
Adverse Event

Japanese encephalitis vaccines (WHO position paper)

[WER 2006, vol. 81, 34/35, pp 331-340](#)
page 332

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

BCG

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 29

An ADT (accelerated degradation test) should be conducted on each lot of BCG vaccine. The number of culturable particles in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C

BCG vaccine (WHO position paper)

[WER 2004, vol. 79, 4, pp 27-38](#)
page 28

The BCG vaccine should be manufactured according to the current recommendations published in the report of the WHO Expert Committee on Biological Standardization.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 22

An ADT should be conducted on each lot of BCG vaccine. The number of CPs (culturable particles) in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C.

General

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 44

The WHO thermostability requirements for mumps and rubella vaccines are similar to those for measles vaccine. At least three containers of monovalent or MMR vaccine are tested by incubation at 37C for seven days, at the end of which each monovalent vaccine or individual vaccine component is titrated in PFUs or CCID50 after selective neutralization, as necessary, of the other components. The geometric mean infectious virus titre must equal or exceed the required minimum number of infective units per human dose (3 log₁₀), and the geometric mean virus titre must not have decreased by more than 1 log₁₀ infective units during incubation.

Statement on vaccine quality (GPV Policy Statement)

[WHO/VSQ/GEN/96.02 Rev. 1](#)
page 1

The Forty-fifth World Health Assembly in 1992 resolved that all vaccines used within national immunization programmes meet WHO requirements (WHA45.17), thus reinforcing these guidelines as a credible goal for all countries.

While some Member States may apply testing procedures which differ in detail from those defined by WHO, nevertheless, they should ensure by national regulation that the products are at least as safe and efficacious as those prepared in accordance with WHO requirements.

Statement on vaccine quality (GPV Policy Statement)

[WHO/VSQ/GEN/96.02 Rev. 1](#)
page 1

Confidence that vaccines are consistently safe and efficacious depends not only on the characteristics of the vaccine product and adherence to standards of Good Manufacturing Practice in its production, but requires continual oversight by an independent and competent National Control Authority (NCA).

Statement on vaccine quality (GPV Policy Statement)

[WHO/VSQ/GEN/96.02 Rev. 1](#)
page 1

WHO responds to requests from the United Nations (UN) or its agencies for an opinion as to the acceptability of a specified vaccine from a specific producer for use in developing country immunization programmes. The responsibility for this process of prequalifying suppliers who will respond to offers to purchase of the UN or its agencies rests at WHO headquarters. The determination is made on a technical basis, after applying a procedure which involves an examination of manufacturing processes, product characteristics and the licensing, control, release, and post-licensing activities of the NCA (National Control Authority.) This procedure has been reviewed by the WHO Expert Committee on Biological Standardization. The list of prequalified suppliers is public. WHO recommends to UN agencies procuring vaccines only those vaccines which have been assessed using the above procedure.

Statement on vaccine quality (GPV Policy Statement)

Many manufacturers produce vaccines which are not purchased by UN agencies and thus may neither require nor seek WHO assessment for prequalification. Countries desiring to purchase these products may seek a statement from WHO as to whether or not these vaccines are of known good quality.

[WHO/VSQ/GEN/96.02 Rev.](#)

[1](#)

page 1

Statement on vaccine quality (GPV Policy Statement)

WHO considers a vaccine to be of known good quality provided:
the NCA (National Control Authority) independently controls the quality of the vaccine in accordance with the six specified functions defined by WHO* and
there are no unresolved confirmed reports of quality-related problems.

[WHO/VSQ/GEN/96.02 Rev.](#)

[1](#)

page 1

* Licensing in accordance with written requirements, review of clinical data, lot release, laboratory testing, inspections for compliance with Good Manufacturing Practice, post-marketing surveillance for field performance, World Health Organization, Technical Report Series 822 (1992).

Thermostability of vaccines

WHO requirement for heat stability of freeze-dried measles vaccine have made a considerable impact on the quality of measles vaccines on the market. This requirement uses two indices of stability:

- (1) Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
- (2) If, during incubation, the virus titre has been decreased, then it shall have done so by not more than 1 log₁₀.

[WHO/GPV/98.07](#)

page 16

Thermostability of vaccines

WHO requirement for yellow fever vaccine stability stipulates that the vaccine should retain 1000 mouse LD₅₀ or the equivalent in plaque-forming units (PFUs) per human dose, and that the mean titre loss should be less than 1 log₁₀ after two weeks incubation at 37C.

[WHO/GPV/98.07](#)

page 20

Thermostability of vaccines

An ADT (accelerated degradation test) should be conducted on each lot of BCG vaccine. The number of culturable particles in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C

[WHO/GPV/98.07](#)

page 29

Thermostability of vaccines

[WHO/GPV/98.07](#)

page 37

WHO requirements for thermostability for OPV:

Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national control authorities are to specify the minimum virus titres per human dose

Thermostability of vaccines

[WHO/GPV/98.07](#)

page 42

Poliomyelitis vaccines were remarkably stable within the pH range 6.5-7.2. A vaccine can be maintained in this pH range by preventing the loss of carbon dioxide from a bicarbonate-containing vaccine, keeping the air space above the vaccine to a minimum, and packing the vaccine in tightly stoppered containers.

Global Advisory Committee on Vaccine Safety, 12 December 2005

[WER 2006, vol. 81, 2, pp 15-19](#)

page 16

WHO is promoting vaccination strategies that economize on the use of antigens to address the current global shortage of influenza vaccines for epidemics and pandemics. That would entail development and licensing of novel antigen-sparing vaccine formulations.

The GACVS agreed to act as a resource for WHO if such a situation were to arise. The Committee made the following recommendations: develop pharmacovigilance guidelines to enable rapid assessment of pandemic influenza vaccines; promote the extension of such guidelines to evaluate seasonal influenza vaccines; develop an authoritative review of the safety and efficacy of inactivated influenza vaccines with adjuvants. It would be assured that regulators from developing countries are included in WHO meetings to promote regulatory collaboration on pandemic influenza vaccine issues and that lessons from the past, such as those from swine influenza vaccine, are taken into account.

Vaccine donations (GPV Policy Statement)

[WHO/VSQ/97.05](#)

page 2

WHO recommends that all countries, including those which receive all their vaccines from UNICEF, exercise at least two essential national control functions: a published set of requirements for licensing, and surveillance of vaccine field performance (monitoring of adverse events following immunization).

Page 4: There is a need for a focal point to check (donated) vaccines upon receipt and the ability to refuse vaccine donations not meeting the criteria. This implies a need for criteria, such as a published set of requirements for licensing, and their application. There is also a need for a system to detect and investigate complaints from the field, essentially the second critical control function, surveillance of vaccine field performance.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)
page 2

Responsible staff must ensure that all vaccines, including those received from UN sources, are licensed for use in their country. They should also ensure that all adverse events following immunization (AEFI) are monitored by an effective field performance surveillance system.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)
page 2

In all cases the lot release certificate from the NRA of the country of origin should be a condition for acceptance of the vaccine and for its subsequent distribution. Note that the manufacturer's own internal lot release cannot be considered as equivalent to the NRA lot release certificate for the purpose of releasing vaccines.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)
page 2

The NRA in the receiving country should undertake lot release procedures for all vaccines that are obtained from non-UN sources, including all vaccines produced and used within the receiving country.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 7

WHO recommends that the manufacturers quality tests be reviewed with possible complementary testing by national regulatory authorities before release of the product for use.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 12

WHO has identified six essential control functions to be undertaken by an effective vaccine regulatory system (National Regulatory Authority or National Control Authority). These are:

- A published set of clear requirements for licensing (of products and manufacturers)
- Surveillance of vaccine field performance (safety and efficacy)
- System of lot release
- Use of laboratory when needed
- Regular inspections of manufacturers for GMP compliance
- Evaluation of clinical performance through authorized clinical trials

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 9

Appendix 18_3 illustrates the variation in the functions of DRAs (Drug Regulatory Authority) to regulate vaccines in countries using different mechanisms to obtain their vaccines. As WHO has set in place procedures to ensure that appropriate regulatory functions are being performed for products which have been found acceptable for purchase by United Nations agencies (WHO/VSQ/97.06), countries receiving vaccines only through United Nations agency purchase (such as WHO or UNICEF), have a lesser responsibility in terms of the essential control functions. For countries sourcing vaccines through production and direct procurement, greater responsibility for ensuring vaccine quality is needed:

If the country is producing vaccines, all six functions should be performed.

For countries which are importing vaccines, fewer functions need be ensured within the authority of the importing country, although it should ensure that the appropriate regulatory activities are being carried out in the country of manufacture.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 9

In assessing applications for marketing authorization (registration) of new products, the DRA (Drug Regulatory Authority) has three options:

- a) to make its own assessment of the documentation submitted regarding the quality, safety, efficacy and product information of the product based on the file submitted by the applicant. This should always be done for products manufactured in the country.
- b) to use assessment protocols from DRAs in other countries as a basis for making its own decision about applications.
- c) to rely on decisions made by DRAs in other countries.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 13

It is recommended that the vaccine regulatory system use the published WHO guidelines on vaccine production developed by the Expert Committee on Biological Standardization and published in the WHO Technical Report Series, as a point of departure.

In the areas of authorizing products for marketing, GMP inspections, and clinical trials, guidelines already promulgated for pharmaceuticals regulation can be used

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 15

Lot release should be based, at minimum, on the review of Summary Lot Protocols which describe the production process in detail. WHO has provided, in each of the guidelines for production of the individual vaccines, model Summary Lot Protocols which can be used.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 15

Post-marketing surveillance by a national regulatory authority encompasses many activities which include:

- 1) The periodic inspections performed to evaluate compliance of manufacturers with GMP and conformance with approved manufacturing processes.
- 2) The continual monitoring of the quality of vaccines through lot release programs and ad hoc assessment of samples collected in the field (less important when lot release is rigorously performed).
- 3) Review and evaluation of adverse reactions to be reported by health care providers.
- 4) Monitoring for effectiveness and efficacy of vaccine preventable diseases.
- 5) Some agencies may include evaluation of vaccine uptake.

