

# Invitation to Manufacturers

27<sup>th</sup> September 2021

## Manufacturers of Antiretroviral (HIV/AIDS), Antihepatitis B and C, Antituberculosis and Antimalarial medicines Are Invited to Submit An Expression of Interest For Product Evaluation by the Global Fund Expert Review Panel

Opening Date: 27<sup>th</sup> September 2021  
Closing Date: 19<sup>th</sup> November 2021  
Reference Number: GF/ERP/Round 24/09-2021

### 01 Background

#### Summary of the Global Fund Quality Assurance Policy

The Global Fund to Fight AIDS, Tuberculosis and Malaria (“Global Fund”) provides grants to support national and global efforts to increase access, care and treatment in approximately 140 countries.

The Global Fund Quality Assurance Policy for Pharmaceutical Products (“QA Policy”<sup>1</sup>) defines uniform and stringent quality requirements applicable to antiretrovirals (ARVs), antituberculosis, and antimalarial pharmaceutical products purchased with Global Fund resources. In principle, these pharmaceutical products can be funded using Global Fund resources if they are in compliance with national regulatory standards as applicable and if:

- prequalified by the WHO Prequalification Programme; **and/or**
- authorized for marketing in a country with a stringent regulatory authority<sup>1</sup> (registration "for export only" is not sufficient) or approved/subject to a positive opinion under one of the following schemes: Canada S.C. 2004, c. 23 (Bill C-9) procedures, or Art. 58 of European Union Regulation (EC/No. 726/2004) or US-FDA tentative approval; **or**
- products of which the dossiers were reviewed and permitted for use for a time limited period by an independent panel of technical experts (the Expert Review Panel).

<sup>1</sup> <https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>

Information about the Expert Review Panel mechanism and process for procurement of Expert Review Panel-reviewed products is available at: <https://www.theglobalfund.org/en/sourcing-management/quality-assurance/expert-review-panel/>

In order to assist Global Fund grant recipients to identify the regulatory status of ARVs, the Global Fund has developed a list of products classified according to the above quality assurance requirements. The current list can be downloaded from: <https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>

## **Summary of the Global Drug Facility Quality Assurance Policy**

In July 2010, the Global Drug Facility (GDF) revised its quality assurance policy and procedures as part of a collaborative process to ensure harmonization with the policies of major multilateral financing mechanisms, including the Global Fund and other organizations (i.e. the Union; the United Nations Children’s Fund (UNICEF), Médecins Sans Frontières) involved in TB control and in particular to:

- ensure global consistency on quality standards set for procurement and supply of anti-TB medicines as well as medical items;
- avoid duplication of effort and ensure optimum utilization of resources.

With the combined objectives to improve the safety, efficacy and quality of products procured by the GDF, the GDF quality assurance system is based on:

- recommendations by WHO/Stop TB Strategy;
- authorization for use by recipient countries;
- recommendations by the relevant WHO Programmes, that is, Prequalification of Medicines Programme (PQP);
- authorization for marketing by a stringent national medicines regulatory authority in the country;
- positive opinion for procurement purposes by an Expert Review Panel, for a specified time period where there are few/no WHO-prequalified or stringent regulatory-approved products available; and
- a quality monitoring program for supplied products, including independent random quality control.

## **Summary of the Unitaid Quality Assurance Policy**

Unitaid's mission is to maximize the effectiveness of the global health response by catalyzing equitable access to better health products for HIV/AIDS, tuberculosis and malaria in low and middle-income countries. Unitaid’s approach is to utilize market interventions to improve public health. In so doing, Unitaid aims to promote “healthy”, dynamic market conditions whereby manufacturers have incentives to invest and innovate, while at the same time supply quality public health products at affordable prices and in acceptable formulations that enable the maximum number of people to access them. By working through markets, Unitaid’s interventions impact not only those countries receiving direct Unitaid support, but also other countries and organisations that can benefit from Unitaid’s global price reductions, improvements in product quality, and innovation. In all cases, Unitaid seeks to find innovative, cost-effective and sustainable market solutions to public health problems. The ultimate goal of Unitaid is to improve the public health of people living in low- and middle-income countries through market-based interventions.

All medicines procured under Unitaid-funded projects are required to be in compliance with Unitaid’s quality assurance policy, which stipulates similar standards as described above and in the relevant sections of the Global Fund quality assurance policy.

