccine are supported by the evidence submitted, leading to a final decision to grant a licence, request further information, or reject the application for the licence.

i) Administration and submission management

A. Discussion

When a file has been received from a manufacturer, importer or agent to support the application for a licence, the first procedures are administrative. The initial check is to make sure that the applicant meets the criteria for a licence holder in the importing country. If the applicant is eligible, then a review of the application form and accompanying documents is made (forms, certifications, cover letters, format, number of copies, language, copies of supporting documents such as GMP certificates, copies of other licences, and list of countries where the product is licensed). The licence document is checked to ensure that technical, facility, clinical and labelling information is included.

If anything is missing in the application, a letter or fax requesting the missing information should be sent, which usually includes a time deadline for receipt. When the information is received, it is also screened to ensure that the requested data has been submitted and that the submission is satisfactory for starting the evaluation process. A rejected submission can be returned to the applicant or can be clearly marked as rejected and archived.

When all the documents have been received and are found satisfactory, they are dated and labelled with a unique receiving number and/or tracking number, which could have a manufacturer code number as part of it. The application number and basic information on the manufacturer and product is then entered into inventory books or computerized databases. These specific numbers will track new applications, updates or supplemental information such as variations to the licence or any new information submitted by the manufacturer for that specific product.

An acknowledgement letter, including the tracking numbers assigned to the file, should be sent to the manufacturer indicating the acceptance date of the file into the assessment queue.

The rationale for waiting until all required documents are received before assigning a tracking number and review start date is that it avoids accepting incomplete applications into the evaluation process and into the NRA's time deadline for internal review.

These log-in procedures and correspondence with manufacturers are an important part of the regulatory apparatus. The log data and correspondence file form the record for a particular manufacturer or vaccine. This process is fairly straightforward; thus the expertise for this administrative part of the regulatory process should remain inside the NRA. The tracking number would be used on all documents, including correspondence between the NRA and the manufacturer. An NRA standard operating procedure should describe the details of the numbering system and how they are assigned.

The next administrative step is the delegation of the submission to a designated NRA staff member and the assignment of the various parts of the submission to the evaluators.

It is important that the submissions are handled and stored securely, and that copies are logged in and out of the registration office to identified reviewers during the evaluation period. Much of the information is proprietary and the NRA is responsible for maintaining confidentiality

Proper management of the application documents submitted for licensing is a major responsibility of the NRA and good management will enhance the reputation of the NRA.

B. Practical approaches

- Set up the inventory and tracking number system, using the existing system for drugs if suitable, or initiating a new vaccine-tracking or biologicals-tracking number system.
- Prepare an SOP and checklists for the screening procedure: application form, required accompanying documents, format, number of copies, language of all sections, completeness.

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- Prepare a format for the acknowledgement letter including the name of the applicant, name of the manufacturer (if different), name of the product, the tracking number for all future correspondence, and the acceptance date for starting the evaluation.
 - Prepare a format for the rejection letter of the initial screen of the submission with comments on what has been found unsatisfactory.
 - Prepare forms for requesting additional information. This could be a checklist type identifying the sections that are incomplete with a “comments” section for details.
 - Prepare instructions for external reviewers for each type of review: can be a checklist format and should include the timeframe for completion.
 - Prepare the format of the letter for request for supplemental information from the manufacturer based on the inadequacies found during the evaluation.
 - Prepare the format of the letter for rejection of the application for licence.
 - Designate an NRA staff member to be responsible for the review of each application for licence.
 - If the application files are to be delivered to the evaluator, prepare written procedures to be followed to ensure there is no unauthorized access to the files. Obtain signatures for delivery and receipt.
 - Prepare an inventory list of the location of all copies of all licence applications.

ii) Technical review of production and quality control

A. Discussion

The written guidelines for manufacturers as to the contents of the file are the guide to what must be evaluated by the NRA, advisers or expert reviewers. There are many examples of such guidelines, some for biological products and some for vaccine in general (51,52,54,58). The most helpful are the requirements published by WHO in the WHO technical report series by the WHO Expert Committee on Biological Standardization (31-44). These WHO documents give a comprehensive guide to the production methods and quality control tests for many vaccines at all stages of production, and provide a reference for reviewing the production of a vaccine.

A WHO model summary protocol for release of each batch of final vaccine is provided with each set of vaccine requirements. This protocol, which is prepared by the manufacturer for each lot of product, is a summary of both the production and control processes. WHO also provides detailed information on potency testing of vaccines (5). The quality control potency test methods performed by the manufacturer can be evaluated against this manual, and other tests can be compared with compendial test procedures published in internationally accepted Pharmacopoeia – *United States Pharmacopoeia (USP)*, *European Pharmacopoeia (EP)*, *British Pharmacopoeia (BP)*. The Pharmacopoeiae also have final product specifications for many vaccines. For products with no WHO or Pharmacopoeial guidance, validation of critical processes and specifications must be reviewed critically.

A flow-chart of the production process should be reviewed first and compared with the WHO requirements or with the country requirements if applicable. A detailed description should give a clear idea of the consecutive steps of the process, indicating the equipment and equipment parameters used at each step, raw materials, media, solutions including quality control and volumes used, the mechanism of transfer of product from step to step, the in-process control tests and specifications, the numbering of the intermediates, storage locations and time, and the sampling for quality control tests on intermediates before proceeding to the next production step.

Bulk batches are often stored for long periods and stability data should be presented to show how long the product remains potent. Final product must have stability data that establishes the expiry date for the product.

A blank batch production record sheet (master formula) should be reviewed to determine the details of the information to be recorded as each batch is manufactured. It should be reviewed to ensure that all materials going into the vaccine are tested before use, that all critical steps in the manufacture are to be initialled and verified by a second operator, and that all materials can be traced back to their origin.

The consistency of production should be assessed by the detailed review of production, in-process tests and quality control tests on 3–5 lots of the vaccine, preferably consecutive lots for a single component vaccine and consecutive bulk batches for a multi-component vaccine. The summary protocols of the production and testing for these should be provided by the manufacturer. In some countries the full batch record is requested. If testing of these consistency lots is required for licensing, then the NRA must have access to an appropriately qualified laboratory to perform these tests (see module 4 on laboratory access).

B. Practical approaches

- Obtain copies of the WHO TRS requirements and summary protocols for all vaccines used in the country (31-44).
- Prepare a basic checklist and/or review form for evaluators to provide the summary of their evaluation.
- Decide on the timeframe for the evaluation.
- Assign the review to one or more qualified reviewers.
- Obtain signatures and commitment to prevent unauthorized access to the files.
- Set milestones for the review process.
- Decide if outside evaluators should deliver only their final report, or if they should communicate problems to the NRA during the review process.

iii) Review of facility operations and GMP

A. Discussion

In addition to the details on production and quality control, information should be included in the licensing file about the facility and its functions and operations:

- company staff structure and key personnel;
- the layout of the premises and equipment in the production and filling areas;
- the support services of air, water, steam, compressed gases, power supply etc.;
- storage areas for quarantine and released raw materials, intermediates or final products;
- the housing of animals used for production and testing;
- all the methods and procedures for controlling the environment and cleaning and maintaining the facility and equipment.

The production process should be reviewed in conjunction with the layout of the facility. Floor plans should be provided along with a listing of the operations carried out in each room. Flow diagrams of the movement of personnel, raw materials, air, intermediate products and waste should be provided to show how production proceeds from step to step.

GMP guidelines from several major countries and from WHO provide the framework for the evaluation of the aspects of good manufacturing practice that can be presented in writing. Although the major evaluation of a vaccine manufacturing facility is done by a GMP inspection during an official on-site inspection, there are many aspects of GMP that can be reviewed during the evaluation of the licensing file. Sufficient information about the facility in the licensing document on organization, personnel, descriptions of processes, documentation and validation, will permit an independent review of GMP, and ensure there is information on the facility and its operations on file.

Evidence for satisfactory compliance with GMP can be gained by review of the official GMP certificates or GMP inspection reports from the NRA of the country of origin submitted by the manufacturer. It is important to obtain the results of all regular GMP inspections and any reports of facility problems that arise for an on-going assessment of the manufacturer's continuing compliance with GMP.

B. Practical approaches

- Check the GMP certificate or GMP inspection report from the NRA of the country of where the product is manufactured for dates, compliance and, any problems reported.
- Review the documents obtained through the WHO certification scheme for quality of pharmaceutical products moving in international commerce.
- Ensure manufacturers are aware that all GMP inspection updates or reports must be forwarded including any non-compliance problems for continuing review of compliance with GMP.

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- Using the GMP guidelines adopted, review the information provided on the facility and facility operations.
 - organization chart to determine the reporting structure and independence of production and quality control;
 - qualifications and job descriptions of key personnel (heads of production, quality control, quality assurance, animal house, plant operations);
 - qualifications of key personnel;
 - facility description and validation;
 - equipment description, validation and calibration;
 - process validation;
 - sanitation and cleaning;
 - campaign procedures, if performed;
 - documentation control;
 - animal care and quarters;
 - environmental monitoring in production and aseptic filling areas;
 - containment, where appropriate.

 - Review flow-charts of production to determine linearity of production flow and concerns for cross-contamination.

iv) Review of pre-clinical and clinical data

A. Discussion

Animal data is usually reviewed by the NRA at the time of clinical trial approval when there is little or no experience with the product in humans. Animal studies are divided into safety and efficacy studies. For safety, the manufacturer plans and carries out toxicity studies looking for potential adverse effects at doses usually much higher than that planned for humans. Efficacy studies are those that look at immunogenicity, route of inoculation, dose response, number of doses needed, and, where possible, protection from challenge with the disease organism. Safety is always monitored even in the efficacy studies.

After the animal studies have provided the basis for proceeding into clinical studies in humans, the manufacturer will prepare a document for the NRA providing data on the manufacture, control, and animal studies and present a study protocol for studies in humans. These clinical trials are divided into phases.

Phase I trials include a small number of subjects to look mainly at safety.

Phase II studies continue to evaluate the safety while determining the dosage and dose regimen, immunogenicity and potential efficacy in a larger group of subjects.

Phase III studies are performed in suitably large numbers of subjects to determine the safety profile in statistically significant numbers, to demonstrate low-level adverse events, to determine the immunogenicity, and efficacy if possible. It is not always possible to show efficacy (reduction of disease) in a clinical trial population where the incidence of disease is low.

Each study is designed based on the results of the previous phase study, and each is submitted to the NRA for filing or for review, depending on the clinical trial review system. General guidelines for the requirements for performing clinical trials (good clinical practice or GCP) have been published by all major industrialized countries, many other countries and WHO (16). Some guidelines are specific to vaccines (61).

All these studies will have been completed before the manufacturer prepares an application for licensing. The animal studies and all phases of clinical studies must be included in the licensing file. However, it is the final phase III trials that will provide the evidence of the immunogenicity and/or protective efficacy of the vaccine. Safety is determined from the data from all the phases of the clinical studies.

