16th Invitation
to Manufacturers of Antituberculosis Medicines
to Submit an Expression of Interest (EOI) for Product Evaluation
to the WHO Prequalification Team: medicines

To support national and global efforts to increase access to and the affordability of care and treatment of tuberculosis, WHO, together with UNICEF, UNAIDS and UNITAID, invites manufacturers of selected pharmaceutical products to submit Expressions of Interest (EOIs) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS 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 for EOI includes 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 INCLUDED IN THE 16TH INVITATION

The ultimate aim of this 16th EOI is to increase the range of selected products and sources available in relation to treatment for tuberculosis. The recommended active ingredients, dosage forms and strengths listed in this document have been identified by WHO’s Global TB Programme for effective treatment of people suffering from tuberculosis. These formulations are included either in the WHO Model List of Essential Medicines¹ and/or in the WHO standard treatment guidelines²

¹ WHO Model List of Essential Medicines. 19th list (April 2015), Revised June 2015


Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - Recommendations for a public health approach. World Health Organization 2013. Available at:
http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1
Guidelines on the management of latent tuberculosis infection. World Health Organization 2015. Available at:
http://apps.who.int/iris/bitstream/10665/85321/1/9789241548908_eng.pdf?ua=1&ua=1
Products included in the WHO Model List of Essential Medicines are those which satisfy the priority health care needs of a population. They are selected on the basis of disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.

Products included in WHO treatment guidelines are selected on the basis of an assessment of the quality of evidence for benefits, harms, costs, and appropriateness for use in a variety of situations, taking into account needs of special populations, and the values and preferences of the groups (professional and patient) using them.

Interested manufacturers are encouraged to submit documentation for recommended dosage forms and strengths, as specified below, of medicinal products in the following categories.

1. **Single ingredient first-line anti-tuberculosis medicines**
   - Ethambutol hydrochloride (E), coated tablet/capsule 200mg; 275mg
   - Ethambutol hydrochloride, coated tablet (scored)/ capsule 400 mg
   - Isoniazid, tablet/capsule 300 mg
   - Pyrazinamide (Z), coated tablet/capsule 250mg
   - Pyrazinamide, tablet/capsule 400 mg; 500 mg
   - Rifampicin, capsule 150 mg; 300 mg
   - Rifabutin, capsule 150 mg
   - Rifapentine, tablets 150 mg
   - Streptomycin, powder for injection 1g (vial)$^3$
   - Streptomycin, powder for injection 0.75 g (vial)$^3$

2. **Fixed dose combination products of first-line anti-tuberculosis medicines**
   - Isoniazid / Rifampicin,
     - coated tablet / capsule 75 mg / 150 mg;
     - coated tablet / capsule 150 mg / 150 mg
     - coated tablet / capsule 150 / 300 mg
   - Ethambutol hydrochloride / Isoniazid,
     - coated tablet /capsule 400 mg / 150 mg
   - Ethambutol hydrochloride / Isoniazid / Rifampicin,
     - coated tablet/capsule 275 mg / 75 mg / 150 mg
   - Isoniazid / Pyrazinamide / Rifampicin,
     - coated tablet/capsule 150 mg / 500 mg / 150 mg
   - Ethambutol hydrochloride / Isoniazid / Pyrazinamide / Rifampicin,
     - coated tablet 275 mg / 75 mg / 400 mg / 150 mg
   - Isoniazid / Pyrazinamide/ Rifampicin,
     - coated tablet/capsule 75 mg / 400 mg / 150 mg

$^3$ With or without diluent water for injection 5 ml vial.
- Isoniazid / Rifapentine,
  disperible tablet 150 mg / 150 mg;
  coated tablet (preferably scored)/capsule 300 mg / 300mg