## 02 Purpose

The purpose of this expression of interest is to invite submissions of product dossiers for review by the Expert Review Panel for which there could be supply bottlenecks, including the cases where there are two or less products of the same formulation available in the global market that are already WHO prequalified or approved by a stringent regulatory authority. This expression of interest may include, as well, some formulations even when there are more than two eligible products in the market, in cases where it has been determined that such products are eligible for distribution to a restricted number of countries only, or when it has been identified that the available production capacity of the qualified products cannot cover the demand.

## 03 Product formulations included in this expression of interest

The recommended active ingredients, dosage forms and strengths ("Formulations") listed in this document are included in the current WHO Model List of Essential Medicines and/or in the most recent WHO standard treatment guidelines for treatment and prevention of the three diseases.

**Antiretroviral formulations and medicinal products for treatment of Hepatitis B and C included in this expression of interest are listed in Annex A.**

**Antituberculosis formulations included in this expression of interest are listed in Annex B.**

**Antimalarial formulations included in this expression of interest are listed in Annex C.**

WHO recommends and endorses the use of medicines in fixed-dose combinations. The Global Fund quality assurance policy strongly recommends that Principal Recipients implement mechanisms to encourage adherence to treatment regimens (including, but not limited to, providing medicines in fixed-dose combinations, once-a-day formulations and/or blister packs, and providing peer education and support), to monitor and contain resistance, and to monitor adverse drug reactions according to existing international guidelines. FDCs are considered as the preferred option when available.

## 04 Eligibility for submission<sup>2</sup>

### **Requirements under CRITERION-1:**

The following criteria must be met in order for products to be accepted for External Review Panel review:

- the manufacturer of the product has submitted an application of the product to the WHO Prequalification Programme and it has been accepted by WHO for review; OR the manufacturer of the product has submitted an application for marketing authorization to a stringent regulatory authority, and it has been accepted for review by the stringent regulatory authority;
- AND the product is manufactured at a site that is compliant with all standards of good manufacturing practice that apply to the relevant product formulation, as verified after inspection by the WHO Prequalification Programme, OR a stringent regulatory authority, OR a regulatory authority participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S)<sup>3</sup>.

### **Requirements under CRITERION-2:**

The following criteria must be met in order for products to be accepted for an External Review Panel review:

<sup>2</sup> Global Fund, [Quality Assurance Policy for Pharmaceutical Products](#) (as amended and restated on 14 December 2010), Point 13

<sup>3</sup> Pharmaceutical Inspection Cooperation Scheme (<http://www.picscheme.org/members.php>)

- the product is manufactured at a site that is compliant with all standards of good manufacturing practice that apply to the relevant product formulation, as verified after inspection by the WHO Prequalification Programme OR a stringent regulatory authority OR a regulatory authority participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S),
- AND it is not listed in the WHO invitation to manufacturers to submit an expression of interest for product evaluation by the WHO Prequalification Programme.

## 05 Submission of documents for Expert Review Panel review under CRITERION-1

All manufacturers interested in submitting applications for review by the Expert Review Panel are requested to submit the following information and material for each product under consideration:

### **For each product awaiting WHO prequalification:**

1. A covering letter expressing interest in submitting the product to the Expert Review Panel for review;
2. An acceptance letter from the WHO Prequalification Programme confirming that the submission for the product has been accepted for review, and stating the WHO reference number assigned by WHO to this specific product;
3. Certification issued by the WHO Prequalification Programme confirming that the site and production line where the product is manufactured comply with all aspects of good manufacturing practice, or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied;
4. A completed Pharmaceutical Product Questionnaire<sup>4</sup> (attached);
5. In lieu of annexes, reference can be made to the dossier submitted for WHO prequalification. Annexes should be submitted in case of any changes or updates;
6. A non-returnable product sample as requested in Section VIII of the questionnaire.

### **For each product awaiting marketing authorization by a stringent regulatory authority:**

1. A covering letter expressing interest in submitting the product to the Expert Review Panel for review;
2. An acceptance letter from the a stringent regulatory authority confirming that the submission for the product has been accepted for review;
3. Certification, issued by a stringent regulatory authority OR a regulatory authority participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S), confirming that the site and production line where the product is manufactured comply with all aspects of good manufacturing practice, or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied;
4. A completed Pharmaceutical Product Questionnaire<sup>4</sup> (attached), and all annexes as applicable;
5. A non-returnable product sample as requested in Section VIII of the questionnaire.