Global Advisory Committee on Vaccine Safety, 1011 June 2004

[WER 2004, vol. 79, 29, pp 269-272](#)
page 270

It was suggested that WHO might serve as a repository for safety reports and as a forum for dialogue and guidance for the technical and scientific standards for adjuvants and their safety, for setting standards for such work, and for defining principles governing regulatory issues in adjuvant safety. The GACVS might collate such information, which should be evaluated and made widely available.

BCG vaccine (WHO position paper)

[WER 2004, vol. 79, 4, pp 27-38](#)
page 28

The BCG vaccine should be manufactured according to the current recommendations published in the report of the WHO Expert Committee on Biological Standardization.

Yellow fever vaccine (WHO position paper)

[WER 2003, vol. 78, 40, pp 349-359](#)
page 355

According to current WHO requirements, a YF (yellow fever) vaccine that has been held at 37 C for 14 days must (i) maintain the minimal potency of >1000 MLD50 per dose and (ii) show a mean loss of titre <1 log 10 MLD50. These requirements necessitate the addition of stabilizers such as sorbitol and gelatin.

Creating national and regional frameworks to support HIV vaccine development in developing countries (Report from a WHO-UNAIDS consultation)

[WHO/IVB/05.17](#)

page 18

WHO's goal is to ensure that 100% of vaccines used in immunization programmes are assured quality vaccines. This means that a country's NRA (national regulatory authority) is independent from vaccine manufacturers, the NRA is fully functional, and that there are no unresolved reported problems with the vaccine.

WHO's Expert Committee on Biological Standards sets international standards for quality, efficacy, and safety. Different groups within (Immunization, Vaccines & Biologicals/Access to Technologies) work together to build capacity of NRAs, and prequalify vaccines for UN agencies. These programmes strengthen and monitor the six regulatory functions required of a functional NRA:

- _a published set of requirements for licensing
- _surveillance data for vaccine field performance
- _a system for lot release
- _use of laboratory when needed
- _regular inspections for GMP
- _an evaluation of clinical performance.

Creating national and regional frameworks to support HIV vaccine development in developing countries (Report from a WHO-UNAIDS consultation)

[WHO/IVB/05.17](#)

page 19

Recent changes in the European regulations established that vaccines produced in Europe for exclusive use outside of Europe will not be licensed by EMEA. As a result of collaboration between EMEA and WHO, article 58 in the new regulation and a detailed procedure have been defined by which EMEA will issue scientific opinion for vaccines used exclusively outside of Europe and considered eligible by WHO. The scientific opinion is intended to mimic the review process for licensing, but the outcome will not be a marketing authorization.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 1

In giving advice to UN agencies on the quality of candidate vaccines or on the continuing quality of vaccines already being purchased, WHO follows a procedure, detailed in document WHO/VSQ/97.06, for evaluating the acceptability in principle of vaccines for purchase. It consists of the following steps:

- 1) Any vaccine producer wishing to supply vaccine to UN purchasing agencies must submit a product summary file to WHO for detailed review.
- 2) In order to verify the consistency of final product characteristics, five consecutive vaccine lots must be independently tested by laboratories contracted by WHO.
- 3) The NRA of the producing country must be assessed by WHO in order to ensure that it is capable of effectively overseeing the quality of vaccines produced in that country.
- 4) Manufacturing facilities must be audited by a WHO team whose members have expertise in the relevant procedures, accompanied by representatives of the local NRA.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)
page 2

The six critical regulatory functions that must be performed by an NRA to ensure the quality of the vaccines they regulate are (as follows):

- Published set of requirements for licensing
- Surveillance of vaccine performance in the field (postmarketing surveillance)
- System of lot release
- Use of laboratory when needed
- Regular inspections for good manufacturing practices
- Evaluation of clinical performance

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)
page 2

Any producing country applying to supply vaccines to UN agencies is automatically required to have an NRA assessment as part of the prequalification process.

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)
page 1

All countries need some sort of NCA, but the governments of countries in which vaccine production takes place need to exercise six critical control functions, and they need to exercise them in a competent and independent manner, backed up with enforcement power. These six functions are:

- A published set of requirements for licensing
- Surveillance of vaccine field performance
- System of lot release
- Use of laboratory when needed
- Regular inspections for Good Manufacturing Practice (GMP) compliance
- Evaluation of clinical performance

Which of these critical control functions is needed in a country depends on vaccine source, as shown (Appendix 12_1.)

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)
page 2

WHO policy is that no technical nor financial support to vaccine production will be provided to facilities unless they have a functional NCA and have developed a strategic plan to achieve viability.

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)

page 4

For some countries, whose local production facility is in the low probability viability category, the first step should be the establishment of an independent and competent National Control Authority, as defined above.

For facilities which are potentially viable, the next step is a viability study to understand where they are, where they want to be, and how to get there. The outcome of such a study will be a strategic plan.

For those facilities which are already viable, and which have already developed a strategic plan, they should specifically address the question of access to new technologies. There are five ways this can be approached:

- Developing strong research and development capacity
- Bulk filling arrangements
- Licensing technology
- Negotiating partnerships for specific products
- Entering into joint venture agreements with a research-based manufacturer

Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation

[WHO/IVB/05.18](#)

page 30

For countries purchasing their own vaccines, the documents and conditions to ensure the quality of vaccine and shipping conditions should be included in the tender specifications. These include: the batch release certificates issued by the NRA in the country of manufacture; the list of countries where the vaccine is licensed; the product file including safety and efficacy data and clinical studies. Vaccine vial monitors (VVMs), cold chain monitor card, packaging and shipping conditions may be considered in this regard by the countries. Technical documents should be reviewed by an expert committee to ensure the quality of the vaccine.

Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation

[WHO/IVB/05.18](#)

page 30

All countries should have an NRA capable of performing at least two functions: licensing and postmarketing surveillance.

Ideally the NRAs need to fulfil six critical control functions, particularly in vaccine-producing countries, and they need to exercise them in a competent and independent manner, backed up with enforcement power.

These six functions are:

- 1) a published set of requirements for licensing,
- 2) surveillance of vaccine field performance,
- 3) system of lot release,
- 4) use of laboratory when needed,
- 5) regular inspections for GMP, and
- 6) evaluation of clinical performance.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 3

Once the four steps described above (31_1) have been satisfactorily completed, WHO must reach an agreement with the local NRA on activities to be performed in connection with vaccines intended for exportation. These activities include the following.

- A) The NRA should agree to release all lots for export on the basis of a review of lot summary protocols. The testing of selected lots for specific parameters is highly encouraged.
- B) The release certificate for UN agencies should follow the recommended model.
- c) The NRA should agree to communicate to WHO all reports of serious adverse events following immunization with vaccines supplied through UN agencies.
- d) The NRA should agree to inform WHO of critical deficiencies in good manufacturing practice, which are identified during its inspections.
- e) The NRA should agree to inform WHO of any recalls or licence withdrawals related to any vaccine supplied through UN agencies.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 3

Once the initial evaluation is completed, the quality of vaccines shipped to countries is monitored through rounds of random testing performed at six-monthly intervals. This is to ensure continuing compliance with WHO requirements and tender specifications. In addition, a full re-evaluation of all prequalified vaccines takes place every two years. This is known as the reassessment process and basically covers the same steps as the initial evaluation described above, as follows:

- 1) Submission by manufacturers of an updated product summary file.
- 2) Testing of vaccine samples.
- 3) Meeting with the appropriate NRA.
- 4) Site visit to the manufacturing facility.

For reassessments however, the waiving of site visits may be considered on a case-by-case basis if certain criteria are met and at least one WHO site visit to the manufacturer has taken place within the previous five years.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

To ensure quality, as well as reliability and availability, it is imperative to purchase only from suitable sources. If vaccines and suppliers are pre-qualified it will ensure that critical criteria are met and eliminate unsuitable bidders, and/or bids of inferior products.

Sources can be pre-qualified as follows:

Registration in country by National Control Authority (NCA): See Regulation and licensing of biological products, WHO Technical Report Series No 858, 1995

International competitive bidding (ICB) procedure: This should be used as a first step for pre-qualifying suppliers if appropriate or if requested by the government. The procedure is that an invitation to bid for pre-qualification is publicly advertised, and responses are reviewed for technical acceptability by the NCA. The NCA will review each vaccine bid on its merits and undertake an appropriate review of the vaccine and the producer.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

In addition to the usual commercial information requested for pre-qualification, the following conditions are critical in selecting vaccine suppliers to ensure that they meet NCA or WHO minimum requirements. The supplier must be a manufacturer (or importer of bulk product for filling, labelling and repackaging) and must provide the following documentation:

- Certificate of registration /licensing in country of origin
- Documentation on quality control (QC) and sampling procedures
- Copy of most recent GMP certification.
- Production and quality control summary protocols.
- Certificate of analysis from NCA in country of origin.
- Statement of licensing status in other countries.

For WHO pre-qualifying sources, see updated list available from WHO/GPV/VSQ1.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

The limited international bidding (LIB) documents should be prepared following standard procedures for drugs, including the minimum requirements for vaccines (NCA or WHO standards). See WHO standards, as published in the WHO Technical Report series.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 11

Pre-qualified sources should be reviewed regularly, with periodic re-confirmation from the NCA or WHO, alternatively issuing an ICB as a requisite to pre-qualification.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 22

An ADT should be conducted on each lot of BCG vaccine. The number of CPs (culturable particles) in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 31

Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national regulatory authorities are to specify the minimum virus titers per human dose

Mumps virus vaccines (WHO position paper)

[WER 2001, vol. 76, 45, pp 346-356](#)

page 352

WHO requirements do not specify the minimum amount of (mumps) vaccine virus that 1 human dose should contain. Rather, this is determined by the national regulatory authority of the country where the vaccine is produced.

