1st Invitation to manufacturers of medicinal products for treatment of substance use disorders, 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 substance use disorders, WHO invites manufacturers of selected pharmaceutical products to submit Expressions of Interest (EOI) for product evaluation.

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 prequalified medicinal products that are considered to be acceptable for procurement by UN organizations and others.

2. Medicinal products included in the 1st Invitation

The aim of this the 1st EOI for 'substance use disorders' is to ensure the availability of quality assured methadone and buprenorphine (opioid agonists) for treatment of opioid dependence, and naloxone for emergency management of opioid overdose.

1. **Methadone** is a synthetic opioid commonly used for opioid agonist maintenance treatment (OAMT) of opioid dependence. This is one of the most effective pharmacological therapies for opioid dependence. Methadone's mechanism of action, like morphine, is mediated by the activation of opioid receptors, principally of the μ type. The pharmacology of methadone has been extensively researched and documented, with adverse effects and drug interactions well characterized. It has been recommended as a key medication for OAMT by WHO since 2009, per Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence, It is included in the WHO Model List of Essential Medicines (EML) 23rd list (2023) as tablet (5 mg; 10 mg (hydrochloride)), oral liquid (5 mg/mL; 10 mg/mL (hydrochloride)) and concentrate for oral liquid (5 mg/mL; 10 mg/mL (hydrochloride)). Due to the possibility of diversion of methadone for non-medical use, it is scheduled as a "narcotic drug," and falls under the Single Convention on Narcotic Drugs (1961). This limits the production, manufacture, export, import, distribution of, trade in, use and possession exclusively to medical and scientific purposes.

2. **Buprenorphine** is a therapeutic alternative to methadone in opioid agonist maintenance treatment (OAMT) of opioid dependence. It is partial agonist with high affinity for μ opioid receptors, with a well-established effectiveness and safety record for treatment of opioid dependence. Buprenorphine is listed as a psychotropic substance, and is currently included in Schedule III of the Convention on Psychotropic Substances (1971), an international control system for psychotropic substances that balances their abuse potential and therapeutic value. This listing is due to the possibility of diversion for non-medical use. Buprenorphine has been recommended by WHO for OAMT since 2009, per Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence, and it is included in the WHO Model List of Essential Medicines (EML) 23rd list (2023) as a therapeutic alternative to methadone.
3. **Naloxone** (n-allylnoroxymorphone) is a semisynthetic competitive opioid antagonist with a high affinity for the μ opioid receptors. It rapidly displaces most other opioids from opioid receptors, and, if administered properly, reverses clinical signs and symptoms of opioid overdose. It can be administered by a variety of routes including intravenously (IV), intramuscularly (IM), subcutaneously (SC) and intranasally (IN). It carries no potential for abuse, although high doses may lead to the development of opioid withdrawal symptoms. Widening the use of naloxone by persons likely to witness an opioid overdose, for acute management of such overdose, is recommended by WHO, per Guidelines on Community management of opioid overdose. Naloxone is also included in the WHO Model List of Essential Medicines (EML) 23rd list (2023) as an antidote used in poisoning (Injection: 400 micrograms [hydrochloride] in 1 mL ampoule).

Products included in the WHO Model List of Essential Medicines 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. Methadone and buprenoprhine are the main products for the pharmacological treatment of opioid dependence. In the near future, based on discussions with Member States, manufacturers and other key stakeholders, other products may be added to the EOI invitation category of substance use disorders.

Interested manufacturers are encouraged to submit documentation for the medicinal product as specified below:

Single ingredient medicines to treat substance use disorders

- **Methadone** (hydrochloride): in tablet (5 mg; 10 mg), oral liquid (5 mg/5mL; 10 mg/5mL) or concentrate for oral liquid (5 mg/mL; 10 mg/mL);
- **Buprenorphine** (hydrochloride): sublingual tablets (0.2 mg, 0.4 mg, 2 mg, 4 mg, 8 mg);
- **Naloxone** (hydrochloride): in vials (0.4 mg and 1 mg per 1 ml) for IV, IM or SC use; prefilled syringes (2 mg/1 ml, 2 mg/2 ml, 2 mg/5 ml) for IM, IV or SC use; and formulations for intranasal use (2 mg/0.1ml, 3 mg/0.1 ml, 4 mg/0.1 ml).

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 Unit – Medicines Assessment Team (PQT/MED) of website at https://extranet.who.int/pqweb.

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 Drug Regulatory Authority (NDRA) may be taken into account during the evaluation conducted by WHO, provided that the NDRA has expertise in the product area. If appropriate, the relevant NDRA 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 NDRA 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 Medicines.

Article 5. References and further information

World Health Organization Model List of Essential Medicines – 23nd List, 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

Executive summary. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2023 (including the 23rd WHO model list of essential medicines and the 9th WHO model list of essential medicines for children). Geneva: World Health Organization; 2024. https://iris.who.int/handle/10665/376570 . License: CC BY-NC-SA 3.0 IGO.

World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009. https://iris.who.int/handle/10665/43948 .

World Health Organization. Community management of opioid overdose. Geneva: World Health Organization; 2014. https://iris.who.int/handle/10665/137462.

mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva: World Health Organization; 2016. https://iris.who.int/handle/10665/250239

World Health Organization and United Nations Office on Drugs and Crime. International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing. Geneva: 2020. License: CC BY-NC-SA 3.0 IGO https://iris.who.int/bitstream/handle/10665/331635/9789240002197-eng.pdf?sequence=1

United Nations Office on Drugs and Crime. The International Drug Control Conventions: Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, Convention on Psychotropic Substances of 1971, United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, with final acts and resolutions. https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/conventions.html

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