Introduction

The 2014 Ebola outbreak is the largest Ebola epidemic in history, which affected multiple countries in West Africa. This epidemic has demonstrated the need for a WHO emergency use assessment and listing procedure (EUAL) for candidate vaccines for use in the context of a public health emergency. The purpose of this extraordinary procedure is to provide guidance to interested UN procurement agencies and national regulatory authorities (NRAs) of relevant WHO Member States. The present document describes the EUAL procedure for candidate vaccines and is primarily aimed at manufacturers of these vaccines in the context of use during a public health emergency. Participation in the procedure is voluntary.

EUAL is not WHO prequalification, and should not be thought of as such.

Rather, EUAL is a special procedure for vaccines in the case of a public health emergency when the community may be more willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options. In such instances, it is paramount to determine the minimal level of information needed prior to making a product available under a time-limited EUAL, while further data are being gathered and evaluated.

WHO recognizes the prime importance of conducting and completing clinical trials of any novel product, including when used in a public health emergency. The inclusion of a product in the EUAL list should not compromise such trials.

WHO has developed the EUAL process to expedite the availability of vaccines needed in public health emergency situations. The EUAL process is intended to assist interested UN procurement agencies and Member States on the acceptability for use of a specific vaccine in the context of a public health emergency, based on a minimum set of available quality, safety, and efficacy data.

It should be noted that it is the sole prerogative of WHO Member States whether or not to allow the emergency use of a candidate vaccine in their country.

Eligibility

In order to qualify for an EUAL, the use of the vaccine must meet the following conditions:

- The disease for which the vaccine is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). The Director-General may authorize use of this procedure for a public health emergency that does not
meet the criteria of a PHEIC if s/he determines that this is in the best interest of public health.

- Based on the contingencies of the specific public health emergency, it is reasonable to consider the vaccine for EUAL assessment (e.g., there is no licensed vaccine for the indication or for a critical subpopulation, e.g. children, or there is a specific vaccine shortage).
- The vaccine is subject to oversight by a NRA that has been assessed as functional by WHO and is willing to provide oversight of batch release and other post-EUAL product safety and manufacturing quality assurance requirements.
- The vaccine is manufactured in compliance with current Good Manufacturing Practices (GMP). If a manufacturer has a documented acceptable history of quality manufacturing of vaccines, WHO may waive the requirement for conducting an on-site inspection.
- The vaccine applicant attests that it intends to complete the development of the product and apply for WHO prequalification. In the ideal situation, the remaining clinical trials and other requisite testing will already be underway at the time of the application for an EUAL. (N.B. A future prequalification application should incorporate all information submitted for the EUAL plus any other information needed to complete a prequalification application.)

WHO may consider reviewing a candidate vaccine for EUAL that does not meet all of the above requirements. In such situations, the application letter and documentation provided to WHO must substantiate the need for the product although it does not meet all eligibility requirements. WHO will conduct a screening of the application and documentation, and will inform the applicant within 5 working days whether the application can be accepted for evaluation. The approximate review time frame will be communicated after the screening process.

By submitting an application the manufacturer will be deemed to have accepted the terms of this procedure.

**Content of the application**

The EUAL process will assess whether, in light of available WHO/international standards, the submitted data demonstrate a reasonable likelihood that the vaccine quality, safety and effectiveness are acceptable, and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC.

The application must be submitted to WHO and must provide the following information:

- Production and quality control information: starting materials (characterization of cell banks, organism seeds, and recombinant constructs), production process, quality control of intermediate and finished products, testing methods, including validation, specifications, and justification, proposed parameters, and values for batch release.
- Evidence of GMP compliance for the manufacturing site(s) where the vaccine is being produced.
- Stability data to demonstrate that the vaccine will maintain the minimum potency considered to be immunogenic/efficacious for the claimed shelf life under the conditions of use.
- Summary information on preclinical and clinical data (safety, immunogenicity, and efficacy, if available). If considered necessary, WHO may require the submission of raw data. If it is not possible to obtain human efficacy data, the applicant will have to justify to WHO’s satisfaction that immunogenicity data are sufficient under the circumstances. This should include correlates of protection, if available. In those cases where human efficacy data and/or correlates of protection are not available at the time of EUAL submission, and WHO decides to include the product in the EUAL list, WHO will require the manufacturer to submit such data and correlates to WHO as soon as they are available.

