

Corrigendum

Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes

This corrigendum is issued to correct the following sentence, in page 9: "...medicinal products that will not be marketed within the European Commission".

It should read: "...within the European Community".

Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes

Immunization, Vaccines and Biologicals



World Health
Organization

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World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland

• *Fax:* + 41 22 791 4227 • *Email:* vaccines@who.int •

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Abbreviations and acronyms

AEFI	adverse event following immunization
BCG	bacille Calmette-Guérin (vaccine)
CHMP	Committee for Medicinal Products for Human Use
CMC	chemistry, manufacturing, control
CTD	common technical document, as defined by the International Conference on Harmonization
DTP	diphtheria-tetanus-pertussis vaccine
DT/TT/Td	products containing diphtheria and tetanus toxoids
EC	European Commission
EMA	the European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
Hib	<i>Haemophilus influenzae</i> type b conjugate vaccine
ICH	International Conference on Harmonization
IPV	inactivated polio vaccine
MA	marketing authorization
MMR	measles-mumps-rubella (vaccine)
NCL	National Control Laboratory
NIP	National Immunization Programme
NRA	National Regulatory Authority
OPV	oral poliovirus vaccine
PAHO	Pan American Health Organization
PSF	product summary file
RF	Revolving Fund

SBA	Summary Basis of Approval (Food and Drug Administration, USA)
SEAR	South-East Asia Region (WHO)
TRS	Technical Report Series (WHO)
UN	United Nations
UNICEF	United Nations Children's Fund
USA	United States of America
VVM	Vaccine Vial Monitor
WHO	World Health Organization

1. General considerations

Many countries without functional¹ national regulatory authorities (NRAs) source their vaccines through United Nations (UN) procurement agencies² that supply vaccines from the list of WHO prequalified products. These countries are thus using, in their public immunization programmes (NIPs), vaccines that meet international standards of quality, safety and efficacy. However, while the WHO prequalification procedure ensures that these vaccines meet WHO recommended standards, it does not replace the oversight role of the NRA of the importing country. WHO recommends that each NRA must have an independent and functional system that covers at least two functions³, even if most or all of the vaccines are sourced through UN agencies. Furthermore, WHO recommends that a priority for countries in this situation should be to strengthen their ability to detect and resolve adverse events following immunization (AEFIs). Other countries import their vaccines through direct procurement, thereby taking advantage of WHO's work in prequalification of products and NRA assessments. Sometimes these countries impose a regulatory approval procedure on products that they buy. However, the regulatory approval activities that ensure a proper product evaluation and facilitate licensing in many developing countries, may require a defined expertise that does not exist, or may be less mature.

¹ Definition of functional NRA is a system independent and functional as assessed against the WHO recommended indicators (according to the main national source of vaccines: domestic production; direct procurement; or UN agency procurement).

See http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm.

² The United Nations Children's Fund (UNICEF) through its Supply Division; the World Health Organization (WHO), which procures through the Revolving Fund (RF) of the Pan American Health Organization (PAHO), through its office in the Americas, etc.

³ Marketing authorization (MA) and licensing activities to give regulatory approval, and postmarketing surveillance, including monitoring of adverse events following immunization (AEFIs).

2. Intent of procedure

This procedure is directed at countries that source their vaccines either through UN agencies or by importing directly from manufacturers using the WHO prequalified list of products, and that wish to ensure that these products are under appropriate regulatory oversight, but may lack the resources to carry out a regulatory approval procedure. Because in executing the prequalification process WHO assures that the necessary regulatory functions are in place, countries that source their vaccines using the WHO prequalified list could expedite the regulatory process for these products by using a fast-track procedure. Such a procedure would recognize the contribution of the WHO prequalification process, while facilitating development of national regulatory capacity. (It is essential, however, to remember the responsibility of all importing countries to develop and implement a system for the detection and resolution of AEFIs). The aim of the expedited procedure is two-fold: a) to propose a methodology that will be in accord with national regulations⁴ and international standards of regulatory approval of products; b) to continue to provide timely access to vaccines used in national immunization programmes that meet standards of assured quality. In addition, it can help NRAs define priorities, including placing more emphasis on adverse event surveillance - the most relevant function for all countries receiving prequalified vaccines from any source.

Six countries from WHO's South-East Asia Region (SEAR)⁵ were selected to participate in an expert committee consultation aimed at identifying issues related to the regulatory approval of UN-sourced vaccines, and formulating recommendations for developing a procedure that would help countries to meet international regulatory standards for the approval of WHO prequalified vaccines, sourced either through UN agencies or procured directly.⁶ This expert consultation reviewed and detailed the modality of a fast-track system for the regulatory approval of UN-sourced vaccines that can address the limited regulatory capacity in some developing countries, and ensure access to assured quality vaccines. It also considered a fast-track process for countries that procure WHO prequalified vaccines directly.

⁴ In the event that national regulations exclude the possibility of an expedited process, countries would need to change these regulations (see Section 11.1) to use the procedure.

⁵ The People's Republic of Bangladesh, the Kingdom of Bhutan, the Republic of India, the Republic of Maldives, the Kingdom of Nepal, and the Democratic Socialist Republic of Sri Lanka.

⁶ WHO Regional Office for South-East Asia, Immunization and Vaccine Development. Expert committee consultation to develop a fast-track mechanism for the licensing of vaccines procured through UN agencies. New Delhi, 13-15 September 2005.