<sup>4</sup> As available at the Global Fund website:

[https://www.theglobalfund.org/media/4325/psm\\_interagencyfinishedpharmaceuticalproduct\\_questionnaire\\_en.docx](https://www.theglobalfund.org/media/4325/psm_interagencyfinishedpharmaceuticalproduct_questionnaire_en.docx)

## 06 Submission of documents for External Review Panel review under CRITERION-2

All manufacturers interested in submitting applications for review by the External Review Panel under *Eligibility Criterion 2* are requested to submit the following information and material for each product under consideration:

1. A covering letter expressing interest in submitting the product to the External Review Panel for review;
2. Certification issued by the WHO Prequalification Programme confirming that the site and production line where the product is manufactured comply with all aspects of good manufacturing practice, or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied;

and/or

3. Certification, issued by stringent regulatory authority OR a regulatory authority participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S), confirming that the site and production line where the product is manufactured comply with all aspects of good manufacturing practice, or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied;
4. A completed Pharmaceutical Product Questionnaire<sup>5</sup>;
5. A non-returnable product sample as requested in Section VIII of the questionnaire.

## 07 Confidentiality

All information provided by manufacturers will be received by the Global Fund and shared with the External Review Panel members for the purpose of facilitating their review of the submission and provision of advice to the Global Fund.

Information provided by manufacturers, review findings and advice provided by the External Review Panel in connection with this expression of interest will be shared with and used by the Global Fund, GDF, Unitaid and the following partners: Médecins sans Frontières, UNICEF, and the United States Agency for International Development (USAID) as the basis for procurement decisions.

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<sup>5</sup> As available at the Global Fund website:  
[https://www.theglobalfund.org/media/4325/psm\\_interagencyfinishedpharmaceuticalproduct\\_questionnaire\\_en.docx](https://www.theglobalfund.org/media/4325/psm_interagencyfinishedpharmaceuticalproduct_questionnaire_en.docx)

## 08 Eligibility

Completeness of the documents submitted to Global Fund Secretariat for External Review Panel review is determined by the Global Fund quality assurance specialist. All the documents listed in the instructions for submission (in annex) must be included by the applicant. Incomplete submissions will not be forwarded to the External Review Panel.

The eligibility of the submissions for External Review Panel review will not be considered by the Global Fund Secretariat. It is the External Review Panel's responsibility to review and to judge the eligibility and whether or not to perform the risk-benefit assessment of the products submitted.

For any product found not to comply with the required standards during previous External Review Panel review, all documentation requested should be re-submitted in full.

## 09 Instructions for submission

**Documentation should be submitted by electronic means ONLY either via CD, USB key or file transfer (because of new IT policy security, please liaise in advance with the contact address above of this EoI to ensure file transfer software is acceptable to Global Fund).** Files should be named to reflect their content as mentioned in this letter (e.g. "Covering Letter.pdf"). For ease of reference, electronically submitted annexes to the questionnaire should be named according to the letters on the list of annexes on page 17 of the questionnaire (e.g. "A.pdf" for information on the formulation of the product). **Please keep the naming of the annexes as short as possible (e.g. "A.pdf").**

**In regards of the technical evaluation, it is mandatory to submit a sample of the finished product offered (one pack of one of the available packaging size is sufficient).**

It is highly recommended that manufacturers send an undertaking with the shipment of sample (sample for technical evaluation) that is sent along with the dossiers, indicating that the samples are sent **for review purpose only**, will not be used on humans or animals have no commercial value and will not be placed in the market. This will ensure smooth passage through customs in the country of origin and in Switzerland.

The deadline for the Submission is the **19<sup>th</sup> November 2021**.