- Proposed labelling.
- A plan to monitor quality, safety and efficacy in the field, and an undertaking to submit any new data to WHO as soon as the new data are available.
- A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

**Minimum data requirements for emergency use listing:**

Specific data requirements may require clarification and discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of their application.

**Manufacturing Quality Data:**

1. Full characterization of cell banks according to WHO TRS 978, and any subsequent updates.
2. Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS.
   
   Process validation and demonstration of consistency of production at the production scale used for the lots to be distributed. If WHO deems it appropriate, interim process validation data based on pilot scale batches can be reviewed.

   *N.B.*, if full characterisation is not possible at the time of submission, adequate justification must be submitted as to why this is not possible, and a plan must be presented to adequately address the data gaps.

3. Justified specifications for starting material, intermediates, and final products.
4. Validation of potency test (or initial interim data as available).
5. Stability data for the vaccine at the production scale of the vaccine to be deployed For vaccines being assessed for emergency use, WHO and if convened, the WHO Ad Hoc Committee for the Emergency Use of Vaccines (AACEUV – see below), will consider suitability of the vaccine in national immunization programme of developing countries (programmatic suitability*) and may consider candidate vaccines with characteristics that would not be accepted for prequalification.
   a. Vaccines requiring storage at less than -20°C are generally not accepted for prequalification. However, under this emergency provision, such vaccines can be considered. Upon receipt of such an application, WHO will evaluate and consider the feasibility of assistance to recipient countries with regard to infrastructure for vaccine storage and distribution at required temperatures.
   b. Routinely, if the vaccine presented for prequalification requires storage below +2°C during its shelf-life period, it should have a minimum period of storage between +2°C and +8°C of 6 months. Under this emergency provision, vaccines with a shelf life at +2 to +8°C of less than 6 months can be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage
period at +2 to +8°C. Upon receipt of such an application, WHO will evaluate and consider the feasibility of providing assistance to recipient countries with regard to infrastructure for vaccine storage and distribution at required temperatures.

c. Routinely, multi-dose vaccines for prequalification should contain adequate preservative, unless they are live-attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency provision does not contain a preservative, adequate information/plans on how such a vaccine could be safely managed in the field should be submitted.

(6) Inspection report(s) from the responsible\(^1\) NRA or from the WHO prequalification team showing compliance with the GMP requirements.

*WHO/IVB/14.10*

**Non-clinical and Clinical Data:**

(1) Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy in the most appropriate animal model. The applicant must justify the choice of animal model. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and an adequate plan and timeline for submitting those data.

(2) Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency.

(3) Preliminary data showing some efficacy— if available. If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, WHO will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide validation data for the surrogate. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review.

**Abbreviated EUAL Assessment**

WHO may in part rely on a previous assessment through another emergency mechanism performed by a functional NRA.

However, as WHO EUAL is designed to provide assurance of the quality, safety, and efficacy of vaccines for use in a current public health emergency, WHO may still undertake some extra assessment activities if deemed necessary.

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\(^1\) An NRA that has been assessed by WHO as functional for vaccine regulatory oversight
Different assessment procedures based on specific circumstances

Based on specific circumstances related to the level of regulatory oversight of the manufacturing of the product and the experience of the manufacturer with regard to prequalification, the contents of the application and the assessment procedure may vary as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>WHO assessment approach</th>
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<tbody>
<tr>
<td>A</td>
<td>• Responsible* NRA has a collaboration agreement with the WHO prequalification programme for streamlining** (or the formalization of an agreement is in process) • Full reports from the responsible NRA with basis for the decision to authorize emergency use are available</td>
<td>WHO, and if convened, the AACEUV will conduct an accelerated review of: - Report(s) from the responsible NRA (Summary basis for the emergency use approval or equivalent) - Programmatic aspects***</td>
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<td>B</td>
<td>• Manufacturer has other prequalified products and successfully sustained prequalification status for 5 years or more</td>
<td>WHO, and if convened, AACEUV will conduct an accelerated review of: - Application (see above for required content) - Programmatic aspects***</td>
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<td>C</td>
<td>• Manufacturer does not have other prequalified products or some of its products have been delisted in the preceding 5 years.</td>
<td>WHO, and if convened, AACEUV will conduct a review of: - Application (see above for required content) - Inspection report from PQ - Programmatic aspects***</td>
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* An NRA that has been assessed by WHO as functional for vaccine regulatory oversight  
** See WHO TRS 978 – Annex 6  
*** WHO/IVB/14.10

