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NATIONAL CONTROL AUTHORITY

*GUIDELINES FOR ASSESSMENT OF
VACCINE QUALITY IN
NON-PRODUCING COUNTRIES*



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GUIDELINES FOR ASSESSMENT OF VACCINE QUALITY
IN NON-PRODUCING COUNTRIES

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immunization. The NCA should also ensure that a written procedure exists for speedy and efficient recall of a batch of a particular vaccine product, should it be found to be compromised in any way.

Table 1 indicates how the critical functions of the national control authorities should be allocated in countries depending on the source of vaccines used for national immunization programmes. The present guidelines deal with countries in the last two categories: those which procure vaccines from independent sources and those who receive vaccines through UNICEF.

Table 1. Critical national control functions, depending on vaccine source

| Function | Production | Production Sharing | Independent Tender | Procured through UNICEF |
|----------------------------|------------|--------------------|--------------------|-------------------------|
| Licensing | | | | |
| Clinical evaluation | | access | access | access |
| Lot release | | | | |
| Lot testing | | | access | access |
| Inspections | | | | |
| Postmarketing surveillance | | | | |

Shaded box means function is essential, "access" means that it can be assured by another entity

2. Objectives

The purpose of these guidelines is to provide a tool that:

- (i) can be used by countries not producing vaccines in the assessment of quality of vaccines procured for use in national immunization programmes;
- (ii) can be used by consultants assisting countries in the assessment of their vaccine demand, supply and financing as part of the development of National Vaccine Supply Plans. The specific indicators to be used during assessment of the national control functions are shown in Table 2.

3. National Control Authority (NCA)

First and foremost, it is important to verify if the country being assessed has a National Control Authority established under appropriate legislation. The law should spell out the *modus operandi* of the authority. In assessing the capacity of national authorities to carry out evaluation and licensing of vaccine products, it is important to look closely at the following:

3.1 Terms of reference

The terms of the NCA should be established by the relevant statutes. The authority should have a mandate to:

- (a) define criteria on which license applications are to be assessed;
- (b) issue, vary and revoke licenses for vaccines and other biological products on grounds of safety, potency and efficacy;
- (c) secure the subsequent safe and effective use of each vaccine product by controlling, through the terms of the license, the content of all labelling (including package inserts, associated prescribing information and advertising) and the channels through which the product may legitimately be supplied.

3.2 Personnel

An NCA may have as few as one or two professionals plus support staff. The professional staff must have a thorough understanding of and practical experience in the different facets of the work. Generally the same skills as for evaluation of general pharmaceutical product applications will be needed.

The responsible officer is accountable for the professional validation and assessment of license applications and for the administrative aspects of licensing, determining priorities and developing timetables for implementation of controls.

3.3 Technical evaluation procedures

The NCA should have clearly defined procedures on how it will proceed with the actual evaluation process. Since the quality of vaccines is subject to stringent international standards, it is recommended that the NCA use the WHO published guidelines for vaccine production as a point of departure. The NCA can obtain information on products manufactured in other countries through application of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (2).

Under the Certification Scheme the manufacturer is required to furnish to the

importer (through his NCA) information that stipulates that:

- (a) the vaccine is registered by the National Control Authority of the manufacturer's country;
- (b) the premises under which it is manufactured meet Good Manufacturing Practice standards (as defined by WHO) and are subject to regular inspection by the NCA; evidence of such recent inspection should be provided in the form of a GMP certificate in the format prescribed by WHO (Appendix A).

The NCA should request this information and process it speedily.

4. *Product Specifications*

Operating within the framework of a National Drugs Policy, and in consultation with the NCA, the immunization programme should draw up a list of recommended vaccines to be used in its immunization activities.

This process can be simplified by referring to the WHO global EPI recommendations on recommended vaccines; reference to the products on the National Essential Drugs and Vaccines List; and local epidemiologic disease data that may demand inclusion of a particular vaccine in certain settings. For example, Japanese encephalitis B and yellow fever vaccines might be included in some countries.

5. *Procurement*

A significant step in the assurance of quality of externally procured vaccines is achieved if the importing country uses vaccine sources licensed and released by competent and independent national licensing and control authorities. UNICEF, with technical advice from WHO, has built considerable experience in this field; countries meeting eligibility criteria may procure vaccines through UNICEF. Member States may choose to use the UNICEF procurement mechanisms if they meet eligibility criteria, or procure from the same sources.