The procedure that follows, defining the implementation of an expedited system for the regulatory approval of imported vaccines that appear on WHO's list of prequalified products for use in national immunization programmes, is intended for use by all concerned NRAs and vaccine manufacturers. Moreover, it will be of interest to UN procurement agencies and to all those working in the area of NRA strengthening.

3. Definitions

Applicability of the expedited procedure. This procedure is applicable to all imported prequalified vaccines that are supplied through a UN agency or are bought using a direct procurement mechanism for use in national immunization programmes. If such a product is directly procured, this procedure is applicable only if the specifications it is required to meet are identical to those outlined in the UN agency tender.

Expedited procedure. An abbreviated regulatory process building on the WHO prequalification procedure, that allows an NRA to provide regulatory approval for imported vaccine products that are included on the WHO list of prequalified products intended for use in national immunization programmes.

Novel and regionally-used vaccines. In the context of this procedure, it includes vaccines that are not considered traditional because they are not the subject of a global WHO recommendation, and might include, but is not limited to, vaccines protecting against Japanese encephalitis B, cholera, typhoid, rabies, meningitis, inactivated polio vaccine (IPV), combination vaccines such as measles-mumps-rubella (MMR), or those containing hepatitis B and/or Hib, as well as other vaccines that may be WHO-prequalified.

Prequalified product. A vaccine product that appears on the list of products on the WHO website⁷ that have been through a published prequalification process to be eligible for purchase by UN agencies for use in national immunization programmes.

Traditional vaccine. Traditional vaccines in the context of this procedure are defined as diphtheria and tetanus toxoids and (whole cell) pertussis vaccine (DTP), bacille Calmette-Guérin (BCG), oral poliovirus vaccine (OPV), products containing diphtheria and tetanus toxoids (DT/Td/TT), measles, hepatitis B, and/or *Haemophilus influenzae* type b conjugate (Hib) vaccines. Yellow fever vaccines are also included, even though they are not used on a global basis, but have been part of the standard package procured by UN procurement agencies.

⁷ http://www.who.int/vaccines-access/quality/un_prequalified/un_prequalified_producers.htm.

4. The prequalification process

WHO provides a service to UNICEF and other UN agencies that purchase vaccines, to determine the acceptability in principle of vaccines from different sources for supply to these agencies. The process in place at WHO to assess the acceptability of candidate vaccines for purchase was published initially in 1987, and was revised in 1988 and in 1989.⁸ It was subsequently revised twice more, in 1996 and 2002, and, based on recommendations made by an advisory committee of experts convened by WHO in April 2004, was replaced by the current document.⁹

Following the evaluation process, WHO issues a list of vaccines which have successfully fulfilled all the established conditions and can thus be taken into consideration for purchase by UN agencies. The system in place has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies. In recent years, it has been recognized that countries also use the list of prequalified vaccines as guidance for reliable sources for purchase.

⁸ WHO Expert Committee on Biological Standardization. Thirty-seventh report. Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 760, Annexes 1 and 2); Thirty-eighth report. Geneva, World Health Organization, 1988 (WHO Technical Report Series, No. 771, Annexes 2 and 3); Thirty-ninth report. Geneva, World Health Organization, 1989 (WHO Technical Report Series, No. 786, Annex 1).

⁹ Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies at http://www.who.int/vaccines-access/quality/vmc/prequalification/pq_%20procedure_5april05_final.pdf.

The purpose of the prequalification assessment is to verify that the vaccines meet the specifications of the relevant UN agency, and are produced and overseen in accordance with the principles and specifications recommended by WHO¹⁰ for good manufacturing practice (GMP), and for good clinical practice (GCP). This is to ensure that vaccines used in national immunization services in different countries are safe and effective for the target population at the recommended schedules, and that they meet particular operational specifications for packaging and presentation.

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

- reliance on the NRA of the country of manufacture which meets the WHO published NRA indicators;¹¹
- general understanding of the product and presentations offered, the production process, quality-control 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 AEFI.

For the evaluation of vaccines, WHO requires information related to the manufacturing company and also to the product itself. The manufacturer provides this information in the Product Summary File (PSF) and during the site visit.

Once the process is complete, and if WHO considers that the outcome is satisfactory,

WHO sends a letter to UNICEF and other UN agencies advising on (a) compliance of the vaccine with both the WHO requirements and the specifications of the relevant UN agency, and (b) the role of the NRA in certifying this fact. This letter will be copied to the manufacturer, the NRA, the National Control Laboratory (NCL) or other entity responsible for lot release, and the relevant WHO regional and country offices. The vaccine will then be included in the WHO list of prequalified vaccines¹² the following month. The prequalified status of a vaccine is normally valid for a period of two years; however, under certain circumstances this status can be extended for up to five years.

¹⁰ WHO Expert Committee on Biological Standardization. Good manufacturing practices for biological products. Geneva, World Health Organization, adopted 1991. (WHO Technical Report Series, No. 822, Annex 1) available at <http://www.who.int/biologicals/publications/trs/areas/vaccines/gmp/en/index.html>, and WHO Expert Committee on Biological Standardization. Guidelines on clinical evaluation of vaccines: regulatory expectations. Geneva, World Health Organization, adopted 2001. (WHO Technical Report Series, No. 924, Annex 1) available at http://www.who.int/biologicals/publications/trs/entity_biologicals_publications_trs_52_en/en/index.html.

¹¹ http://www.who.int/vaccines-access/vaccine_regulation/nras/nrastrengthening.htm.