The review of the clinical data for licensing should check that the study was submitted to the NRA and was reviewed and approved by an ethical review committee, that the protocol for the study was followed and the performance was according to good clinical practice, and that the number of subjects was statistically significant for the safety, immunogenicity and efficacy determinations.

The studies to be evaluated in detail are those using the dose and intended population to be immunized in the importing country. There should be a check on the age groups vaccinated, the dose schedule followed, use with other vaccines in the immunization schedule, possible interference with other vaccine efficacy, and the spectrum of adverse reactions seen in the vaccinees. This is to ensure that the clinical results will apply to the potential vaccinees.

B. Practical approaches

- Obtain general reference documents on clinical trial guidelines by other countries and WHO, guidelines on clinical trials of vaccines, WHO information booklets (for example, the *Immunological basis for immunization covers seven vaccine preventable diseases* (WHO/EPI/Gen/93.11-18)), and guidelines on good clinical practice (16).
- Contact existing clinical advisory committees to determine the expertise available for review of vaccine clinical data in the licensing file.
- Identify potential outside experts for clinical review, determine their eligibility based on qualifications, potential conflict of interest and availability.
- Maintain updated list of qualified experts.
- Prepare confidentiality agreements with external experts where needed.
- Provide evaluators with the appropriate documents to aid their review.
- Prepare checklists of the important evaluation criteria for clinical data for the evaluators. A list of items could be the following:
 - General (for all studies)
 - a) Clinical protocol title and number
 - b) Phase of the study
 - c) Dates of start and completion of the trial
 - d) Objectives of the trial

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- e) NRA approval granted
 - f) Ethical review committee approval obtained
 - g) Name and qualifications of responsible investigator(s)
 - h) Number of subjects planned
 - i) Ages, race
 - j) Inclusion and exclusion criteria
 - k) Location of study, single site or multi-site trial
 - l) Doses given
 - m) Dose schedule
 - n) Consent given for each subject
 - o) Blinded/unblinded/randomized
 - p) Controlled/uncontrolled/placebo controlled/historical controls, alternate product control
 - q) Product name
 - r) Product presentation studied (single dose, multidose vials)
 - s) Number of lots used, and lot numbers
 - t) Statistical parameters to be used
 - u) Adherence to protocol, amendments to protocol
 - v) Were the required number of subjects recruited?
- Safety
 - a) Numbers evaluated
 - b) Adverse reactions observed
 - c) Number, grade, severity, time, duration, dose relationship
 - d) Physicians decision on cause of reaction
 - e) Comparison to expected reactions of other similar vaccines
 - f) Review of manufacturer's statistical evaluation and conclusions on safety
 - g) Compatibility with other vaccines given at same time.
 - Immunogenicity
 - a) Numbers evaluated
 - b) Dose and dose schedule
 - c) Method for taking and storing samples
 - d) Method for testing samples: same test for all? If not, comparability of tests used?
 - e) Best dose, best schedule in pivotal (phase III) studies
 - f) Potential for boosting other vaccines of the same type
 - g) Interchangeability with other vaccines of the same type
 - h) Interference with other vaccines to be given at the same time

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- Efficacy
 - a) Reduction of disease or other clinical markers
 - b) Numbers studied
 - c) Dose and schedule
 - d) Statistical analysis of the efficacy endpoints
 - e) Comparison to other, similar vaccines
 - f) Suitability for the importing country:
 - i) Is the % protection sufficient for the country's needs?
 - ii) Is the schedule compatible with the national immunization programme?
 - iii) Is the clinical data applicable to the population to be immunized?
 - iv) Will additional pivotal clinical studies be needed before licensing?
 - g) Requirement for bridging studies – e.g. for different populations or for different schedules or for interactions with other vaccines – who does them, costs involved
 - h) Requirement for postmarketing studies – e.g. safety or efficacy in the local population – who does them, costs involved
 - i) Suitability for the private market if it exists.

v) **Review of labelling and leaflets**

A. Discussion

Each country has requirements for the information to be included on the individual container label, the box label and on the information leaflet. WHO also has published label requirements (22) and UNICEF has specific requirements for labelling and packaging. The NRA of each country will have to inform the manufacturer of the national requirements for language and the information to be included on the labels and in the leaflet.

Some countries require that the manufacturer submit copies of the approved package leaflet from countries where the product is licensed. This can be a useful way to determine what kind of information is required by other countries. The NRA usually reviews the labels and leaflet internally and compares the leaflet information with the evaluators' technical and clinical summaries. Any discrepancies must be checked.

B. Practical approaches

- Obtain published guidelines on labelling of medicines from WHO and other countries.
- Ensure access to publications such as Martindales (UK), Physician's desk reference (USA) and others that print out the leaflet and prescribing information of most licensed products in the respective countries.
- Maintain a file of package leaflets and company brochures for various vaccines.
- Prepare national guidelines for the labels and leaflet information including language required.

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- Prepare a checklist for label review indicating what information should be included on the vial and on the box.
 - Compare the leaflet information with the licensing file to ensure the information for users is consistent with the data in the file.

vi) **Final assessment and issuing of the licence(s)**

A. Discussion

When the technical, facility, clinical and label reviews and recommendations have been completed by or reported to the NRA, an overall assessment must be made for the final decision on granting the licence(s).

A summary report by the NRA should give the conclusions of each of the evaluation reports and the decision on the issuing of a licence, rejection of the application, or a request for supplemental information.

This decision can be made in conference with the advisory committees and the decision submitted to management for ratification.

B. Practical approaches

- Prepare the summary sheet for compiling the conclusions of each of the evaluators.
- Determine any conditions to the licence, such as the requirement for lot release, expiry date of the licence, and any other conditions for maintaining the licence (full information of all GMP inspections, licence updates, renewals or changes in the country of origin).
- Submit the final decision to the NRA person responsible for issuing the licence or rejecting the licence application.
- Design the licence document, ensuring all required information is included.

It must set out, *inter alia*, the name of the product, the dosage form, the quantitative formula including excipients per unit dose, shelf life, storage conditions, and packaging characteristics. It also contains all the information approved for health professionals and the public, the sales category, name and address of the licence-holder, and the period of validity of the licence (18).

WHO has published documents which give guidance for establishing a licensing system for medicinal products existing on the market (15,17). This involves identifying all the existing manufacturers and importers, preparing a list of biological products which will be licensed, and preparing guidelines for the provisional registration of these products. A specific date needs to be established after which products can no longer be legally distributed. Any new products would be subject to the newly established licensing system. Rapid screening of products and manufacturers for provisional licences will ensure that necessary products remain on the market. The screening should be sufficient to leave acceptable products on the market and remove unsuitable products.

5. Criteria for departures from the normal review process (all countries)

A. Discussion

There can be specific cases where a vaccine that has not been licensed in the importing country is urgently needed by that country. Emergency situations such as epidemics or outbreaks, a critical delay in vaccine delivery from the current supplier, a rejected shipment, and so on, may be a reason for an exception. All efforts to obtain a vaccine in an emergency situation should be directed towards a vaccine from another UN supplier or from a country with a well-recognized NRA, and expedited lot release of the emergency supplies of vaccine should be carried out (see module on Lot Release).

Another exception could be to permit immediate review of a product that is needed to treat a specific population or to meet a specific deadline for an immunization programme. The approval process should meet the same criteria, but the review time could be shortened by giving priority scheduling to the product or by permitting the reviewers and advisory committees to concentrate on an expedited review (“fast tracking”).

During the introduction of the licensing process, exceptions can be made for vaccines already on the market so they may receive provisional licences and continue to be sold on the market until the licensing process is fully in place (15,17) (see details in section 4 above).

If there are unusual cases where emergency supplies are required for a small number of people or individuals, policies for “emergency drug release” or “release on compassionate grounds” on an individual-patient basis have been instituted by some countries. Specific records and report forms are required. These products are imported without licence when no other treatment is available. The NRA of the importing country approves these under the terms of the policy on a case-by-case basis.

B. Practical approaches

- Identify legal requirements for permitting exceptions.
- Identify and train the responsible person(s) for reviewing and approving exceptions.
- Review possible exceptions and prepare guidelines for each potential situation.
- Prepare guidelines and conditions for provisional licensing (see section 4 above).
- Review the situations for emergency drug release and establish the criteria and report forms.
- Prepare an information letter for health care community.

6. Written guidelines for variance to license (all countries)

A. Discussion

In addition to the written guidelines for manufacturers regarding the contents of their original application for a licence, there should also be specific written guidelines for the information that must be submitted to the NRA when there is a change to the facilities, to the procedures for manufacturing or quality control, or to the clinical use that would affect the conditions of the licence or require a variation (revision or amendment) to the licence.

Such changes to the product or its production can be in several categories:

- major changes to the facility, manufacturing methods, source materials or testing procedures,
- moderate changes that affect the product or come into contact with the products, and
- minor changes not affecting the product.

The major and moderate changes must be assessed and approved by the NRA(s) that granted the licence; and the licence must be amended or revised (variation).

Some minor changes are “notifiable” or do not need prior NRA approval before implementing the change. The manufacturer must notify the NRA of these changes. This can be done for each change or in annual updates to the licence (renewal or periodic updates).

Another type of change is the addition of a new or changed indication (a new dosage regimen, a different population, different age group, etc.) which must be supported by clinical data. Although the approval of the clinical trials in the country of origin would not need to be made in the importing country, there must be a review showing that the clinical trials were properly approved and controlled in compliance with good clinical practice (16) as was done during the assessment of clinical data during the initial licence review. The results must support the new indication, and the changes should be suitable for the importing country’s use of the product. This may affect the labelling of the product and will change the package leaflet text in the importing country. New clinical data may be required if changes in the dose regimen including dose, route, frequency or timing are proposed (17).

It must be clearly stated what procedures must be followed for submission of these changes and whether permission from the NRA is required before implementing the changes. Manufacturers must have specific guidance on the requirements for variance so that they can prepare and present the new information in the most timely and cost-effective manner. The review time should be clearly stated for each type of change, depending on the change and the evaluation that must be made by the NRA. Significant changes in the manufacturing process may require major modifications to the existing licence, as well as the submission of new lots of product to demonstrate consistency of manufacture, and new clinical data (17).

In the case of imported vaccines licensed and released in the country of origin, the requirements for approval of a change and variation to the licence will be done according to the approved procedure in place in that country. However, it must be a condition of the licence in the importing country that their NRA be informed of the submission and response to an application for a variation to a licence in the country of origin. The written guidelines for manufacturers on variation to licences that are issued by the importing country should indicate that an application must also be made for a variation to the licence. It is understood that manufacturers will apply initially to their own NRA, but that all changes submitted for approval in country of origin must be communicated to the importing country NRA, along with the approval documents from the NRA in the country of origin. These will be assessed for making the appropriate amendments (variation) to the licence in the importing country.