6. *Monitoring of Vaccine Receipt and Distribution*

6.1. *Stock control*

The staff of the immunization programme should develop systematic stock control procedures that allow vaccines to be used on a FIRST-TO-EXPIRE-FIRST-OUT basis. Strict adherence to this system should be enforced at all levels of the distribution network, through appropriate training of supervisory personnel and store-keepers.

The monitoring of vaccines by expiry date and batch/lot number throughout the distribution system is useful in event of a manufacturer's recall for reasons of potency, toxicity, adverse event or contamination.

6.2. Assessment of vaccine quality during breaks in the cold chain

It is almost impossible to fool-proof breakdown in the cold chain system at all times. Accidents can occur, exposing vaccine to extremes of temperature not recommended by the manufacturer. The assistance of a control laboratory may be requested in the case of cold chain breakdown, if the quantity of vaccine involved is sufficiently large (Appendices B and C). Cold chain staff should be able to rapidly detect and respond to cold chain failures. There should be written instructions on how to proceed.

6.3. Points of intervention for assurance of quality in the cold chain

- At the port of entry
- On unpacking vaccine
- On storage at the central store
- On reception at the health facility
- On storage at the health facility

The most important initial point for comprehensive quality assurance intervention is after the vaccine arrives at the central store. The following questions should be answered:

- i) Is the vaccine in the shipment the correct one ordered?
- ii) Is the vaccine labelled and packaged according to the appropriate guidelines?
- iii) Is the vaccine temperature within labelled guidelines?
- iv) Are there any 3M vaccine monitors and Freeze-Watch indicators in the shipment if included in the procurement specifications?
- v) Can it be assured that the vaccine was not exposed to high temperatures (above 8°C) for prolonged periods before it arrived?
- vi) Were aluminum adsorbed (tetanus toxoid, DTP, hepatitis B) vaccines protected against freezing? These vaccines are rapidly damaged by a single freezing event.
- vii) Was the shipment transported without delay anywhere on its way to the central store?

During storage further quality assurance interventions should be planned on the basis of answering the following questions:

- i) Has the vaccine storage temperature stayed between 2-8°C?
- ii) Has the vaccine been protected from exposure to high temperatures during storage?
- iii) Can it be assured that aluminum-adsorbed vaccines have never been frozen as

- per recording thermometers or Freeze-Watch monitors?
- iv) Is there sufficient shelf-life remaining, as indicated by the expiry date, to allow for distribution time?
 - v) Are the vaccine labels still on the vials?
 - vi) Is the vaccine free from visible signs of contamination?
 - vii) Is the vaccine still fit for intended use?

If the answer to any of these questions is no, intervention must proceed.

7. *Development of Procedures for Destruction of Vaccines*

The NCA should have written protocols for destruction of and accountability of doses of vaccine judged to be unfit for use after an assessment following cold chain failure, suspected damage during transportation or upon expiry. Adequate records should be maintained.

8. *The Inspectorate*

The NCA should have a functional inspectorate section for regular inspection of vaccines at the port of entry into the country. Spot checks in the cold chain would assist in strengthening of the quality monitoring system.

9. *Postmarketing Surveillance*

Postmarketing surveillance of vaccines serves to monitor and assess safety and efficacy during widespread use of the products. To date this aspect has received little attention in immunization programmes around the world.

Adverse events, though rare, occasionally follow immunization with vaccines. Some of these events are due to the intrinsic characteristics of the vaccines. Some can be traced to programme problems such as poor handling or administrative technique. Some occur coincidentally after immunization due to other causes, and some may be due to changes in vaccine strain. An example of this is the case of BCG lymphadenitis in Zimbabwe in the late 1980s (8); cases declined on reverting to the original supplier. Some serious events have been recorded as a result of mishandling of vaccines and poor administrative techniques. Indeed, in rapidly expanding programmes reactions due to programmatic causes may predominate (3). As many of these impact injection safety, thorough investigation, analysis and action is required.

The detection of serious adverse events following immunization is important to the success of a programme since the occurrence of such events can influence the community's acceptance of immunization. The system should be built on the concept of spontaneous reporting and should motivate reporters through feedback on the outcome of specific case investigations.

The responsibility for monitoring product safety and efficacy in the field rests with the NCA, but the immunization programme needs to participate actively in the process, being the best source of data. Thus, investigation of reports should be a collaborative effort.