¹² The current list may be consulted at http://www.who.int/vaccines-access/quality/un_prequalified/un_prequalified_producers.htm.

5. Activities to be in place for registration/marketing approval of a product by an NRA (WHO definition of functions)

According to the WHO definitions of NRA functions, for marketing approval of a product and continuing regulatory oversight, the following activities should be in place for an NRA overseeing production: review of the CMC file (chemistry, manufacturing, control), corresponding to Module 3 of the Common Technical Document (CTD); assessment of GMP compliance of the facility and of the production procedure, ongoing after marketing; continuing review of variations and changes submitted to the product registration file; review of appropriate clinical data; continuing review of product safety-first through clinical trials and after marketing through a functional AEFI system; lot release; and development, validation, standardization and use of tests that correlate with efficacy (laboratory correlates of efficacy), such as the measles potency test, or if none, with consistency (eg. immunogenicity test for acellular pertussis potency).¹³

¹³ It should be noted that the procedure covers general pre-approval activities by the NRAs using it. Post-approval activities will derive from the updates received from WHO and the UN procuring agency (Annex 1c), and will include also those activities already in place in the countries for products undergoing the full regulatory approval process.

6. Activities that are assured for WHO prequalified products

The WHO prequalification process ensures that the functions listed in the preceding paragraph are executed by the producer's NRA. In addition, WHO reviews clinical data to make sure that they are applicable to the immunization schedule recommended for general use on a global basis, and for the epidemiological situations in different WHO regions. If not, WHO may choose to prequalify the product and provide detailed information on the scope of applicability of the vaccine, as well as providing a disclaimer stating that prequalification of a vaccine does not imply a recommendation for use in all countries and referring to WHO position papers reflecting use recommendations. These products are referred to in the procedure that follows as “prequalified products not recommended for global use”. To date there are no such products.

The producer's NRA is responsible for continuing communication with WHO regarding GMP compliance, variations, failures in the lot-release process, and AEFI, all of which should be communicated by the manufacturer. However, assurance of continued compliance with specifications is done only through random laboratory testing, not on a lot-by-lot basis, unless this is done by the producer's NRA as part of the lot-release process. Manufacturers may produce several products of a certain type, complying with different specifications of packaging, presentation and potency. If the product is procured directly, in the application of the fast-track process it should be ensured that the product in question has specifications identical to those specified in the UN agency tender.

7. Special case for vaccines approved through EMEA scientific opinion process

Article 58 of Regulation (EC) No 726/2004¹⁴ establishes a mechanism whereby the European Medicines Agency (EMA) may give a scientific opinion rather than a Marketing Authorization (MA), in the context of cooperation with WHO, for the use of certain medicinal products that will not be marketed within the European Commission (EC). GMP inspections are coordinated by the EMA but carried out by the competent authority in the country of manufacture. GCP inspections and good laboratory practice (GLP) inspections for preclinical testing are carried out by the inspectorates of member states. The manufacturer must commit to report and record any AEFIs to the competent authorities where the product is marketed, and to the EMA. Batch control is done by the manufacturer and may be recommended to be done by an official medicines control laboratory. All recalls and defects that restrict supply, are to be reported to competent authorities in the countries where the products are marketed. As is the case for products receiving an MA through the EMA centralized process, European Public Assessment Reports (EPARs) will be available, and coordinated by EMA following a positive final scientific opinion.

For products that receive such a scientific opinion from EMA in lieu of a marketing authorization, and thereafter receive WHO prequalification for as long as the vaccines continue to be prequalified, there would be no significant change from the procedure outlined below, except that the granting of the scientific opinion would be conditional on the manufacturer's commitment to conduct active surveillance of AEFI in countries procuring the vaccine directly. The importing NRA would also need to ensure that those reports were received directly from the manufacturer.

¹⁴ Committee for Medicinal Products for Human Use. Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community. EMA/CHMP/5579/04, 23 May 2005.

8. Responsibilities of the importing country's NRA under the expedited review procedure

NRAs that elect to use the expedited procedure have a responsibility to follow the review time frames and conditions as outlined in the procedure. In the event that the manufacturer's application is disapproved, these NRAs agree to provide WHO (with a copy to the procuring agency if applicable), with a detailed justification. Should WHO find such a disapproval justified, this may trigger an investigation into the product, and a review of its prequalification status. However, if the disapproval is not justified, this could jeopardize future supply of the indicated product through the given UN agency route. NRAs electing to use this expedited review procedure will not require more information from manufacturers or relevant distributors than that defined below.

It will be understood that the implementation process for such a procedure will take time. All products cannot be reviewed at the same time, even using an expedited review procedure. Thus countries, in adopting this procedure, need to build in a transition period of one or two years to ensure that all necessary products can eventually be reviewed without threatening the national vaccine supply. Moreover, the review process should not be construed as a means to block import of any prequalified vaccine sourced through a UN agency for use in national immunization programmes.

Note that some, but not all, countries that procure vaccines directly, in order to enter into the procurement process require the presence within the country of a licensed agent. Countries wishing to undertake this expedited review procedure for imported prequalified products which are directly procured, should ensure that nothing in their procurement regulations is inconsistent with the principles stated herein.

9. Responsibilities of WHO under the expedited review procedure

WHO agrees, under both scenarios 1 and 2, to inform all countries that have indicated their intent to use this process, of any changes in the prequalification status of the products, together with a brief explanatory statement. This information can be provided on the supplementary form included in Annex 1c. Such statements will be based on ongoing communication with the manufacturer and the NRA, as well as the reassessment process for prequalification by WHO.