B. Practical approaches

- Review existing guidelines for variance to licences published by other major manufacturing countries: Australia, Canada, the EU and the USA (see, for example, reference 58).
- Establish a list of type of changes (variations) that must be submitted.
- Define the timeframe for review and approval of each type of change.
- Prepare an application form for variance to a licence.
- Draft documents to indicate the procedure to follow for each type of variation (guidelines for variation to a licence).
- Inform manufacturers at the time of initial licensing that all variations submitted to the NRA of their country must also be submitted for approval of the variation.

7. Criteria for the selection and use of expert committees (all countries)

A. Discussion

During the review of the documentation submitted for evaluation for the licence, there are many categories of expertise needed to review the various parts of the file. The use of advisory committees or other experts for technical and clinical sections is a common way to increase the expertise available to the NRA. For an importing country, these committees are a necessary adjunct to the in-house staff expertise. The criteria for selecting committee members must be clearly laid out:

- who is eligible (qualifications, availability, conflict of interest, specific expertise);
- how the committees are formed (large panel of various experts regularly available, specific experts convened on an individual product basis);
- how confidentiality of the manufacturer's information will be maintained;
- compensation if applicable; and
- timeframes and deadlines.

If expertise cannot be obtained inside the country, experts can be recruited from other countries including other NRAs. Other NRAs or WHO may also be helpful in identifying suitable experts.

The NRA should have guidelines for outside experts and standing advisory committees stating what is expected in the report, the time frame and deadlines, and signing of confidentiality agreements where appropriate. If the expert is not a government official, bound by government confidentiality and conflict of interest guidelines, the manufacturer may need be consulted for approval of the expert's qualifications and confidentiality statements.

The statement signed by expert advisers to WHO participating in the team for the pre-qualification of vaccine for supply to UN agencies (WHO/VSQ/97.06) is a suitable model for the preparation of conflict-of-interest and confidentiality statements for outside experts. The provisions of the WHO form are summarized in the following:

- i) In the course of the discharging of the functions of auditing a manufacturer the expert agrees to the following:
 - to treat proprietary information from WHO or the manufacturer as confidential and not use the information except in discharging the duties of auditing;
 - to refrain from disclosing or providing the information to anyone not also bound by confidentiality unless the information was known to the expert before disclosure by WHO or the manufacturer, or was in the public domain at the time of disclosure, or has become part of the public domain through no fault of the expert; or has become available from a third party not in breach of any legal obligations of confidentiality.
- ii) The expert also agrees not to communicate the deliberations or decisions to any third party without permission from WHO.
- iii) The expert confirms that he/she has no financial interest or relationship with a party that may have a commercial interest in the information disclosed, or may have a vested interest in the outcome of the assessment of the vaccine.
- iv) The provisions also indicate that the manufacturer has the right to object to the participation of the expert and if this cannot be resolved by WHO, the agreement with the expert can be revised or cancelled.

B. Practical approaches

- Prepare a list of specific expertise needed to evaluate the vaccines to be imported.
- Obtain a list of members of existing advisory committees for the drug regulatory authorities and their qualifications to evaluate technical and clinical documentation for vaccines to be imported.
- Approach government, hospital and university professionals in appropriate disciplines to determine their interest and to invite them to submit a *curriculum vitae* (CV) to apply to join advisory committees or serve as independent expert reviewers.
- Develop guidelines for the advisers and experts to understand their role, responsibilities, time lines, estimated input and period of membership.
- Prepare official confidentiality and conflict-of-interest statement.

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- Evaluate the qualifications and expertise of the applicants and appoint or recommend for appointment to the advisory committees.
 - Prepare a list of qualified independent experts and their expertise for future contracts.

8. List of licensed products and manufacturers (all countries)

A. Discussion

Each country should maintain a list of products and manufacturers that are licensed to be on the market. This list should be available to all potential customers of vaccines. If there is a private market for vaccine in the country, the list should be accessible to the health profession and/or to the public. If vaccines are restricted to government or national immunization programmes, the list should be available to the departments involved, including the procurement and financial departments in charge of tendering and purchasing. In some countries this is published in an official gazette, as a separate government publication, or more recently is listed on the Internet (see web sites in References). Access to these lists can give confirmation of the licensing status of various vaccines in individual countries.

B. Practical approaches

- Find out the formal mechanism for publishing the list of drugs.
- Determine if vaccines are already listed.
- If not, contact the appropriate department to arrange the process of including vaccines.
- Make arrangements for communications with the department responsible for publishing the listings regarding the publication schedule and procedure for listing newly licensed products, licence renewals, revocation of licences, and rejection of applications for licences.
- Obtain the published list of licensed vaccines from other countries for reference.

Module 3:

Lot release

Introduction

Lot release is the process of reviewing each individual batch of a licensed product before giving approval for its release onto the market. This process is carried out for vaccines and other biological drugs in most countries. The release involves the review of manufacturer's production data and quality control test results by the national regulatory authority, and may or may not include laboratory testing by the national control laboratory, or by an agency or contracted laboratory performing tests for the NRA (see module 4 on laboratory access). The requirements for testing can depend on the legal requirements, the type of product, the manufacturer, the production and control history of the product, post-marketing history, the risk assessment of the product, the intended population, and other factors making up the product profile.

Because biological drugs such as vaccines are complex molecules that cannot be chemically defined, and because of the inherent variability of biological systems, each production run of a biological product can be considered unique. Therefore, these products are subject to scrutiny by national regulatory authorities on a lot-by-lot basis. The initial review of vaccine lots is done during the licensing process when the methods of manufacture and testing, and the consistency of production of several (usually consecutive) lots are evaluated. The requirements for the information and format of the data and samples to be submitted for lot release are established during the licensing evaluation and are included as a condition of the licence.

Once licensed, biological products are released lot by lot by the NRA, based on a review of the approved summary protocol of the manufacturing steps and test results from the full manufacturing and control process, not just the final product QC release test results.

The independent control of vaccine lots is especially important as vaccines are given to large numbers of healthy infants and children and must be safe and effective for public health programmes. WHO has published production and control requirements for most currently available vaccines in their technical report series documents (31-44). These include models of summary lot protocols and model certificates of release for the NRA.

Indicators have been developed by WHO for the regulatory function of lot release performed by the NRA and are listed below. All of the indicators are applicable for countries that produce and/or procure vaccines.

Indicators: lot release

- **Based at minimum on protocol review (obligatory requirement for summary lot protocol as part of specification for procurement) and lot release certificate from the NRA of the country of origin (all countries).**
- **Written procedure and criteria for lot-release process (checklist, sampling, guidelines) (all countries).**
- **Access to product file, national control laboratory report (if applicable) and inspection reports and complaints in case of problems (all countries).**
- **Records kept of lot-release data for analysis of consistency of quality, and continual review and scientific dialogue with the manufacturers on issues of quality test results (all countries).**
- **Written criteria for exemption from lot release (all countries).**

The following sections will present a discussion of the background and rationale for each indicator. Then they will look at some practical approaches which can be developed into course exercises or used as a list of activities for a newly developing NRA to assess progress or needs in the function of lot release.

1. Based at minimum on protocol review (obligatory need for summary lot protocol as part of specification for procurement) and lot release certificate from the NRA of the country of origin (all countries)

A. Discussion

In countries where vaccines are manufactured, the NRA is responsible for the release of each lot of vaccine based on the manufacturer's results and on their review and testing according to the conditions of the licence.

For countries importing vaccine it is recommended that a condition of the licence be that the product is licensed and lot released by the regulatory authorities in the country of origin. The licence should specify that the submission of the lot release certificate from the NRA of the country of origin as well as the manufacturing summary of production and control (WHO summary protocol or similar model for national criteria) is a requirement for lot release by the NRA of the importing country.

For a country that imports all its vaccine, there may be no necessity to have a fully functioning NCL for vaccine testing and release but to have access to a suitable laboratory when needed (see module 4 on laboratory access). For routine lot release, the importing NRA should perform the following for a minimum but sufficient assessment of a product imported from a country with a well-recognized regulatory authority:

- Check the incoming shipment, in particular with regard to the transport conditions.
- Take samples if required.
- Ensure the accompanying documentation is complete.

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- Review the manufacturer's summary protocol and release test results in detail.
 - Check the labelling, packaging and leaflet against the conditions of the licence conditions.
 - Receive and review the certificate of release from the manufacturer's NRA.

If vaccines manufactured in countries with less recognized NRA/NCL functions have been evaluated and granted licences by the NRA of the importing country, a decision must be taken during licensing on the samples for laboratory testing which will be required for each lot in addition to the review of the summary protocol. The decision must ensure that each lot of vaccine meets the official national criteria, preferably the WHO criteria of assured quality.

The NRA will need to approve the format and contents of the summary protocol at the time of licensing. Manufacturers must be informed at the time the licence is granted that the specified summary protocol must be prepared and submitted for each lot, together with a copy of the release from their NRA.

If an importing country plans to perform tests on incoming vaccine lots, the policy on which tests should be undertaken should be documented. If only a proportion of batches can be tested (e.g. due to a shortage of animals or human resources, or based on the test results in the summary lot protocol) the scientific basis for this should be established (e.g. every fourth or tenth batch of a particular product, or one final lot from each bulk lot, or all lots that have test results outside certain documented limits).

Vaccines purchased through UNICEF are pre-qualified by WHO for sale to UN agencies. Although the usual checking of the shipment, receipt of the summary protocol, NRA release certificate and other supporting documentation must be verified for each lot, these lots may be exempted from the detailed protocol review process by the NRA of the importing country. The additional evaluation of both the manufacturer and the NRA by WHO, regular re-assessments by WHO, and the requirements for lot release by the NCL of the country of manufacturer ensures these vaccines are of assured quality.

B. Practical approaches

- Decide on the national requirements for release of vaccines purchased from UN agencies, imported from countries with well-recognized NRAs, and for situations where vaccines may need to be imported from countries with unknown NRA functions.
- If testing is to be performed on imported products in addition to the detailed review of the summary lot protocol, develop a written policy for the products from each manufacturer.

2. Written procedure and criteria for lot-release process (checklist, sampling, guidelines) (all countries)

A. Discussion

There are several instruction documents to be developed by the NRA. They are of two types:

- those prepared as guides for the manufacturers, to provide them with the details of the documents, level of detail of data, and samples to be submitted;
- those for the internal procedures carried out by the NRA for lot release. The latter include the administrative procedures for checking incoming shipments, logging in the information, assigning a receiving (tracking) number, acknowledging receipt of the information, assigning of the protocol review, the protocol review procedure, record keeping and reporting of the decision, and the issuance of the certificate of lot release or rejection of the lot.