Submissions should be sent to the following Address of the TGF QA team:

**HealthProductQualityAssurance@theglobalfund.org**

Should you have any further questions, please send an e-mail to the following email address: [HealthProductQualityAssurance@theglobalfund.org](mailto:HealthProductQualityAssurance@theglobalfund.org)

## Annex A - Antiretroviral formulations and medicines to treat hepatitis

**Dossiers for individual components of WHO-recommended fixed-dose-combinations<sup>6</sup> that are not yet included in the List of Pharmaceutical Products Found Compliant with the Global Fund Quality Assurance Policy can be submitted as well to the Expert Review Panel until such time as the development of the fixed-dose combinations is finalized.**

### **Antiretrovirals as fixed-dose combinations for pediatric use:**

#### Nucleoside/Nucleotide Reverse Transcriptase Inhibitors plus Protease Inhibitors: (CRITERION-1):

- Lamivudine /Abacavir mini tablets/granules 15 mg/30 mg co-mixed with Lopinavir/Ritonavir mini tablets/ granules (heat stable) 40 mg/10 mg

#### Protease Inhibitors (CRITERION-1):

- Darunavir/Ritonavir, 120 mg/20 mg, tablet (heat stable)

#### Nucleoside/Nucleotide Reverse Transcriptase Inhibitors plus Integrase Inhibitors (CRITERION-1):

- Lamivudine/Abacavir/Dolutegravir, 30 mg/60 mg/5 mg, tablet (dispersible)

### **Antiretrovirals as single-ingredient formulations for use in children (until pediatric fixed-dose combinations become available)**

#### Solid formulations of Integrase Inhibitors (CRITERION-1):

- Raltegravir, 25 mg, tablet (scored and chewable)

#### Integrase Inhibitors (CRITERION-1):

- Dolutegravir, 10 mg, tablet (scored and dispersible)

### **Antiretrovirals as single-ingredient formulations for use in adults and adolescents (until fixed-dose combinations become available):**

#### Non-Nucleoside Reverse Transcriptase Inhibitors (CRITERION-1):

- Efavirenz, 400 mg, tablet
- Etravirine, 200 mg, tablet

### **Antiretrovirals as fixed-dose combinations for adults and adolescents:**

#### Protease Inhibitors (CRITERION-1):

- Darunavir/Ritonavir, 300 mg/50 mg, 400 mg/50 mg, tablet (heat stable)

- Nucleotide Reverse Transcriptase Inhibitors plus Non-nucleoside Reverse Transcriptase Inhibitors plus Integrase Inhibitors (CRITERION-1):

- Emtricitabine/ Tenofovir disoproxil fumarate (TDF)/Dolutegravir, tablet 200 mg/300 mg/50 mg

<sup>6</sup> WHO, June 2016. [Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection](#) ; WHO, April 2016. [New recommendations in the updated WHO Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection](#)

## **Medicines to treat Hepatitis B and Hepatitis C**

### Hepatitis B single-ingredient formulations for use in adults and adolescents (CRITERION-1):

- Entecavir, 0.5 mg tablet, 1 mg tablet (scored)
- Tenofovir, 150 mg, 200 mg, tablet (preferably dispersible)

### Hepatitis B single-ingredient paediatric formulations (CRITERION-1):

- Entecavir, 0.05 mg/ml, oral solution

### Hepatitis C Fixed-dose combination for use in adults (CRITERION-1):

- Sofosbuvir/ Daclatasvir, 400 mg/60 mg and 400 mg/30 mg, tablet
- Sofosbuvir/ Velpatasvir, 400 mg/100mg, tablet
- Glecaprevir/Pibrentasvir, 100 mg/40mg, tablet

### Hepatitis C Fixed-dose in children 12 - 17 years (CRITERION-1):

- Sofosbuvir/ Ledipasvir, 400 mg/90 mg, tablet
- Sofosbuvir/ Daclatasvir, 400 mg/60 mg, tablet
- Glecaprevir/Pibrentasvir, 100 mg/40 mg, tablet

### Hepatitis C Fixed-dose in children 6 - 12 years (CRITERION-1):

- Sofosbuvir/ Daclatasvir, 400 mg/60 mg, tablet (scored)

### Hepatitis C single-ingredient for use in adults and in children 12 - 17 years (CRITERION-1):

- Ribavirin, 200 mg, 400 mg, 600 mg, capsule



## B - Antituberculosis formulations

The formulations included in this category are inclusive of all groups of anti-TB medicines.

**Preferred standard packaging specifications:** for all the solid dosage products the preferred standard packaging specifications are:

- Blister of 10, 14 or 28 tablets, 3, 6 or 24 blisters in a box (i.e. 672 tablets in a box or 100 tablets in a box)

However, this does not preclude the manufacturer from submitting dossiers for other pack sizes.