WHO will also distribute to all countries using this process for fast-track approval under either scenario 1 or scenario 2, information relating to decisions not to purchase the product, that are based on product quality, product packaging, or any other conditions which may impact its suitability for use in a national immunization programme, which have been reported to WHO by UN procurement agencies. This information will be provided to NRAs by WHO on the supplementary form provided in Annex 1c.

10. Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes

This procedure is intended for countries that source their vaccines through UN agencies, or who are using information from the WHO prequalification process as a basis for selection of vaccines for use in their national immunization programmes, importing them through direct procurement. It provides guidance on how NRAs of such countries can build on the processes in place for the WHO prequalification process to expedite the granting of regulatory review for such products. *It is important to recognize that this procedure describes only the regulatory review process and is not intended to abrogate or otherwise affect any post-approval activities that may be in place in the countries using it.* It is intended that the importing country would receive information on changes and variations and the relevant regulatory actions that would impact the product's approval through the WHO prequalification status. Although the procedure applies to both traditional, and novel and regional vaccines as defined in the definitions section, there is a difference in the provisions for traditional vaccines, and for the others. There has been many years of experience with the use of traditional vaccines, plus there is a thorough knowledge of production processes, related adverse reactions, validated laboratory tests that correlate with performance, and clinical data in epidemiological situations reflecting use in all countries. On the other hand, the novel vaccines and those for regional or limited use, have had a shorter history of use, limited to only some countries, and there may be geographical and epidemiological implications in their field performance that have not yet been explored [see Sections 10.3.1(o) and 10.3.2(n)].

Countries may choose to adopt all or part of the procedure as part of their national regulations for regulatory review of these specific products. WHO should be kept informed of their experience with its use.

10.1 **Changing national regulations.** In order to provide for a regulatory basis to put in place an expedited process, countries should ensure that their national regulations define conditions where it will be possible to shorten the normal regulatory approval process. Many countries already have as part of their national legislative basis, a provision for such an expedited regulatory review. Where this is not defined, countries may need to amend their regulations to allow for such a change. Each country must determine the most appropriate manner of accomplishing this. However, a change in the implementing regulations for the national drug law or its equivalent, may be the most appropriate pathway. For some countries, this may entail a change in the regulations defining the role and activities of the NRA and/or the relevant affiliated institutions, e.g. the National Control Laboratory (NCL). For others, it may entail a legislative change accompanied by a guideline, or by a guideline alone. The present procedure can be adapted for that purpose. WHO can provide support to countries in examining their legislative framework to determine how best to accomplish this change should it be necessary. Countries should ensure that the time frame for implementation, including a transitional period, is included in their national procedures.

Moreover, those countries aiming to use the expedited review process under scenario 2, direct procurement of prequalified vaccines, should ensure that nothing in their national procurement regulations would interfere with the use of this process.

10.2 **Criteria for use.** This procedure is intended to apply to traditional and novel vaccines, and vaccines used regionally as defined above, for use in the following situations.

10.2.1 **Scenario 1.** For an expedited review of vaccines that are WHO-prequalified and are sourced from a UN agency.

10.2.2 **Scenario 2.** For an expedited review of imported vaccines that are WHO-prequalified and are procured directly, provided that the same specifications as provided in the UN agency tender are included in the national tender (see Annex 1b). In this case, regulatory approval can be granted only based on confirmation that the product in question meets the UN agency tender specifications, and the product supplied has demonstrated consistency in meeting them (tender specifications are provided in form Annex 1b, which can be requested from WHO through the manufacturer).

To trigger the process, an importing NRA may invite a manufacturer to submit an application form for review of a given vaccine, along with samples of products, lot release certificates, and the corresponding summary lot protocols of three final lots of product derived from three consecutive bulk lots. A complete description is given in Annex 1a, along with the application form, and the complementary information to be provided by WHO (Annex 1b). Annex 3 provides suggested implementation steps for putting in place this expedited review procedure.

10.3 NRA responsibilities for the expedited process

NRAs electing to use this process agree to follow the steps outlined below and to notify WHO of the outcome. More details are provided in Section 5 (Conditions and review time frames). NRAs electing to use this process will not require additional information beyond that detailed below for approval under this process. **In the case of suspected problems with the quality of the vaccine being supplied, additional information will be required.**

Since the process described below differs significantly from a normal review process because of the recognition of the work already done by the manufacturer's NRA and by WHO, the review of the file will not require review by experts in different subjects. An examination of the checklist in Annex 1d will illustrate this. Therefore, the file for an expedited review should only go to a designated person or group within the NRA. Because the process rests so heavily on visual inspection and review of summary lot protocols to ensure that the product meets tender specifications, a possibility in some countries is to refer the entire process to the group charged with lot release of a particular vaccine, or group of vaccines; for example the NCL.

10.3.1 **Scenario 1.** Countries that are importing vaccines that are prequalified through a UN agency, would be required to follow the following steps. [In the case of novel vaccines and those for regional use, please see also Section 10.3.1(o)].

10.3.1(a) Ensure that the regulations on product approval allow for the possibility of an expedited regulatory review of products meeting the criteria defined below.