Guidelines for manufacturers/importers

The guideline document for the manufacturer should provide specific information on the requirements for release of each lot for each vaccine. All activities that require input or action on the part of the manufacturer should be clearly identified with a written list of directions for the manufacturers to follow so that they know exactly what is required of them for lot release. The guide should include:

- a reference to the official mandate of the NRA to perform lot release,
- directions for a request for release and other required documentation,
- the acknowledgement of receipt at the NRA (fax or mail),
- the expected timeframe for release, and
- the format of the lot release certificate and how it should be sent to the manufacturer/importer (fax or mail).

The official mandate will be a reference to the relevant parts of the law of the country that cover the lot release of vaccines. This should include definitions that indicate if vaccines are treated as a separate category of products or are included in the overall definition of a drug.

A clear description of the information to be included in a covering letter (or form) from the manufacturer or importer, and the required signatures of an identified responsible person for requesting lot release is a necessary part of ensuring that the lot-release process is standardized and efficient.

The documentation required to accompany each lot should be clearly identified. Copies of the approved summary protocol (recommended to be based on the WHO model summary protocol) with additional data if the country has internal requirements, copies of the labels for each lot, the package leaflet, and the certificates of release of the lot by the NRA of the country of origin should be included. The requirements to report test failures, repeat tests, criteria for repeat testing and methods calculations of the final results, and any reprocessing that occurred during manufacture of the lot should be clearly set out in the instructions for preparing the summary lot protocol.

The summary protocol must contain sufficient data to permit the NRA to redo the calculations – pass/fail results are not sufficient. The preparation and use of new standards or in-house references should also be submitted. There may be other documents such as customs forms, copies of the purchase orders or tenders for the vaccine, and copies of any other documentation required by the importing country.

The manufacturer should also know the number of vaccine vials that will be taken as samples from the shipment by the NRA.

The manufacturers/importers should know the expected turn-around time for release of each vaccine lot. If the release is on summary protocol alone, this shouldn't take more than a week or two for the administrative procedures. However, the time may depend on several factors: the customs clearance procedures; the time of receipt of the documents by the NRA (in advance of product shipment, or accompanying the product shipment); the administrative procedures; the time for review of the summary lot protocol; as well as consideration of the additional workload for the NRA staff. If any testing is required by law, WHO recommends that the minimum testing be performed, such as the visual inspection of the vial (appearance and colour of the product, container and closure, review of the vial label and packaging). If the NRA is required to inspect the vaccine shipments as they arrive at customs or at the importer/purchaser, this could add time to the release process.

Finally, the manufacturer should be informed of any requirements for submitting information about each licensed product for the files to give a complete product profile. This would include the number of repeat tests.

Internal NRA guidelines and forms

The NRA must develop criteria and prepare written procedures and documents for the lot-release process. The summary lot protocols approved at licensing will be the technical document on which a lot will be evaluated for release. If the importing country has requirements in addition to the recommended WHO summary protocol requirements, the summary protocol should include these. The additional data could be provided on a separate information sheet for the country-specific requirements, or a composite summary protocol could be developed.

A log-in form should be prepared with spaces for all the required information and data, and for signatures and dates to be kept as the record of the incoming lot and the approval or rejection of its release. The log-in procedure would:

- record the dates, information, accompanying documentation, and samples for each lot received,
- assign a unique receipt number for each lot for traceability, and
- identify the NRA reviewer, the review deadline, the results of the review, and date the release certificate was issued or denied.

Dates of receipt of any additional information or contact/correspondence with the manufacturer/importer regarding the lot shipment should be cross-referenced with the tracking number.

An internal NRA SOP for the lot-release process should be prepared to describe the sequential steps in the process, to clearly identify the persons responsible for each step, and to make reference to all the documents and forms or checklists used in the process. The standard form of a SOP is provided in WHO/VSQ/97.01 (2). Lot release requires a certain amount of administrative and clerical procedures as well as the review of the manufacturer's data. The SOP should give details on all these steps.

To standardize the review of the information submitted in the summary protocol, checklists should be prepared for each vaccine with spaces to check off the information for each section of the vaccine's approved summary protocol. There should be a section for label review, and space to write any comments and to record any discrepancies or problems found during review. All contact with the manufacturer to clarify issues should be noted on the checklist or a signed dated record attached to it. The checklist form should include space for the receipt number (tracking number) for full traceability.

Once the general vaccine summary protocol checklist has been decided, a *master summary protocol checklist* should be prepared for each licensed vaccine listing the specific cells, strains, seed lots, media and materials, etc. approved for use in the production and testing. Protocol review checklists should include test specifications and possibly the source of the specification (licence, WHO, pharmacopoeia) so it is clear whether a batch meets the licence specification. Each checklist and master checklist should be reviewed and approved by the senior NRA official responsible for vaccine release before it is put into routine use.

These master checklists are used to compare the submitted information in the manufacturer's summary protocol for each lot, against the procedures, materials, tests and specifications approved during licensing, and expiry date verification, and signature verification. Copies of the approved labels and leaflets should also be available for label and leaflet review.

The official lot release certificate must also be designed. WHO provides model release certificates for most vaccines (31-44) and also general type certificates (see Annex 2 of ref 7; Appendix 3 of ref 15; and Appendices 1 & 2 of ref 18). Annex 2 of ref 7 is the "Model Certificate for the release of vaccines acquired by United Nations Agencies" and has been included as Annex 1 to this manual. These models can be adopted by an NRA or used as a basis for designing their own certificates.

The release certificate should include any national requirements in addition to the recommended WHO model release certificate. The wording should clearly indicate the technical requirements that have been met: WHO requirements, national requirements or both.

In vaccine producing countries, the manufacturer submits the required samples and documents directly to the NRA/NCL for their evaluation. For importing countries, the shipment of the vaccine lot usually arrives at the port of entry addressed to the purchaser. Depending on the laws of the country, the NRA may make the initial check of the product at the port of entry, or at the importer's warehouse.

A checklist should be prepared for the initial NRA verification of the incoming shipments, if this is done at the port of entry. If sample vials are taken during this verification, there should be a record of the number taken and the transport conditions, and this information should be added to the log-in sheet.

The NRA will have to ensure that the storage conditions and quarantine status of the product shipment are satisfactory during the time until the lot is released to the purchaser. If laws require that customs maintain the product until release, then the customs storage conditions must be adequate for all expected imported vaccine and access should be restricted. If product is shipped to the importer or to the purchaser, then there must be a mechanism whereby the NRA can ensure the product is properly stored and quarantined until release. These procedures should be written into an SOP with a checklist to record the process. Inspections of these storage facilities should be made at regular intervals. The national drug regulatory authority could be of assistance. WHO has published guidelines for the performance and specifications for cold rooms and freezer rooms that can be consulted (47).

Training

Training in the lot-release procedures is necessary to ensure that the transition to lot release goes smoothly and efficiently, and that each new NRA employee is prepared for their role in the procedures of lot release.

Although it is the manufacturer who will prepare the summary lot protocols, the NRA staff responsible for the summary lot-protocol review must be given experience in the review of these documents before implementing routine lot release. The staff responsible for a specific vaccine should compare the WHO models with the technical file to review the specifications at each of the manufacturing steps listed on the summary protocol. The staff should be involved in the preparation of the checklists and master checklists for each vaccine and each manufacturer including the approved specifications. The person responsible for receipt and log-in of incoming lot documents and samples should be given instructions on the activities involved and the timeframes.

Instructions will need to be prepared and communicated to the manufacturers in advance of the implementation to give them time to prepare the newly required documentation. If the WHO model summary protocol is to be used, the instructions can be a reference to the appropriate WHO TRS. If a country-specific summary protocol has been prepared, then the manufacturers will need to receive official copies for each of their vaccines and time to review and ask any questions regarding the new lot-release procedure.

Information must also be communicated to the purchasers of vaccine and to the immunization programmes to give them advance instructions on the procedures and timetable for implementation for lot release, and to incorporate the new procedures into their routine receipt and delivery operations. They should check that a copy of the lot release certificate from the NRA has been supplied to show that the lot has been released for distribution.

Implementation of a lot release programme

Parallel to the preparation of information letters, SOPs, guidelines, documents and training, plans for implementation of the lot release programme must be prepared. The schedule must be decided and the details communicated to the suppliers and purchasers.

Plans for implementation of the start-up of the lot release programme must be carefully considered. It is important to ensure that lot release proceeds efficiently from the start, and that as little interruption as possible occurs in the supply of vaccine to purchasers and immunization programmes. It is never easy to impose new restrictions on suppliers, so it is important to make the transition as easy as possible. The preparation of instructions and training as described above is the first step.

An estimation of the number of lots of each type of vaccine that will be received per year can be made from recent years' purchases and/or from immunization programme projections. These numbers should be the basis for estimating the workload for the NRA. The workload for individual staff of the NRA should also be estimated to determine changes in responsibilities or if new staff will be required. If large numbers of lots of vaccines are imported, it may be expedient to set up a phase in the programme where vaccines enter the lot release programme at defined intervals. Depending on the vaccines and suppliers, this can be done by product or by manufacturer. This will permit the NRA staff to accommodate to the increased workload and to become familiar with the lot-release process.

It is important that the decision on the timeframe for implementing lot release be considered very carefully. It is better to overestimate the time from receipt of a vaccine to its release at the beginning of the lot release programme and later reduce the time, than to underestimate and then have to deal with delays and perhaps reduce the credibility of the NRA.

B. Practical approaches

- Prepare the guidelines for the manufacturers and/or importers on the procedure for submitting a vaccine lot for release and the required level of detail of production and control data to be submitted.
- Determine the contents and format of the request release letter/form.
- Prepare and approve the NRA SOP for the internal lot-release procedures with a flow-chart of the process, identification of the persons responsible, and indication of the required signatures and counter signatures.
- Prepare a list of the required supporting documents to be shipped with each lot of each vaccine from every manufacturer.
- Prepare a log-in sheet with defined fields for the information to be recorded for each vaccine lot received for approval for release. These would include:
 - Product name
 - Manufacturer
 - Name, signature, title and date of request
 - Date of receipt

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- Lot number
 - Lot size
 - Receipt (tracking) number assigned
 - Date of manufacture
 - Date of expiry
 - Storage conditions
 - Dose and pharmaceutical form
 - Presentation (doses/vial)
 - Diluent
 - Diluent lot number
 - Summary protocol received
 - Labels and leaflet received
 - Samples received, number of vials
 - Assigned reviewer
 - Assessment required
 - Deadline for assessment
- Prepare an acknowledgement of receipt fax form for the manufacturer.
 - Prepare instructions for the staff for the log-in of each vaccine lot arriving for lot release, including assigning a receipt (tracking) number, and acknowledgement of receipt to the supplier.
 - Prepare a checklist for the recording of the review of the summary protocol for each vaccine, including specifications for each test.
 - Prepare master checklists for each licensed vaccine.
 - Design the official national certificate of release, and a form for rejection of a lot for release.
 - Prepare a master file for each licensed vaccine with copies of the licence conditions (expiry date, special requirements, etc), approved summary protocol, master checklist, and list of all documents required to be submitted for lot release for that vaccine.
 - Establish a filing system for the completed checklist lot reviews for each licensed vaccine.
 - Train the personnel in the recommendations published by WHO for the production and control of specific vaccines to give them a working knowledge of the vaccines they will be evaluating for lot release. Specialized expertise is required for the review of viral vaccines, bacterial vaccines and combination vaccines.
 - Deliver training sessions describing the roles and responsibilities of those involved in or affected by lot release during the implementation phase:
 - NRA staff
 - Manufacturers/importers
 - Customs officials (if procedures change)
 - Immunization programmes.

