

# **Emergency Use Assessment and Listing Procedure (EUAL) for candidate in vitro diagnostics (IVDs) for use in the context of a public health emergency**

## **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 in vitro diagnostics (IVDs) 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 for candidate IVDs and is primarily aimed at manufacturers of these IVDs 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 IVDs in the case of a public health emergency when the community may be willing to tolerate less certainty about the performance and safety of products, given the morbidity and/or mortality of the disease and the shortfall of diagnostic 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 procedure to expedite the availability of IVDs needed in public health emergency situations. The EUAL procedure is intended to assist interested UN procurement agencies and Member States on the acceptability for use of a specific IVD in the context of a public health emergency, based on a minimum set of available quality, safety, and performance 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 IVD in their country.

## Eligibility

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

- The disease for which the IVD is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). In a public health emergency that does not rise to the level of a PHEIC, the Director-General may authorize use of this procedure 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 IVD for EUAL assessment *e.g.*, there are no IVDs that have undergone comprehensive premarket regulatory assessment for the indication or for a critical subpopulation (*e.g.*, children), or there is a specific IVD shortage.
- The applicant must be the legal manufacturer of the product. A condition for the EUAL of a “re-branded<sup>1</sup>” product is that the original product manufacturer and the “re-brander” explicitly consent to the public disclosure by WHO of this “re-branding” arrangement.
- The IVD is manufactured under a functional quality management system (QMS) and the manufacturer has the capacity to meet expected demand.
- The IVD manufacturer attests that it intends to complete the validation and verification of the product and apply for WHO prequalification. In the ideal situation, the remaining prequalification 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 in the EUAL plus any other information needed to complete a prequalification application).

WHO may issue an Expression of Interest (EOI) regarding IVDs that might be eligible for an EUAL assessment. Such an EOI may be either open-ended or for a fixed period of time. The EOI will identify those IVDs that are to be prioritized in the EUAL process. This prioritization procedure will take into account any target product profiles (TPP) established by WHO for IVDs in response to the public health emergency. If the application is not for a priority product but for a product that may still be of interest during the public health emergency, WHO may choose to assess the product, but those fitting the priority criteria (for example, one fulfilling a WHO TPP) will be assessed first.

WHO may consider reviewing a candidate IVD 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.

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<sup>1</sup> A product that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a “rebranded” product is identical in every aspect to the product manufactured by the original manufacturer, except that the product is labeled with the “rebranded” product name and purchaser identifier.

## **Content of the application and minimum data requirements for emergency use listing:**

The EUAL procedure will assess, against current WHO/international standards, where available if the submitted evidence is sufficient to demonstrate that the benefits of using the IVD outweigh the foreseeable risks and uncertainties in the context of a PHEIC. As such, the EUAL process will consist of:

- A desktop review of selected manufacturing and QMS documentation;
- A review of any existing documentary evidence of safety and performance; and
- A limited laboratory evaluation of relevant performance and operational characteristics of the product.

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.

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

### **Labelling:**

- Labels (all components, kit, instrument(s) and/or box labels);
- Instructions for use (IFU) and user manual of instrument(s) (if applicable); and
- Any other instructional materials provided to the user.
- Proposed labelling
- A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

### **Product Performance Specification, and Associated Validation and Verification Studies**

Studies in support of the intended use are requested. Where they exist, these would include:

- Specimen type
- Accuracy of measurement: trueness and precision studies.
- Analytical sensitivity
- Analytical specificity: interference and cross reactivity studies
- Traceability of calibrators and control material values
- Measuring range of the assay
- Validation of assay cut-off
- Validation of assay procedure – reading time
- Stability (excluding specimen stability)

- Claimed shelf life
- In-use stability
- Shipping stability
- Robustness Studies
- Evaluation of potential biohazard issues associated with the design and use of the product
- Clinical evidence (evidence of relevant performance characteristics such as clinical or diagnostic sensitivity and specificity) depending on the feasibility of conducting such studies given the emergency circumstances
- This list may be subject to change to meet the needs of a particular disease state of IVD TPP.

For each study to be submitted, the following must be provided:

- Study description, study identifier, product identifier (*e.g.*, lot numbers), IFU version used, the date of initiation and the date of completion;
- A summary of the study findings including a conclusion that clarifies how the study objectives have been met; and
- The study protocol and full report.

### **Quality management systems requirements**

- Evidence of implementation of a manufacturing quality management system (*e.g.*, ISO 13485:2003 certificate and most recent regulatory (or certification body) audit report, quality manual, exclusions or non-applications, list of valid quality management documentation, management review report);
- Details of the production workflow including QC points (in process and final release activities);
- Critical supplier list including supplied products (components/raw materials) and services;
- Details on the experience with the product (when was the product developed and when was it first placed on the market, if applicable);
- Details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch/lot size).

### **The assessment process – a triaged activity**

The assessment process itself is generally a sequential process with applications that do not pass a step not being eligible to continue in the process; however, the process will be flexible depending on the individual situation. This however, does not preclude preparatory planning for subsequent steps. At each step, the assessment considers the potential benefits weighed against known or predictable risks.

## **STEP 1 – QMS Review**

A review of the manufacturer's QMS documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, the recommendation will be to proceed, request further documentation, or to terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the legal manufacturer, that there is evidence of an adequate QMS in place, and that the requisite manufacturing capability exists.

## **STEP 2 – Dossier Review**

The second step is the assessment of the documentary evidence of safety and performance. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUAL assessment. Based on the submitted documentation, a risk based judgment will be made on whether there is a favorable benefit/risk profile. An initial evidence base that includes studies using banked specimens from previous studies, relevant studies in the literature, and studies using contrived specimens to supplement testing of clinical specimens including representative analytes may be acceptable in the absence of complete analytical and/or clinical performance studies, if this evidence base provides a reasonable assurance of safety and performance.