10.3.1(b) Check the prequalification status of the product. This should be provided in the application by the manufacturer using the form provided in Annex 1b (information to be provided by WHO). If there are limitations on the use of the product as indicated in Annex 1b, i.e. if the products are prequalified but not recommended for global use, the procedures defined in Section 10.3.1(o) should also be followed.

10.3.1(c) Ensure that the necessary documents are provided. For scenario 1 products, this should be limited to product samples, product inserts, NRA lot release certificates from the country of origin, a list of countries where the product is licensed and marketed, and summary lot protocols of three final lots derived from three consecutive bulk lots for consistency determination. A sample manufacturer's application form is provided in Annex 1a.

10.3.1(d) Conduct a visual inspection of the samples supplied for consistency determination with respect to colour, freedom from particulates, vial size, vial filling, stoppers, labels, etc.

10.3.1(e) Check that the specifications met by the product provided in the summary lot protocol match those in the appropriate WHO Technical Report Series (referred to in the UN agency tender document, and referenced in the form provided in Annex 1b).

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- 10.3.1(f) Review the product leaflet against the model insert (obtainable from WHO; provided with the application form by the manufacturer in Annex 1b).
 - 10.3.1(g) Review the product label and inner box against the appropriate WHO Technical Report Series publication (referred to in the UN agency tender document, and referenced in the form provided in Annex 1b).
 - 10.3.1(h) Review the samples, label, and inner box for consistency, and also that they match the description supplied in the summary lot protocols.
 - 10.3.1(i) Assure the presence of the Vaccine Vial Monitor (VVM) and of other items as specified in the WHO *Guidelines on the international packaging and shipping of vaccines*.¹⁵
 - 10.3.1(j) Prepare a report based on the review indicating compliance or non-compliance with national norms and the tender specifications. The checklist provided in Annex 1d may be used for this purpose.
 - 10.3.1(k) If compliant, issue the *Certificate of Approval* and add the product to the list of authorized products.
 - 10.3.1(l) Notify WHO and the manufacturer of the outcome, and copy to the UN procurement agency. In the event of disapproval of the application, provide a detailed justification to WHO, with a copy to the UN procurement agency.¹⁶
 - 10.3.1(m) Upon receipt of updated information from WHO, including information from the UN procurement agency (information in form provided in Annex 1c), add this information to the product file. No further action will be necessary unless WHO recommends that the prequalification status be withdrawn.
 - 10.3.1(n) For countries that are receiving their vaccines ONLY through UN procurement, any additional steps should be omitted, as they duplicate the prequalification process.

¹⁵ WHO/IVB/05.23.

¹⁶ Notifications should be made through the WHO representative who will forward through the respective WHO Regional Office to the Prequalification Officer, World Health Organization Quality, Safety and Standards, IVB, Avenue Appia, 1211 Geneva 27, Switzerland, email vaccines@who.int.

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- 10.3.1(o) If the vaccine is not on the list of traditional vaccines, refer to the information on prequalification status provided on the form contained in Annex 1b. If there are restrictions on the use of the product (for example, if prequalification is given only for use in a particular geographical region), and your country is not included in the area of restricted use, the existing clinical data will need to be reviewed. This can be done effectively through one of the regional fora convened by WHO, and WHO assistance in the provision and review of clinical data should be requested.¹⁷
- 10.3.2 **Scenario 2.** For countries importing prequalified vaccines through direct procurement [for novel vaccines and those for regional use, please see Section 10.3.2(n)].
- 10.3.2(a) Ensure that the regulations on product approval allow for the possibility of an expedited regulatory review for products that meet the criteria defined below. Note that national procurement guidelines may contain special conditions governing the procurement of products for national immunization programmes. For example, some countries require that the sponsor must have a national representative participate in the procurement process. The aim of this procedure is to ensure that the regulatory approval process should be as streamlined as possible for a prequalified product; thus, countries using this procedure for regulatory review of directly-procured prequalified products should ensure that the process discussed below is consistent with their procurement guidelines. If not, then the guidelines should be altered prior to embarking on its use.
- 10.3.2(b) Check the prequalification status of the product. This should be provided by the manufacturer as part of the application using the form provided in Annex 1b. If there are limitations on the use of the product as indicated in Annex 1b, that is if the products are prequalified but not recommended for global use, carry out the procedures defined in Section 10.3.2(n).

¹⁷ Request to the Regulatory Pathways Officer, World Health Organization, IVB, Avenue Appia, 1211 Geneva 27, Switzerland, email vaccines@who.int. Note that in this case the time frame for approval may be extended (see Section 5).

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- 10.3.2(c) Ensure that the necessary documents are provided. This should include product samples, product inserts, lot release certificates, and summary lot protocols of three consecutive lots for consistency determination (see the form in Annex 1a). Additional documentation, including verification that the NRA and the manufacturer are providing WHO with ongoing verification of GMP compliance, AEFI monitoring, and control of variations, and that WHO has reviewed the clinical data for appropriateness for the national epidemiological situation, can be sought from WHO when the manufacturer applies for expedited regulatory review.¹⁸
 - 10.3.2(d) Conduct a visual inspection of the samples supplied for consistency determination with respect to colour, freedom from particulates, vial size, vial filling, stoppers, labels, etc.
 - 10.3.2(e) Check that specifications provided in the summary lot protocol match those in the appropriate Technical Report Series, and those in the national tender, if different. Note that the product specifications must be the same as that for the UN procurement agency tender (provided on the form in Annex 1b by WHO, and included with the manufacturer's application). Review the lot-release data provided to ensure compliance with the specifications.¹⁹
 - 10.3.2(f) Review the product leaflet against the model insert (obtainable from WHO on the form in Annex 1b).
 - 10.3.2(g) Review the product label and inner box against the appropriate WHO Technical Report Series publication.
 - 10.3.2(h) Review the sample, label, and inner box for consistency, and also that they match the descriptions supplied on the summary lot protocols.
 - 10.3.2(i) Assure the presence of the Vaccine Vial Monitor and of other items as specified in the WHO *Guidelines on the international packaging and shipping of vaccines*.²⁰ [It is assumed that countries would include this in their procurement specifications - see Section 10.3.2(e)].
 - 10.3.2(j) Prepare a report based on the review, indicating compliance or non-compliance with national norms and the tender specifications. The checklist provided in Annex 1d may be used for this.

