Norms and standards

Assessing new medical products in health emergencies: the EUAL procedures

Development and regulatory approval of medical products typically take many years. When an unprecedented Ebola outbreak devastated West African countries and kept on spreading, there were no approved vaccines, medicines or rapid diagnostic tests available to combat the disease. A WHO-convened ethical panel reached consensus that in this special situation, and provided certain conditions were met, it was ethical to use investigational products.

In the months that followed, WHO not only convened global players to accelerate R & D for Ebola, but also developed rules on how to identify those investigational products that can be used in an emergency – with the agreement of the competent regulatory authority – while they are being studied further. The Emergency Use Assessment and Listing (EUAL) procedures are the first of their kind of a global nature. They are a step ahead in ensuring that the world is prepared for future emergencies.

Unmet medical needs

New medical products are approved every year to treat the diseases that continue to threaten the world’s populations, such as cancer or diabetes. Research and development (R & D) and regulatory approval of new products typically take many years and require long-term planning of investments.

Ebola outbreaks have been known to occur since 1976 (1), but they were always quickly contained with infection control measures. When an Ebola outbreak was confirmed in March 2014, there was no approved medical product for the prevention or treatment of Ebola virus disease. However, this outbreak turned out to be unprecedented in size and complexity, with over 27 000 cases and 11 000 deaths on record in the most recent WHO Ebola Situation report (2). On 8 August 2014 the WHO Director-General declared the Ebola outbreak to be a public health emergency of international concern.

Vaccines, treatments and diagnostics were now urgently needed to contain the outbreak, save lives and relieve suffering. On 11 August 2014 a WHO-convened panel reached consensus that in the particular circumstances of the Ebola outbreak, and provided certain conditions are met, it is ethical to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention (3).

WHO leadership

The panel of independent experts who reviewed WHO’s response to the Ebola outbreak has commended the Organization for stepping up to fill a void
at a critical stage of the Ebola outbreak (4). WHO’s Ebola R & D team successfully convened international partners to fast-track the development of needed products and provided leadership in the conduct of trials for candidate vaccines and in the use of experimental therapeutics such as drugs and blood products.

When this race for time began, there was no guidance available on how to test any candidate products in an emergency situation, or how to regulate them. The Regulation group of the WHO Ebola R & D team rose to the task and worked against the clock to propose a new model for rapid assessment of investigational vaccines, medicines and diagnostics to be used in emergencies. The Emergency Use Assessment and Listing (EUAL) procedures were published for comment on 10 March 2015. A consultation period of four weeks followed, leading to useful input being received from regulators, industry and other stakeholders. The final EUAL procedures were published on 10 July 2015 (5).

The EUAL procedures

The EUAL procedures are reproduced in Attachment 1. They define a voluntary pathway for manufacturers to have their as yet unregistered products listed as acceptable for use in a public health emergency, based on a minimum set of available quality, safety, and efficacy data. It is then up to the regulatory authorities of target countries to authorize the use of the listed products in their territories.

WHO regulatory experts have long-standing experience in identifying the best options of providing needed treatment when stringently approved products are out of reach. The WHO Prequalification Team (PQT) assesses vaccines, medicines and diagnostic products for use in UN and donor-funded programmes. The head of the Ebola R&D Regulation group and most of its members came from PQT, and the group could thus draw on a vast amount of experience with regulation and manufacturing of medical products. The EUAL procedures are the outcome of team work across all three product categories that were needed to address the Ebola crisis.

In this context it is important to note that there are fundamental differences between WHO prequalification and the EUAL procedure. Prequalification focuses mainly on the ongoing quality of products whose safety and efficacy – or performance for diagnostics – have been demonstrated upfront. EUAL, on the other hand, is based on assessment of available data for yet unproven candidate products that are to be used in an emergency while additional safety and efficacy data are being generated.

So far, four Ebola diagnostic tests have been listed under this procedure (6), and WHO has published an interim guidance document for Ministries of Health and
other organizations on factors to consider in the selection and use of available in vitro diagnostic (IVD) assays for Ebola virus disease (7). As the world is on the verge of an effective Ebola vaccine (see page 345), the VSV-EBOV vaccine could also become a candidate for EUAL.

**Preparedness for future emergencies**

Lessons have been learned from the Ebola outbreak. The Ebola Interim Assessment Panel has noted that research and development for neglected diseases remains inadequate, and has recommended that WHO should play a central convening role in research and development efforts in future emergencies.

New health emergencies will certainly arise. Three new pathogens have emerged since the year 2000 – SARS, H7N9 avian influenza and the MERS coronavirus – and in May 2015 the WHO Director General warned that the threat from avian influenza is persisting to the point where the world should be on high alert (8).

Reforms and assured core funding will be required for WHO to fully play its normative role in a complex and changing health architecture. Whatever the framework will be to manage future public health emergencies, the EUAL procedures will be a valuable tool to guide manufacturers and regulatory professionals in bringing new medical products promptly to affected populations.