3. Access to product file, and national control laboratory to guide particular areas of scrutiny in lot release and to inspection reports, complaints in case of problems (all countries)

A. Discussion

During the review of the summary protocols, the NRA staff will need to have access to other documents to keep up-to-date with all the information on each specific vaccine product. These will include the licensing file, licence updates/renewals, approved variances to the licence, complaint files, adverse event reports, and facility inspection reports that have been received for the product. The licensing file (product file) should be consulted to crosscheck the manufacturing and control testing information on the summary protocol with the methods approved in the licence. Complaints can identify problems that have occurred, which can be checked during the lot-release process. Adverse-event reports linked to vaccine quality should be communicated to the staff in charge of lot release to determine if a more detailed scrutiny of new lots of the vaccine could identify potential problems. Inspection reports would identify problems at the manufacturing facility that might affect the quality of vaccines and lead to a more detailed evaluation of certain lot(s) of vaccine.

Those responsible for licensing, facility GMP inspections, and field surveillance should communicate any changes in the licence conditions or problems encountered with a vaccine to those responsible for lot release. It is important that each vaccine lot is evaluated for release under the current licence conditions and with full knowledge of the safety, quality and efficacy of the vaccine.

B. Practical approaches

- Make agreements for accessing information from the NRA staff responsible for other vaccine data such as complaints of adverse events following immunization (AEFI), inspection reports, and licensing files. A regular system of notifications between various departments should be instituted.
- If the staff responsible for lot release are not part of the quality evaluation team for licensing, the individuals responsible for the release of specific vaccines can be given the task of reviewing the product files to become familiar with the manufacture and control procedures for each manufacturer of that vaccine.
- Regularly update the master file for each licensed vaccine (see 2B) with copies of (or cross-references to) inspection reports, a list of all AEFI and complaints for specific lots of the vaccine, and a list of all licence renewals/updates and approved licence amendments or variations to the licence.

4. Records kept of lot release data for analysis of consistency of quality, and continual review and scientific dialogue with the manufacturers on issues of quality test results (all countries)

A. Discussion

In addition to release of each vaccine lot into the country, the NRA of the importing country should evaluate the results of the manufacturer's test data for all lots submitted for release, to determine any changes or trends in the manufacturing, in-process tests or QC release test results over time. For a country importing vaccines and releasing lots based on the summary protocol, the analysis will be mainly a review of the trends in the manufacturer's data over time for individual products, and a comparison between the manufacturer's data and that from the NRA of the country of origin if the certificate of release provides details of the test results. Any significant changes in quality must be evaluated and discussed with the manufacturer or with the NRA of the country of origin to determine the potential impact on vaccine safety and efficacy. Investigations into such changes should determine whether any changes in source materials, production methods or testing are involved.

A sufficient number of lots of each vaccine will be required before any trends can be identified, therefore, this analysis would follow after the actual lot-release system has been implemented and several lots of a specific vaccine had been submitted for release. Plans for performing trend analysis of the data should be made in advance. Contact with other NRAs with well-functioning NCLs would be advisable, including the national DRA that may have expertise in trend analysis.

The plans should include decisions on the relevant parameters to be analysed for each vaccine, the methods to be used, and trends and/or criteria that are considered significant for individual vaccines. For assays where reference vaccines are used, the reference vaccine values will show the consistency of the manufacturer's test method, and the individual vaccine lot results will show the consistency of manufacture.

Exactly which parameters are important are based on the knowledge of the product/assay involved. Usually only one or two parameters are tracked – always including potency. The data can be graphically represented showing the mean and 2 or 3 standard deviation points from that mean as lines on the graph. This allows consistency and the trends can be easily monitored visually. Computer analysis could also be done if suitable programs are available or can be developed. The analysis procedure should be documented defining the course of action to be followed if trends or unexpected deviations occur.

B. Practical approaches

- Contact WHO or other well-recognized regulatory authorities to request advice on statistically appropriate trend analysis for specific vaccines.
- Begin with graphical record of the results of potency tests for each lot and the corresponding values for the reference vaccine over time.

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- Identify courses or reference books on biostatistics that present information on trend analysis for biological products. Train appropriate staff in trend analysis.
 - Investigate the availability for obtaining or developing a computer data analysis program for trend analysis.
 - Update the master file for each vaccine with the results of trend analysis.

5. Written criteria for exemption from lot release (all countries)

A. Discussion

There are situations when the NRA of the importing country can or may need to exempt vaccines from lot release.

One is procurement of vaccine through UNICEF. The WHO pre-qualification procedure for approval for sale to UN agencies requires that the vaccine is licensed in the importing country and that each lot of vaccine is accompanied by the certificate of lot release from the NRA of the country of origin. For EPI vaccines purchased through UNICEF, the vaccine should be licensed in the importing country, but the detailed scrutiny of each lot is not considered mandatory. However, the summary protocol of each lot must be received; the shipment checked for correct transport conditions, correct labels, correct accompanying documentation; samples taken if required, and logged into the NRA inventory.

A second situation may also occur. In general, all industrialized countries with well-recognized NRA/NCLs, subject their domestically manufactured biological products to lot-by-lot release. In the last few years, new provisions have been introduced in several of these countries where regulation of biological products has been long-standing and many manufacturers have a long history of satisfactory production and control of their biological products. These provisions permit a manufacturer to apply for or meet new criteria for exemption from lot release (56). The manufacturer is required to report the lots distributed at predetermined intervals. Generally, vaccines do not fit into this category for exemption, but the situation could arise. Because any vaccine qualifying for this exemption would be a very well characterized vaccine with a very successful history of compliance and consistent production under strict and effective regulations, the exemption indicates a high quality product. Such a vaccine could be ineligible for licensing by an importing country that has a requirement for lot release by the NRA of the country of origin. In order not to reject such vaccines from licensing or lot release, the NRA of the importing country would need to create an exemption for such products, to revise or delete the requirement for NRA release in the country of origin. Instead it would release the lot in the importing country on the manufacturer's summary protocol alone. There should be a condition that the required reports of all lots manufactured and released should also be submitted to the NRA of the importing country for its files.

Each situation where lot release can be waived should be pre-determined, and made on strict criteria. The manufacturers of imported vaccine must be fully informed of the criteria; they should be instructed to notify the NRA of any changes to the lot-release requirements in their own country that would affect the conditions of licensing in the importing country.

B. Practical approaches

- Prepare a list of situations and criteria when a vaccine can be exempted from lot release.
- Set the conditions for accepting a vaccine that is no longer subject to lot release in the country of origin. This may include specifying only certain countries with well-respected NRA functions, advice from WHO for each case, requiring lot release in the importing country, and requiring annual lists of the vaccine lots distributed worldwide.
- Prepare an exemption form to be used in these approved situations. A copy of the exemption form for a permanent exemption should be filed in the master file for the vaccine. An exemption for specific lots should be attached to the file for the individual lot.

Module 4:

Evaluation of testing laboratory/laboratory access

Introduction

National regulatory authorities need to be able to assess the quality of vaccines and other pharmaceutical products by performing tests on products in certain situations. This testing can be a requirement to corroborate the manufacturer's test results during the evaluation for licensing or for a variation to a license. It can be a requirement for lot release for certain products according to the regulations in the manufacturer's country. It can be testing of products for which there has been a complaint or a report and investigation of an adverse event. Some regulatory authorities evaluate the stability of vaccines by performing certain tests at the end of a product's shelf life.

In order to do this, the national regulatory authorities must have access to suitable laboratories where these tests can be performed.

A well-functioning laboratory for vaccines is a key resource for the vaccine regulatory system (20). The staff have the expertise in vaccinology which can help in regulatory decisions, such as the evaluation of marketing authorizations and review of clinical trial data.

A functioning laboratory is a necessary part of the national regulatory authority operations of a country that manufactures vaccines. This may be a laboratory which is an integral part of the regulatory authority, a separate agency or institute reporting to the NRA, or a contracted laboratory service. The basic requirement is that an NRA must have access to a suitable laboratory to carry out its functions. Whatever the laboratory organization, there are specific quality criteria that must be met to adequately perform the testing functions to ensure that the quality of vaccines to be used for immunization programmes or for the private market meets national standards.

The establishment of a laboratory is a long and costly process, and involves complex, expensive laboratory tests, which must be standardized, validated and interpreted. Staff with training and expertise in complex, demanding procedures can remain proficient only if tests are performed on a regular basis. Tests that are done only occasionally must be revalidated.

For vaccine-importing countries with newly developing regulatory authorities, the routine testing of vaccines is not considered necessary for lot release of vaccines purchased from: UN agencies; or countries with a well recognized NRA, if the vaccine is licensed and lot released in the country of origin (see module 3 on lot release).

However, there may be situations where vaccine samples must be tested. This may include testing of vaccine lots for licensing; stability testing; random field samples; complaint samples; samples from an adverse event investigation; or requirements in the law of the importing country that require samples of vaccine lots to be tested. A laboratory might also be required to properly store samples of vaccines for the NRA. The NRA of a vaccine-importing country needs access to suitable laboratories in these instances. These laboratories should meet relevant criteria for the tests they will perform. The NRA of the importing country should be prepared to evaluate and contract the laboratory services they need to ensure the quality and safety of vaccines.

Several different laboratories may be needed to provide the range of expertise required to be prepared for testing the different vaccines imported. The national drug regulatory authority should be contacted to see what laboratory facilities and test procedures are available. Laboratories could be outside the country if the expertise needed were not available within the importing country. If the NRA has any collaborative contacts with other well-functioning and recognized NCLs, they could be approached to provide laboratory assistance when needed and have the advantage of an already existing laboratory quality system (LQS) for vaccine testing. WHO could be contacted to suggest a suitable laboratory.

The following indicators list the activities and procedures that are considered essential for a laboratory carrying out the testing of vaccines within the regulatory system. All are essential for laboratory functions and together make up a laboratory quality system. For the NRAs of countries where vaccine is manufactured the indicators refer to their own laboratory operations. When NRAs contract out laboratory operations, whether in vaccine-producing or vaccine-procuring countries, these indicators apply but with the slightly different emphasis of overseeing the laboratory operations of the independent laboratories.

