Promoting the
QUALITY OF MEDICINES Plus

Invitation to Local Pharmaceutical Manufacturers to submit Expression of Interest (EOI) for the Manufacturer of NTD Products

Title: Request for submission of EOI for manufacturers of neglected tropical diseases (NTD) products toward WHO prequalification.

Issue Date: September 30, 2021

Closing Date: December 31, 2021

Background and Rationale

The Promoting the Quality of Medicines Plus (PQM+) program, funded by the U.S. Agency for International Development (USAID), provides technical support through a cooperative agreement to manufacturers of essential medicines in low- and middle-income countries (LMICs) to improve their compliance with Good Manufacturing Practices (GMP) and to meet requirements to manufacture pharmaceutical products in an effort to increase access to quality-assured essential medicines. PQM+ provides technical support to selected potential manufacturers and suppliers of essential medicines by improving their capabilities to meet the prequalification requirements for pharmaceutical products.

Neglected tropical diseases (NTDs) are among the leading causes of morbidity and mortality worldwide, with more than 1 billion people (nearly one-eighth of the world's population) suffering from one or more forms of illness related to NTDs. These diseases affect the world's most vulnerable populations, almost exclusively poor people living in LMICs. Increasing access to quality-assured medicines to treat NTDs is a key strategic response to reducing the NTD burden, one of USAID's main priority areas as implemented through the PQM+ program.

PQM+ invites interested manufacturers to submit an expression of interest (EOI) application for evaluation to receive technical support toward WHO prequalification for the supply of quality-assured medicines to increase access to affordable quality-assured treatment for NTDs. This EOI is designed particularly for manufacturers of:

- Ivermectin 3 mg tablet (unscored)
- Albendazole 400 mg tablet (chewable, preferably scored)
- Praziquantel 600 mg tablet (scored)
- Mebendazole 500 mg tablet (chewable)
- Diethylcarabamazine citrate 50mg (unscored) or 100 mg (scored) tablet
- Tetracycline eye ointment HCL 1%
- Azithromycin 50 mg tablet and 500 mg tablet
- Azithromycin powder for oral suspension (POS)

Upon successful acceptance for technical assistance, PQM+ will continue to work with the applicant to complete their application for WHO prequalification submission. PQM+ also will consider 50 percent funding to cover the cost of relevant *in vivo* bioequivalence (BE) studies.

Scope of Work

<u>Ivermectin 3 mg tablet (unscored)</u>
Through its research and development (R&D) experimental study, collaboration with a contract research organization (CRO), and review of the applicable literature, the applicant should

characterize the ivermectin drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the active pharmaceutical ingredient (API) quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Albendazole 400 mg chewable tablet (preferably scored)
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the albendazole drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Praziquantel 600 mg tablet (scored)
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the praziquantel drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Mebendazole 500 mg tablet (chewable)
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the mebendazole drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Diethylcarabamazine citrate, 50mg (unscored) or 100 mg (scored) tablet
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the diethylcarbamazine drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Tetracycline eye ointment HCL 1%
Through its R&D experimental study and review of the applicable literature, the applicant should characterize the tetracycline drug substance—including solubility, polymorph, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Azithromycin liquid: 50 mg and 500 mg tablet
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the azithromycin drug substance—including solubility, polymorph composition, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Azithromycin powder for oral suspension (POS)
Through its R&D experimental study, collaboration with a CRO, and review of the applicable literature, the applicant should characterize the azithromycin drug substance—including solubility, polymorph composition, and other physico-chemical and microbiological properties—to identify the API quality attributes that affect the performance of the finished drug product. In addition, the recipient should demonstrate manufacturing capabilities and provide supporting documents for manufacturing, process validation, analytical method validation, stability study, dissolution profile study, and other GMP and product dossier requirements as part of monitoring the performance of the project and deliverables of the project milestone.

Evaluation Procedures of All Manufacturers

The technical support following the selection of a manufacturer toward WHO prequalification assessment procedure includes:

- Production activities for the manufacture of the product;
- 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 APIs, and finished product;
- Assessment of clinical testing organizations related to bioequivalence of the product for compliance with good clinical practices and good laboratory practices; and
- Review of proposed pricing range (per tablet) of quality-assured product.

Selection Criteria

The selection of an applicant is based on technical evaluation of the main requirements described on the pages that follow, where the applicant should provide supporting evidence to demonstrate previous experience in developing analytical methods for the study of pharmaceutical drug substances characterization, formulation, and manufacturing development; ability in scale-up of production;, and appropriate system-based quality management, including the Good Laboratory Practices (GLP) and GMP, to manufacture pharmaceutical products.

Technical Evaluation Criteria

To facilitate the review of the application, applicants must organize their response with supporting documents in the order that follows.

Criteria	Maximum Points
I. Drug substance and material suppliers	30
• Access to drug master file (DMF) of the API • API supplier's GMP status • Finished pharmaceutical product (FPP) manufacturer's API characterization and control of drug substance	
II. Capability and experience in product development, submission, and BE batches	30
• Formulation and drug product component • Manufacturing process and scale-up • Stability study, including stress stability study and accelerated and long-term conditions • Bio-batch and characterization against comparators	
III. **Capability for manufacturing and product dossier development**	20
• Manufacturing site GMP compliance status, certification, and summary of CAPA plan for any recent GMP inspection • Scale-up and commercial manufacturing • Product dossier compilation in Common Technical Document (CTD) format	
IV. Capabilities for project management and implementation planning	20
• Applicant team roles and responsibilities • Sufficient resources and commitment for sharing any costs with PQM+ (e.g., bioequivalence studies) • Project monitoring and procedures • Estimated pricing range for finished quality-assured product (per tablet or tube)	
Total Possible Score:	**100**

How to Submit an EOI

Interested manufacturers are required to complete Annex I for each product and provide the required information with supporting documents for PQM+ evaluation by December 31, 2021 to frederick.meadows@usp.org and TFB@usp.org. Although one manufacturer may express interest for more than one product, funding support for BE study in the future may not be provided to a single company for more than one product. Thus, an applicant who wishes to submit an application for more than one product should indicate their priority of interest for the support in the cover letter to be submitted in response to the EOI.

Annex I: Application Checklist for Submission of an EOI

Product Name: _____

Manufacturer Name: _____

Manufacturer address and country: _____

S/N	Document type	Confirm availability		Document reference / attachment number
		Yes	No	
1	Cover page			
2	Drug substance and material supplier			
3	Access to DMF of the API from the supplier			
	API supplier/manufacturer GMP compliance			
	FPP manufacturer API characterization, solubility, polymorph, and control of drug substance			
4	Capability and experience in product development, submission, and bio-batch production			
5	Formulation and drug product component			
	Manufacturing process and scale-up			
	Stability study, including stress stability study			
	Accelerated and long-term conditions (30°±2°C / 75±5%)			
	Bio-batch production and characterization against comparators			
6	Manufacturing and product dossier development			
	Manufacturing site GMP compliance certification			
	Summary of recent GMP inspection and corrective and preventive action (CAPA) plan			
	Scale-up and commercial manufacturing			
	Product dossier compilation in CTD			
7	Project management implementation plan			
8	Applicant's team roles and responsibilities to manage projects related to the EOI			
	Resources available and commitments for provision of funding toward cost-sharing			
	Project monitoring and procedures			

Authorized signature _____

Name and title_____

Date _____