**Acknowledgements**

WHO wishes to thank all those who contributed to the development of the EUAL procedures, including the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA), GlaxoSmithKline (GSK), Janssen-Cilag, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and others as well as WHO’s own staff and consultants. Without their dedicated work and constructive input, the EUAL procedures could not have been put forward at a time when they were urgently needed.

**References**

8. WHO Director-General’s speech at the Sixty-eighth World Health Assembly. 18 May 2015.
Attachment 1: Emergency Use Assessment and Listing Procedures (EUAL) for candidate vaccines, medicines and diagnostics

Introduction

The 2014–15 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 / medicines / 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 member states. The present document describes the EUAL for candidate [vaccines / medicines / IVDs] and is primarily aimed at manufacturers of these medicines 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 medicines in the case of a public health emergency when the community may be 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 procedure to expedite the availability of [vaccines / medicines / 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 [vaccine / medicine / IVD] 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 [vaccines / medicines / IVDs] in their country.

**Vaccines**

**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).

**Medicines**

**Eligibility**

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

- The disease for which the medicine 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 medicine for EUAL assessment (e.g., there are no licensed medicines for the indication or for a critical subpopulation).

**Diagnostics**

**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.)
### EUAL – Vaccines (continued)
- 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 (e.g., children), or there is a specific medicine shortage.

- The medicine (both API and FFP) is manufactured in compliance with current Good Manufacturing Practices (GMP). If a manufacturer has a documented acceptable history of quality manufacturing of medicines, WHO may waive the requirement for conducting an on-site inspection.
- The 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 in the EUAL plus any other information needed to complete a prequalification application.)

WHO may consider reviewing a candidate medicine 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 promptly inform the applicant 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.

### EUAL – Medicines (continued)
- The applicant must be the legal manufacturer of the product. A condition for the EUAL of a “rebranded” 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.

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1. 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.
**EUAL – Vaccines (continued)**

- 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.

**EUAL – Medicines (continued)**

**Content of the application**

The EUAL procedure will assess whether, in light of available WHO/international standards, the submitted data demonstrate a reasonable likelihood that the medicine 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:
- Certificate(s) or other acceptable evidence of GMP compliance for the relevant manufacturing site(s) used in the production of the product,
- Stability data to demonstrate that the medicine will maintain the minimum potency considered necessary for the claimed shelf-life under the conditions of use,
- Sufficient chemistry, manufacturing, and controls data to assure the quality of the product for its intended purpose,
- Summary information on all preclinical and clinical data. If it has not been possible to obtain efficacy data in humans, the applicant should provide all other available data substantiating to WHO’s satisfaction, the claim of the medicine’s efficacy and safety under the conditions of the foreseen use. This should include any surrogates (validated or otherwise) that are thought to be predictive of ultimate clinical benefit. In these cases, where human efficacy data are not available at the time of EUAL submission, and WHO decides to include

**EUAL – Diagnostics (continued)**

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 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
EUAL – Vaccines (continued)

- 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

EUAL – Medicines (continued)

- the product in the EUAL list, WHO will require the manufacturer to submit such data 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 patients 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) Information on the active ingredient(s) and finished product, including characterization, composition, preparation, controls (specifications), known and potential impurities. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the safety/efficacy profile of the product should also be provided.
(2) Stability data for the finished product at a scale commensurate with safe use under the conditions of a public health emergency. For medicines being assessed for emergency use, WHO and the WHO Ad Hoc Committee for the Emergency Use of

EUAL – Diagnostics (continued)

- 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
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**EUAL – Vaccines (continued)**

suitability\(^1\) 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.

\(^1\) WHO/IVB/14.10

**EUAL – Medicines (continued)**

Medicines (AACEUM – see below), if convened, will consider suitability of the medicine in light of WHO treatment guidelines and may consider candidate medicines with characteristics that would not be accepted for prequalification.) and (3) Inspection report(s) from an NRA or from a prequalification inspection (or paper assessment) showing compliance with the GMP requirements. (Based on the acceptability of the NRA report, WHO may or may not need to perform its own assessment of GMP compliance.)

**Non-clinical and Clinical Data:**

(1) All relevant in vitro and in vivo pharmacodynamic data, e.g., on microbiologic activity (including any modeling performed).

(2) Data demonstrating efficacy in animal model(s) under well-controlled and documented conditions. The preferred model for prediction of efficacy in humans depends on the disease and may vary according to the medicine’s mechanism of action. The applicant must justify the choice of animal model.

a. Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.

b. All available evidence of the medicine’s activity in vitro and in other animals, together with

**EUAL – Diagnostics (continued)**

- 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 the current 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
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 imminent availability 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 pharmacokinetics and efficacy in humans against other diseases will be evaluated. Data provided should give reasonable assurance that an inefficacious regimen will be excluded.

3. A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be efficacious in the relevant animal model.

4. A safety assessment should be provided for the drug at the exposure level proposed for treatment of the disease, considering non-clinical and, if available, clinical data. If human PK trials or studies in other indications at the exposure level proposed for treatment of the disease have been conducted, assessment of safety using standard parameters (e.g., adverse events, clinical laboratory monitoring, etc.) will serve as the most meaningful assessment of safety, supplemented by any other non-clinical and clinical data at different exposure levels. Safety results from animal studies, as well as relevant in vitro data should be assessed with respect to safety in humans. and

5. Clinical data demonstrating safety and efficacy at the dose to be used and initial acceptable efficacy and safety in the population where the medicine will be used in the context of the

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.
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<table>
<thead>
<tr>
<th>EUAL – Vaccines (continued)</th>
<th>EUAL – Medicines (continued)</th>
<th>EUAL – Diagnostics (continued)</th>
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<tr>
<td>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.</td>
<td>public health emergency. If large scale study results are not available, WHO will consider whether the preponderance of evidence from the pre-clinical and early human studies, and any other information of which it is aware, justifies reliance on an unvalidated surrogate thought to be reasonably likely to predict clinical efficacy. In such cases the emergency use listing can proceed provided there are trials underway which it is expected will provide clinical validation of the surrogate.</td>
<td>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.</td>
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<tr>
<td>Different assessment procedures based on specific circumstances</td>
<td>Abbreviated EUAL Assessment</td>
<td>Abbreviated EUAL Assessment</td>
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<tr>
<td>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:</td>
<td>WHO may in part rely on a previous assessment through another emergency mechanism, if the review of the other emergency mechanism is deemed to be of a satisfactory standard. However, WHO EUAL is designed to provide a level of assurance of the quality, safety, and efficacy of these medicines 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.</td>
<td>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.</td>
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<tr>
<td><strong>Category A</strong></td>
<td><strong>Abbreviated EUAL Assessment</strong></td>
<td><strong>Abbreviated EUAL Assessment</strong></td>
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<tr>
<td><strong>Criteria:</strong></td>
<td>WHO assessment approach:</td>
<td>WHO assessment approach:</td>
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<td>• Responsible{superscript}2 NRA has a collaboration agreement with the WHO prequalification programme for streamlining{superscript}3 (or the formalization of an agreement is in process)</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)</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)</td>
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<tr>
<td>• Full reports from the responsible NRA with basis for the decision to authorize emergency use are available</td>
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**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.

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**WHO Decision on 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 AACEUM 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.

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**Norms and standards**

WHO/IVB/14.10

The criteria are included in the Terms of Reference of the AACEUD

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

**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 medicines 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.
Existing international regulatory authorities of adverse events that may cause death or serious deterioration in the health of the patient, user, or another person. This means that users must be encouraged to report all such issues. Those responsible must characterize reports in a change of safety and/or efficacy 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.

Post-emergency-use-listing safety monitoring for medicines granted EUAL
Existing international regulatory standards prescribe that marketing authorization holders notify national regulatory authorities of adverse events that may cause death or serious deterioration in the health of the patient, user, or another person. This means that users must be encouraged to report all such issues. Those responsible must characterize reports in a change of safety and/or efficacy 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.
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 terms of their severity, with serious and unexpected adverse events to be reported immediately to the relevant national regulatory authorities and to WHO. In countries without adequate capacity for this activity, WHO can receive notification of reports and help ensure appropriate evaluation and dissemination of the information.

For EUAL medicines, appropriate post-EUAL monitoring mechanisms must be in place to allow for the timely evaluation of adverse events and notification to WHO and the relevant NRAs.

WHO will ensure that any necessary corrective action is implemented and that users are informed through a safety notice. WHO reserves the right to issue an information notice for users, if at any time, WHO deems that the applicant is not responding to a post-listing safety issue 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

| EUAL – Vaccines (continued) |
| EUAL – Medicines (continued) |
| EUAL – Diagnostics (continued) |

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/

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:

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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 ante dating 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).
**EUAL – 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.

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**EUAL – Medicines**

**General notes**
- The medicinal products included in this list are investigational medicinal 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 investigational medicinal product 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 medicinal product in their country. This list is updated regularly. Investigational medicinal 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 medicines 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.

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**EUAL – 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.
Any interested UN procurement agency and Member States intending to use the EUAL list of investigational 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 based on information that may subsequently become available to it.

The list is not an exhaustive list of medicinal 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.

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).

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### Norms and standards

**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**

### EUAL – Vaccines (continued)

- 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.

### EUAL – Medicines (continued)

- 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.

### EUAL – Diagnostics (continued)

- 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.

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**Disclaimer to the WHO EUAL List of Candidate Medicinal Products**

1. **Inclusion in this list does not constitute an endorsement of the 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 medicines 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 medicinal products (including investigational medicinal products) may affect their quality, efficacy and safety.**

4. **WHO disclaims any and all liability and responsibility**

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**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.

7 July 2015