Indicators: evaluation of testing laboratory/laboratory access

- **Commitment to a laboratory quality system from management (all countries)**
- **Designation of a quality manager (all countries)**
- **Existence of a quality manual (all countries)**
- **Documentation of procedures in place (including document control, SOPs, study plans for control of specific products, retest policy) (all countries)**
- **Equipment documentation in place (including commissioning records, operation manuals and logs, calibration and maintenance schedules, validation protocols) (all countries)**
- **Staff training plan developed and implemented (all countries)**
- **Existence of an audit and review system (all countries)**
- **Validation procedures in place for all tests (all countries)**
- **Existence of a laboratory safety programme (all countries)**
- **Appropriate use, calibration and maintenance of standards and reference reagents (all countries)**

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- **Monitoring and analysis of laboratory data trends on a product-by-product basis and appropriate corrective action as required** (all countries)
 - **Participation in proficiency schemes and collaborative studies** (all countries).

This module on laboratory access will discuss each of the indicators and how each applies to the NRAs of countries that contract out needed laboratory services. Each indicator will have a discussion section on the background and a section on practical approaches.

1. Commitment for a laboratory quality system from management (all countries)

A. Discussion

In order to run a laboratory or evaluate contracted laboratory services, a laboratory quality system must be in place for the activities and operations involved. Management must support this, financially and ideologically, in order for the NRA to carry out its functions successfully.

An NRA that is contracting all its services needs to have a commitment from management to support the decisions of the NRA for the laboratory functions it considered essential. This would be to support the formal evaluation process established for identifying qualified laboratories, and to accept the decision-making process for issuing, renewing or rescinding contracts for laboratory services, based on the predetermined criteria adopted for the contract process.

B. Practical approaches

- Prepare a written list of criteria for the identification of a qualified laboratory, and the criteria for evaluation of the laboratory services offered with a rationale for the decisions.
- Prepare the estimated costs of specific laboratory test services needed on a yearly basis with a rationale for these estimates.
- Meet with management to get a commitment to the plans and costs of laboratory services.
- WHO has published guidelines for contracting laboratory support for regulation of vaccines (11). These guidelines present steps in the selection of a laboratory and are summarized here. Management's support for all of these activities should be obtained.

Taken from Annex 4 of
Regulation of vaccines: building on existing drug regulatory authorities (11)

1	Draw up the terms of reference (TOR) for the laboratory services desired	Tests to be performed Methods and standardization of tests Capacity of the laboratory Turnaround time Price Reporting of results: raw data, interpretation of data Provisions for maintenance of confidentiality
1b	Identify the budget for the contract	Cost the services Find the funds
2	Establish selection criteria (to be set out before requests for proposals (RFP) are prepared)	Recommendations of other users of the laboratory Price of each test (equipment, materials and staff time) History of experience with the test Sample shipment logistics Responses to the request for proposal Results of previous evaluations
3	Assemble a list of possible qualified laboratories	List to include: name of laboratory; name of contact person; address; telephone number; fax number. Potential choices: NCL of a well functioning NRA with expertise in vaccine testing Proficiency tested laboratory from WHO regional networks An accredited laboratory with proven proficiency in desired test(s)
4	Carry out the contracting process	Responsible department (normally procurement entity) to determine: name of body issuing the RFP person who will sign contract person to authorize payments person to make payments contract for specific number of tests or a specific period of time Prepare the RFP according to established procedures to include the detailed terms of reference Send RFP to qualified laboratories Evaluate the proposals received by special committee or jointly with the NRA based on pre-established criteria including weighting factors choose laboratory with most responsive offer and best price
5	Evaluation of the performance of the laboratory	Responsiveness to the national needs for testing and meeting timeframes Ease of interpretation of raw data provided Reliability of data provided (trend analysis, auditing by NRA)

2. Designation of a quality manager (all countries)

A. Discussion

For the NRA contracting out laboratory services, a quality manager should be designated to be responsible for coordinating the evaluation of potential laboratories, dealing with the department preparing requests for proposals and contracts, and evaluating the proposals and the performance of the laboratories.

This quality manager would be responsible for determining quality policy, objectives, responsibilities as it applies to the contracting of laboratory services, ensuring the contracted laboratories and data generated meet the terms of the contract, and ensuring that samples for testing are shipped appropriately to the laboratory(ies). Responsibilities would also include hiring or training of NRA staff in the necessary topics to be able to effectively assess the laboratory results and laboratory operations, and assigning of staff to evaluate specific test procedures, and results.

The major responsibility will be the contracting procedures. In order to contract laboratory services from other laboratories, the NRA manager must consider first what testing services are needed for routine or emergency situations. Potential laboratories must be identified that can provide the services that will or may be needed. Existing government laboratories such as the drug regulatory control laboratories would have suitable staff and facilities for chemical, biochemical and some microbiological tests for sterile products. Other possibilities would be government diagnostic laboratories or university laboratories working in immunology, microbiology, or with the relevant vaccine-controlled infectious disease(s). These labs could be contracted to perform immunological or potency tests. If animals are needed for testing procedures, then a laboratory with appropriate segregated housing and treatment quarters would be needed as well as an approved supplier of the species required. If bacteria, cells or virus stocks are needed for testing, these should be prepared and stored under conditions reviewed and approved by the NRA to ensure they meet requirements of the test. If any specific safety precautions are required in the performance of a contracted test, the NRA should ensure that the laboratory is exercising these precautions.

Several administrative procedures must be established for contracting laboratory services. The NRA must judge in advance if there is any potential conflict of interest from other operations or contracts at the laboratory. A contract with each independent laboratory providing services should be formally made, identifying the responsible manager and outlining the terms of the agreement for laboratory testing. There must be an agreement on the performance of the test according to national or WHO criteria for LQS:

- performing tests according to the approved SOPs;
- recording and signing of all data;
- predetermined criteria for repeat testing;
- a specific time frame for completing the tests;
- maintenance of confidentiality of the vaccine source and results of the tests; and
- disposition of the data (8).

The contract should include a statement that the NRA can audit the laboratory and the test data at their discretion. The laboratory should also be given an approximate idea of the extent and frequency of testing that will be expected.

The NRA manager should evaluate the qualifications of the staff available, and provide or oversee the preparation of SOPs and data record sheets for the tests required. The laboratory should prepare documentation for the operation, maintenance and calibration of each piece of equipment, perform appropriate qualification/validation, and maintain records of the status and use of the equipment, especially if the equipment is not dedicated to the tests for the NRA.

B. Practical approaches

- Designate a staff member with suitable experience in laboratory operations as coordinator of laboratory service contracts.
- Prepare a job description of the manager including duties and responsibilities for planning, establishing, implementing, monitoring, and budgeting the operations for contracting laboratory services.

3. Existence of a quality manual (all countries)

A. Discussion

A quality manual is an NRA document that describes the quality policy, objectives, responsibilities, and the organization of the NRA activities that are related to vaccine quality. This document should describe the plans for each potential situation that would require vaccine testing and various circumstances for contacting manufacturers or the NRA of the country of origin on vaccine quality. The manual should cover all the activities and documents prepared that relate to the evaluation and qualification of contract laboratories, setting terms of reference, preparing requests for proposals, evaluating proposals, choosing laboratories, preparing contracts, and evaluating laboratory results for the purposes of assessing vaccine quality in specific situations.

WHO provides guidance on these contracting procedures (see section 1 above and 11).

B. Practical approaches

- Prepare a quality manual covering all activities performed within the NRA related to vaccine quality including a description of the situations where testing facilities would be needed.
- Include in the quality manual, a list of requirements for evaluating potential contract laboratory services. The following is an example of the type of information needed.

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- i) Identify situations where access to a laboratory is necessary. The possibilities are:
- initial licensing
 - variance to the license involving a change to the product or test methods
 - complaints
 - adverse event investigation
 - random field samples
 - stability testing
 - sample storage
 - confirmation of data on summary lot protocols
 - investigation of trends or aberrant results from summary lot protocols.
- ii) Identify the expertise and qualifications of the staff required for various vaccine tests:
- biochemical tests
 - chemical tests
 - immunological tests
 - microbiological/sterility tests
 - cell culture tests
 - animal tests.
- iii) Identify the conditions of an acceptable laboratory:
- qualifications of the staff
 - responsible manager
 - agreement to perform according to NRA requirements for LQS/GLP:
SOPs, assay validations, retest criteria, suitable storage of biological starting materials and references/standards, record keeping, testing of raw materials, segregation of materials from other laboratory work, equipment documentation and calibration, safety precautions when applicable.
 - agreement on NRA auditing
 - agreement to testing timeframes and deadlines, and priority handling if requested
 - confidentiality
 - no conflict of interest.
- iv) Identify the contractual requirements for different labs and prepare contracts in accordance with legal requirements. Contracts should include the right of the NRA to audit the laboratory.
- v) Training NRA staff for auditing of labs, animal quarters and tests results. Preparation of specific auditing checklists for each contracted laboratory.
- vi) Identify internationally recognized NRA laboratories for assistance with serious problems.

4. Documentation of procedures in place (including document control, SOPs, study plans for control of specific products, re-test policy) (all countries)

A. Discussion

When a contracted laboratory performs testing, the NRA would be responsible for:

- providing the methods to be used for the tests to be performed, particularly for tests that need to be put in place, or
- for assessing the adequacy of the standard operating procedures and the record sheets prepared by the contracted laboratory, in accordance with the contract for each specific test.

Detailed information on the assays should be provided to the laboratories as part of the terms of reference when putting out the request for proposals. Thus the laboratories will know what procedures must be followed, and what documentation must be prepared for the proposal.

B. Practical approaches

- Obtain copies of Pharmacopoeia (USP, EP) and other publications for standardized methods.
- Obtain the WHO laboratory manual (5) which gives detailed instructions for potency tests for vaccines used in immunization programmes.
- Obtain the *WHO guide to good manufacturing practices requirements Part 1 (2)* and the WHO guide for LQS (8) for guidance on the procedures to be in place in contract laboratories.

5. Equipment documentation in place (including commissioning records, operation manuals and logs, calibration and maintenance schedules, validation protocols) (all countries)

A. Discussion

In a similar fashion, the NRA must describe in detail the requirements for equipment specifications, documentation, maintenance, qualification, and calibration in a request for proposal (RFP) so that the laboratories can respond adequately. The NRA must evaluate this information to choose the most appropriate laboratory.

B. Practical approaches

- Obtain the *WHO guide to good manufacturing practices requirements Part 1 (2)*, Part 2: (3) and the WHO guide for LQS (8) for guidance on the equipment procedures to be in place in contract laboratories.

6. Staff training plan developed and implemented (all countries)

A. Discussion

The quality manager responsible for contracted laboratory testing must ensure that staff assigned to evaluate the proposals for specific vaccine tests, for evaluating laboratories and laboratory results, and for evaluating or interpreting laboratory results have the qualifications and training to make these assessments. Alternatively, or in addition to the internal expertise available, experts or advisory committees with the appropriate expertise and already qualified for the licensing of specific vaccines could be used for the evaluation of test procedures, results and interpretation of contracted tests. Such outside experts should be subject, as appropriate, to confidentiality agreements and conflict of interest guidelines. WHO provides an example of such an agreement for consultants contracted to participate in the assessment of the acceptability of vaccines for purchase by UN agencies (see WHO/VSQ/97.06, Annex 1). (7)

The NRA must be familiar with the test procedures required for the vaccines they import. These procedures are reviewed during the licensing process (see module on licensing). WHO-recommended potency test procedures are provided in detail in WHO's manual of laboratory methods (5), many general test procedures are found in *Pharmacopoeia*, and the manufacturer provides the QC release procedures in the licensing application documents. These standard operating procedures (SOPs) need to be provided to the contracted laboratory for training their staff in the procedures to be prepared for testing product when required. Validation of the assays could be planned by the NRA in conjunction with the laboratory manager following the WHO GMP training guide on validation (3). The NRA should also give guidance on criteria of the expected performance of staff in different assays and on re-training/re-validation to be undertaken if tests are performed infrequently. It is generally accepted that compendial tests such as those described in pharmacopoeias or WHO requirements, as well as manufacturer's product specific assays have been validated during their development, but each laboratory needs to determine satisfactory performance of such assays.

Access to a suitable laboratory or laboratories for testing of vaccines when the need arises requires significant input and preparation on the part of the NRA. Although the testing is conducted elsewhere, the NRA is still responsible for the correct performance and documentation of the tests contracted out. Therefore the training of the NRA staff to give them adequate knowledge in the various test procedures and in auditing of laboratories and reviewing test data is an essential part of using a contract laboratory.

B. Practical approaches

- Make a list of NRA staff with the appropriate experience and expertise to be responsible for specific vaccine testing contracts.
- Identify additional expertise or training required to oversee and evaluate the required contracted tests.

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- Prepare a training programme for NRA staff.
 - Make arrangements for accessing experts from the drug regulatory authority or other advisers for laboratory evaluations and product evaluations and/or training of vaccine staff.

7. Existence of an audit and review system (all countries)

A. Discussion

The NRA will be responsible for overseeing the performance of the laboratories performing tests on contract. This should include an established procedure for auditing the laboratories and the data generated as part of the evaluation of the ongoing performance of a contracted laboratory. Detailed files on each contracted laboratory should be maintained and regularly updated by the NRA.

The NRA staff must be trained sufficiently in the various vaccine assays to be able to review and evaluate test results and to audit the contracted laboratories. The WHO GTN manual on laboratory quality systems (8) and the quality control section in the WHO guide to inspections of biologics manufacturers can be consulted (ref. 4). GTN courses specifically for the NRA staff of vaccine-procuring countries are available for training on licensing, lot release, laboratory access, and adverse events following immunization (see GTN web site address in References).

B. Practical approaches

- Obtain and review section 2.12 in the WHO guide for a quality systems manual in a control laboratory (8) and section 5.0 of the WHO guide for inspections of manufacturers of biological products (4) to identify the procedures for auditing a laboratory.
- Train NRA staff to perform an audit of the laboratory and the data records to ensure that the procedures are being performed according to the contract.
- Access expertise in laboratory auditing from the national drug regulatory authority or other outside experts that can aid or train vaccine staff in laboratory auditing.

8. Validation procedures in place for all tests (all countries)

A. Discussion

Each assay used to perform a quality control test on a vaccine must be a validated procedure demonstrating the accuracy, precision, reproducibility, linearity, sensitivity, specificity, and robustness appropriate to the test in question (3). In the case of contracted laboratory tests, the NRA should ensure that all laboratories on the qualified list perform validated procedures or agree to validate the procedures as part of the contract. The NRA should ensure that the tests contracted out are validated by the appropriate validation scheme.

As mentioned previously, it is generally accepted that compendial tests such as those described in pharmacopoeias or WHO requirements have been validated during their development, but each laboratory needs to determine satisfactory performance of such assays. This could also be the case where tests have been developed by a manufacturer, are product specific and have been validated by a manufacturer, e.g. *in vitro* potency testing of hepatitis B vaccines. The NRA could then specify the manufacturer's documented method and require demonstration of satisfactory implementation and performance of such a test by the contracted laboratory.

B. *Practical approaches*

- Obtain the WHO manual for laboratory tests for vaccines (5) and the WHO guide for validation (ref. 4), make a list of the procedures to be contracted, and determine the appropriate validation study needed for each contracted test.
- Provide the validation information as part of the terms of reference in the request for a proposal to qualified laboratories.
- Include the review of the validation of the assay(s), either performed or proposed in the evaluation of the proposals during the decision on choosing the laboratory.

9. Existence of a laboratory safety programme (all countries)

A. *Discussion*

The NRA should ensure that the laboratory performing tests on contract is aware of any risks associated with the product being tested or reagents used during the performance of the test. Appropriate safety precautions for personnel, the community and the environment should be practised in the laboratory.

Other hazardous substances handled in the contracted laboratory should be identified to avoid any potential contamination of the vaccine that could compromise the vaccine test results.

B. *Practical approaches*

- Make a list of each vaccine and the potential risks to laboratory personnel from chemical, biological or radiochemical origin from the organism, reference materials or test materials.
- Obtain a list of hazardous agents used in the contracted laboratories to identify any special handling of the vaccine samples in the laboratory. Examples would be radio-immunoassays, microbiological assays, reference organisms.
- Request the laboratory to prepare emergency procedures for potential exposure to any new hazards introduced into the laboratory with the vaccine test procedures.
- Vaccination of contract laboratory staff.

10. Appropriate use, calibration and maintenance of standards and reference reagents (all countries)

A. Discussion

The standard preparations and reference reagents that will be used by the contract laboratories must be approved by the NRA. The NRA should obtain and provide them with the appropriate WHO or international references/standards (63), and must review the laboratory's data establishing the values and approve the in-house preparation before it is used for testing. Alternately, the NRA could request the help of another NRA/NCL to provide references or standards.

Where product-specific reference materials have to be used for potency tests of vaccines, the NRA should obtain these reference materials from the manufacturer.

B. Practical approaches

- Obtain the catalogue of biological standards and reference material from the National Institute for Biological Standards and Control (NIBSC), the WHO international laboratory for biological standards. Contact details: NIBSC, PO Box 1193, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QH, United Kingdom; email: standards@nibsc.ac.uk; or web site www.nibsc.ac.uk/catalog/standards.
- Contact other NCLs regarding the availability of accessing their reference materials or for cooperation in producing reference materials.
- Include the production of national reference materials to the contracted laboratories, ensuring that the materials produced are sufficiently evaluated before being put into use.

11. Monitoring and analysis of laboratory data trends on a product-by-product basis and appropriate corrective action as required (all countries)

A. Discussion

The data that is generated by the contracted laboratory belongs to the NRA and the raw data and results should be transmitted to the NRA. Any data analysis, when required, would be the responsibility of the NRA to perform.

The NRA will need to decide whether copies of the records are maintained (in confidence) by the contract lab, or if the complete records of each individual testing request are transferred when completed to the NRA's vaccine files. Data generated by the contract testing should be added to the NRA's routine analysis of each vaccine as outlined in the module on lot release (see the discussion and practical approaches for indicator 4 of the lot release module).

12. Participation in proficiency schemes and collaborative studies (all countries)

A. Discussion

Proficiency schemes are used to compare the test results for a specific product performed in a number of chosen laboratories. They can be designed to use either the test methods routinely performed in each laboratory or to use a specified procedure supplied to the participating laboratories. WHO establishes their values for international reference materials in collaborative studies. These reference materials are then made available to national regulatory authorities and manufacturers for establishing their own national or manufacturer's in-house reference materials. These schemes can determine the sensitivity of assays used in different labs to detect borderline acceptable titres of coded samples of vaccine. Proficiency schemes usually invite well-known laboratories to participate in the initial comparisons and, when the range of variation of results has been established, to extend the participation to a wider selection of laboratories.

Laboratories performing testing on contract for national regulatory authorities should be willing to participate in proficiency schemes if invited to do so, and the NRA should consider making this a condition of the contract. The NRA could also consider identifying several other NCLs that would be willing to test a panel of coded vaccines and reference materials in parallel with the contract laboratory, as either a pre-qualification procedure for a contract laboratory or as an on-going assessment of their performance. This could identify strengths and potential weaknesses in the methodologies of a laboratory.

B. Practical approaches

- Contact WHO regarding the potential for participation on proficiency schemes.
- Contact other NCLs for determining the possibility of identifying a potential group of laboratories to test a panel of vaccine samples with the express purpose of evaluating the initial acceptability or continuing acceptability of each as an approved contract laboratory.
- Include participation in proficiency schemes as a condition of a contract for a testing laboratory.

References

WHO/VSQ documents

- 1 *National control authority: Guidelines for assessment of vaccine quality in non-producing countries* WHO/VSQ/95.1
- 2 *A WHO guide to good manufacturing practices (GMP) requirements. Part 1; Standard operating procedures and master formulae* WHO/VSQ/97.01
- 3 *A WHO guide to good manufacturing practices (GMP) requirements. Part 2: Validation* WHO/VSQ/97.02
- 4 *Guide for inspection of manufacturers of biological products* WHOVSQ/97.03
- 5 *Manual of laboratory methods* WHO/VSQ/97.04
- 6 *Vaccine donations: GPV policy statement* WHO/VSQ/97.05
- 7 *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies.* WHO/VSQ/97.06
- 8 *Guide for a quality systems manual in a control laboratory (for GTN by PAHO/SIREVA)* WHO/VSQ/98.04

WHO/V&B documents

- 9 *Informal consultation of experts on national regulation of vaccines* WHO/V&B/99.08
- 10 *Review of existing documents on planning, performance and assessment of clinical studies on vaccines* WHO/V&B/99.09
- 11 *Regulation of vaccines: Building on existing drug regulatory authorities* WHO/V&B/99.10