Each NCA should develop its own system of postmarketing surveillance. The system adopted should be able to detect, register and analyze unusual clustering of serious adverse events or clinical syndromes (which could indicate a lack of efficacy) after immunization. Prompt reporting is crucial to trigger timely responses from the NCA and manufacturers. The NCA needs to define the type of adverse events related to immunization that require monitoring and prepare protocols for response to these events and the action to be taken. The basic principles of field investigations of cases of infectious diseases are followed.

Postmarketing surveillance requires mobilization of personnel in different parts of the health care system. Collaboration with other sectors of the Ministry of Health (Disease Surveillance; Health Information System) is mandatory if the adverse events system is to be effective.

Prior to taking action in relation to reported specific cases, it is important to:

- examine the clinical data to confirm the diagnoses and outcome;
- search whether additional similar vaccine-associated cases can be detected;
- examine which specific vaccine errors in handling or administration techniques could be implicated by the reports; and
- suggest the need for further data collection, such as whether similar problems are being observed in children not recently vaccinated, or if there is a need for laboratory data.

Many records may have to be accumulated before conclusions regarding causation of event by the vaccine in question can be drawn.

10. Conclusions

National Control Authorities in countries procuring vaccines are responsible for the review of data and for making decisions on the safety and efficacy of vaccines used in immunization programmes. Working in collaboration with the national immunization programme, the NCA assures that vaccine quality is maintained until the product reaches the end user. To achieve these goals each vaccine-importing country needs to first establish a National Control Authority whose scope depends on its particular needs. That NCA must then address a number of priority activities:

- i) Adoption of licensing requirements and a licensing system for vaccines.
- ii) Development of a list of vaccines (specifications) which takes into account epidemiological need and demonstrated product efficacy. This should be undertaken in reference to national documents such as the Essential Drugs List and the WHO/EPI recommendations.
- iii) Provision of the necessary elements to the NCA for assurance of the quality of vaccines during procurement.
- iv) Recognition of the conditions affecting vaccine quality (the potency of vaccines declines rapidly with exposure to ultraviolet light, extreme temperatures and to disinfectants), and taking the necessary preventive action through control of the cold chain to avoid compromise of quality.
- v) Assuring access to a testing laboratory should the need to use this facility arise (See Appendices B and C).
- vi) Establishment of a system for postmarketing surveillance to monitor and assess safety during widespread use, and in particular to investigate reported cases of post-immunization problems.
- vii) Establishment of a system that takes action to withdraw questionable vaccines from use when the need arises.
- viii). Establishment of collaborative mechanisms between the NCA and the national immunization programme for achievement of the above activities.

All countries regardless of their vaccine source need to assume responsibility for product licensing and postmarketing aspects (see Table 1). In addition all countries need to be able to access laboratory testing facilities and clinical data on efficacy to assure the quality of vaccines used nationally. Countries that are procuring independently (not through UNICEF) by tender need to set up mechanisms for lot release of vaccines.

REFERENCES

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Table 2.

**Indicators for monitoring of vaccine quality
in nonproducing countries**

| Parameter/Objective | Indicators | Status |
|----------------------------------|---|--------|
| National Control Authority (NCA) | <p>NCA established by law</p> <p>Written procedures on requirements for vaccine registration</p> <p>Availability of adequate resources for the efficient functioning of the NCA</p> <p>Adequate staff and technical support from national experts</p> <p>Effective and meaningful communication with other NCAs</p> <p>Procedures for recall of vaccines from the field</p> <p>Procedures for destruction of non-useable vaccines</p> <p>Evidence of liaison with WHO when quality problems arise</p> | |
| Vaccine product specifications | <p>List of registered EPI and other vaccines</p> <p>Evidence of the use of a simple, accessible and manageable system for evaluation of clinical data</p> <p>Evidence of the link between EPI epidemiological data and the national health information system</p> <p>Updates of specifications as information on newer and improved vaccines becomes available</p> | |

| Parameter/Objective | Indicators | Status |
|----------------------------------|--|--------|
| Procurement | <p>Written procedures for vaccine procurement</p> <p>Rules for restricted or open tender procedures</p> <p>Up to date information on sources and prices of vaccines</p> <p>Procedures for handling of vaccine donations</p> | |
| Preshipment assurance of quality | <p>Evidence of product registration in producing country</p> <p>Summary of manufacturers' protocols defining manufacturing process</p> <p>Evaluation of manufacturers' procedures and protocols</p> <p>Batch/lot Quality Control Certificates from NCA that vaccine meets WHO requirements</p> <p>Evaluation of shelf-life specifications and stability</p> <p>Evidence of GMP compliance by the manufacturers</p> | |
| Distribution/Use | <p>Written procedures for quality monitoring in the cold chain</p> <p>Written procedures on how to handle cold chain failures</p> | |

| Parameter/Objective | Indicators | Status |
|-----------------------------|---|--------|
| Inspectorate | <p>Availability of vaccine production inspectors to the NCA</p> <p>Spot checks on vaccine license holders to ensure compliance with the operating terms of licenses</p> | |
| National Control Laboratory | Access to a laboratory in case testing is necessary | |
| Postmarketing surveillance | <p>Establishment of a surveillance systems for adverse reactions to vaccines post-immunization</p> <p>Inclusion of case investigations in this system</p> <p>Monitoring by the system of -BCG lymphadenitis -injection site abscesses -severe local reactions</p> <p>Availability of reporting forms to health facilities</p> <p>Existence of written guidelines on responses and action to confirmed adverse events following immunizations</p> | |

General instructions

Please refer to the guidelines for further information on how to complete this form and on the implementation of the Scheme. Forms should be completed using a typewriter to ensure legibility. A cross should be placed in boxes as appropriate to indicate which options apply. Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

- 1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
- 2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
- 3 A qualitative listing of other ingredients contained in the dosage form should be appended.
- 4 When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is entered on the product licence.
- 5 Specify whether the person responsible for placing the product on the market:
 - (a) manufactures the active ingredients and the finished dosage form;
 - (b) manufactures the finished dosage form;
 - (c) packages and/or labels a finished dosage form manufactured by an independent company; or
 - (d) is involved in none of the above.
- 6 Indicate, when applicable, if the licence is provisional, pending technical review.
- 7 This refers to the document, prepared by certain national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
- 8 In this circumstance, permission for issuance of the certificate is required from the product licence holder.
- 9 Please indicate the reason the applicant has provided for not requesting registration:
 - (a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
 - (b) the product has been reformulated with a view to improving its stability under tropical conditions;
 - (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
 - (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
 - (e) any other reason, please specify.
- 10 The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those adopted by the Twenty-eighth World Health Assembly in its resolution WHA 28.65 (see WHO Official Records, No. 226, 1975, Annex 12, Part 1). Proposals for the amendment of these requirements are included in the Thirty-second Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 822, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).
- 11 This section is to be completed when the product licence holder or applicant conforms to status (c) or (d) as described in note 5 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and to indicate the extent and nature of any controls exercised over each of these parties.

APPENDIX B

The National Control Laboratory (NCL)

National Drugs Control Laboratories are fairly common in most Member States. Although these laboratories can analyze general pharmaceutical products, the capability to handle biological products is rare. Therefore, the role of the NCL in the assurance of the quality of vaccines in nonproducing countries is limited. Indeed the establishment of facilities dedicated to vaccine testing cannot be justified in most countries, until they have reached a level of development where they are moving towards local production (9).

Where local testing facilities have been developed, the laboratory may wish to devote its resources to critical areas during cold chain failures such verification of identity and potency testing for oral polio vaccine, which is particularly heat-labile.

Appendix C shows the number of doses involved during cold chain failure justifying a potency test and the number of doses needed for the test as recommended by WHO. Vaccine potency testing is a lengthy and costly procedure and therefore is justified only rarely.

In any case, facilities for potency testing will rarely be available in most National Control Laboratories of developing countries, and some collaborative arrangements may have to be made with external laboratories.

Whenever laboratories exist in the same geographical region, it may be useful to assess their ability to network and the move towards harmonization of vaccine test requirements and protocols. Exchange of information on vaccine testing to ensure that countries are using similar protocols should also be encouraged.

APPENDIX C

NUMBER OF DOSES OF VACCINE JUSTIFYING POTENCY TEST

| Vaccine | Number of doses involved | Number of doses for test | Lead time for results |
|------------------------------|--|--------------------------|-----------------------|
| OPV | 20,000 | 20 | 1 month |
| Measles (freeze-dried) | 20,000 | 20 | 1 month |
| Yellow Fever (freeze-dried) | 20,000 | 20 | 1 month |
| BCG (freeze-dried) | 20,000 | 20 | 3 months |
| Diphtheria-pertussis-tetanus | 200,000 | 20 | 3 months |
| Tetanus toxoid | 50,000 | 20 | 3 months |
| Hepatitis-B | | | |
| Poliomyelitis (inactivated) | Until potency test is established Do not retest | | |

Source: WHO/EPI/MLM/91.5