

21st Invitation to Manufacturers of Antituberculosis Medicines 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 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 21st INVITATION

The ultimate aim of this 21st 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. 21st edition (June 2019)

<https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1>

WHO Model List of Essential Medicines for Children. 7th edition (June 2019) <https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1>

² WHO guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05; <https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1>, accessed 21 May 2019)

WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. (Licence: CC BY-NC-SA 3.0 IGO; <https://www.who.int/publications/i/item/9789240007048>, accessed 23 June 2020). Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. World Health Organization 2014; available at: http://www.who.int/tb/publications/childtb_guidelines/en/

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition 2016. Geneva: World Health Organization; 2016. (https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1, accessed 21 May 2019)

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 the needs of special populations, and the values and preferences of the groups (health care providers 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.

While specific paediatric formulations are listed in section 4 (FDCs) and 5 (single-dose format), it should be noted that some formulations listed in the other sections may be used for children too, with the purpose of reducing pill burden or taking advantage of the score line to adjust dosing. When this is the case, a footnote is added to provide more details, with specific references to the WHO guidelines.

TB and HIV programmes are fully supportive of the corresponding EOI. While the product Sulfamethoxazole/Trimethoprim/Isoniazid/Pyridoxine tablet 800 mg/ 160 mg/ 300 mg/25 mg is included in the HIV EOI³ under Section 5.3. Antiprotozoal, antifungal and antimycobacterial agents, we want to emphasize the importance of this product for prevention of TB, the leading cause of death among people with HIV.

1. Single ingredient first-line anti-tuberculosis medicines

- Ethambutol, film-coated tablet (scored)/capsule 400 mg)
- Isoniazid, tablet (scored)/capsule 300 mg
- Pyrazinamide, tablet 400 mg (scored) or 500 mg (scored)⁴
- Rifampicin, capsule 150 mg; 300 mg
- Rifabutin, capsule/tablet 150 mg
- Rifapentine, tablet 300 mg (scored)

2. Fixed dose combination products of first-line anti-tuberculosis medicines⁶

- Ethambutol hydrochloride/Isoniazid/Pyrazinamide/Rifampicin,
coated tablet 275 mg/75 mg/400 mg/150 mg
- Ethambutol hydrochloride/Isoniazid/Rifampicin,
coated tablet/capsule 275 mg/75 mg/150 mg
- Isoniazid/Rifampicin,
coated tablet/capsule 75 mg/150 mg;

Latent TB Infection: Updated and consolidated guidelines for programmatic management World Health Organization 2018. Available at: <http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en>

³ 16th Invitation to Manufacturers and Suppliers of Medicinal Products for HIV Infections and Related Diseases to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team: medicines (https://extranet.who.int/prequal/sites/default/files/documents/EOI-HIV_February2019_0.pdf, accessed 6 June 2019)

⁴ These formulations can also be used for children weighing 24 Kg or more to reduce pill burden. See page 97 of the WHO consolidated guidelines on the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7; <https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 21 May 2019)

⁶ The FDC 'Sulfamethoxazole/Trimethoprim/Isoniazid/Pyridoxine tablet 800 mg/ 160 mg/ 300 mg/25 mg' is not included here, even though it is relevant for TB patients, as it is already included in the HIV EOI available at: https://extranet.who.int/prequal/sites/default/files/documents/EOI-HIV_February2019_0.pdf, accessed 6 June 2019

coated tablet/capsule 150 mg/300 mg

- Isoniazid 300 mg/Rifapentine 300 mg, tablet (scored)