Ad hoc Advisory Committee for the Emergency Use of Vaccines (AACEUV)

As part of the evaluation of an EUAL application, WHO may (but does not have to (*)) convene a meeting of the ad hoc advisory committee for the emergency use of vaccines (AACEUV) to assess the information in the product EUAL application and other information available to the committee. Upon completion of its review, the committee will issue an opinion and provide advice to WHO on the acceptability of the vaccine for emergency use in the context of the public health emergency.
This opinion will be advisory to WHO. The final decision whether or not to include a product in the EUAL list will rest with WHO.

The Committee will be selected by the Essential Medicines and Health Products Department of WHO primarily from suitably qualified members of other standing advisory committees, relevant WHO expert panels, and other suitably qualified experts, including representatives from the NRA in the country of manufacture and NRA(s) from the country/-ies in which the product would be used). If possible, the committee should have at least two representatives from the geographical area(s) of the public health emergency. All members of the AACEUV will be required to complete the WHO Declaration of Interest form for WHO experts.

If the committee cannot develop an opinion by consensus, any dissenting views must be noted in the report.

(*) the criteria are included in the Terms of Reference of the AACEUV

**WHO Decision on Emergency Use Listing**

WHO may, prior to including a product in the list, consult and/or coordinate with relevant NRA(s) and other parties, as appropriate.

The decision made by WHO (in its sole discretion) to include a vaccine in the list is based on:

- information and documentation submitted which provide sufficient evidence (at the time of the assessment) regarding quality, safety, and efficacy/effectiveness and,
- a risk/benefit analysis,

for use in a PHEIC.

WHO will subject to the protection of confidential information of the applicant publish a report of its assessment on the WHO website.

The EUAL list will be accompanied by general notes and disclaimers as outlined in Annex 1. In this connection, it should be noted that inclusion in the EUAL list does not constitute an endorsement, or warranty of the fitness, by WHO of any product for a particular purpose, including in regard to its safety and/or efficacy. The relevant authorities of WHO Member States shall be and remain exclusively responsible for authorizing the use of listed vaccines during a public health emergency in their country.

The validity of an emergency use listing in the context of a public health emergency will generally be for 12 months. All decisions for an emergency use listing will be reassessed within 12 months (or sooner, if further data or other information become available that could alter the original opinion). When deemed necessary and warranted based on available data and information, the emergency use listing can be extended. Products may be taken off the EUAL list if new data or information become available that change the benefit-risk profile of the product or immediately upon declaration by the WHO Director-General that there no longer is a PHEIC. Manufacturers are required to supply any new information/data to WHO as soon as it is available.

As WHO is responsible for the EUAL assessment, the ownership of the above mentioned reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any confidential information of the applicant (i.e. information that is to be
considered confidential in accordance with the terms set forth below). Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and with relevant intergovernmental organizations to the extent possible and appropriate, under obligations of confidentiality.

WHO reserves the right:

- to terminate an assessment, if applicant fails to provide WHO with all the required information.
- to delist a product in case of fraud, misrepresentation, withholding of information by the applicant/manufacturer.

The applicant must inform WHO of any changes/variations regarding the formulation, presentation, methods of manufacture or quality control, specifications, facilities, or any other aspects which might result in a change of safety and/or efficacy/effectiveness of the vaccine.

**Post-emergency-use-listing safety monitoring for vaccines granted EUAL**

Existing international regulatory standards prescribe that marketing authorisation holders notify national regulatory authorities of adverse events following immunization (AEFI). Those events include, in particular, death, hospitalization, or long-term disability. National authorities (regulatory agencies and immunization programs in particular) should also assemble a national database of AEFI. In addition, national authorities should have a mechanism in place that allows manufacturers to be informed about AEFIs related to their products. Similarly, WHO must be informed about all vaccine safety concerns in respect of a vaccine included in the list. The applicant must characterize reports in terms of severity, and immediately report serious AEFIs to the relevant national regulatory authorities and WHO. For reports received by WHO from immunisation programmes or procurement agencies, WHO will inform the respective applicants also to help insure appropriate further investigation.

