

40th Invitation to manufacturers of Active Pharmaceutical Ingredients (API) to submit an Expression of Interest (EOI) for API evaluation to the WHO Prequalification Unit (PQT)

To support national and global efforts to increase access to and the affordability of care and treatment of priority diseases and to support reproductive health, the WHO invites manufacturers of selected APIs to submit Expressions of Interest (EOIs) for API evaluation.

1. PROCEDURE FOR THIS INVITATION TO EOI

The current invitation is published in accordance with the *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products*, adopted in 2008 by the 43rd WHO Expert Committee on Specifications for Pharmaceutical Preparations, as part of the report of this Committee, published as No. 953 of the WHO Technical Report Series in 2009.

Assessment of APIs submitted under this Invitation will include evaluation of:

- active pharmaceutical ingredient master files (APIMFs), which must include the data and information as specified in the Guidelines on active pharmaceutical ingredient master file procedure.
- manufacturing sites, which must adhere to good manufacturing practices (GMP) applicable to the manufacture of APIs.

If evaluation demonstrates that an API and its corresponding manufacturing site(s) meet WHO recommended standards, it will be included in a list of APIs that are considered to be acceptable for incorporation into finished pharmaceutical products. APIs for which an APIMF has already been assessed and accepted by WHO, and the relevant manufacturing site(s) has(have) been inspected by WHO or a member of the Pharmaceutical Inspection Co-operation Scheme (PICs) in the previous three years and found to comply with WHO GMP requirements for the manufacture of the particular API, may be included in the list without prior reassessment or re-inspection.

2. APIs INCLUDED IN THIS INVITATION

The ultimate aim of this invitation is to increase the range and availability of selected APIs which have been found to meet WHO-recommended quality standards. Those APIs and their manufacturing sites which are found to meet the quality standards recommended by WHO will be included in a published list of APIs which have, at the time of their evaluation and inspection by WHO, been found to be acceptable, in principle, for use in the production of finished pharmaceutical products (FPPs). It remains the ultimate responsibility of the manufacturer of the FPP to ensure that the API is suitable for the manufacture of a specific pharmaceutical product.

Expressions of Interest are invited for the APIs listed below. APIs added to this invitation are indicated in red and APIs now removed are struck-through.

APIs for products used in the treatment of HIV/AIDS and related diseases

- Abacavir
- Amphotericin B
- Atazanavir
- Benzathine benzylpenicillin
- Cabotegravir
- Clindamycin
- Dapivirine
- Darunavir
- Dolutegravir
- Efavirenz
- Emtricitabine
- Ethinylestradiol
- Etravirine
- Fluconazole
- Flucytosine
- Ganciclovir
- Isoniazid
- Lamivudine
- Lenacapavir
- Levonorgestrel
- Lopinavir
- Nevirapine
- Pyridoxine
- Pyrimethamine
- Rilpivirine
- Ritonavir
- Sulfadiazine
- Sulfamethoxazole
- Tenofovir alafenamide
- Tenofovir disoproxil fumarate
- Trimethoprim
- Valganciclovir
- Zidovudine

APIs for products used in the treatment of hepatitis B and C

- Daclatasvir
- Entecavir
- Glecaprevir
- Ledipasvir

- Pibrentasvir
- Ribavirin
- Sofosbuvir
- Tenofovir disoproxil fumarate
- Velpatasvir

APIs for products used in the treatment of malaria

- Amodiaquine
- Artemether
- Artesunate
- Dihydroartemisinin
- Lumefantrine
- Mefloquine
- Piperaquine
- Primaquine
- Pyrimethamine
- Pyronaridine
- Quinine (hydrochloride)
- Sulfadoxine
- Tafenoquine

APIs for products used in the treatment of tuberculosis

- Bedaquiline (fumarate)
- ~~Clavulanate (as an acid or a salt with an acceptable salt former)~~
- Clofazimine
- Cycloserine
- Delamanid
- Ethambutol
- Ethionamide
- Isoniazid
- Levofloxacin
- Linezolid
- Moxifloxacin
- Para-aminosalicylate sodium (PAS Sodium)
- Pretomanid
- Prothionamide
- Pyrazinamide
- Pyridoxine
- Rifabutin
- Rifapentine

- Rifampicin
- Terizidone

APIs for reproductive health products

- Benzathine benzylpenicillin
- Benzylpenicillin
- Carbetocin
- Desogestrel
- Estradiol cypionate
- Estradiol valerate
- Ethinylestradiol
- Etonogestrel
- Levonorgestrel
- Magnesium sulphate
- Medroxyprogesterone acetate
- Mifepristone
- Misoprostol
- Norethisterone enanthate
- Norgestrel
- Oxytocin
- Procaine benzylpenicillin
- Progesterone
- Tranexamic acid
- Ulipristal acetate

APIs for products used in the treatment of neglected tropical diseases

- Albendazole
- Amphotericin B
- Arpraziquantel
- Azithromycin
- Clarithromycin
- Diethylcarbamazine citrate
- Fexinidazole
- Ivermectin
- Mebendazole
- Miltefosine
- Moxidectin
- Paromomycin
- Praziquantel
- Rifampicin
- Sodium stibogluconate (SB⁵⁺)

APIs for products used in the treatment of diarrhoea

- Zinc (sulfate or gluconate)

APIs for products used in the treatment of influenza

- Baloxavir
- Oseltamivir
- Zanamivir

APIs for products used in the treatment of COVID-19

- Baricitinib
- Dexamethasone
- Molnupiravir
- Nirmatrelvir
- Remdesivir
- Ritonavir

APIs for products used in the treatment of multi-drug-resistant bacterial infections

- Cefiderocol (sulfate toxylate)

APIs for products used in treatment of apnoea in preterm infants

- Caffeine citrate

APIs for products used in treatment of bacterial infections in children

- Amoxicillin
- Nitrofurantoin

3. HOW TO SUBMIT AN EXPRESSION OF INTEREST

Interested manufacturers are encouraged to submit expressions of interest for API evaluation by sending the required documentation, arranged according to the information provided on the WHO PQT website at <https://extranet.who.int/pqweb/>

4. QUALITY ASSESSMENT PROCEDURE FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST BY A MANUFACTURER

A quality assessment addresses whether the API meets the requirements recommended by WHO and is manufactured in compliance with good manufacturing practices (GMP).

The quality assessment procedure established by WHO is based on the following principles:

- a general understanding of the production and quality control activities of the manufacturer of the API;
- assessment of data and information on the API, submitted by the manufacturer, which includes the manufacturing process, material specifications, test data and results, including changes and variations;
- assessment of the API manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key starting materials or intermediates and the final APIs during and after;
- purification through compliance with WHO GMP;
- random sampling and testing of APIs;
- control of storage and distribution;
- handling of complaints and recalls; and
- monitoring of complaints from relevant United Nations agencies and national medicines regulatory authorities of WHO Member States.

WHO will collaborate with NMRAs and other organizations on quality assessment and site inspections. WHO recommends that manufacturers of APIs expressing interest in participating in the prequalification of APIs should inform and ask the relevant NMRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the national medicines regulatory authority with the necessary authorization to discuss the API files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant API and that the API meets WHO recommended standards, the API (as produced at the specified manufacturing site) is added to the WHO List of Prequalified Active Pharmaceutical Ingredients.

5. REFERENCES AND FURTHER INFORMATION

For further information, please visit the WHO PQT website at <https://extranet.who.int/pqweb> or contact the Team directly at prequal@who.int.