Mumps virus vaccines (WHO position paper)

Due to its known low effectiveness, the Rubini-strain (mumps) vaccine should not be used in national immunization programmes. Persons previously immunized with the Rubini-strain vaccine should receive a dose of an effective mumps vaccine to ensure protection.

[WER 2001, vol. 76, 45, pp 346-356](#)
page 354

Temperature sensitivity of vaccines

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log₁₀ (162).

[WHO/IVB/06.10](#)
page 25

Temperature sensitivity of vaccines

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log₁₀.

[WHO/IVB/06.10](#)
page 29

Temperature sensitivity of vaccines

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log₁₀.

[WHO/IVB/06.10](#)
page 25

Temperature sensitivity of vaccines

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log₁₀.

[WHO/IVB/06.10](#)
page 29

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

Additional information on the safety of different mumps vaccine strains is available from country experiences with use of mumps vaccine in mass campaigns and routine settings. These data should be reviewed by the GACVS and the resulting conclusions included in the revision of the WHO mumps position paper.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

The WHO secretariat should make special efforts to collaborate with industry to increase global availability of MMR vaccines that contain strains of mumps vaccines with the best safety profile.

Tetanus vaccine (WHO position paper)

[WER 2006, vol. 81, 20, pp 198-208](#)
page 202

According to WHO requirements*, the potency of monovalent tetanus toxoid shall be no less than 40 IU (determined in guinea-pigs or in mice) per dose (0.5 ml), and at least 40 IU (determined in guinea-pigs) or 60 IU (determined in mice) per dose when tetanus toxoid is used in combination with diphtheria and whole-cell pertussis vaccines.

* Requirements for diphtheria, tetanus, pertussis and combined vaccines. WHO Technical Report Series, No. 800, 1990, Annex 2; Recommendations for diphtheria, tetanus, pertussis and combined vaccines (Amendments 2003). WHO Technical Report Series, No. 927, 2005, Annex 5.

State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)
page 89

A number of cell-culture based rabies vaccines are being developed in China and India on Vero cells, human diploid cells (HDC), or duck embryo cells. These vaccines however have not yet been prequalified by WHO and may require further assessment in terms of safety and efficacy before they can be traded internationally.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 3

Training should be a dynamic process, in respect to both, the training an employee receives during his or her career with a firm, and in terms of ensuring that training programmes and materials keep pace with job requirements and performance expectations.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)

page 5

World Health Organization, good manufacturing practices for pharmaceutical products*: main principles - Personnel

(T)here must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded as written descriptions.

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibility placed on any one individual should not be so extensive so as to present any risk to quality.

All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Good Manufacturing Practices for pharmaceutical products: main principles. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908. Annex 4).

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)

page 13

Training curricula should be written for operation, maintenance and laboratory personnel, supervisors, managers, and also for temporary employees and contractors.

New employees are also an important audience so that they understand the rationale for the strict method of operation within the vaccine manufacturing industry.

New employees are not truly competent to work in a regulated industry that makes critical products like vaccines until they have been trained and have demonstrated that they know and can perform what is required of them.

Employees whose activities take them into production areas or into control laboratories (including maintenance and cleaning staff), and other personnel whose activities could impact on the quality of the product should receive work-specific training at the time of joining the company and on a continuing basis. The work-specific area training should cover three aspects:

GMP training (GMP training should be provided to ensure that employees understand and follow the GMP requirements applicable to their jobs.)
on-the-job training - standard operating procedures (SOPs) and technical skills training. (The supervisor is responsible for this training, and it is based on the SOPs and the acquisition of technical skills needed for the job. It is particularly important at this stage to teach the trainee not only what he/she should do and how, but why it must be done in such a way and in no other.)
safety training.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 17

(For good manufacturing practice requirements,) supervisor training should be conducted to guarantee that supervisors be adequately trained in:

- the areas they are going to supervise;
- the SOPs used in their department;
- their responsibilities under GMP, especially their responsibility for training, for reviewing documents, and for reviewing safety procedures to avoid danger to their staff.

Managers and supervisors need to be trained in their responsibilities under GMPs and good laboratory practice (GLPs) for non-clinical studies. They should also be updated in GMP trends. The manager training programme should guarantee that new managers be trained and that existing managers remain familiar with their assigned functions.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 19

(For good manufacturing practice requirements) Trainers training

Typically, trainers (both those who teach to groups in classrooms, as well as those who work individually with people during structured on-the-job training) should have an understanding of how adults learn and in providing effective feedback to trainees.

On-the-job and SOP trainers should be recognized experts in the area or in the tasks that they perform. They should also understand the best ways to teach tasks and procedures.

Group trainers should have presentation skills to use various training media (e.g. slides, overheads, flipcharts), methods (e.g. discussions, games, case studies, lectures), and know how to respond to questions and difficult situations.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 19

For good manufacturing practice requirements) Ongoing training:

Ongoing training should include:

GMP: New guidelines, current GMP changes and their interpretation and biopharmaceutical industry trends, including short reviews of specific GMP topics that may be applicable to current work-related issues and challenges.

On-the-job training: Employees should be trained when a new SOP or method is issued, when a procedure or method is changed and requires users to perform differently, and when new equipment or instruments are to be used. If the performance according to a procedure or job task has degraded, the requirements should be reviewed and coaching given as needed to return the performance to the desired level.

Safety training: Periodic reinforcement is necessary for protecting staff from hazards. This training should also be implemented in case of changes or modifications of the safety regulations, changes or modifications of the technological process, work resources, raw materials, materials, new potential risks or other factors that could affect the workers safety and health.

Each company should determine the frequency for the ongoing training and the established frequency must guarantee that employees remain familiar with the specific tasks required by their job.

Remedial training:

Remedial training should be planned when specific deficiencies related to training are identified during the performance of a job or task, or during the investigation of a deviation or an out-of-specification result, accident or near-accident.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 22

For good manufacturing practice requirements) Job-change training:

Work-specific training (GMP, on-the-job and safety training) should be conducted for the employees new needs, taking into account the previous knowledge, skills and attitudes that they have developed.

Temporary employee and contractor training:

Temporary employees and contractors whose work takes them into production areas or quality control laboratories and those whose work can impact the quality of the product must be trained.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 51

(When implementing training to support good manufacturing practice (GMP)), for each training course, it is recommended that:

- minimum trainer requirements are established;
- each trainer attends a train-the-trainer course;
- the QC/QA unit analyse and approve the trainers; and
- the trainers qualification be documented.

During the design of the training programme, training records should also be designed. Quality assurance should audit training records periodically. It is advisable to keep the following training documents:

- training requirements
- employee-training records
- training attendance records.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 2

The assessment (prequalification) procedure established by WHO for vaccines is based on the following principles:

- reliance on the national regulatory authority (NRA) of the country of manufacture because it meets the published WHO NRA indicators (http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm);
- general understanding of the product and presentations offered, production process, quality control (QC) methods and relevance for the target population of available clinical data;
- assurance of production consistency through application of GMP specifications;
- random check-testing of vaccines by independent WHO-contracted laboratories to monitor compliance with tender specifications on a continuing basis;
- monitoring complaints from the field and assisting in the investigation of adverse events following immunization (AEFI).

Since reliance upon effective regulatory oversight by the NRA of the country of manufacture plays a critical role in the system (procedure for assessing acceptability of vaccines for purchase by United Nations agencies), manufacturers shall: (a) inform their NRA (national regulatory authority) of their application to WHO for the vaccine prequalification by sending a copy to the NRA of the application letter sent to WHO; (b) request the NRA to participate/collaborate in the process; and provide the NRA with the necessary authorization to discuss the relevant files with WHO representatives.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 2

As vaccines purchased by UN agencies need to meet WHO recommendations or guidelines (whichever is available), novel vaccines for which such guidelines are not available cannot be evaluated. In cases where a vaccine is made available for a disease of public health importance, the development of such guidelines will be prioritized by WHO and, as soon as a draft document becomes available, this can be used for evaluation for prequalification purposes.

WHO will define, in consultation with UN purchasing agencies and other relevant partners, which vaccines are priority for prequalification and will make this information publicly available. This exercise is required in order to focus the use of resources. The priorities will be redefined at regular intervals to ensure that efforts are put into evaluating those vaccines that are of highest public health importance and most needed in developing countries

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 3

The following are the conditions for acceptance of applications:

The candidate vaccine falls under the category of priority products as defined by UN purchasing agencies and other partners e.g. the Global Alliance for Vaccines and Immunization (GAVI).

The NRA of the producing country is found to meet all the critical indicators defined for prequalification purposes following a WHO independent assessment (http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm).

Furthermore, during the prequalification process, the WHO team will establish an agreement with the NRA for appropriate lot release of all vaccines to be supplied through UN agencies, and sharing of information in case of serious GMP deviations, AEFIs, or withdrawals due to quality issues.

If the vaccine finishing (packaging; or filling/packaging; or formulation/filling/packaging) and distribution are performed in a country different from that of bulk manufacturing, the NRA of the country where the finished product is manufactured must comply with the above-mentioned requirements and commit to perform all post-marketing regulatory functions.

A marketing authorization (MA) has been granted by the relevant NRA and the post-marketing regulatory oversight is conducted by the NRA of the country of manufacture or that of the country of finishing and distribution. Alternatively, if it is intended that the European Medicines Agency (EMA) Scientific Opinion* should serve as a surrogate of the MA, the Guideline on Procedural Aspects regarding the Committee for Medicine Products for Human Use (CHMP) Scientific Opinion should be followed in the context of cooperation with WHO for the evaluation of medicinal products intended exclusively for markets outside the community.

* Licensing regulations in the European Union prevent the granting of marketing authorizations to those medicinal products which are not to be used in the European Union territory.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 4

WHO reserves the right to terminate the assessment (of acceptability of vaccines for purchase by UN agencies) if, at any time, it is considered that insufficient information has been provided to enable effective completion of the assessment.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 6

During the review of the file (procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies,) emphasis will be placed on assessing the suitability of the vaccine for the immunization services where it is intended to be used, taking into account composition, presentations offered, recommended schedules and clinical data available, labelling (including vaccine vial monitors VVMs), information provided on package inserts (which shall not contradict WHO model inserts), and packaging and shipping procedures, which shall be in accordance with the latest revision of the WHO International guidelines on packaging and shipping of vaccines (WHO/IVB/01.05 or later version).

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 7

WHO will request the manufacturer to submit to WHO an appropriate number of samples (25 at minimum and 200 at maximum) each of not less than three final lots, for consistency testing. These lots will have been produced after a date defined by WHO and formulated from consecutive bulk lots (in the case of combined vaccines, consecutive bulks will be specified by WHO for one of the components). These samples shall be accompanied by the respective lot-summary protocols.

In some cases, samples of bulk material, and samples of the manufacturers reference vaccine may be requested. WHO will send the vaccine samples to its contracted laboratories for testing. Tests undertaken will be the most relevant to reflect the quality, safety and efficacy of the vaccine. Usually potency and toxicity are tested; however, depending on the nature of the vaccines, other relevant tests can be performed. They must have been produced under full-scale production conditions, and be a representative sample of the product intended to be marketed through UN agencies.

To promote the independence and impartiality of the testing, the list of WHO's contracted laboratories will be kept confidential.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 7

The main objectives of the site visit are to assess that the vaccine complies with WHO recommendations for production and control, that it meets the UN tender specifications (which reflect the needs of the immunization programmes at country level), that the company has an adequate quality assurance (QA) system in place, and that the relevant vaccine/s is/are produced in compliance with WHO-recommended GMP.

Site visits are required for all manufacturers applying for the prequalification of new products to be evaluated for purchase by UN agencies. They are necessary as part of the initial evaluation, as follow-up to corrective actions taken by the manufacturer following WHO recommendations and for reassessment purposes. They may also be deemed necessary as a result of complaints or reports of serious AEFI if a quality problem is suspected.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 8

As part of the assessment, WHO will negotiate an agreement with the relevant NRA for exchange of information regarding results of national inspections, variations to the licence or cancellations, rejection of lots, recalls and withdrawals, interruptions in production, information on AEFI reported or other matters that could affect the normal supply of vaccine to UN agencies.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 9

The prequalified status of a vaccine is normally valid for a period of two years; however, under certain circumstances, this status can be extended up to five years.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 10

Special considerations for (assessing the acceptability of) vaccines formulated and filled by different manufacturers in the same or different countries:

a) Commodity transaction: sale and purchase of bulk vaccine on the open market. Bulk manufacturers and finished product manufacturers working under this type of arrangement would not be eligible to undergo the prequalification process for the products in question.

B) Contract manufacturing: a contract manufacturer is a facility that is subcontracted by a vaccine manufacturer to do one or more steps of the process. The vaccine manufacturer is responsible for the product and shall ensure that all steps of the manufacturing process are performed in accordance with the licence specifications and in compliance with GMP.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 12

In agreement with UN purchasing agencies or other partners, the fast-track procedure (for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies) can be considered in the following situations:

An acute shortage* of a vaccine that puts at risk the global supply of routine immunization programmes. (*As agreed with UN purchasing agencies and other partners.)

An emergency situation or outbreak of a disease for which there is no prequalified vaccine, or its availability is not sufficient and an additional source of the same vaccine is required.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 13

Under special circumstances, the prequalification evaluation can be initiated before the national licence is granted. This provision can be applied, in agreement with the UN purchasing agencies and other partners, under the following circumstances:

The vaccine is a priority vaccine for introduction into the routine immunization programme; and

Availability of the vaccine in question is a substantial limiting factor for the timely introduction of the vaccine into routine immunization programmes.

This provision does not apply to novel vaccines not yet introduced in the immunization programme.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 13

In some cases, vaccines that are manufactured in one country (country A) can be finished (packaged, or filled, labelled and packaged, or formulated, filled, labelled and packaged) in a different country (country B) by the same or different manufacturer. The vaccine would then be distributed only from the country where the finished product is manufactured (country B). In such cases, the vaccine must have been licensed in country B, the regulatory authority of country B must have been assessed by WHO and found to meet all the critical indicators as defined by WHO for prequalification purposes and must have agreed to exercise the ongoing regulatory overseeing of the product for export through UN agencies

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 15

Reassessments (of the acceptability, in principle, of vaccines for purchase by United Nations agencies) will be done in the following situations:

- i) At regular intervals, usually every two years, with the possibility of an extension of up to five years for vaccines that have been prequalified for more than two years, and have been reassessed at least once after initial evaluation.
- ii) If the vaccine fails to meet the WHO recommendations and/or the specifications of the offer to bid.
- iii) When no supply to the UN has taken place for a period equal to, or greater than, two years.
- iv) In the case of a suspension of production, after production is reestablished and before purchase by the UN agencies.
- v) When, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made.

Samples of lots supplied through UN agencies will be selected, at regular intervals (at least once a year), for independent testing of final product characteristics.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 17

The cost of the activities required to assess the acceptability, in principle, of candidate vaccines for UN agency purchase is covered by the manufacturers.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 18

(l)f, in the opinion of the manufacturer, any information to be submitted to WHO and its expert team members in the course of the (re)assessment procedure (for acceptability of vaccines for purchase by United Nations agencies) includes confidential information; the manufacturer must advise WHO thereof in writing, prior to or at the same time as the disclosure, duly identifying the confidential information in question. Notwithstanding the foregoing, WHO and its expert team members will treat all information submitted to them either as written documents or during site visits as confidential, in accordance with the terms set forth below.

WHO will treat information so identified contained in the product summary file and information disclosed during site visits as confidential and proprietary to the manufacturer and, in this connection, take all reasonable measures to ensure (a) that such information (the Confidential Information) is not used for any other purpose than the (re)assessment procedure described in this document, and (b) that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein. WHO and/or its expert team members will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- a) was known to them prior to any disclosure by the manufacturer; or
- b) was in the public domain at the time of disclosure by the manufacturer; or
- c) has become part of the public domain through no fault of WHO and/or any of its expert team members; or
- d) has become available to WHO and/or any of its expert team members from a third party not in breach of any legal obligations of confidentiality to the manufacturer.

Japanese encephalitis vaccines (WHO position paper)

[WER 2006, vol. 81, 34/35, pp 331-340](#)

page 332

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

Influenza

Global Advisory Committee on Vaccine Safety, 12 December 2005

[WER 2006, vol. 81, 2, pp 15-19](#)
page 16

WHO is promoting vaccination strategies that economize on the use of antigens to address the current global shortage of influenza vaccines for epidemics and pandemics. That would entail development and licensing of novel antigen-sparing vaccine formulations.

The GACVS agreed to act as a resource for WHO if such a situation were to arise. The Committee made the following recommendations: develop pharmacovigilance guidelines to enable rapid assessment of pandemic influenza vaccines; promote the extension of such guidelines to evaluate seasonal influenza vaccines; develop an authoritative review of the safety and efficacy of inactivated influenza vaccines with adjuvants. It would be assured that regulators from developing countries are included in WHO meetings to promote regulatory collaboration on pandemic influenza vaccine issues and that lessons from the past, such as those from swine influenza vaccine, are taken into account.

JE

Japanese encephalitis vaccines (WHO position paper)

[WER 2006, vol. 81, 34/35, pp 331-340](#)
page 332

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

MMR

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

The WHO secretariat should make special efforts to collaborate with industry to increase global availability of MMR vaccines that contain strains of mumps vaccines with the best safety profile.

Measles

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 16

WHO requirement for heat stability of freeze-dried measles vaccine have made a considerable impact on the quality of measles vaccines on the market. This requirement uses two indices of stability:

- (1) Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
- (2) If, during incubation, the virus titre has been decreased, then it shall have done so by not more than 1 log₁₀.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 25

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log₁₀ (162).

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 25

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log₁₀.

Mumps

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 44

The WHO thermostability requirements for mumps and rubella vaccines are similar to those for measles vaccine. At least three containers of monovalent or MMR vaccine are tested by incubation at 37C for seven days, at the end of which each monovalent vaccine or individual vaccine component is titrated in PFUs or CCID₅₀ after selective neutralization, as necessary, of the other components. The geometric mean infectious virus titre must equal or exceed the required minimum number of infective units per human dose (3 log₁₀), and the geometric mean virus titre must not have decreased by more than 1 log₁₀ infective units during incubation.

Mumps virus vaccines (WHO position paper)

[WER 2001, vol. 76, 45, pp 346-356](#)
page 352

WHO requirements do not specify the minimum amount of (mumps) vaccine virus that 1 human dose should contain. Rather, this is determined by the national regulatory authority of the country where the vaccine is produced.

Mumps virus vaccines (WHO position paper)

Due to its known low effectiveness, the Rubini-strain (mumps) vaccine should not be used in national immunization programmes. Persons previously immunized with the Rubini-strain vaccine should receive a dose of an effective mumps vaccine to ensure protection.

[WER 2001, vol. 76, 45, pp 346-356](#)
page 354

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

Additional information on the safety of different mumps vaccine strains is available from country experiences with use of mumps vaccine in mass campaigns and routine settings. These data should be reviewed by the GACVS and the resulting conclusions included in the revision of the WHO mumps position paper.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

Policy

Thermostability of vaccines

The WHO thermostability requirements for mumps and rubella vaccines are similar to those for measles vaccine. At least three containers of monovalent or MMR vaccine are tested by incubation at 37C for seven days, at the end of which each monovalent vaccine or individual vaccine component is titrated in PFUs or CCID50 after selective neutralization, as necessary, of the other components. The geometric mean infectious virus titre must equal or exceed the required minimum number of infective units per human dose (3 log₁₀), and the geometric mean virus titre must not have decreased by more than 1 log₁₀ infective units during incubation.

[WHO/GPV/98.07](#)
page 44

Statement on vaccine quality (GPV Policy Statement)

The Forty-fifth World Health Assembly in 1992 resolved that all vaccines used within national immunization programmes meet WHO requirements (WHA45.17), thus reinforcing these guidelines as a credible goal for all countries.

While some Member States may apply testing procedures which differ in detail from those defined by WHO, nevertheless, they should ensure by national regulation that the products are at least as safe and efficacious as those prepared in accordance with WHO requirements.

[WHO/VSQ/GEN/96.02 Rev. 1](#)
page 1

Statement on vaccine quality (GPV Policy Statement)

Confidence that vaccines are consistently safe and efficacious depends not only on the characteristics of the vaccine product and adherence to standards of Good Manufacturing Practice in its production, but requires continual oversight by an independent and competent National Control Authority (NCA).

[WHO/VSQ/GEN/96.02 Rev. 1](#)
page 1

Statement on vaccine quality (GPV Policy Statement)

WHO responds to requests from the United Nations (UN) or its agencies for an opinion as to the acceptability of a specified vaccine from a specific producer for use in developing country immunization programmes. The responsibility for this process of prequalifying suppliers who will respond to offers to purchase of the UN or its agencies rests at WHO headquarters. The determination is made on a technical basis, after applying a procedure which involves an examination of manufacturing processes, product characteristics and the licensing, control, release, and post-licensing activities of the NCA (National Control Authority.) This procedure has been reviewed by the WHO Expert Committee on Biological Standardization. The list of prequalified suppliers is public. WHO recommends to UN agencies procuring vaccines only those vaccines which have been assessed using the above procedure.

[WHO/VSQ/GEN/96.02 Rev.](#)

[1](#)

page 1

Statement on vaccine quality (GPV Policy Statement)

Many manufacturers produce vaccines which are not purchased by UN agencies and thus may neither require nor seek WHO assessment for prequalification. Countries desiring to purchase these products may seek a statement from WHO as to whether or not these vaccines are of known good quality.

[WHO/VSQ/GEN/96.02 Rev.](#)

[1](#)

page 1

Statement on vaccine quality (GPV Policy Statement)

WHO considers a vaccine to be of known good quality provided:
the NCA (National Control Authority) independently controls the quality of the vaccine in accordance with the six specified functions defined by WHO* and
there are no unresolved confirmed reports of quality-related problems.

[WHO/VSQ/GEN/96.02 Rev.](#)

[1](#)

page 1

* Licensing in accordance with written requirements, review of clinical data, lot release, laboratory testing, inspections for compliance with Good Manufacturing Practice, post-marketing surveillance for field performance, World Health Organization, Technical Report Series 822 (1992).

Thermostability of vaccines

WHO requirement for heat stability of freeze-dried measles vaccine have made a considerable impact on the quality of measles vaccines on the market. This requirement uses two indices of stability:

- (1) Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
- (2) If, during incubation, the virus titre has been decreased, then it shall have done so by not more than 1 log₁₀.

[WHO/GPV/98.07](#)

page 16

Thermostability of vaccines

WHO requirement for yellow fever vaccine stability stipulates that the vaccine should retain 1000 mouse LD₅₀ or the equivalent in plaque-forming units (PFUs) per human dose, and that the mean titre loss should be less than 1 log₁₀ after two weeks incubation at 37C.

[WHO/GPV/98.07](#)

page 20

Thermostability of vaccines

[WHO/GPV/98.07](#)

page 29

An ADT (accelerated degradation test) should be conducted on each lot of BCG vaccine. The number of culturable particles in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C

Thermostability of vaccines

[WHO/GPV/98.07](#)

page 37

WHO requirements for thermostability for OPV:

Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national control authorities are to specify the minimum virus titres per human dose

Thermostability of vaccines

[WHO/GPV/98.07](#)

page 42

Poliomyelitis vaccines were remarkably stable within the pH range 6.5-7.2. A vaccine can be maintained in this pH range by preventing the loss of carbon dioxide from a bicarbonate-containing vaccine, keeping the air space above the vaccine to a minimum, and packing the vaccine in tightly stoppered containers.

Vaccine donations (GPV Policy Statement)

[WHO/VSQ/97.05](#)

page 2

WHO recommends that all countries, including those which receive all their vaccines from UNICEF, exercise at least two essential national control functions: a published set of requirements for licensing, and surveillance of vaccine field performance (monitoring of adverse events following immunization).

Page 4: There is a need for a focal point to check (donated) vaccines upon receipt and the ability to refuse vaccine donations not meeting the criteria. This implies a need for criteria, such as a published set of requirements for licensing, and their application. There is also a need for a system to detect and investigate complaints from the field, essentially the second critical control function, surveillance of vaccine field performance.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)

page 2

Responsible staff must ensure that all vaccines, including those received from UN sources, are licensed for use in their country. They should also ensure that all adverse events following immunization (AEFI) are monitored by an effective field performance surveillance system.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)
page 2

In all cases the lot release certificate from the NRA of the country of origin should be a condition for acceptance of the vaccine and for its subsequent distribution. Note that the manufacturer's own internal lot release cannot be considered as equivalent to the NRA lot release certificate for the purpose of releasing vaccines.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

[WHO/IVB/04.16-20](#)
page 2

The NRA in the receiving country should undertake lot release procedures for all vaccines that are obtained from non-UN sources, including all vaccines produced and used within the receiving country.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 7

WHO recommends that the manufacturers quality tests be reviewed with possible complementary testing by national regulatory authorities before release of the product for use.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 12

WHO has identified six essential control functions to be undertaken by an effective vaccine regulatory system (National Regulatory Authority or National Control Authority). These are:

- A published set of clear requirements for licensing (of products and manufacturers)
- Surveillance of vaccine field performance (safety and efficacy)
- System of lot release
- Use of laboratory when needed
- Regular inspections of manufacturers for GMP compliance
- Evaluation of clinical performance through authorized clinical trials

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 9

Appendix 18_3 illustrates the variation in the functions of DRAs (Drug Regulatory Authority) to regulate vaccines in countries using different mechanisms to obtain their vaccines. As WHO has set in place procedures to ensure that appropriate regulatory functions are being performed for products which have been found acceptable for purchase by United Nations agencies (WHO/VSQ/97.06), countries receiving vaccines only through United Nations agency purchase (such as WHO or UNICEF), have a lesser responsibility in terms of the essential control functions. For countries sourcing vaccines through production and direct procurement, greater responsibility for ensuring vaccine quality is needed:

If the country is producing vaccines, all six functions should be performed.

For countries which are importing vaccines, fewer functions need be ensured within the authority of the importing country, although it should ensure that the appropriate regulatory activities are being carried out in the country of manufacture.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 9

In assessing applications for marketing authorization (registration) of new products, the DRA (Drug Regulatory Authority) has three options:

- a) to make its own assessment of the documentation submitted regarding the quality, safety, efficacy and product information of the product based on the file submitted by the applicant. This should always be done for products manufactured in the country.
- b) to use assessment protocols from DRAs in other countries as a basis for making its own decision about applications.
- c) to rely on decisions made by DRAs in other countries.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 13

It is recommended that the vaccine regulatory system use the published WHO guidelines on vaccine production developed by the Expert Committee on Biological Standardization and published in the WHO Technical Report Series, as a point of departure.

In the areas of authorizing products for marketing, GMP inspections, and clinical trials, guidelines already promulgated for pharmaceuticals regulation can be used

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 15

Lot release should be based, at minimum, on the review of Summary Lot Protocols which describe the production process in detail. WHO has provided, in each of the guidelines for production of the individual vaccines, model Summary Lot Protocols which can be used.

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)

page 15

Post-marketing surveillance by a national regulatory authority encompasses many activities which include:

- 1) The periodic inspections performed to evaluate compliance of manufacturers with GMP and conformance with approved manufacturing processes.
- 2) The continual monitoring of the quality of vaccines through lot release programs and ad hoc assessment of samples collected in the field (less important when lot release is rigorously performed).
- 3) Review and evaluation of adverse reactions to be reported by health care providers.
- 4) Monitoring for effectiveness and efficacy of vaccine preventable diseases.
- 5) Some agencies may include evaluation of vaccine uptake.

BCG vaccine (WHO position paper)

[WER 2004, vol. 79, 4, pp 27-38](#)

page 28

The BCG vaccine should be manufactured according to the current recommendations published in the report of the WHO Expert Committee on Biological Standardization.

Yellow fever vaccine (WHO position paper)

[WER 2003, vol. 78, 40, pp 349-359](#)

page 355

According to current WHO requirements, a YF (yellow fever) vaccine that has been held at 37 C for 14 days must (i) maintain the minimal potency of >1000 MLD50 per dose and (ii) show a mean loss of titre <1 log 10 MLD50. These requirements necessitate the addition of stabilizers such as sorbitol and gelatin.

Creating national and regional frameworks to support HIV vaccine development in developing countries (Report from a WHO-UNAIDS consultation)

[WHO/IVB/05.17](#)

page 18

WHO's goal is to ensure that 100% of vaccines used in immunization programmes are assured quality vaccines. This means that a country's NRA (national regulatory authority) is independent from vaccine manufacturers, the NRA is fully functional, and that there are no unresolved reported problems with the vaccine.

WHO's Expert Committee on Biological Standards sets international standards for quality, efficacy, and safety. Different groups within (Immunization, Vaccines & Biologicals/Access to Technologies) work together to build capacity of NRAs, and prequalify vaccines for UN agencies. These programmes strengthen and monitor the six regulatory functions required of a functional NRA:

- _a published set of requirements for licensing
- _surveillance data for vaccine field performance
- _a system for lot release
- _use of laboratory when needed
- _regular inspections for GMP
- _an evaluation of clinical performance.

Creating national and regional frameworks to support HIV vaccine development in developing countries (Report from a WHO-UNAIDS consultation)

[WHO/IVB/05.17](#)

page 19

Recent changes in the European regulations established that vaccines produced in Europe for exclusive use outside of Europe will not be licensed by EMEA. As a result of collaboration between EMEA and WHO, article 58 in the new regulation and a detailed procedure have been defined by which EMEA will issue scientific opinion for vaccines used exclusively outside of Europe and considered eligible by WHO. The scientific opinion is intended to mimic the review process for licensing, but the outcome will not be a marketing authorization.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 1

In giving advice to UN agencies on the quality of candidate vaccines or on the continuing quality of vaccines already being purchased, WHO follows a procedure, detailed in document WHO/VSQ/97.06, for evaluating the acceptability in principle of vaccines for purchase. It consists of the following steps:

- 1) Any vaccine producer wishing to supply vaccine to UN purchasing agencies must submit a product summary file to WHO for detailed review.
- 2) In order to verify the consistency of final product characteristics, five consecutive vaccine lots must be independently tested by laboratories contracted by WHO.
- 3) The NRA of the producing country must be assessed by WHO in order to ensure that it is capable of effectively overseeing the quality of vaccines produced in that country.
- 4) Manufacturing facilities must be audited by a WHO team whose members have expertise in the relevant procedures, accompanied by representatives of the local NRA.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 2

The six critical regulatory functions that must be performed by an NRA to ensure the quality of the vaccines they regulate are (as follows):

- Published set of requirements for licensing
- Surveillance of vaccine performance in the field (postmarketing surveillance)
- System of lot release
- Use of laboratory when needed
- Regular inspections for good manufacturing practices
- Evaluation of clinical performance

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 2

Any producing country applying to supply vaccines to UN agencies is automatically required to have an NRA assessment as part of the prequalification process.

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)

page 1

All countries need some sort of NCA, but the governments of countries in which vaccine production takes place need to exercise six critical control functions, and they need to exercise them in a competent and independent manner, backed up with enforcement power. These six functions are:

- A published set of requirements for licensing
- Surveillance of vaccine field performance
- System of lot release
- Use of laboratory when needed
- Regular inspections for Good Manufacturing Practice (GMP) compliance
- Evaluation of clinical performance

Which of these critical control functions is needed in a country depends on vaccine source, as shown (Appendix 12_1.)

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)

page 2

WHO policy is that no technical nor financial support to vaccine production will be provided to facilities unless they have a functional NCA and have developed a strategic plan to achieve viability.

Ensuring the quality of locally produced vaccines and the viability of local production (GPV Policy Statement)

[WHO/VSQ/98.03](#)

page 4

For some countries, whose local production facility is in the low probability viability category, the first step should be the establishment of an independent and competent National Control Authority, as defined above.

For facilities which are potentially viable, the next step is a viability study to understand where they are, where they want to be, and how to get there. The outcome of such a study will be a strategic plan.

For those facilities which are already viable, and which have already developed a strategic plan, they should specifically address the question of access to new technologies. There are five ways this can be approached:

- Developing strong research and development capacity
- Bulk filling arrangements
- Licensing technology
- Negotiating partnerships for specific products
- Entering into joint venture agreements with a research-based manufacturer

Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation

[WHO/IVB/05.18](#)

page 30

For countries purchasing their own vaccines, the documents and conditions to ensure the quality of vaccine and shipping conditions should be included in the tender specifications. These include: the batch release certificates issued by the NRA in the country of manufacture; the list of countries where the vaccine is licensed; the product file including safety and efficacy data and clinical studies. Vaccine vial monitors (VVMs), cold chain monitor card, packaging and shipping conditions may be considered in this regard by the countries. Technical documents should be reviewed by an expert committee to ensure the quality of the vaccine.

Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation

[WHO/IVB/05.18](#)

page 30

All countries should have an NRA capable of performing at least two functions: licensing and postmarketing surveillance.

Ideally the NRAs need to fulfil six critical control functions, particularly in vaccine-producing countries, and they need to exercise them in a competent and independent manner, backed up with enforcement power.

These six functions are:

- 1) a published set of requirements for licensing,
- 2) surveillance of vaccine field performance,
- 3) system of lot release,
- 4) use of laboratory when needed,
- 5) regular inspections for GMP, and
- 6) evaluation of clinical performance.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 3

Once the four steps described above (31_1) have been satisfactorily completed, WHO must reach an agreement with the local NRA on activities to be performed in connection with vaccines intended for exportation. These activities include the following.

- A) The NRA should agree to release all lots for export on the basis of a review of lot summary protocols. The testing of selected lots for specific parameters is highly encouraged.
- B) The release certificate for UN agencies should follow the recommended model.
- c) The NRA should agree to communicate to WHO all reports of serious adverse events following immunization with vaccines supplied through UN agencies.
- d) The NRA should agree to inform WHO of critical deficiencies in good manufacturing practice, which are identified during its inspections.
- e) The NRA should agree to inform WHO of any recalls or licence withdrawals related to any vaccine supplied through UN agencies.

Ensuring the quality of vaccines at country level: Guidelines for health staff

[WHO/V&B/02.16](#)

page 3

Once the initial evaluation is completed, the quality of vaccines shipped to countries is monitored through rounds of random testing performed at six-monthly intervals. This is to ensure continuing compliance with WHO requirements and tender specifications. In addition, a full re-evaluation of all prequalified vaccines takes place every two years. This is known as the reassessment process and basically covers the same steps as the initial evaluation described above, as follows:

- 1) Submission by manufacturers of an updated product summary file.
- 2) Testing of vaccine samples.
- 3) Meeting with the appropriate NRA.
- 4) Site visit to the manufacturing facility.

For reassessments however, the waiving of site visits may be considered on a case-by-case basis if certain criteria are met and at least one WHO site visit to the manufacturer has taken place within the previous five years.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

To ensure quality, as well as reliability and availability, it is imperative to purchase only from suitable sources. If vaccines and suppliers are pre-qualified it will ensure that critical criteria are met and eliminate unsuitable bidders, and/or bids of inferior products.

Sources can be pre-qualified as follows:

Registration in country by National Control Authority (NCA): See Regulation and licensing of biological products, WHO Technical Report Series No 858, 1995

International competitive bidding (ICB) procedure: This should be used as a first step for pre-qualifying suppliers if appropriate or if requested by the government. The procedure is that an invitation to bid for pre-qualification is publicly advertised, and responses are reviewed for technical acceptability by the NCA. The NCA will review each vaccine bid on its merits and undertake an appropriate review of the vaccine and the producer.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

In addition to the usual commercial information requested for pre-qualification, the following conditions are critical in selecting vaccine suppliers to ensure that they meet NCA or WHO minimum requirements. The supplier must be a manufacturer (or importer of bulk product for filling, labelling and repackaging) and must provide the following documentation:

- Certificate of registration /licensing in country of origin
- Documentation on quality control (QC) and sampling procedures
- Copy of most recent GMP certification.
- Production and quality control summary protocols.
- Certificate of analysis from NCA in country of origin.
- Statement of licensing status in other countries.

For WHO pre-qualifying sources, see updated list available from WHO/GPV/VSQ1.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 8

The limited international bidding (LIB) documents should be prepared following standard procedures for drugs, including the minimum requirements for vaccines (NCA or WHO standards). See WHO standards, as published in the WHO Technical Report series.

Guidelines for the international procurement of vaccines and sera

[WHO/VSQ/98.05](#)

page 11

Pre-qualified sources should be reviewed regularly, with periodic re-confirmation from the NCA or WHO, alternatively issuing an ICB as a requisite to pre-qualification.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 22

An ADT should be conducted on each lot of BCG vaccine. The number of CPs (culturable particles) in vaccine incubated at 37C for 28 days should be not less than 20% of that in the vaccine stored at 4C.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 31

Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national regulatory authorities are to specify the minimum virus titers per human dose

Mumps virus vaccines (WHO position paper)

[WER 2001, vol. 76, 45, pp 346-356](#)

page 352

WHO requirements do not specify the minimum amount of (mumps) vaccine virus that 1 human dose should contain. Rather, this is determined by the national regulatory authority of the country where the vaccine is produced.

Mumps virus vaccines (WHO position paper)

[WER 2001, vol. 76, 45, pp 346-356](#)

page 354

Due to its known low effectiveness, the Rubini-strain (mumps) vaccine should not be used in national immunization programmes. Persons previously immunized with the Rubini-strain vaccine should receive a dose of an effective mumps vaccine to ensure protection.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 25

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log₁₀ (162).

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 29

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log10.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 25

WHO requirement for heat stability of freeze-dried measles and measles-containing vaccines . . . uses two indices of stability:

1. Freeze-dried vaccine should retain at least 1000 live virus particles in each human dose at the end of incubation at 37C for seven days; and
2. If, during incubation, the virus titer has been decreased, then it shall have done so by not more than 1 log10.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)

page 29

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log10.

Tetanus vaccine (WHO position paper)

[WER 2006, vol. 81, 20, pp 198-208](#)

page 202

According to WHO requirements*, the potency of monovalent tetanus toxoid shall be no less than 40 IU (determined in guinea-pigs or in mice) per dose (0.5 ml), and at least 40 IU (determined in guinea-pigs) or 60 IU (determined in mice) per dose when tetanus toxoid is used in combination with diphtheria and whole-cell pertussis vaccines.

* Requirements for diphtheria, tetanus, pertussis and combined vaccines. WHO Technical Report Series, No. 800, 1990, Annex 2; Recommendations for diphtheria, tetanus, pertussis and combined vaccines (Amendments 2003). WHO Technical Report Series, No. 927, 2005, Annex 5.

State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)

page 89

A number of cell-culture based rabies vaccines are being developed in China and India on Vero cells, human diploid cells (HDC), or duck embryo cells. These vaccines however have not yet been prequalified by WHO and may require further assessment in terms of safety and efficacy before they can be traded internationally.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)

page 3

Training should be a dynamic process, in respect to both, the training an employee receives during his or her career with a firm, and in terms of ensuring that training programmes and materials keep pace with job requirements and performance expectations.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)

page 5

World Health Organization, good manufacturing practices for pharmaceutical products*: main principles - Personnel

(T)here must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded as written descriptions.

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibility placed on any one individual should not be so extensive so as to present any risk to quality.

All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Good Manufacturing Practices for pharmaceutical products: main principles. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908. Annex 4).

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)

page 13

Training curricula should be written for operation, maintenance and laboratory personnel, supervisors, managers, and also for temporary employees and contractors.

New employees are also an important audience so that they understand the rationale for the strict method of operation within the vaccine manufacturing industry.

New employees are not truly competent to work in a regulated industry that makes critical products like vaccines until they have been trained and have demonstrated that they know and can perform what is required of them.

Employees whose activities take them into production areas or into control laboratories (including maintenance and cleaning staff), and other personnel whose activities could impact on the quality of the product should receive work-specific training at the time of joining the company and on a continuing basis. The work-specific area training should cover three aspects:

GMP training (GMP training should be provided to ensure that employees understand and follow the GMP requirements applicable to their jobs.)
on-the-job training - standard operating procedures (SOPs) and technical skills training. (The supervisor is responsible for this training, and it is based on the SOPs and the acquisition of technical skills needed for the job. It is particularly important at this stage to teach the trainee not only what he/she should do and how, but why it must be done in such a way and in no other.)
safety training.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 17

(For good manufacturing practice requirements,) supervisor training should be conducted to guarantee that supervisors be adequately trained in:

- the areas they are going to supervise;
- the SOPs used in their department;
- their responsibilities under GMP, especially their responsibility for training, for reviewing documents, and for reviewing safety procedures to avoid danger to their staff.

Managers and supervisors need to be trained in their responsibilities under GMPs and good laboratory practice (GLPs) for non-clinical studies. They should also be updated in GMP trends. The manager training programme should guarantee that new managers be trained and that existing managers remain familiar with their assigned functions.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 19

(For good manufacturing practice requirements) Trainers training

Typically, trainers (both those who teach to groups in classrooms, as well as those who work individually with people during structured on-the-job training) should have an understanding of how adults learn and in providing effective feedback to trainees.

On-the-job and SOP trainers should be recognized experts in the area or in the tasks that they perform. They should also understand the best ways to teach tasks and procedures.

Group trainers should have presentation skills to use various training media (e.g. slides, overheads, flipcharts), methods (e.g. discussions, games, case studies, lectures), and know how to respond to questions and difficult situations.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 19

For good manufacturing practice requirements) Ongoing training:

Ongoing training should include:

GMP: New guidelines, current GMP changes and their interpretation and biopharmaceutical industry trends, including short reviews of specific GMP topics that may be applicable to current work-related issues and challenges.

On-the-job training: Employees should be trained when a new SOP or method is issued, when a procedure or method is changed and requires users to perform differently, and when new equipment or instruments are to be used. If the performance according to a procedure or job task has degraded, the requirements should be reviewed and coaching given as needed to return the performance to the desired level.

Safety training: Periodic reinforcement is necessary for protecting staff from hazards. This training should also be implemented in case of changes or modifications of the safety regulations, changes or modifications of the technological process, work resources, raw materials, materials, new potential risks or other factors that could affect the workers safety and health.

Each company should determine the frequency for the ongoing training and the established frequency must guarantee that employees remain familiar with the specific tasks required by their job.

Remedial training:

Remedial training should be planned when specific deficiencies related to training are identified during the performance of a job or task, or during the investigation of a deviation or an out-of-specification result, accident or near-accident.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 22

For good manufacturing practice requirements) Job-change training:

Work-specific training (GMP, on-the-job and safety training) should be conducted for the employees new needs, taking into account the previous knowledge, skills and attitudes that they have developed.

Temporary employee and contractor training:

Temporary employees and contractors whose work takes them into production areas or quality control laboratories and those whose work can impact the quality of the product must be trained.

A WHO guide to good manufacturing practice (GMP) requirements - Part 3: Training

[WHO/IVB/05.24](#)
page 51

(When implementing training to support good manufacturing practice (GMP)), for each training course, it is recommended that:

- minimum trainer requirements are established;
- each trainer attends a train-the-trainer course;
- the QC/QA unit analyse and approve the trainers; and
- the trainers qualification be documented.

During the design of the training programme, training records should also be designed. Quality assurance should audit training records periodically. It is advisable to keep the following training documents:

- training requirements
- employee-training records
- training attendance records.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 2

The assessment (prequalification) procedure established by WHO for vaccines is based on the following principles:

- reliance on the national regulatory authority (NRA) of the country of manufacture because it meets the published WHO NRA indicators (http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm);
- general understanding of the product and presentations offered, production process, quality control (QC) methods and relevance for the target population of available clinical data;
- assurance of production consistency through application of GMP specifications;
- random check-testing of vaccines by independent WHO-contracted laboratories to monitor compliance with tender specifications on a continuing basis;
- monitoring complaints from the field and assisting in the investigation of adverse events following immunization (AEFI).

Since reliance upon effective regulatory oversight by the NRA of the country of manufacture plays a critical role in the system (procedure for assessing acceptability of vaccines for purchase by United Nations agencies), manufacturers shall: (a) inform their NRA (national regulatory authority) of their application to WHO for the vaccine prequalification by sending a copy to the NRA of the application letter sent to WHO; (b) request the NRA to participate/collaborate in the process; and provide the NRA with the necessary authorization to discuss the relevant files with WHO representatives.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 2

As vaccines purchased by UN agencies need to meet WHO recommendations or guidelines (whichever is available), novel vaccines for which such guidelines are not available cannot be evaluated. In cases where a vaccine is made available for a disease of public health importance, the development of such guidelines will be prioritized by WHO and, as soon as a draft document becomes available, this can be used for evaluation for prequalification purposes.

WHO will define, in consultation with UN purchasing agencies and other relevant partners, which vaccines are priority for prequalification and will make this information publicly available. This exercise is required in order to focus the use of resources. The priorities will be redefined at regular intervals to ensure that efforts are put into evaluating those vaccines that are of highest public health importance and most needed in developing countries

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 3

The following are the conditions for acceptance of applications:

The candidate vaccine falls under the category of priority products as defined by UN purchasing agencies and other partners e.g. the Global Alliance for Vaccines and Immunization (GAVI).

The NRA of the producing country is found to meet all the critical indicators defined for prequalification purposes following a WHO independent assessment (http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm).

Furthermore, during the prequalification process, the WHO team will establish an agreement with the NRA for appropriate lot release of all vaccines to be supplied through UN agencies, and sharing of information in case of serious GMP deviations, AEFIs, or withdrawals due to quality issues.

If the vaccine finishing (packaging; or filling/packaging; or formulation/filling/packaging) and distribution are performed in a country different from that of bulk manufacturing, the NRA of the country where the finished product is manufactured must comply with the above-mentioned requirements and commit to perform all post-marketing regulatory functions.

A marketing authorization (MA) has been granted by the relevant NRA and the post-marketing regulatory oversight is conducted by the NRA of the country of manufacture or that of the country of finishing and distribution. Alternatively, if it is intended that the European Medicines Agency (EMA) Scientific Opinion* should serve as a surrogate of the MA, the Guideline on Procedural Aspects regarding the Committee for Medicines Products for Human Use (CHMP) Scientific Opinion should be followed in the context of cooperation with WHO for the evaluation of medicinal products intended exclusively for markets outside the community.

* Licensing regulations in the European Union prevent the granting of marketing authorizations to those medicinal products which are not to be used in the European Union territory.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 4

WHO reserves the right to terminate the assessment (of acceptability of vaccines for purchase by UN agencies) if, at any time, it is considered that insufficient information has been provided to enable effective completion of the assessment.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 6

During the review of the file (procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies,) emphasis will be placed on assessing the suitability of the vaccine for the immunization services where it is intended to be used, taking into account composition, presentations offered, recommended schedules and clinical data available, labelling (including vaccine vial monitors VVMs), information provided on package inserts (which shall not contradict WHO model inserts), and packaging and shipping procedures, which shall be in accordance with the latest revision of the WHO International guidelines on packaging and shipping of vaccines (WHO/IVB/01.05 or later version).

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 7

WHO will request the manufacturer to submit to WHO an appropriate number of samples (25 at minimum and 200 at maximum) each of not less than three final lots, for consistency testing. These lots will have been produced after a date defined by WHO and formulated from consecutive bulk lots (in the case of combined vaccines, consecutive bulks will be specified by WHO for one of the components). These samples shall be accompanied by the respective lot-summary protocols.

In some cases, samples of bulk material, and samples of the manufacturers reference vaccine may be requested. WHO will send the vaccine samples to its contracted laboratories for testing. Tests undertaken will be the most relevant to reflect the quality, safety and efficacy of the vaccine. Usually potency and toxicity are tested; however, depending on the nature of the vaccines, other relevant tests can be performed. They must have been produced under full-scale production conditions, and be a representative sample of the product intended to be marketed through UN agencies.

To promote the independence and impartiality of the testing, the list of WHO's contracted laboratories will be kept confidential.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 7

The main objectives of the site visit are to assess that the vaccine complies with WHO recommendations for production and control, that it meets the UN tender specifications (which reflect the needs of the immunization programmes at country level), that the company has an adequate quality assurance (QA) system in place, and that the relevant vaccine/s is/are produced in compliance with WHO-recommended GMP.

Site visits are required for all manufacturers applying for the prequalification of new products to be evaluated for purchase by UN agencies. They are necessary as part of the initial evaluation, as follow-up to corrective actions taken by the manufacturer following WHO recommendations and for reassessment purposes. They may also be deemed necessary as a result of complaints or reports of serious AEFI if a quality problem is suspected.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 8

As part of the assessment, WHO will negotiate an agreement with the relevant NRA for exchange of information regarding results of national inspections, variations to the licence or cancellations, rejection of lots, recalls and withdrawals, interruptions in production, information on AEFI reported or other matters that could affect the normal supply of vaccine to UN agencies.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 9

The prequalified status of a vaccine is normally valid for a period of two years; however, under certain circumstances, this status can be extended up to five years.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)
page 10

Special considerations for (assessing the acceptability of) vaccines formulated and filled by different manufacturers in the same or different countries:

a) Commodity transaction: sale and purchase of bulk vaccine on the open market. Bulk manufacturers and finished product manufacturers working under this type of arrangement would not be eligible to undergo the prequalification process for the products in question.