¹⁸ A reporting form for providing the necessary information is provided in the list of documents, Annex 1b.

¹⁹ In special cases, testing may be carried out at the National Control Laboratory to confirm compliance with specifications, but only if the appropriate tests are validated. Disputes should be referred to WHO for an opinion based on an investigation of the testing methodology and quality assurance system.

²⁰ WHO/IVB/05.23.

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- 10.3.2(k) If compliant, issue the *Certificate of Approval* and add the product to the list of authorized products.
 - 10.3.2(l) Notify WHO and the manufacturer of the outcome. In the event of disapproval of the application, provide a detailed justification to WHO.²¹
 - 10.3.2(m) Upon receipt of updated information from WHO (information on the form provided in Annex 1c), or from the manufacturer and his NRA, add this information to the product file. No further action is necessary unless WHO recommends that the prequalification status be withdrawn.
 - 10.3.2(n) If the vaccine is not on the list of traditional vaccines, refer to the information on prequalification status provided on the form contained in Annex 1b. If there are restrictions on the use of the product (e.g. if prequalification is given only for use in a particular geographical region), and your country is not included in the area of restricted use, the existing clinical data will need to be reviewed. This can be done effectively through one of the regional fora convened by WHO, and WHO assistance should be requested for the provision and review of clinical data.²²

10.4 Documentation needs. The form in Annex 1a is the application for regulatory review using the expedited procedure for imported vaccines used in national immunization programmes, to be provided by the manufacturer to the importing country NRA. The form in Annex 1b is the initial information provided by WHO to the importing country NRA through the manufacturer, verifying the prequalification process and duration and conditions, if any, for prequalification, and providing specifications. The form in Annex 1c is for use by WHO to regularly update the importing country NRA should there be changes in the prequalification status, based on assessments by WHO and/or the UN procurement agency. The form in Annex 1d is a sample checklist that can be used for reporting the results of the product assessment in the fast-track process, and for reporting to WHO.

10.5 Conditions and review time frames. The guiding principle is to build on the WHO prequalification process and conserve NRA time and resources. For this reason, when this expedited regulatory review process is used, countries should consider limiting the amount of user fees levied for vaccines imported through UN agencies and for directly procured imported vaccines. Note that notification to WHO (with a copy to the UN procurement agency, if relevant, and justification if the decision is negative), should follow the same time frames for the review process as indicated below.

²¹ Notifications should be made through the WHO representative who will forward through the respective WHO Regional Office to the Prequalification Officer, World Health Organization Quality, Safety and Standards, IVB, Avenue Appia, 1211 Geneva 27, Switzerland, email vaccines@who.int.

²² Request to the Regulatory Pathways Officer, World Health Organization, IVB, Avenue Appia, 1211 Geneva 27, Switzerland, email vaccines@who.int. Note that in this case the time frame for approval may be extended (see Section 5).

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- 10.5.1 **Scenario 1.** Countries using this expedited review procedure must provide timely notification, which will be product and manufacturer specific, of the disposition of the expedited procedure to the manufacturer and to WHO (with a copy to the UN procurement agency). This notification should be dated and sent²³ at least 30 working days after receipt from the manufacturer of a complete information package, as defined in Annex 1a. Information to be provided by WHO on the form in Annex 1b as outlined in part 10.4 of this procedure, should be provided by the manufacturer as part of the application. The form in Annex 1d can be used for reporting if desired. In the special case of products covered by Section 10.3.1(o), for which the clinical data must be reviewed, a total of 120 working days may be provided.
- 10.5.2 **Scenario 2.** In the case of imported products that are procured directly, Section 10.5.1 will apply in its entirety, except in the special case of products covered by Section 10.3.2(n), for which the clinical data must be reviewed, a total of 120 working days may be provided. In addition, a total of 90 working days will be allowed in the event that the importing country's NCL²⁴ tests for compliance with specifications, when the specifications differ from those in the UN tender, and this only provided the laboratory has the ability to perform the appropriate validated test(s) (see Section 10.3.2(e), footnote 19). However, in no case should the review time exceed a total of 120 working days.
- 10.5.3 In the event that the information provided by the manufacturer is not complete, the process will be halted pending supply of the necessary documentation.
- 10.5.4 WHO should be notified of the results of the expedited regulatory process, in addition to the applicant manufacturer. In the event that the application is disapproved, WHO must receive a detailed justification for the disapproval within the timelines for the review process as outlined in Section 5, as this casts doubt on the prequalification process itself, and has implications for vaccine supply.
- 10.5.5 The period of validity of the regulatory approval should be limited to that normally provided by the importing NRA, so long as the prequalified status remains valid. Normally this will be reviewed every two years, and, provided WHO has been informed of the use of this expedited review procedure, the importing NRA will be notified in the event of a prequalification status change. If for any reason the prequalification status is withdrawn, the regulatory approval in the country using the expedited process would automatically be terminated pending a full investigation. Alternatively, a normal regulatory approval process could then be executed by the NRA.

²³ Notifications should be made through the WHO representative who will forward through the respective WHO Regional Office to the Prequalification Officer, World Health Organization Quality, Safety and Standards, IVB, Avenue Appia, 1211 Geneva 27, Switzerland, email vaccines@who.int.

²⁴ Or a duly authorized contract laboratory acting on its behalf.

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- 10.5.6 This process does not apply to vaccines being imported for private sector use. The process advocated is specifically linked to use of the imported vaccines in national immunization programmes, and may differ from those in place for products for private sector use.
- 10.5.7 NRAs should not use non-approved status to block entry of prequalified products procured by UN agencies for their national immunization programmes under this expedited review process.
- 10.6 **Mechanisms.** The process will be triggered when an NRA, having ensured that its national regulations allow a waiver of the normal review process, instructs manufacturers to apply for regulatory approval for prequalified products that are being imported, using the forms contained in Annexes 1a and 1b. It is expected that NRAs adopting this procedure will impose a transition period to cover the period from inception until all eligible products are approved.

The provision of this information will signal that the process has started. The act of the manufacturer's requesting the form in Annex 1b to be sent to a country from WHO, will indicate a country's intention to use the process for a specific product. WHO should copy the information provided on Form 1b to the relevant UN procurement agency, to cover products sourced through that agency.

If the decision is not positive, the importing country NRA will provide WHO with detailed justification (see Section 5.4). The appropriate UN procurement agency will be sent a copy of this information. If changes in regulatory approval or prequalification status of the product in question take place, WHO will provide updated information to the NRA applying the expedited review process or to report any other information which might impact the suitability of the product for use in national immunization programmes (e.g. any serious AEFI that is vaccine related). This information, to be provided on the form found in Annex 1c, will be provided by WHO, with relevant input from the UN procurement agency.

As new vaccines are prequalified on a regular basis, NRAs applying the expedited review process should monitor the WHO list of prequalified vaccines on a monthly basis, so that they can contact the manufacturer(s) should they wish to initiate the review process.²⁵

Annex 2 provides a proposed sequence of steps an NRA can take to implement this process.

²⁵ The WHO prequalification products list is updated monthly at http://www.who.int/vaccines-access/quality/un_prequalified/un_prequalified_producers.htm.

Annex 1:

List of documents

1a. Expedited review application form

Part 1. General information

- 1.1 Information about the manufacturer: include name and address of the manufacturing site(s), telephone and facsimile numbers, 24-hour telephone numbers and e-mail addresses of principal contacts. If the application is being submitted by a distributor within the importing country, this information should also be provided for the distributor.
- 1.2 Name of officer responsible (pharmacist responsible) and contact addresses, telephone numbers, and e-mail addresses, if not provided in Part 1.1.
- 1.3 Names and addresses, including telephone and facsimile numbers, and e-mail addresses of principal contacts for this particular product, of the National Regulatory Authority, and of the National Control Laboratory (or designated contract laboratory if different).

Part 2. Vaccine composition, presentation, and schedules

- 2.1 Name of the product; both generic name and brand name if applicable.
- 2.2 Composition of the product.
- 2.3 Description of the presentation, including diluent if applicable; forms, dose sizes, types of containers, Vaccine Vial Monitor (VVM) type used, and description of application devices (e.g. syringes, droppers) to be delivered with the vaccine, if applicable.
- 2.4 Schedule recommended, and administration route.

Part 3. Provided with this application

Samples of vials, ampoules of diluents, labels, boxes, package inserts and corresponding labelling to be provided in preferred language (selection of English, French, Spanish, Russian, or Portuguese, according to preference of the importing country):

- 10 units each of the following three final lots produced from three consecutive bulk lots of product, including relevant packaging listed above;

- copy of package insert;
- NRA batch release certificates for the three final lots listed above;
- summary lot protocols for the three final lots listed above;
- prequalification status form filled in and signed by WHO (see Annex 1b).

Date submitted:

Name and title of person
submitting application (typed):

1b. Form for provision of prequalification status and specifications requested from WHO

Information provided to: _____
(name and country of NRA using expedited review procedure for this product)

The product: _____

Manufactured by: _____

Located at: _____
(include any additional clarification needed for the manufacturing site)

Distributed by: _____ (if relevant)

Under the ongoing regulatory oversight of: _____
(insert name of National Regulatory Authority and National Control Laboratory as applicable)

Provided in: _____ dose (vials/ampoules) supplied:

- with diluent in (vials/ampoules);
- with syringes (description);
- with droppers.

WHO-prequalified as of: _____ (date)

The following conditions (if any), are attached to the prequalification status:

The prequalification status will be reassessed in: _____ (month, year) unless a decision, based on history, is made to waive the reassessment process. WHO will advise the recipient of this form if, as a result of the reassessment, or for any other reason the prequalification status is withdrawn.

The vaccine listed above meets the following specifications: (insert packaging specifications, relevant TRS documents, and product specifications if different from those stated in the TRS, and VVM type).

A copy of the sample product insert for the product is attached.

As part of the granting of prequalification status, the manufacturer and the NRA agree to keep WHO updated on an ongoing basis relative to verification of ongoing GMP compliance, AEFI monitoring, and control of variations. In the event that prequalification and/or national regulatory approval are withdrawn, WHO will provide the addressee named above with a notification to that effect, along with a brief summary statement explaining the reason for withdrawal.

Signed below by the WHO designated officer responsible for prequalification of vaccines:

Date:

Name and title (typed):

cc: UN procurement agency

1c. Form for updating information on regulatory status, packaging and other information that may impact the product's continuing suitability for use in national immunization programmes, for use by WHO

Information provided to: _____
(name and country of NRA using expedited review procedure for this product)

The product: _____

Manufactured by: _____

Located at: _____
(include any additional clarification needed for the manufacturing site)

Distributed by: _____ (if relevant)

Under the ongoing regulatory oversight of: _____
(insert name of National Regulatory Authority and National Control Laboratory as applicable)

Provided in: _____ dose (vials/ampoules) supplied:

- with diluent in (vials/ampoules);
- with syringes (description);
- with droppers.

WHO-prequalified as of: _____ (date)

The following conditions (if any), are attached to the prequalification status:

On the basis of information provided to WHO and the UN procurement agency by the manufacturer and the NRA, or as a result of reassessment activities by WHO, the product has undergone a suspension of prequalification status due to:

- withdrawal from the market;
- withdrawal of national regulatory approval;
- unsatisfactory reassessment;
- unsatisfactory field performance.

Additional comments: _____

Date:

Name and title of
WHO Prequalification Officer:

1d. Checklist for reporting product compliance

(Form to be used for national regulatory approval and sent as report to WHO within 30 working days of receipt of information.¹ Send via WHO country representative and respective Regional Office, to Prequalification Officer ivb@who.int).

Name of product: _____

Manufacturer: _____

Presentation: _____

Prequalification Status: _____
(Date) (Conditions)

Product received in (Country): _____

- through UN procurement;
- through direct procurement _____
(name of distributor if applicable).

Lot numbers assessed for consistency and conformity:

- Application form complete including WHO documentation of prequalification status;
- Summary Lot Protocols reviewed and indicated compliance with specifications in:
 - UN tender;
 - TRS number.
- Product leaflet consistent with sample product insert;
- Product label and inner box match TRS number;
- Product label, samples, and inner box consistent with each other;

¹ Except in cases of products for which clinical data review is needed (products prequalified with conditions indicated in Form 1b), for which the time frame is extended to a total of 120 working days.

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- Product label, samples, and inner box match Summary Lot Protocols;
 - VVM and relevant temperature-monitoring devices present (as per WHO/IVB/05.23);
 - If relevant,² information on clinical data that were reviewed and found satisfactory by a national or international committee of experts available (provide mechanism, e.g. expert national or international panel, regional forum, etc.);

Other observations: _____

Decision:

Product is approved for distribution in (country name): _____ until (month/year): _____ or WHO prequalification status lapses, whichever comes first.

Product is NOT approved for distribution (attach detailed justification).

Date: Name and title of officer responsible:

Send via WHO country representative and respective Regional Office to Prequalification Officer, vaccines@who.int, with a copy to UN procurement agency, unless product received through direct procurement.

² Only for products prequalified with conditions indicated in Form 1b.

Annex 2:

Proposed Implementation Plan

- 1) Review national regulations, procurement process (if relevant), vaccine import procedures, and any other processes that might be affected by adoption of the procedure, *Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes*.
- 2) In the event that changes are needed, implement them so that the procedure can be adopted. The changes should be kept as simple as possible, and WHO can assist with this process.
- 3) Adapt (if necessary) and adopt the procedure as part of the national regulatory process applying to vaccines for use in national immunization programmes. Note that as this process may take some time, countries may wish to start the process using the final draft guidelines.
- 4) Adapt and print the necessary forms (Annexes 1a, 1b, and 1d). Note that Annex 1c is for use by WHO.
- 5) Build in a transition period during which all prequalified vaccines eligible for the immunization programme can receive regulatory review. There will be no differentiation between nationally non-approved and approved vaccines sourced from UN agencies.
- 6) Select one or more manufacturers to start the process. These could be selected based on the proportion of current vaccines produced by them, with the intention that all products should be covered in as short a time as possible. Contact each manufacturer to inform them that the NRA is now accepting applications for the expedited review procedure, and provide the national forms.
- 7) Receipt of the application from the manufacturer. Note that the provision of information from WHO indicates that WHO has added your NRA to its tracking system for the expedited review process.
- 8) Review the application and provide Form 1d to WHO and to the manufacturer (with a copy to the UN procurement agency, if applicable), within the required time frames. If the decision is negative, provide appropriate justification.
- 9) Add the product information to the national approved drug list and monitoring system.
- 10) Select a second manufacturer and repeat the process, until all the prequalified suppliers providing vaccines for the national immunization programme have received expedited regulatory review.



The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested (*Initiative for Vaccine Research*).

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards (*Quality Assurance and Safety of Biologicals*).

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented (*Vaccine Assessment and Monitoring*).

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies (*Access to Technologies*).

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives (*Expanded Programme on Immunization*).

Department of Immunization, Vaccines and Biologicals

Family and Community Health

World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: +41 22 791 4227

Email: vaccines@who.int

or visit our web site at: <http://www.who.int/vaccines-documents>



World Health
Organization