WHO TRS publications: general/regulatory

- | | | |
|----|--|-----------------------------|
| 12 | <i>Guidelines for developing national drug policies</i>
<i>Update</i> | WHO, 1988
WHO/DAP/95.9 |
| 13 | <i>WHO certification scheme on the quality of pharmaceutical products moving in international commerce</i> | WHO TRS 790, 1990 Annex 5 |
| 14 | <i>Guiding principles for small national drug regulatory authorities</i> | WHO TRS 790, 1990 Annex 6 |
| 15 | <i>Guidelines for national control authorities on quality assurance for biological products</i> | WHO TRS 822, 1992 Annex 2 |
| 16 | <i>Guidelines on good clinical practice (GCP) for trials on pharmaceutical products</i> | WHO TRS 850, 1995 Annex 3 |
| 17 | <i>Regulation and licensing of biological products in countries with newly developing regulatory authorities</i> | WHO TRS 858, 1995 Annex 1 |
| 18 | <i>Guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce.</i> | WHO, TRS 863, 1996 Annex 10 |
| 19 | <i>Guidelines on import procedures for pharmaceutical products</i> | WHO TRS 863, 1996 Annex 12 |
| 20 | <i>National drug regulatory legislation: guiding principles for small drug regulatory authorities</i> | WHO TRS 885, 1999 Annex 8 |
| 21 | <i>Training activities: List of training programmes for drug regulators</i> | WHO TRS 885, p 12 |

WHO TRS publications: GMP

- | | | |
|----|--|----------------------------|
| 22 | <i>Good manufacturing practices for biological products</i> | WHO TRS 822, 1992 Annex 1 |
| 23 | <i>Good manufacturing practices for pharmaceutical products</i> | WHO TRS 823, 1992, Annex 1 |
| 24 | <i>Good manufacturing practices: Guidelines on validation of manufacturing processes</i> | WHO TRS 863, 1996 Annex 6 |
| 25 | <i>Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans</i> | WHO TRS 863, 1996 Annex 7 |

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- 26 *Good manufacturing practices: authorized person - role, functions and training* WHO TRS 885, 1999 Annex 4

WHO TRS publications: General biologicals

- 27 *General requirements for the sterility of biological substances amendment 1995* WHO TRS 530, 1973 Annex 4
WHO TRS 872, 1998 Annex 3
- 28 *Guidelines for the preparation, characterization and calibration of national or laboratory working standards and reference reagents for biological substances* WHO TRS 800, 1990 Annex 4, Part B
- 29 *Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology* WHO TRS 814, 1991, Annex 3
- 30 *Requirements for the use of animal cells as in vitro substrates for the production of biologicals* WHO TRS 878, 1998 Annex 1

WHO TRS publications: Vaccine requirements

- 31 *Requirements for meningococcal polysaccharide vaccine* WHO TRS 594, 1976 Annex 2
- 32 *Requirements for poliomyelitis vaccine (inactivated)* WHO TRS 673, 1982 Annex 2
- 33 *Requirements for dried BCG vaccine, revised 1985* WHO TRS 745, 1987 Annex 2
Amendment 1987 WHO TRS 771, 1988 Annex 2, 3, 12
- 34 *Requirements for rabies vaccine (inactivated) for human use produced in continuous cell lines* WHO TRS 760, 1989 Annex 9
Amendment WHO TRS 840, 1994 Annex 5
- 35 *Requirements for hepatitis B vaccines made by recombinant DNA techniques* WHO TRS 786, 1989 Annex 2
Amendment WHO TRS 889, 1999 Annex 4
- 36 *Requirements for poliomyelitis vaccine, oral, revised 1989* WHO TRS 800, 1990 Annex 1
- 37 *Requirements for diphtheria, tetanus, pertussis and combined vaccines* WHO TRS 800, 1990 Annex 2
Revised 1989
- 38 *Requirements for Haemophilus Type b conjugate vaccines* WHO TRS 814, 1991 Annex 1

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|----|--|--|
| 39 | <i>Requirements for Vi polysaccharide typhoid vaccine</i> | WHO TRS 840, 1994 Annex 1 |
| 40 | <i>Requirements for measles, mumps and rubella vaccines and combined vaccine (Live)</i>
<i>Note</i> | WHO TRS 840, 1994 Annex 3

WHO TRS 848, 1994 |
| 41 | <i>Requirements for hepatitis A vaccine (inactivated)</i> | WHO TRS 858, 1995 Annex 2 |
| 42 | <i>Requirements for hepatitis B vaccine prepared from plasma, revised 1994</i> | WHO TRS 858, 1995 Annex 3 |
| 43 | <i>Requirements for yellow fever vaccine, revised 1995</i> | WHO TRS 872, 1998 Annex 2 |
| 44 | <i>Guidelines for the production and control of the acellular pertussis Component of monovalent or combined vaccines</i> | WHO TRS 878, 1998 Annex 2 |

Other WHO documents

- | | | |
|----|---|---|
| 45 | Thermostability of vaccines | WHO/GPV/98.07 |
| 46 | <i>Assurance of vaccine quality: Will international laboratory networks help?</i> | WHO task force on situation analysis, CVI, April 1994 |
| 47 | <i>Equipment performance specifications and test procedures: E1: cold rooms and freezer rooms</i> | WHO/EPI/LHIS/97.03 |
| 48 | <i>Marketing authorization of pharmaceutical products with special reference to multi-source (generic) products</i> | WHO/DMP/RGS/98.5 |

Other regulatory agency publications

- | | | |
|----|---|--|
| 49 | Federal Food and Drugs Act of 1906

Federal Food, Drug and Cosmetic Act of 1936

Public Health Act | USA: Department of Health and Human Services, Food and Drug Administration |
| 50 | Code of Federal Regulations (CFR), Title 21 Food and drugs
Subchapter F - Biologics, parts 600–680
Licensing and Standards, parts 600, 601, 610 | USA: Department of Health and Human Services |

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- | | | |
|----|--|--|
| 51 | Guidance for industry: Content and format of chemistry, manufacturing and controls information and establishment description for a vaccine or related product | USA, FDA, Center for Biologics Evaluation and Research (CBER), 01/99, web site |
| 52 | Guidance for industry - changes to an approved application: biological products | USA, FDA, Center for Biologics Evaluation and Research (CBER) web site |
| 53 | Food and Drugs Act and Regulations Part C Drugs, schedule D Biologics | Canada, Health Protection Branch, Therapeutic Products Programme |
| 54 | <i>Guideline: Preparation of human new drug submissions</i> | Canada, Health Protection Branch, Therapeutic Products Programme
Document H42-2/38-1990 |
| 55 | Policy issues: Management of drug submissions | Canada, Health Protection Branch, Therapeutic Products Programme (web site under Policies) |
| 56 | Draft policy: Review/testing/approval of biologics drug lots | Canada, Health Protection Branch, Therapeutic Products Programme (web site under Policies) |
| 57 | Therapeutic Substances Act, 1953

Therapeutic Goods Act, 1996, 1989, and amendments

Therapeutic goods regulations

Therapeutic goods order and determinations | Australia, Therapeutic Goods Administration |
| 58 | Australian guidelines for the registration of drugs, 1994

Australia: Applying to list a new drug product in the Australian registry of therapeutic goods, or vary previously listed drug products
TGA web site for publications. | Australia, Therapeutic Goods Administration |
| 59 | <i>The rules governing medicinal products in the European Union, Vol. 1-9</i> | European Union: Directives, notices, guidelines |
| 60 | Notice to applicants: Application for a variation. | European Union: Medicinal products for human use. Procedures for marketing authorization, Vol. 2 notices |

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- | | | |
|----|---|---|
| 61 | Note for guidance on clinical evaluation of new vaccines | European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit. Document CPMP/EWP/463/97 draft |
| 62 | <i>ASEAN Manual for inspection of GMP</i> | Association of South East Asian Nations, 1988 |
| 63 | <i>Catalogue of biological standards and reference material</i> | National Institute for Biological Standards and Control (NIBSC) |

Forms

Reference

- | | |
|---|--|
| Model certificate of a pharmaceutical product | Ref. 18, Appendix 1 |
| Model statement of licensing status of pharmaceutical product | Ref. 18, Appendix 2 |
| Model batch certificate of a pharmaceutical product | Ref. 18, Appendix 3 |
| Provisions for team members participating in WHO missions to assess acceptability, in principle, of vaccines for purchase by UN Agencies | Ref. 7, Annex 1 |
| Model certificate for the release of vaccines acquired by United Nations Agencies (revised 1988) | Ref. 7, Annex 2 |
| Model certificate of approval of a biological product | Ref. 15, Appendix 1 |
| Model certificate for release of a lot or lots of a biological product | Ref. 15, Appendix 2 |
| Summary protocol for the routine batch release of virus vaccines and model certificate for the release of virus vaccine by National Control Authorities | WHO TRS 872, 1998 Annex 4 |
| USA: Application to market a new drug, biologic or an antibiotic drug for human use (and instructions) | USA. Form FDA 356h (see FDA web site) |
| Canada: Drug submission application for: human, veterinary or disinfectant drugs (and instructions) | Canada: Form HPB/DGPS 3011 (5-99) (see TPP web site) |
| Canada: Quality information summary - biologicals. Forms part 1-4 | Canada: Forms on the TPP web site |

Web sites

WHO (World Health Organization): www.who.int

Documents are posted at: www.who.int/vaccines-documents

PAHO (Pan American Health Organization): www.paho.org

FDA, CBER (USA): www.fda.gov/cber

Guidelines: www.fda.gov/cber/guidelines.htm

Downloadable documents: www.fda.gov/cber/cberftp.html

FDA: Code of Federal Regulations (CFR): www.access.gpo.gov/nara/cfr

HPB, TPP (Canada): www.hc-sc.gc.ca/hpb-dgps/therapeut/

(search the site for downloadable publications, policies, forms, etc)

EMA (European Medicines Evaluation Agency, EU):

www.eudra.org/emea.html

TGA (Australia): www.health.gov.au/tga/tgapubs (publications)

ICH: International conference on harmonization

(Topics and Guidelines) www.pharmweb.net/pwmirror/pw9/ifpma/ich5.html

Annex 1:

Model certificate for the release of vaccines acquired by United Nations agencies (revised 1988)

(To be completed by the national control authority of the country where the vaccines have been manufactured, and to be sent by the vaccine manufacturer to UNICEF.)

The following lots of¹ vaccine produced by² in³, whose numbers appear on the labels of the final containers, meet all national requirements.⁴ Part A⁵ of Requirements for Biological Substances No.⁶ (Requirements for¹, published in 19..... [if applicable, revised 19....., addendum 19.....]) and Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, published in 1959; revised 19.....).⁷

Lot No.	Expiry date	Lot No.	Expiry date
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As a minimum, this certificate is based on examination of the manufacturing protocol.

The Director of the National Control Laboratory (or Authority as appropriate)⁸

Name (typed)

Signature

Date

¹ Indicate type of vaccine (measles, oral poliomyelitis, tetanus, diphtheria-tetanus, diphtheria-pertussis-tetanus, BCG).

² Name of manufacturer.

³ Country.

⁴ If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the national control authority.

⁵ With the exception of the provisions on shipping, which the national control authority may not be in a position to control.

⁶ Indicate the reference number of the relevant Requirements for Biological Substances published by WHO.

⁷ These requirements were revised in 1965; a further revision is in preparation for consideration by the WHO Expert Committee on Biological Standardization in 1989.

⁸ Or his or her representative.