Call for Expression of Interest

Invitation to manufacturing companies with generic formulations of Liposomal Amphotericin B (L-AmB) to submit an expression of interest (EOI) in receiving technical, regulatory and/or financial support to accelerate the commercialization of a quality assured product.

Issue Date: 5th July 2022
Deadline for Questions: 15th July 2022
Closing Date: 26th July 2022

Disclaimer Notice and Confidentiality

This call for Expression of Interest (EoI) is issued by Unitaid for planning and design purposes. It should not be regarded as a Call for Proposals or Request for Tender. Any information submitted in response to this EoI is provided to Unitaid on a voluntary basis. The submission of information should not establish any expectation that Unitaid and/or its partners will provide financial or technical support to respondents. Unitaid shall be under no obligation to procure any of the services or products described in this document and the issuing of this EoI call shall not be construed as a commitment by Unitaid to engage in commercial or other business relations.

Unitaid will assess the information provided by respondents to this EoI and may use it to support strategic and planning decisions within its project portfolio, or for its own internal purposes, including but not limited to, the design of future Calls for Proposals or other solicitations.

Any confidential information submitted in response to this EoI should be clearly marked as such by the respondent on the completed form. Unitaid will take all reasonable measures to maintain the confidentiality of information marked confidential. Information marked confidential will not be shared with other entities or individuals outside Unitaid, including technical partners, without the respondent's written authorization. This confidentiality commitment will not apply if the information concerned, or any part of it: (a) was known to Unitaid prior to any disclosure by the respondent; or (b) was in the public domain at the time of disclosure by the respondent; or (c) becomes part of the public domain through no fault of Unitaid; or (d) becomes available to Unitaid from a third party who is not in breach of any legal obligation of confidentiality to the respondent.

Information not marked as confidential may be shared with other entities or individuals outside Unitaid without the respondent's written authorization, provided it has first been anonymized and/or aggregated by Unitaid to deter identification of individual companies (e.g., used without specifying individual Company names, product names, geographical location).

Overview

This call for Expression of Interest (EOI) is to solicit interest from manufacturing companies ("Companies") with generic formulations of Liposomal Amphotericin B (L-AmB) in advanced stages of development and/or ready for commercialization for technical, regulatory and/or financial support to accelerate the commercialization of a quality assured product. This EoI process will help Unitaid to determine how to improve access to quality assured L-AmB in low- and middle-income countries (LMICs) at an affordable price[1].

Cryptococcal meningitis is the most frequent cause of adult meningitis in areas with a high prevalence of human immunodeficiency virus (HIV) and is the second leading cause of HIV-related death worldwide, with the majority of deaths occurring in sub-Saharan Africa. Despite widened access to antiretroviral therapy, there is a persistent burden of advanced HIV disease in the sub-Saharan African region. Cryptococcal meningitis causes an estimated 100,000 AIDS-related deaths worldwide per annum, three-quarters of which occur in sub-Saharan Africa[2,3].

L-AmB is well suited for use in short-course induction treatments of cryptococcal meningitis because it can be given at higher doses owing to a lower incidence of drug-induced toxic effects, has a long tissue half-life, and effectively penetrates brain tissue. The concept of a single high-dose intravenous infusion of L-AmB has been established in the treatment of visceral leishmaniasis. More recently, the AMBITION trial demonstrated that single-high dose liposomal amphotericin B combined with flucytosine, and fluconazole is non-inferior to the WHO-recommended treatment for HIV-associated cryptococcal meningitis and is associated with fewer adverse events[4]. L-AmB is now the WHO recommended first line treatment for cryptococcal meningitis. L-AmB is also clinically used for a wide variety of other indications such as severe and/or deep systemic mycoses e.g., systemic aspergillosis, histoplasmosis, mucormycosis, talaromycosis, candidiasis and as empiric therapy for febrile neutropenia.

This call for Expression of Interest (EOI) is issued by Unitaid., which is a hosted partnership of World Health Organization (WHO). Unitaid is also working on the issues addressed in this Call with its partners Drugs for Neglected Tropical Diseases (DNDi) and Clinton Health Access Initiative (CHAI). This coalition of partners aims to leverage their collective capabilities and partnerships with other relevant not-for-profit organizations to accelerate access to a generic L-AmB products in LMICs. Subject to the confidentiality arrangements described above, Unitaid may request DNDi and/or CHAI to review EOI submissions and provide technical support.