3. Single ingredient second-line anti-tuberculosis medicines

- Amikacin, solution injection 500 mg/2 ml vial, amp; powder for injection 1g vial, ³
- Bedaquiline (fumarate), tablet 100 mg
- Capreomycin, powder for injection 1g, vial³
- Capreomycin, powder for injection 500 mg, vial³
- Clofazimine, capsule 50 mg and 100 mg; tablet 100 mg (scored)
- Cycloserine, capsule 250 mg
- Delamanid, tablet 50 mg
- Ethionamide, tablet/capsule 125mg, 250 mg (scored)
- Gatifloxacin, tablet 200 mg; 400 mg (scored)
- Kanamycin, solution for injection 1 g; powder for injection 1g, vial³
- Kanamycin, solution for injection 500 mg; powder for injection 500 mg, vial³
- Levofoxacin, tablet/capsule 250 mg; tablet 500 mg (scored); tablet 750 mg
- Linezolid, coated tablet 600 mg (scored)
- Linezolid, oral powder for suspension (20 mg/ml) 240 ml, bottle.
- Moxifloxacin tablet (scored)/capsule 400 mg
- Protonamide, tablet/capsule 250 mg
- Para-Aminosalicylic Acid (PAS) sachets, 4 g granules
- PAS Sodium 100 g jar granules, 4g/9.2 g sachets granules; powder for oral solution, sachets
- Terizidone, tablet/capsule, 250 mg; 300 mg.

4. Solid dosage formulations for children, preferably dispersible or crushable tablets, in fixed
dose combination format:

- Rifampicin 75 mg / Isoniazid 50 mg / Pyrazinamide 150 mg
- Rifampicin 75 mg / Isoniazid 50 mg

5. Solid dosage formulation for children, in single dose format:

- Delamanid, tablet 50 mg (dispersible)
- Ethambutol hydrochloride tablet 100 mg (scored and dispersible); 50 mg (scored and dispersible)
- Isoniazid tablet 100 mg (scored and dispersible); 50 mg (scored and dispersible)
- Pyrazinamide tablet 150 mg (scored and dispersible);
- Cycloserine capsule 125 mg;
- Levofoxacin tablet 100 mg (scored and dispersible);
- Moxifloxacin tablet 100 mg (scored and dispersible);
- Linezolid tablet 150 mg (scored and dispersible);
- Ethionamide tablet 125 mg (scored and dispersible);

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 in the section on Procedures & Fees on the WHO Prequalification Team: medicines website at https://extranet.who.int/prequal.

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

The quality assessment is undertaken to assess 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.

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 PQTm, please visit the PQTm website at: https://extranet.who.int/prequal. Should you have any questions relating to the procedure for responding to an EOI, please write to PQTm at its email address: prequal@who.int. Your question(s) will be directed to the prequalification team member who can best advise you.

For further information on WHO treatment guidelines, please consult:


OTHER REFERENCES (PUBLISHED LITERATURE AND OTHER REPORTS):

1. Management of tuberculosis in children and new treatment options
   B.J. Marais1, H.S. Schaaf and P.R. Donald
   Infectious Disorders – Drug Targets, 2011, 11, 144-156

2. Treatment of paediatric TB: revised WHO guidelines
   Stephen M. Graham
   Paediatric Respiratory Reviews 12 (2011) 22–26

3. Antituberculosis drug-induced hepatotoxicity in children
   Peter R. Donald
   Paediatric Reports 2011; 3:e16

4. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations.

5. European Medicines Agency concludes review of dose recommendations for anti-tuberculosis medicines used in children – press release
6. Pharmacokinetic Analyses of Fixed-Dose Drug Combinations for Paediatric Tuberculosis

7. Pharmacokinetic Simulations of a Fixed-Dose Ethambutol Formulation for Paediatric Tuberculosis

   Paediatric Respiratory Reviews 12 (2011) 31–38

9. J.A. Seddon, A.C. Hesseling, B.J. Marais et al
   Paediatric use of second-line anti-tuberculosis agents: a review

    Am J Respir Crit Care Med. 2010 Sep 1;182(5):684–92.

