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 medicines 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 medicines 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 medicines 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 medicine 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 medicine in their country.
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 a medicine for EUAL assessment e.g., there are no licensed medicines for the indication or for a critical subpopulation (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.

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 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 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 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 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.

Abbreviated EUAL Assessment

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.
Ad hoc Advisory Committee for the Emergency Use of Medicines (AACEUM)

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 medicines (AACEUM) 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 medicine for emergency use in the context of the public health emergency. This opinion will be advisory to WHO. The final decision whether or not to include a product in the EUAL list will rest with WHO.

The Committee will be selected by the Essential Medicines and Health Products Department of WHO primarily from suitably qualified members of other standing advisory committees, relevant WHO expert panels, and other suitably qualified experts, including representatives from the NRA in the country of manufacture and NRA(s) from the country/-is 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.

*see Terms of Reference of the AACEUM

WHO Decision on Emergency Use Listing

Upon making a decision (in its sole discretion) to include a candidate medicine in the list of products deemed to have an acceptable quality, safety and effectiveness, which outweigh the foreseeable risks, in the context of use in a public health emergency of international concern, WHO will - subject to 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 benefit-risk profile of the product, or immediately
upon declaration by the WHO Director-General that there no longer is a PHEIC. Applicants are required to supply any new information/data to WHO as soon as it is available.

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

WHO reserves the right:

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

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

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

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

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

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

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

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

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

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

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

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

NOTES AND DISCLAIMERS

EUAL List of candidate medicinal products

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 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.

Listing of products in the EUAL list

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

- Any interested UN procurement agency and Member States intending to use the EUAL list of investigational 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 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 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.