### **Single ingredient (criterion 1):**

#### Paediatric- Friendly Formulations

- Bedaquiline 20 mg, tablet, or dispersible tablet (preferably scored)
- Clofazimine 50 mg, tablet or dispersible tablet
- Cycloserine 125 mg, capsule
- \*Delamanid 25 mg, tablet or dispersible tablet
- Ethambutol 100 mg, chewable or dispersible tablet
- \*Linezolid 150 mg, dispersible tablet
- Rifapentine 150 mg, dispersible tablet (scored)

#### Adult Formulations

- Bedaquiline 100 mg, tablet
- Clofazimine 100 mg, tablet (preferably scored)
- \*Delamanid 50 mg tablet
- Pretomanid 200 mg, tablet
- Rifabutin 150 mg, capsule or tablet
- \*Rifapentine 300 mg, tablet (scored)

#### Fixed-dose combinations:

- \*Rifampicin / Isoniazid / Pyrazinamide, 75 mg / 50 mg / 150 mg, dispersible tablet
- Rifampicin / Isoniazid, 75 mg / 50 mg, dispersible tablet
- \*Isoniazid / Rifapentine, 300 mg / 300 mg, capsule or tablet or scored tablet

\* These formulations are eligible for the *Ad hoc* Review Process:

<https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>

## Annex C - Antimalarial formulations

### **Formulations included under eligibility (CRITERION-1):**

#### Artemisinin-based fixed-dose oral combination formulations

- Artesunate + Mefloquine,
  - o 25/50 mg, tablet
  - o 100/200 mg, tablet
- Dihydroartemisinin + Piperaquine,
  - o 60 mg + 480 mg, tablet (preferably scored)
  - o 80 mg + 640 mg, tablet (preferably scored)
  
- Artesunate + Pyronaridine, 60 mg +180 mg, tablet

#### Artemisinin-based **fixed dose combination oral pediatric formulations, dispersible:**

- Artemether + Lumefantrine, 40 mg + 240 mg, tablet (preferably scored)
- Artesunate + Mefloquine, 25 mg + 50 mg, tablet
- Artesunate + Pyronaridine, 20 mg +60 mg, tablet
  
- Dihydroartemisinin + Piperaquine,
  - o 20 mg + 160 mg, tablet (scored)
  - o 30 mg + 240 mg, tablet
  - o 40 mg + 320 mg, tablet

#### Combination antimalarial medicines in co-blistered formulations, **dispersible:**

- Amodiaquine + Sulfadoxine / Pyrimethamine :
  - o 75 mg + 250 mg /12.5 mg, tablet
  - o 150 mg + 500 mg / 25 mg, tablet
  - o 76.5 mg + 250 mg / 12.5 mg, tablet
  - o 153 mg + 500 mg / 25 mg, tablet

### Artemisinin-based single-ingredient formulations

#### -Artesunate

- suppositories 50 mg
- suppositories 200 mg
- Powder for injection (IV/IM) 30 mg, 120 mg (vial) with appropriate reconstitution agents and diluents.

#### Artemether, oily injection

- injection 20 mg/ml
- injection 40 mg/ml
- injection 80 mg/ml
- injection 100 mg/ml

### Annex C - Antimalarial formulations

#### **Formulations included under eligibility (CRITERION-1):**

#### Other antimalarial medicines

- Primaquine (as base)
  - o 2.5 mg, tablet (preferably dispersible for paediatric use)
  - o 5 mg, tablet (scored) (preferably dispersible for paediatric use)
  - o 7.5 mg, tablet (scored) (preferably dispersible for paediatric use)
  - o 15 mg, tablet (scored)

#### **Formulations included under eligibility (CRITERION-2)**

#### Single-ingredient medicines

- Chloroquine tablet 100 mg, 150 mg, 300 mg, base (as phosphate or sulphate)
- Quinine sulphate tablet 125 mg, 500 mg
- Quinine dihydrochloride injection (IV/IM) 300 mg/ml, 600mg/2ml.

**\*END\***

#### *Additional consulted reference guidelines:*

WHO policy brief (WHO, July 2019) Update of recommendations on first- and second-line antiretroviral regimens

WHO guidelines (WHO, July 2018) Optimal formulary and limited-use list for paediatric ARVs.

WHO guidelines (WHO, July 2018) Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection.