2nd Invitation to Manufacturers of therapeutics against Ebola Virus Disease to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit

To support national and global efforts to increase access to and affordability of products for treatment of Ebola Virus Disease. WHO invites manufacturers of this pharmaceutical product to submit Expressions of Interest (EOI) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS INVITATION TO EOI

The current Invitation is published in accordance with the *Procedure for Prequalification of Pharmaceutical Products*, adopted in 2001 by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations, and amended subsequently as part of the 45th report of the Committee, published as No. 961 of the WHO Technical Report Series in 2011.

Assessment of product(s) submitted under this Invitation will include evaluation of:

- product dossiers, which must include product data and information as specified in the guidelines for submission (see Procedures & Fees)
- manufacturing sites, which must adhere to good manufacturing practices (GMP)
- clinical sites (if applicable), which must adhere to good clinical practices (GCP).

If evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the list of medicinal products that are considered to be acceptable for procurement by UN organizations and others.

ARTICLE 2. MEDICINAL PRODUCTS INVITED

The aim of this Invitation is to increase the range of selected products and sources available in relation to management of Ebola Virus Disease.

Neutralizing Antibodies

In a randomized controlled study, the PALM trial[1], Zaire ebolavirus glycoprotein-directed human monoclonal antibodies demonstrated mortality benefit in patients with infection caused by Zaire ebola virus. Atoltivimab, maftivimab, and odesivimab-ebgn (three monoclonal antibodies in one product) and ansuvimab (one monoclonal antibody) showed superior results to other treatments given. The study included adults and children.

The recommended dose of atoltivimab, maftivimab, and odesivimab-ebgn is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg, diluted and administered as a single intravenous infusion. The higher concentration (with the current approved dosage of 150mg/Kg) allows a reduction of the volume per Kg to be administrated, especially in children.

The recommended dose of ansuvimab-zykl is 50 mg/kg reconstituted, further diluted, and administered as a single intravenous infusion.

Interested manufacturers are encouraged to submit documentation for recommended dosage forms as specified below.

Neutralizing antibody products

- A combination of atoltivimab, 241.7 mg, maftivimab 241.7 mg, and odesivimab 241.7 mg per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL) in a single-dose vial
- A combination of atoltivimab, 483.3 mg, maftivimab 483.3 mg, and odesivimab 483.3 mg per 14.5 mL (33.33 mg/33.33 mg/33.33 mg per mL)
- Ansuvimab-zykl 400 mg as lyophilized powder in single-dose vial

For details on specific requirements for neutralizing antibody products see:
https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products

ARTICLE 3. HOW TO SUBMIT AN EXPRESSION OF INTEREST

In order to submit an expression of interest for product evaluation, the manufacturer must send the requested documentation, arranged according to the information provided on the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) website in the Procedures and Fees section.

ARTICLE 4. QUALITY ASSESSMENT PROCEDURE FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST BY A MANUFACTURER

The quality assessment is undertaken to evaluate whether the pharmaceutical product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with good manufacturing practices (GMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to GMP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with good clinical practices and good laboratory practices, as appropriate;
- random sampling and testing of medicines supplied.

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant starting materials, the finished pharmaceutical product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Medicinal Products.

ARTICLE 5. REFERENCES AND FURTHER INFORMATION

1. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

   N Engl J Med, 12 December 2019

   https://www.nejm.org/doi/full/10.1056/NEJMoa1910993