3. Single ingredient second-line anti-tuberculosis medicines

- Amikacin, solution injection 500 mg/2 ml vial, ampoule
- Bedaquiline, tablet 100 mg
- Clofazimine, tablet 50 mg (unscored) and 100 mg (preferably scored)^{8,9}; capsule 50 mg and 100 mg;
- Cycloserine, capsule 250 mg
- Delamanid, tablet 50 mg (preferably dispersible)
- Ethionamide, film-coated tablet 250 mg (scored)
- Gatifloxacin, tablet 200 mg, 400 mg (scored)
- Imipenem/Cilastatin combined with clavulanate; 500 mg/500 mg/125 mg in vial for IV use¹⁰
- Meropenem combined with clavulanate; 1000 mg/125 mg in vial for IV use^{10, 11}
- Levofloxacin, tablet/capsule 250 mg; tablet 500 mg (scored); tablet 750 mg (scored)
- Linezolid, coated tablet 600 mg (scored)
- Moxifloxacin tablet (scored)/capsule 400 mg
- Para-aminosalicylic Acid (PAS), 4 g, granules, sachet
- PAS, 4 g (as sodium salt), granules, sachet
- Protionamide, film-coated tablet (scored)/capsule, 250 mg
- Streptomycin, powder for injection, 1g (vial)¹²
- Terizidone, tablet/capsule, 250 mg; tablet 500 mg (scored)
- Pretomanid, tablet, 200 mg¹³

4. Solid dosage formulations for children, in fixed dose combination format¹⁴

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- Rifampicin 75 mg/Isoniazid 50 mg, dispersible tablets
- Rifampicin 75 mg/Isoniazid 50 mg/Pyrazinamide 150 mg, dispersible tablets.

⁸ Both 50 mg and 100 mg capsules and tablets are currently being used for patients under 15 years old too (see page 96 of the consolidated guidelines)

⁹ If a dispersible formulation of either 50 mg or 100 mg can be developed (even considering the highly hydrophobic nature of Cfz), that should be considered too.

¹⁰ Formulations of both imipenem/cilastatin and meropenem can be developed, if the combination with clavulanate (as an acid or a salt with an acceptable salt former) is not possible.

¹¹ For both adult and paediatric use.

¹² With or without diluent water for injection 5 ml vial.

¹³ For use only as part of the BPaL regimen under operational research conditions. The BPaL regimen comprises three components that are used as a package with pretomanid administered at 200 mg once daily, bedaquiline administered at 400 mg once daily for the first 2 weeks of treatment (days 1–14) and then 200 mg three times a week thereafter, and linezolid at 1200 mg per day.

¹⁴ All paediatric formulations should ideally be palatable (ie, formulations that easily disperse in small volumes of water and have a pleasant taste to facilitate administration in young children).

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

- Bedaquiline, tablet 20 mg (scored and dispersible)
- Cycloserine minicapsule 125 mg
- Ethambutol hydrochloride tablet 100 mg (scored and dispersible)
- Ethionamide tablet 125 mg (scored and dispersible)
- Isoniazid tablet 100 mg (scored and dispersible)
- Levofloxacin tablet 100 mg (scored and dispersible)
- Linezolid tablet 150 mg (scored and dispersible)
- Linezolid, oral powder for suspension (20 mg/ml), 240 ml bottle
- Moxifloxacin tablet 100 mg (scored and dispersible)
- Pyrazinamide tablet 150 mg (dispersible)¹⁶
- Rifapentine, tablet 150 mg (scored and dispersible)¹⁷

6. Medicines to support TB treatment

- Pyridoxine (vitamin B6), tablet 50 mg (scored);¹⁸ tablet 10 mg (scored)¹⁹

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 [Procedures & Fees](#) in the medicines section of the WHO prequalification 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

¹⁶ For children 24-34 Kg, WHO encourages the use of the 400 mg or 500 mg (scored) tablets (listed in Section 1) to reduce the pill burden. (See page 97 of the WHO consolidated guidelines on the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7; <https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 21 May 2019).

¹⁷ If scored and dispersible, Rifapentine 300 mg (section 1) can be used in paediatric patients too.

¹⁸ Pyridoxine is given with isoniazid in patients at risk (such as those with HIV, malnutrition).

¹⁹ Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in <5 year olds and 25 mg od in >4 year olds).