B) Contract manufacturing: a contract manufacturer is a facility that is subcontracted by a vaccine manufacturer to do one or more steps of the process. The vaccine manufacturer is responsible for the product and shall ensure that all steps of the manufacturing process are performed in accordance with the licence specifications and in compliance with GMP.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 12

In agreement with UN purchasing agencies or other partners, the fast-track procedure (for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies) can be considered in the following situations:

An acute shortage* of a vaccine that puts at risk the global supply of routine immunization programmes. (*As agreed with UN purchasing agencies and other partners.)

An emergency situation or outbreak of a disease for which there is no prequalified vaccine, or its availability is not sufficient and an additional source of the same vaccine is required.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 13

Under special circumstances, the prequalification evaluation can be initiated before the national licence is granted. This provision can be applied, in agreement with the UN purchasing agencies and other partners, under the following circumstances:

The vaccine is a priority vaccine for introduction into the routine immunization programme; and

Availability of the vaccine in question is a substantial limiting factor for the timely introduction of the vaccine into routine immunization programmes.

This provision does not apply to novel vaccines not yet introduced in the immunization programme.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 13

In some cases, vaccines that are manufactured in one country (country A) can be finished (packaged, or filled, labelled and packaged, or formulated, filled, labelled and packaged) in a different country (country B) by the same or different manufacturer. The vaccine would then be distributed only from the country where the finished product is manufactured (country B). In such cases, the vaccine must have been licensed in country B, the regulatory authority of country B must have been assessed by WHO and found to meet all the critical indicators as defined by WHO for prequalification purposes and must have agreed to exercise the ongoing regulatory overseeing of the product for export through UN agencies

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 15

Reassessments (of the acceptability, in principle, of vaccines for purchase by United Nations agencies) will be done in the following situations:

- i) At regular intervals, usually every two years, with the possibility of an extension of up to five years for vaccines that have been prequalified for more than two years, and have been reassessed at least once after initial evaluation.
- ii) If the vaccine fails to meet the WHO recommendations and/or the specifications of the offer to bid.
- iii) When no supply to the UN has taken place for a period equal to, or greater than, two years.
- iv) In the case of a suspension of production, after production is reestablished and before purchase by the UN agencies.
- v) When, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made.

Samples of lots supplied through UN agencies will be selected, at regular intervals (at least once a year), for independent testing of final product characteristics.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 17

The cost of the activities required to assess the acceptability, in principle, of candidate vaccines for UN agency purchase is covered by the manufacturers.

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

[WHO/IVB/05.19](#)

page 18

(l)f, in the opinion of the manufacturer, any information to be submitted to WHO and its expert team members in the course of the (re)assessment procedure (for acceptability of vaccines for purchase by United Nations agencies) includes confidential information; the manufacturer must advise WHO thereof in writing, prior to or at the same time as the disclosure, duly identifying the confidential information in question. Notwithstanding the foregoing, WHO and its expert team members will treat all information submitted to them either as written documents or during site visits as confidential, in accordance with the terms set forth below.

WHO will treat information so identified contained in the product summary file and information disclosed during site visits as confidential and proprietary to the manufacturer and, in this connection, take all reasonable measures to ensure (a) that such information (the Confidential Information) is not used for any other purpose than the (re)assessment procedure described in this document, and (b) that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein. WHO and/or its expert team members will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- a) was known to them prior to any disclosure by the manufacturer; or
- b) was in the public domain at the time of disclosure by the manufacturer; or
- c) has become part of the public domain through no fault of WHO and/or any of its expert team members; or
- d) has become available to WHO and/or any of its expert team members from a third party not in breach of any legal obligations of confidentiality to the manufacturer.

Japanese encephalitis vaccines (WHO position paper)

[WER 2006, vol. 81, 34/35, pp 331-340](#)

page 332

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

Polio

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 37

WHO requirements for thermostability for OPV:
Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national control authorities are to specify the minimum virus titres per human dose

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 42

Poliomyelitis vaccines were remarkably stable within the pH range 6.5-7.2. A vaccine can be maintained in this pH range by preventing the loss of carbon dioxide from a bicarbonate-containing vaccine, keeping the air space above the vaccine to a minimum, and packing the vaccine in tightly stoppered containers.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 31

Each final lot of OPV must undergo the accelerated degradation test to confirm that its stability is satisfactory. Representative final containers of the vaccine have to be incubated at 37C for 48 hours. The total virus content in both exposed and unexposed vials is determined concurrently with that of a trivalent reference preparation. The vaccine passes the test if the loss on exposure is not greater than a factor of 100.5 infectious units per human dose. The national regulatory authorities are to specify the minimum virus titers per human dose

Rabies

State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)
page 89

A number of cell-culture based rabies vaccines are being developed in China and India on Vero cells, human diploid cells (HDC), or duck embryo cells. These vaccines however have not yet been prequalified by WHO and may require further assessment in terms of safety and efficacy before they can be traded internationally.

Rubella

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 44

The WHO thermostability requirements for mumps and rubella vaccines are similar to those for measles vaccine. At least three containers of monovalent or MMR vaccine are tested by incubation at 37C for seven days, at the end of which each monovalent vaccine or individual vaccine component is titrated in PFUs or CCID50 after selective neutralization, as necessary, of the other components. The geometric mean infectious virus titre must equal or exceed the required minimum number of infective units per human dose (3 log₁₀), and the geometric mean virus titre must not have decreased by more than 1 log₁₀ infective units during incubation.

SAGE

Global Advisory Committee on Vaccine Safety, 12 December 2005

[WER 2006, vol. 81, 2, pp 15-19](#)
page 16

WHO is promoting vaccination strategies that economize on the use of antigens to address the current global shortage of influenza vaccines for epidemics and pandemics. That would entail development and licensing of novel antigen-sparing vaccine formulations.

The GACVS agreed to act as a resource for WHO if such a situation were to arise. The Committee made the following recommendations: develop pharmacovigilance guidelines to enable rapid assessment of pandemic influenza vaccines; promote the extension of such guidelines to evaluate seasonal influenza vaccines; develop an authoritative review of the safety and efficacy of inactivated influenza vaccines with adjuvants. It would be assured that regulators from developing countries are included in WHO meetings to promote regulatory collaboration on pandemic influenza vaccine issues and that lessons from the past, such as those from swine influenza vaccine, are taken into account.

Global Advisory Committee on Vaccine Safety, 1011 June 2004

[WER 2004, vol. 79, 29, pp 269-272](#)
page 270

It was suggested that WHO might serve as a repository for safety reports and as a forum for dialogue and guidance for the technical and scientific standards for adjuvants and their safety, for setting standards for such work, and for defining principles governing regulatory issues in adjuvant safety. The GACVS might collate such information, which should be evaluated and made widely available.

SAGE - recommend to WHO

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

Additional information on the safety of different mumps vaccine strains is available from country experiences with use of mumps vaccine in mass campaigns and routine settings. These data should be reviewed by the GACVS and the resulting conclusions included in the revision of the WHO mumps position paper.

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 214

The WHO secretariat should make special efforts to collaborate with industry to increase global availability of MMR vaccines that contain strains of mumps vaccines with the best safety profile.

Schedule

Mumps virus vaccines (WHO position paper)

[WER 2001, vol. 76, 45, pp 346-356](#)
page 354

Due to its known low effectiveness, the Rubini-strain (mumps) vaccine should not be used in national immunization programmes. Persons previously immunized with the Rubini-strain vaccine should receive a dose of an effective mumps vaccine to ensure protection.

Tetanus

Tetanus vaccine (WHO position paper)

[WER 2006, vol. 81, 20, pp 198-208](#)
page 202

According to WHO requirements*, the potency of monovalent tetanus toxoid shall be no less than 40 IU (determined in guinea-pigs or in mice) per dose (0.5 ml), and at least 40 IU (determined in guinea-pigs) or 60 IU (determined in mice) per dose when tetanus toxoid is used in combination with diphtheria and whole-cell pertussis vaccines.

* Requirements for diphtheria, tetanus, pertussis and combined vaccines. WHO Technical Report Series, No. 800, 1990, Annex 2; Recommendations for diphtheria, tetanus, pertussis and combined vaccines (Amendments 2003). WHO Technical Report Series, No. 927, 2005, Annex 5.

VPD Surveillance

Regulation of vaccines: building on existing drug regulatory authorities

[WHO/V&B/99.10](#)
page 15

Post-marketing surveillance by a national regulatory authority encompasses many activities which include:

- 1) The periodic inspections performed to evaluate compliance of manufacturers with GMP and conformance with approved manufacturing processes.
- 2) The continual monitoring of the quality of vaccines through lot release programs and ad hoc assessment of samples collected in the field (less important when lot release is rigorously performed).
- 3) Review and evaluation of adverse reactions to be reported by health care providers.
- 4) Monitoring for effectiveness and efficacy of vaccine preventable diseases.
- 5) Some agencies may include evaluation of vaccine uptake.

Yellow Fever

Thermostability of vaccines

[WHO/GPV/98.07](#)
page 20

WHO requirement for yellow fever vaccine stability stipulates that the vaccine should retain 1000 mouse LD50 or the equivalent in plaque-forming units (PFUs) per human dose, and that the mean titre loss should be less than 1 log₁₀ after two weeks incubation at 37C.

Yellow fever vaccine (WHO position paper)

[WER 2003, vol. 78, 40, pp 349-359](#)
page 355

According to current WHO requirements, a YF (yellow fever) vaccine that has been held at 37 C for 14 days must (i) maintain the minimal potency of >1000 MLD50 per dose and (ii) show a mean loss of titre <1 log₁₀ MLD50. These requirements necessitate the addition of stabilizers such as sorbitol and gelatin.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 29

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log₁₀.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 29

(Yellow fever vaccines) meeting the WHO stability guidelines show a minimum mouse potency titer (or an equivalent potency in PFU) of greater than 1000 units after exposure to 37C for 14 days, and their loss in potency during this exposure is less than 1 log₁₀.