In some jurisdictions, minimizing potential harm of an IVD approved through an emergency authorization mechanism is achieved by active post-market surveillance. However, it cannot be always be assumed that, in the public health emergency settings this EUAL process serves, that there are sufficient resources and institutions in place for any consistent effective surveillance. It will be critical for the manufacturer to detail what, if any, post-emergency-use-listing safety monitoring activities are planned if the EUAL is granted.

The outcome of this step will determine if the application will proceed to step 3, whether further documentation should be requested, or whether the application should be terminated.

## **STEP 3 – Performance Evaluation**

When needed and where possible, WHO will work with relevant partners and WHO Collaborating Centres to undertake a limited performance evaluation to verify critical analytical and clinical performance characteristics of the product and to make preliminary assessments regarding its utility in different settings. Protocols will be drafted and comment sought from the participating WHO laboratories or WHO Collaborating Centres, and where time permits, more widely. Ethics approval both from WHO and in country will be sought, as appropriate. Special attention will be paid to the suitability of use for the intended setting.

Acceptance criteria will be established for the critical performance characteristics, but will take into account the limitations of the scale of the evaluation, and the potential clinical utility of the IVD in the context of the PHEIC.

If the acceptance criteria have been met, the application will be deemed to have successfully met WHO laboratory performance requirements for EUAL.

## **Abbreviated EUAL Assessment**

Some submissions submitted for WHO EUAL may have undergone a previous assessment through other emergency mechanisms, for example, the US FDA Emergency Use Authorization (EUA) process. Where this is the case, it is not the intent of WHO to undertake duplicative work, if the review of the other emergency mechanism is deemed to be of a satisfactory standard. The ability to waive aspects of the EUAL assessment in these circumstances can be applied to any of the three steps. In situations where independently generated performance data are available, WHO may also consider using these data in place of or to reduce the extent of a WHO-coordinated performance evaluation.

However, WHO EUAL is designed to provide a level of assurance of the quality, safety, and performance of these assays for the primary purpose of use in the setting of a current public health emergency. This focus means that WHO may still undertake some extra assessment activities if deemed necessary.

## **Ad hoc Advisory Committee for the Emergency use of IVDs (AACEUD)**

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 IVDs (AACEUD) 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 on the acceptability of the IVD 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 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 include 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

Upon making a decision (in its sole discretion) to include a candidate IVD in the EUAL list of products deemed to have benefits that outweigh the foreseeable risks and uncertainties for use in a public health emergency of international concern, 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 IVDs during a public health emergency in their country.

WHO may, prior to including a product in the list, consult and/or coordinate with relevant NRAs and other parties as appropriate. The validity of an emergency use listing in the context of a public health emergency will generally be for 12 months. All decisions to grant 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 or 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 safety or performance 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 to the product, including its design, labelling or manufacture, or to the quality management system, or any other aspects which might affect the safety, quality or performance of the product.

## Post-emergency-use-listing safety monitoring for IVDs granted EUAL

Existing international regulatory standards prescribe that manufacturers notify national regulatory authorities of adverse events<sup>2</sup> that may cause death or serious deterioration in the state of health of the patient, user, or another person. This means that users must be encouraged to report all quality issues, both administrative and technical, to manufacturers. Manufacturers must characterize complaints in terms of their severity (i.e. serious, moderate, mild) with serious and moderate adverse events to be immediately reported to the relevant national regulatory authorities and WHO. In countries without adequate capacity for this activity, WHO can receive notification of complaints and ensure appropriate evaluation and dissemination of the information.

For IVDs included in the EUAL list, appropriate post-EUAL monitoring mechanisms must be in place to allow for the timely notification and evaluation of adverse events to WHO and the relevant NRAs. The WHO IVD complaint form should be completed as much as possible and sent to WHO. The form is available at the following WHO web address

[http://www.who.int/diagnostics\\_laboratory/postmarket/en/](http://www.who.int/diagnostics_laboratory/postmarket/en/)

WHO will ensure that any necessary field safety corrective action is implemented and that users are informed through a field safety notice. WHO reserves the right to issue an information notice for users, if at any time, WHO deems that the manufacturer is not responding to a complaint in a timely and scientifically sound manner. If a quality issue related to safety or performance 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

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<sup>2</sup> An adverse event is defined as a product defect (*i.e.* malfunction or failure, deterioration in characteristics or performance, or inadequacy of labeling or of instructions for use) that, directly or indirectly, has led or might have led to serious medical consequences, namely death or serious deterioration in the state of health of the patient, user or another person.



- (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 in vitro diagnostics

#### General notes

- The in vitro diagnostics included in this list are **investigational diagnostic** products. They have **not** been granted marketing authorization by a stringent regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific in vitro diagnostic 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 in vitro diagnostic product in their country. This list is updated regularly. Investigational diagnostic products 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 in vitro diagnostics (IVDs) 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.
- The list is not an exhaustive list of diagnostic products 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 requirements.
- 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 in vitro diagnostics in the EUAL list

- WHO may recognize the emergency evaluation and approval of diagnostic 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 (EMA) and Health Canada (HCnda).

## Suggestions relating to procurement

- Any interested UN procurement agency and Member States intending to use the EUAL list of diagnostic products 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 in vitro Diagnostic Products

1. Inclusion in this list does not constitute an endorsement of the diagnostic products listed. WHO explicitly disclaims any warranty of the fitness of any listed investigational product 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 in vitro diagnostics (IVDs) 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 in vitro diagnostic products (including investigational in vitro diagnostic products) 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.