2nd Invitation to manufacturers of second and third anti-tuberculosis medicines to submit an Expression of Interest (EoI) for product evaluation by Expert Review Panel (ERP)

July 2010

I. Background

In 2008, GDF initiated a revision and expansion of its Quality Assurance Policy and Procedures as part of a collaborative process to ensure harmonization with the policies of two major multi-lateral financing mechanisms (i.e. The Global Fund and UNITAID), and other organizations (i.e. The Union; 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 efforts among organizations involved in TB control.

With the mission of ensuring the safety, efficacy and quality of products provided by GDF, the quality assurance system is based on:

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

II. Purpose of this invitation for EoI

The purpose of this invitation for EoI is to invite submissions of anti-tuberculosis product dossiers -second and third-line - for review by the ERP for which there are

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less than 3 products[1] of the same formulations that are WHO Prequalified or SRA approved or ERP reviewed are available in the global market.

III. Product Formulations included in 2nd EoI

The recommended active ingredients, dosage forms and strengths ("Formulations") listed in this document have been identified by WHO's Department of tuberculosis as vital to effective treatment for people suffering from tuberculosis. These Formulations are included either in the WHO Model List of Essential Medicines[2] and/or in the WHO standard treatment guidelines[3] or in National/institutional Guidelines.

In addition to above this invitation for EoI also invites submissions of dossiers of anti-tuberculosis drugs a) to treat XDR-TB (extensively drug resistant tuberculosis) and b) second line anti-TB drugs produced and used solely in INDIA for review by the ERP.

IV. Eligibility Criteria for ERP review in accordance with Global Drug Policy 2010

IV. 1. Eligibility criterion 1:

a) Requirements:

The following criteria are required to be fulfilled by the manufacturer for being accepted for ERP review under this *criterion.* This criterion has been in force from the beginning of the ERP process and was adopted by Global Drug Facility in 2008.

> *1. the manufacturer of the product has submitted an application for pre-qualification of the product by 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 any SRA[4] (Stringent Regulatory Agency), and it has been accepted for review by the SRA,*
>
> and

[1] INN, strength, dosage form, type of packaging (HPDE container or Alu/PvC foil blister or Alu/ALU foil strips)
[2] WHO Model List of Essential Medicines. 16th list, March 2009
http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en.pdf
WHO Model List of Essential Medicines. For Children. Second list, March 2009
http://www.who.int/selection_medicines/committees/expert/17/second_children_list_en.pdf
[3] WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. WHO/HTM/TB/2008.402
http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html

[4]Defined as either: an ICH[4] member country, an ICH observer or any country whose regulatory authority is associated with an ICH member through a legally binding mutual recognition agreement, or be approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Art. 58 of European Union Regulation (EC9 No. 726/2004) or United States FDA tentative approval. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use: www.ich.org

2. *the product is manufactured at a site that is compliant with all standards of Good Manufacturing Practice (GMP) that apply to the relevant product formulation, as verified after inspection by the WHO Prequalification Programme OR any SRA OR a regulatory authority participating to the Pharmaceutical Inspection Cooperation Scheme (PIC/S)*[5]**.**

b) Formulations included in this invitation for EoI under Eligibility Criterion-1

The formulations included in this category are:

b.1. Single ingredient Second Line drugs:

- Amikacin, solution injection 500 mg/2 ml vial/ampoule
- Amikacin, powder for injection 1g vial/ampoule
- Capreomycin, powder for injection 1g, vial/ampoule
- Cycloserine, capsule 250 mg -Loose tablets in HDPE container and Blister pack
- Ethionamide, tablet 250 mg, tablet, Loose tablets in HDPE container and Blister pack
- Kanamycin, powder for injection 500 mg and 1g vial, preferably 80 vials per box.
- Levofloxacin, tablet 250 mg, tablet 500 mg, tablet 750 mg, Loose tablets in HDPE container and Blister pack or Alu/Alu strip, preferably 10 tabs per foil strip, 9 strips in a box.
- Moxifloxacin, tablet 400 mg Loose tablets in HDPE container and Blister pack or Alu/Alu strip, preferably 10 tabs per strip, 9 strips in a box.
- Ofloxacin, tablet 200 mg and 400mg tablet, Loose tablets in HDPE container and Blister pack
- Prothionamide, tablet 250 mg Loose tablets in HDPE container and Blister pack
- Para-Aminosalicylic Acid (PAS) sachets, 4 g granules,

[5] www.picscheme.org http://www.theglobalfund.org/documents/psm/List_of_Countries_ICH.pdf

- Para-Aminosalicylic PAS Sodium 100 g jar; preferably 4 g granules sachets, 250 sachets per box; powder for oral solution in sachet.
- Terizidone, capsule/tablet, 300 mg Loose capsules/container and Blister pack

Note: the word "Preferably" wherever used for packs, indicates the most preferred type of packing and/or packing size. However, this does not preclude manufacturers to submit dossiers for other pack sizes.

c) Submission under Eligibility Criterion-1:

All manufacturers interested in submitting applications for review, by the ERP under *Eligibility criterion-1* for products listed, are requested to submit the following information and material for each product under consideration.

For each product awaiting WHO-prequalification:

- A covering letter expressing interest to submit the product to the ERP for review
- 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.
- Certification, issued by WHO Prequalification Medicine programme confirming that the site and production line where the product is manufactured comply with all aspects of Good Manufacturing Practice (GMP), or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied.
- A completed Pharmaceutical Product Questionnaire (as available at http://www.stoptb.org/gdf/drugsupply/resource_materials.asp) 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.
- A non-returnable product sample as requested in Section VIII of the questionnaire

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

- A covering letter expressing interest to submit the product to the ERP for review

- An acceptance letter from the SRA confirming that the submission for the product has been accepted for review

- Certification, issued by a regulatory authority which is a member, observer or associate of ICH or a member of PIC/S, confirming that the site and production line where the product is manufactured comply with all aspects of Good Manufacturing Practice (GMP), or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied

- A completed Pharmaceutical Product Questionnaire as available at (http://www.stoptb.org/gdf/drugsupply/resource_materials.asp), and all annexes as applicable

- A non-returnable product sample as requested in Section VIII of the questionnaire

Documentation should be submitted in hard copy (on paper) and electronically, except for annexes to the Pharmaceutical Product Questionnaire, which should be submitted electronically only.

VI.2.Eligibility criterion 2:

a) Requirement:

The following criteria are required to be fulfilled by the manufacturer for being accepted for ERP review under *Eligibility criterion-2*.

1. These Formulations are included either in the WHO Model List of Essential Medicines and/or in the WHO standard treatment guidelines or in National/institutional Guidelines
2. The product is manufactured at a site that is compliant with all standards of Good Manufacturing Practice (GMP) that apply to the relevant product formulation, as verified after inspection by the WHO Prequalification Programme OR an SRA OR a regulatory authority participating to the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

b) Formulations included in this invitation for EoI under Eligibility Criterion-2

The formulations included in this category are:

b.1. Third line anti-tuberculosis drugs used for the treatment of extensively drug resistant (XDR-TB):

- Amoxicillin/Claulanate 875/125mg and 500/125mg Tablets, Loose tablets in HDPE container and Blister pack
- Clofazimime 50mg, 100mg tablet Loose tablets in HDPE container and Blister pack
- Clarithromycin 500mg Tablet Loose tablets in HDPE container and Blister pack
- Linezolid 600 mg, tablets Loose capsules/container and Blister pack
- Thiacetazone 150mg Tablet Loose tablets in HDPE container and Blister pack

b.2. Second and third line anti-tuberculosis drugs used solely in INDIA.

- Amikacin, powder for injection 750 mg vial, preferably 80 vials per box
- Capreomycin, powder for injection 500 mg vial, preferably 80 vials per box
- Capreomycin, powder for injection 750 mg, vial, preferably 80 vials per box
- Kanamycin, powder for injection 750 mg, vial, preferably 80 vials per box.
- Ethionamide, tablet 125 mg Loose tablets in HDPE container and foil strip of 10 tablets, 9 strips per box
- Para-Aminosalicylic Sodium (PAS), sachets 10 g granules, preferably 100 sachets per box.

Note: the word "Preferably" wherever used for packs, indicates the most preferred type of packing and/or packing size. However, this does not preclude manufacturers to submit dossiers for other pack sizes.

c) Submission:

All manufacturers interested in submitting applications for review, by the ERP under *Eligibility criterion-2*, for products listed, are requested to submit the following information and material for each product under consideration.

- A covering letter expressing interest to submit the product to the ERP for review
- Certification, issued by WHO Prequalification Medicine programme confirming that the site and production line where the product is manufactured comply with all aspects of Good Manufacturing Practice (GMP), or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied.

  And/or

- Certification, issued by a regulatory authority which is a member, observer or associate of ICH or a member of PIC/S, confirming that the site and production line where the product is manufactured comply with all aspects of Good Manufacturing Practice (GMP), or a letter describing arrangements made to obtain such certification and stating the date when it will be supplied
- A completed Pharmaceutical Product Questionnaire as available at (http://www.stoptb.org/gdf/drugsupply/resource_materials.asp .
- A non-returnable product sample as requested in Section VIII of the questionnaire

Documentation should be submitted in hard copy (on paper) and electronically, except for annexes to the Pharmaceutical Product Questionnaire, which should be submitted electronically only.

V. Additional informations/instructions to the applicant

1. Completeness of the documents submitted to Global Drug Facility Secretariat for ERP review is screened by **the Global Drug Facility QA officer and/or designated person**. All documents indicated under (c) submission should be sent by the applicant. Incomplete submission will not be forwarded to ERP.

2. The eligibility of the submissions for the ERP review will not be done at the Global Drug Facility Secretariat. It is under the ERP responsibility to review and to judge the eligibility as to whether to perform or not the risk benefit assessment of the submitted dossiers.

3. For any product not found to comply with the required standards during previous ERP review, all documentations requested should be re-submitted in full.

4. The applicant is requested to indicate clearly under which Eligible Criterion (1, or 2) the product has been submitted for this ERP review.

5. Only dossiers for products listed above should be submitted. Out of list dossiers will not be forwarded to the ERP.

Electronic documentation should be submitted on a CD. 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 corresponding to the letters on the list of annexes (A. to Z.) on page 17 of the questionnaire (e.g. "A.pdf" for information on the formulation of the product; "X1.pdf", "X2.pdf" etc. for certificates of analysis for APIs from the API manufacturer).

The information provided with the submission will be received by the Global Drug Facility and will be shared with the ERP members for the purposes of facilitating the ERP review of the submission and recommendation to GDF and relevant partners such as the Global Fund.

Submissions should be sent by surface mail to the following address:

Paloma Marroquín Lerga

Techncial officer

The Global Drug Facility

Stop TB Partnership Secretariat

World Health Organization

20, Avenue Appia, CH-1211 Geneva 27

The deadline for submission is the **15 September 2010**, 17:00 h Geneva time.

Subsequent invitations for EoI will be published from time to time according to needs.

VI. Further information and enquiries

Guidelines on the application process for ERP review will be made available on the Global Drug Facility's website. Kindly direct any enquiries to:

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Technical officer

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Geneva, **12 July 2010**