1. Summary of the Target Product

This EoI is open to generic manufacturers (Companies) that have a liposomal amphotericin B (L-AmB) formulation for parenteral use in advanced stages of development in order to accelerate widespread access to this product. An interested Company should be willing to generate and share data on critical quality product attributes, drug product composition, in vitro characterization of liposome to support sameness (liposome composition, morphology and number of lamellar, lipid bilayer phase transitions,

[1] Target price comparable to current public sector access price in LMICs with high burden of cryptococcal meningitis.
2 https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2021/10/2021-CHAI-HIV-Market-Report.pdf
3 https://msfaccess.org/breakthrough-cryptococcal-meningitis-treatment-gives-gilead-another-opportunity
[4] Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. Available at https://www.nejm.org/doi/full/10.1056/NEJMoa2111904

liposome size distribution, electrical surface potential or charge, and in vitro leakage rates), and in-vitro and, at least, pilot in-vivo bioequivalence studies with AmBisome (Gilead Ltd) as reference product. This information should comply with the WHO Guidance Document released on 06 July 2021 "Notes on the Design of Bioequivalence Study: Amphotericin B (liposomal)" and/or, the "Draft Guidance on Amphotericin B" released by the FDA on Aug 2020.

2. Intent of the EoI

This EoI is designed to identify opportunities to establish a healthy market for L-AmB by mitigating potential risks associated with the development and commercialization of a quality-assured generic L-AmB product, with a focus on LMICs.

The expected volume of procurement by global procurers, such as the Global Fund, PAHO and PEPFAR, once generic manufacturers enter the market, is likely to depend on the speed with which manufacturers:

(1) file regulatory dossiers with WHO Prequalification (PQ) and Expert Review Panel (ERP) or applicable Stringent Regulatory Authority (SRA).
(2) receive favorable decisions from the required Quality Assurance mechanisms to be eligible for procurement by the target countries.
(3) if the supplier is applying for a WHO PQ instead of SRA approval, demonstrate commitment to achieve WHO PQ[5] after a favorable ERP recommendation; and
(4) can ensure capacity to supply projected needs within agreed manufacturing lead times.

In this context, Unitaid is also seeking to understand the extent to which Companies may be interested in potentially receiving technical and/or financial support, such as: regulatory assistance for registration and/or WHO Prequalification; support for pharmacokinetic (PK)/ bioequivalence (BE) studies; support for WHO expert review panel quality assurance review; or or an advance market commitment for partner-funded procurement volumes.

Companies are required to indicate willingness to collaborate on a wide range of activities, which may include some or all the following:

- Provision of a report that includes information on status of formulation development, analytical method development and validation, bioequivalence studies, and stability studies.
- Preparation and submission of a regulatory dossier for an SRA or the WHO Prequalification Programme (WHO PQ) and the Expert Review Panel (ERP)[6] as well as other stringent regulatory authorities.
- Preparation and submission of a plan for regulatory filings and product commercialization in LMICs.
- Production and supply planning/commitment to cover at least 5 years (through 2027) that ensures capacity to supply target market within a mutually agreed manufacturing lead time; and

[5] Once WHO prequalification is achieved additional procurement volumes may be realized from other buyers (national and international)
[6] Expert Review Panel (ERP) is an independent technical body composed of external technical experts, hosted by WHO Department of Essential Medicines and Pharmaceutical Policies, to review the potential risks/benefits associated with the use of FPPs that are not yet WHO-prequalified or SRA-authorized and to advise the Global Fund in its decision on whether to allow grant funds to be used to procure FPP

- Willingness to supply product at or below a ceiling price to be finalized in the award contract on a continuous basis, for qualified orders within a validity period.

3. Instructions to interested parties

a. Expression of Interest (EoI):

i. All EoIs must be submitted in English and be signed by an authorized representative of the Company.

ii. EoI responses must comprise the Excel Sheet provided together with a Cover Letter and will not be considered if either of these components is missing. The Cover Letter should include a statement confirming the Company's interest and willingness to engage further on a future solicitation to achieve the desired objectives of this Call.

iii. The following documents shall be completed in full and submitted with the EoI response:

- A Vendor Information Form, using the template provided in Annex A, providing information on the vendor as an entity (legal and organizational), and describing concisely and briefly the vendor's expertise and experience relevant to the requirements and criteria described above.
- A self-declaration form, using the form provided in Annex B.

iv. EoIs should be submitted via e-mail with the subject line **Expression of Interest EoI–L-AmB** to Unitaid-proc@who.int

b. Timeline and Information Session

The timeline for the EoI process is described below.

Call for Expression of Interest released	5th July 2022
Questions Deadline for Manufacturers (submission via email only)	15th July 2022
Q&A Response Document Released	18th July 2022
EoIs Due	26th July 2022

**Late submissions will not be accepted.*

c. Questions and clarifications

i. A formal period during which any questions regarding this EoI are answered will follow the posting of the EoI on UNGM. (Please reference above for timeline). Questions may be sent via email to Unitaid-proc@who.int.

ii. All enquiries must be received via email by the stipulated deadline for questions. All questions and responses will be published on the UNGM.

iii. It will not be possible to engage in telephone enquiries.

d. Eligibility

The call is open to generic manufacturers who meet the following criteria:

i. Manufacturer has previously submitted dossiers to WHO PQ, US FDA or other stringent regulatory authority and received approval **OR** manufacturer has provided confirmation by external consultant or organization[7] that the manufacturer has a facility able to pass a USFDA or WHO PQ audit with little to no updates required **and** that the manufacturer has the appropriate personnel in place, internal or external, to prepare a product dossier that could be approved by USFDA or WHO PQ.

ii. Manufacturer's production facility operates under current Good Manufacturing Practice (cGMP) and manufacturing site/unit has been inspected and approved for GMP by WHO PQ or USFDA/SRA

iii. Manufacturer has the proven ability to manufacture Liposomal Amphotericin B at commercial scale

e. Costs of preparing documents

Any costs associated with preparing and submitting an EoI will be borne by the Company.

[7] A CV for the external consultant or details about the external organization should be provided showing their prior experience in obtaining USFDA or WHO PQ facility and dossier approvals.

Annex A – Vendor Information Form

To be returned by [26th July 2022] to Unitaid-proc@who.int

NOTICE:

- *Companies can only participate in solicitations of WHO/Unitaid after completing their basic registration (free of charge) at the United Nations Global Marketplace (www.ungm.org).*
- *As you express interest in the planned solicitation by submitting this response form, please verify that your company is registered under its full legal name on the United Nations Global Marketplace (www.ungm.org) and that your application has been submitted to WHO/Unitaid.*

Company Information to be provided by the Vendor expressing interest			
UNGM Vendor ID Number:			
Legal Company Name: *(Not trade name or DBA name)*			
Company Contact:			
Address:			
City:		State:	
Zip:		**Country:**	
Telephone Number:		Fax Number:	
Email Address of focal person:		**Company Website:**	
Corporate information:			
Company **mission statement**			
Service commitment to customers and measurements used			
Organization structure (include description of those parts of your organization that would be involved in the performance of the work)			
Relevant **experience** (how could your expertise contribute to Unitaid/WHO's needs for the purpose of this EOI) – *Please attach reference and contact details*			
Staffing information			
Company's current commitment and initiatives in support of sustainability (in particular in relation to carbon footprint, e.g.: overall company carbon footprint, past/ongoing initiatives to reduce carbon emissions, compensation of emissions/offsetting). Please include any relevant certification or supportive documentation, if any.			

Entity Name:	
Mailing Address:	
Name and Title of duly authorized representative:	
Date:	
Signature:	

Annex B - Vendor's Self Declaration Form

To be returned by [26th July 2022] to Unitaid-proc@who.int

<**Full legal name of Vendor**> (the "Vendor") hereby declares to the World Health Organization (WHO) that:

a. it is not bankrupt or being wound up, having its affairs administered by the courts, has not entered an arrangement with creditors, has not suspended business activities, is not the subject of proceedings concerning the foregoing matters, and is not in any analogous situation arising from a similar procedure provided for in national legislation or regulations.

b. it is solvent and in a position to continue doing business for the period stipulated in the contract after contract signature, if awarded a contract by WHO.

c. it or persons having powers of representation, decision making or control over the Vendor have not been convicted of an offence concerning their professional conduct by a final judgement.

d. it or persons having powers of representation, decision making or control over the Vendor have not been the subject of a final judgment or of a final administrative decision for fraud, corruption, involvement in a criminal organization, money laundering, terrorist-related offences, child labor, human trafficking, or any other illegal activity.

e. it is in compliance with all its obligations relating to the payment of social security contributions and the payment of taxes in accordance with the national legislation or regulations of the country in which the Vendor is established.

f. it is not subject to an administrative penalty for misrepresenting any information required as a condition of participation in a procurement procedure or failing to supply such information;

g. it has declared to WHO any circumstances that could give rise to a conflict of interest or potential conflict of interest in relation to the current procurement action.

h. it has not granted and will not grant, has not sought and will not seek, has not attempted and will not attempt to obtain, and has not accepted and will not accept any direct or indirect benefit (finanical or otherwise) arising from a procurement contract or the award thereof; and

i. it adheres to the UN Supplier Code of Conduct.

The Vendor understands that a false statement or failure to disclose any relevant information which may impact upon WHO's decision to award a contract may result in the disqualification of the Vendor from the bidding exercise and/or the withdrawal of any proposal of a contract with WHO. Furthermore, in case a contract has already been awarded, WHO shall be entitled to rescind the contract with immediate effect, in addition to any other remedies which WHO may have by contract or by law.

Entity Name:	
Mailing Address:	
Name and Title of duly authorized representative:	
Date:	
Signature:	