For vaccines included in the list, appropriate post-EUAL monitoring mechanisms must be established by the applicant to allow for the timely evaluation of adverse events and notification to WHO and the relevant NRAs. This includes ensuring the existence of a spontaneous AEFI reporting system, and the possibility of conducting active surveillance studies in order to investigate specific concerns, either because they were identified as signals during the product clinical evaluation or due to other considerations.

If a safety issue related to a vaccine included in the list cannot be resolved to WHO’s satisfaction, WHO reserves the right to revoke the emergency use listing of the product.

**Confidentiality**

WHO will treat all information to which it will gain access as part of the EUAL procedure and which has been marked by the applicant as confidential and proprietary, in accordance with the terms set forth below.

Except as explicitly otherwise provided herein, WHO will take all reasonable measures to ensure:
• that confidential information is not used for any purpose other than as described in this document; and
• that such information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO will not, however, be bound by any obligations of confidentiality and restrictions on use to the extent it is clearly able to demonstrate that any part of the confidential information:

(a). was lawfully in its possession and known to it prior to disclosure by the applicant hereunder, as evidenced by documents antedating the date of disclosure; or

(b). was in the public domain or the subject of public knowledge at the time of disclosure hereunder; or

(c). becomes part of the public domain or the subject of public knowledge through no fault of WHO; or

(d). becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to the applicant in respect thereof; or

(e). was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or

(f). is required to be disclosed by law, provided that WHO shall in such case immediately notify the applicant in writing of such obligation and shall provide adequate opportunity to the applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).
Annex 1

NOTES AND DISCLAIMERS

EUAL List of candidate vaccines

General notes

- The vaccines included in this list are investigational vaccines. They have not been granted marketing authorization by a functional regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific investigational vaccine in the context of a Public Health Emergency of International Concern (PHEIC). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data, an agreed plan for their further evaluation and a plan for their subsequent prequalification. It is the sole prerogative of national authorities to decide whether or not to allow the emergency use of a candidate vaccine in their country. This list is updated regularly. Investigational vaccines are added to the list as and when (following the voluntary participation by relevant manufacturers) the available data on such products are evaluated and, if necessary, relevant sites are inspected by WHO, and are - at the time of evaluation - found to meet the requirements outlined in the Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency. WHO cannot in respect of any listed product represent that these requirements will continue to be met. WHO may suspend or remove products from the list based on information that may subsequently become available to it (including information on failure of the responsible NRA to exercise independent and appropriate regulatory oversight).
- The list is not an exhaustive list of vaccines that may be used in a PHEIC. It reflects those investigational products which have been submitted to WHO for evaluation by interested parties.
- The fact that certain investigational products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above mentioned standards and operational specifications.
- Inclusion in the list does not imply any approval by WHO of the products and manufacturing sites in question (which is the sole prerogative of national authorities).
- This list may not be used by manufacturers and suppliers for commercial or promotional purposes.

Listing of products in the EUAL list

- WHO may recognize the emergency evaluation and approval of products by regulatory authorities that apply stringent standards for quality, similar to those recommended by WHO, such as, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMEA) and Health Canada (HCnda).
Suggestions relating to procurement

- Any interested UN procurement agency and Member States intending to use the EUAL list of investigational vaccines for procurement should ensure that only products from the manufacturing sites mentioned in this list are supplied to it.
- Organizations using this list for procurement should perform other aspects of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities and other related aspects, including the emergency use approval by national authorities in relevant countries.

Disclaimer to the WHO EUAL List of Candidate Vaccines

1. Inclusion in this list does not constitute an endorsement of the vaccine products listed. WHO explicitly disclaims any warranty of the fitness of any listed investigational vaccines for a particular purpose, including in regard to its safety and/or efficacy.

2. WHO does not furthermore warrant or represent that:
   a. the list is complete or error free; and/or that
   b. the listed investigational products which have been found to meet the requirements outlined in the Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency will continue to do so; and/or that
   c. the investigational products listed have obtained emergency use approval for their specified use or any other use in any country of the world, or that their emergency use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.

3. In addition, WHO wishes to alert procuring organizations that the improper storage, handling and transportation of vaccines (including investigational vaccines) may affect their quality, efficacy and safety.

4. WHO disclaims any and all liability and responsibility for any injury, death, loss, damage or other prejudice of any kind whatsoever that may arise as a result of or in connection with the procurement, distribution and use of any investigational product included in the list.