- 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: 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:

1. WHO guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05; <https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1>, accessed 21 May 2019)
2. WHO consolidated guidelines on the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7; <https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 21 May 2019)
3. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. (Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/i/item/9789240006997>, accessed 23 June 2020)
4. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition 2016. Geneva: World Health Organization; 2016. (https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1, accessed 21 May 2019)
5. Latent TB Infection: Updated and consolidated guidelines for programmatic management World Health Organization 2018. Available at: <http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>
6. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>

Other references (published literature and other reports):

1. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.03; http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf?ua=1).
2. Graham SM, Grzemska M, Gie RP. 2015. The background and rationale for a new fixed-dose combination for first-line treatment of tuberculosis in children. *IJTL*, 19(S1):1:2015: S3-S8(6) DOI: <http://dx.doi.org/10.5588/ijtld.15.0416>
3. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05; https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/).
4. Fixed-dose combinations for the treatment of TB in children. Factsheet. Geneva: World Health Organization; 2018 (https://www.who.int/tb/FDC_Factsheet.pdf).
5. TB Alliance and Unitaid. New Pathways for Childhood TB Treatment. Lessons from the STEP-TB Project; (https://www.tballiance.org/sites/default/files/child-resources/New_Pathways_for_Childhood_TB_Treatment.pdf)
6. Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. UNICEF and WHO; 2017 (https://www.who.int/tb/areas-of-work/children/WHO_UNICEFchildhoodTBFDCs_Statement.pdf?ua=1).
7. Management of Drug-Resistant Tuberculosis in Children: A Field Guide. 4th ed. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; 2019 (http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf).
8. Svensson EM et al. Relative bioavailability of bedaquiline tablets suspended in water: Implications for dosing in children. *Br J Clin Pharmacol*. 2018 Jun 27. doi: 10.1111/bcp.13696.
9. Achar J et al. Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis. *Emerg Infect Dis*. 2017 Oct;23(10). doi: 10.3201/eid2310.17030.
10. Garcia-Prats AJ et al. Clinical and cardiac safety of long-term levofloxacin in children treated for multidrug-resistant tuberculosis. *Clin Infect Dis*. 2018 May 16. doi: 10.1093/cid/ciy416.
11. Diallo T et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. *N Engl J Med*. 2018 Aug 2;379(5):454-463. doi: 10.1056/NEJMoa1714284.
12. Assefa Y et al. 3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review. *Eur Respir J*. 2018 Jul 11;52(1). pii: 1800395. doi: 10.1183/13993003.00395-2018.
13. Cruz AT, Starke JR. Completion Rate and Safety of Tuberculosis Infection Treatment with Shorter Regimens. *Pediatrics*. 2018 Feb;141(2). pii: e20172838. doi: 10.1542/peds.2017-2838.
14. Cruz AT, Garcia-Prats AJ, Furin J, Seddon JA. Treatment of Multidrug-Resistant Tuberculosis Infection in Children. *Pediatr Infect Dis J*. 2018 Oct; 37(10):1061-4.
15. Dheda K, Chang KC, Guglielmetti L, Furin J, Schaaf HS, Chesov D, et al. Clinical management of adults and children with multidrug-resistant and extensively drug-resistant tuberculosis. *Clin Microbiol Infect*. 2017;23(3):131-40

16. Harausz EP, Garcia-Prats AJ, Law S, Schaaf HS, Kredo T, Seddon JA, et al. (2018) Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis. *PLoS Med* 15(7): e1002591. <https://doi.org/10.1371/>
17. Harausz EP, Garcia-Prats AJ, Seddon JA, Schaaf HS, Hesselning AC, Achar J, et al. New and Repurposed Drugs for Paediatric Multidrug-Resistant Tuberculosis. Practice-based Recommendations. *Am J Respir Crit Care Med*. 2017;195(10):1300-10.
18. Schaaf, HS., Garcia-Prats, A., McKenna, L. and Seddon, J. Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children. *Expert Review in Clinical Pharmacology* 2018, 11(3): 233-44.
19. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM et al. Treatment of highly drug-resistant pulmonary tuberculosis. *New Eng J Med*. 2020;382(10):893–902.