1st Invitation

to manufacturers of *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs)

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 the affordability of care and treatment of tuberculosis, WHO, together with UNICEF, UNAIDS, UNITAID and the Stop TB Partnership Global Drug Facility invites manufacturers of selected *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs) to submit Expressions of Interest (EOIs) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS EOI

Assessment of product(s) submitted under this Invitation for EOI will include, but not be limited to:

- Assessment of product dossiers, which must meet WHO technical guidance on quality, safety and efficacy or performance;
- Inspection of manufacturing sites, which must adhere to current good manufacturing practices (cGMP) and good distribution practices (GDP);
- Inspection of clinical sites (if applicable), which must adhere to current good clinical practice (cGCP) and current good laboratory practices (cGLP).
- Assessment during dossier assessment and/or inspection of ability to meet relevant operational packaging and presentation specifications; and adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines.

If evaluation demonstrates, as determined by WHO, that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, the product (as manufactured at the specified manufacturing site[s]) will be included in the WHO list of prequalified products that are considered to be acceptable, in principle, for procurement by interested United Nations agencies and WHO Member States.

ARTICLE 2. INCLUDED IN THIS INVITATION

Over a quarter of the global population is infected with *Mycobacterium tuberculosis* complex (MTBC), with high prevalence in some regions. WHO currently recommends three types of tests for detection of TB infection: tuberculin skin tests (TSTs), interferon-gamma release assay (IGRA), and Mtb antigen-based Skin Tests (TBSTs).

The TBSTs use recombinant antigens, such as ESAT6 and CFP10, and are administered via intradermal injection. TBSTs elicit a cellular immune response to Mtb-specific antigens, inducing a delayed-type hypersensitivity reaction in individuals with TB infection. The immune response is measured 48–72 hours after administration as induration in millimetres. Based on available evidence, WHO issued recommendations on the use of TBSTs for the diagnosis of TB infection, as these tests offer accuracy comparable to IGRAs and surpass that of TSTs.

WHO classifies TBSTs as biotherapeutic products (BTPs) for diagnostic use, evaluated under the same regulatory principles as medicinal products. The aim of this Expression of Interest (EOI) is to promote access to biotherapeutic

products, including similar biotherapeutic products (SBPs), that contain the recombinant dimer of *Mycobacterium tuberculosis* early secretory antigenic target (rdESAT-6) and recombinant culture filtrate protein (rCFP-10).

Interested manufacturers are encouraged to submit documentation for the medicinal product used within the approved indication as specified below:

- Mtb-specific antigens rdESAT-6 and rCFP-10, 0.1 micrograms / 0.1 mL, solution for injection (0.05 micrograms rdESAT-6 and 0.05 micrograms rCFP-10) for intradermal administration.

This invitation is limited to: -

- Mtb-specific antigens rdESAT-6 and rCFP-10, or the corresponding SBPs, that have been approved by a stringent regulatory authority (SRA) and marketed in the country of registration; and which will be assessed via an Abridged Assessment pathway. The Abridged Assessment will include a verification of the data, to be provided by the applicant, demonstrating that the product submitted for WHO prequalification is the same as that approved by the SRA. In addition, the applicant should submit evidence that the product sought to be prequalified under this pilot procedure adheres to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines and meets relevant operational packaging and presentation specifications.

- Mtb specific antigens rdESAT-6 and rCFP-10 SBPs (based on a Reference biotherapeutic product (RBP) approved by an SRA) that have not been registered by SRAs and which will be assessed via a Full Assessment pathway.

  In case the product is claimed to be an SBP, the Full Assessment will include an evaluation of data, to be submitted by the applicant, demonstrating similarity of the SBP to a suitable RBP in terms of quality characteristics, biological activity, safety and efficacy. Demonstration of similarity between an SBP and RBP. should be based on scientific evidence and a comprehensive similarity exercise. The applicant must provide WHO with the necessary evidence to support all aspects for a successful SBP qualification. A similarity exercise (i.e., a head-to-head comparison of the SBP against a reference biotherapeutic product that, in turn, has been registered/licensed by an SRA on the basis of a full dossier with comprehensive data on nonclinical and clinical studies) will be required. The similarity exercise(s), starting with comparison of quality characteristics, of the SBP and RBP represents the prerequisite for the reduction of the non-clinical and clinical data set required for licensure of the SBP and prequalification

ARTICLE 3. HOW TO SUBMIT AN EOI

In order to submit an expression of interest for product evaluation, the manufacturer must send the required documentation, arranged according to the information provided on the WHO Prequalification Team website https://extranet.who.int/prequal/medicines or by writing to prequalbiosimilar@who.int mailbox.

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

The quality assessment is undertaken to assess whether the diagnostic 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.

Previous evaluation conducted by the relevant national medicines regulatory authority (NMRA) may be taken into account during the evaluation conducted by WHO, provided that the NMRA has expertise in the product area. If appropriate, the relevant NMRA may be invited to collaborate with WHO on the quality assessment. Any manufacturer who submits a product for evaluation, is therefore encouraged to authorize its NMRA to discuss relevant product files with WHO representatives, during assessments and inspections, if required (subject to appropriate confidentiality provisions, if necessary).

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

For further information on WHO medicines prequalification, please visit the WHO prequalification website at: https://extranet.who.int/prequal. Should you have any questions relating to the procedure for responding to an EOI, please email: prequalbiosimilar@who.int. Your question(s) will be directed to the prequalification team member who can best advise you.

For further information on WHO diagnostic guidelines for TB infection, please consult:

WHO consolidated guidelines on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
module 3: diagnosis: tests for TB infection

WHO operational handbook on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
WHO operational handbook on tuberculosis. Module 3

All consolidated WHO guidelines and operational handbooks can also be found on: https://tbksp.org/en.

For the latest WHO Model List of Essential Diagnostics, please consult:

The selection and use of essential in vitro diagnostics: report of the fourth meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2022 (including the fourth WHO model list https://iris.who.int/bitstream/handle/10665/373322/9789240081093-eng.pdf)

Other references:

World Health Assembly (WHA) adopted Resolution WHA 67.21 on “Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy” https://iris.who.int/bitstream/handle/10665/162867/A67_R21-en.pdf

WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23, https://extranet.who.int/prequal/sites/default/files/document_files/WHO_IVB_05.23_eng.pdf

WHO model list of essential medicines
WHO Model Lists of Essential Medicines

WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009
Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, TRS No 977

WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, Technical Report Series No. 987, 2014
Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, TRS No 987

Guidelines for the preparation of a contract research organization master file, Annex 7, Technical Report Series No. 957, 2010
TRS 957 - Annex 7: WHO guidelines for the preparation of a contract research organization master file

WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, Technical Report Series No. 1011, 2018.
Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, TRS No 1011