10th Invitation to Manufacturers of Reproductive Health Products 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 medicinal products for reproductive health, WHO, together with UNFPA, invites manufacturers of selected pharmaceutical products to submit Expressions of Interest (EOIs) for product evaluation. (The first Invitation for EOI for reproductive health products was published in October 2006.)

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. PRODUCTS INCLUDED IN THE 10TH INVITATION

The ultimate aim of this 10th Invitation is to increase the range of selected products and sources available in relation to reproductive health. The medicinal products listed herein have been identified by WHO Department of Reproductive Health and Research, and the Reproductive Health Supplies Coalition as vital to effective prevention and treatment. These products are included in the WHO Model List of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf?ua=1), in the WHO reproductive health guidelines Family Planning and Contraception (http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/) and Preventing Unsafe abortion (http://www.who.int/reproductivehealth/publications/unsafe_abortion/en/) and in the WHO Integrated Management of Pregnancy and Childbirth (IMPAC) guideline.

Products included in the WHO Model List of Essential Medicines are those 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 onto 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. Oral hormonal contraceptives

- ethinylestradiol + desogestrel, tablet 30 micrograms +150 micrograms
- ethinylestradiol + levonorgestrel, tablet 30 micrograms + 150 micrograms
- levonorgestrel, tablet 30 micrograms
- levonorgestrel, tablet 750 micrograms (pack of two); 1.5 mg (pack of one)
- norethisterone, tablet 350 micrograms
- norgestrel, tablet 75 micrograms
- desogestrel, tablet 75 micrograms
- ulipristal acetate tablet 30 mg

2. Injectable hormonal contraceptives

- medroxyprogesterone acetate, depot injection 150 mg/ml, in 1-ml vial
- medroxyprogesterone acetate + estradiol cypionate, injection 25 mg + 5 mg
- norethisterone enanthate, injection 200 mg
- norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg
- depot medroxyprogesterone acetate (DMPA-SC), subcutaneously administered injection 104 mg/0.65 mL

3. Implantable contraceptives

- Levonorgestrel, two rod hormone releasing implant, each rod containing 75 mg (150 mg in total)
- Etonogestrel, implant, 68 mg of etonogestrel

4. Hormonal intra-uterine device

- Levonorgestrel intra-uterine system (Intrauterine system with reservoir containing 52 mg of levonorgestrel)

5. Intravaginal contraceptives

- Progesterone vaginal ring (Progesterone-releasing vaginal ring containing 2.074 g of micronized progesterone)

6. Utero-tonics

- misoprostol 25 microgram tablet
- oxytocin, injection 10 IU, 1-ml
- mifepristone 200 mg tablet (only to be used in combination with misoprostol)
- mifepristone 200 mg tablet co-packaged with 4 tablets of misoprostol 200 microgram[1]
- misoprostol 200 microgram tablet[2]
- heat-stable carbetocin, injection 100 microgram/ml – in 1 ml ampoule

7. Prevention and treatment of eclampsia

- Magnesium sulphate, injection 500 mg/ml, in 2ml and 10ml ampoule or vial

8. Treatment of maternal syphilis and prevention of congenital syphilis

Adult formulations

- Benzathine benzylpenicillin 2.4 million units per dose in vial for reconstitution and intramuscular injection
- Benzathine benzylpenicillin 1.2 million units per dose in vial for reconstitution and intramuscular injection

Paediatric formulations

- Benzylpenicillin 150,000 units in vial for reconstitution and intravenous administration
- Procaine benzylpenicillin 150,000 units in vial for reconstitution and intramuscular administration
- Benzathine benzylpenicillin 150,000 units in vial for reconstitution and intramuscular administration

9. Antifibrinolytics

- Tranexamic acid 100 mg/ml – in 5 or 10 ml ampoule

ARTICLE 3. HOW TO SUBMIT AN EOI

In order to submit an expression of interest for product evaluation, the applicant must send the requested documentation, arranged according to the information provided on the WHO Prequalification Team - medicines website at https://extranet.who.int/prequal

[1] Mifepristone (200mg) administered orally; misoprostol (4X200µg) administered either sublingually or vaginally
[2] Misoprostol administered either orally, sublingually or vaginally depending on the indication

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

The quality assessment is undertaken to evaluate whether the 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 products 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 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

For further information on the WHO Prequalification Team: medicines, please visit PQT's website at: https://extranet.who.int/prequal. If you have any questions relating to the procedure for responding to an EOI, please write to the 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 Family Planning and Contraception guidelines, please consult WHO website at: (http://www.who.int/reproductivehealth/publications/family_planning/en

For further information on WHO recommendations for induction of labour, please consult WHO website at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241501156/en/

For further information on WHO recommendations for prevention and treatment of postpartum haemorrhage, please consult WHO website at: https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1

For further information on WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage, please consult WHO website at https://apps.who.int/iris/bitstream/handle/10665/259379/WHO-RHR-17.21-eng.pdf;jsessionid=7B41D1D9A257D890CB1B8C5DD2826B93?sequence=1

For further information on WHO safe abortion, please consult WHO website at: http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/

and

http://www.who.int/reproductivehealth/publications/unsafe_abortion/clinical-practice-safe-abortion/en/

World Health Organization. WHO Guidelines for the treatment of *treponema pallidum* (syphilis). 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf.