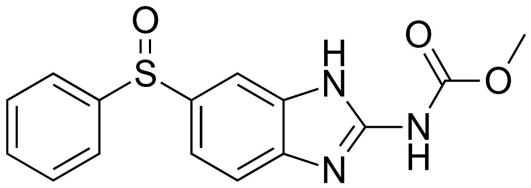
DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Pharmaceutical Development for Oxfendazole



CAS 53716-50-0

Dated: 21 November 2016

DNDi
Drugs for Neglected Diseases *initiative*

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1. PURPOSE

The evaluation is requested by DND*i* (Drugs for Neglected Diseases *initiative*).

Oxfendazole is currently being profiled by DND*i* for the treatment of filarial infections with the aim to start Phase I clinical studies in H2 2017. The compound is registered for veterinary use, however First In Human studies have been performed recently by an independent research group.

In order to progress its own clinical trials, DND*i* is now seeking a Contract Development and Manufacturing Organization (CDMO) offering ideally an integrated platform of pharmaceutical development and manufacturing capabilities to cover both Drug Substance and Drug Product activities.

2. RFP INSTRUCTIONS

2.1. General information

a) DND*i* invites you as a Service Provider to submit one proposal covering API process development and GMP manufacture, clinical formulation development and manufacture, as well as associated analytical development and quality control services.

b) This entire RFP and all the related discussions, meetings, information exchanges and subsequent negotiations that may occur are subject to the confidentiality terms and conditions of the Intent to Participate attached as Annex 1.

c) All bidders are required to complete and send return the Intent to Participate letter.

d) The issuance of this Request for Proposal in no way commits DND*i* to make an award. DND*i* is under no obligation to justify the reasons of its service provider's choice following the competitive bidding. DND*i* could choose not to justify its business decision to the participants of the RFP.

e) DND*i* reserves the right to:

- Reject any proposal without any obligation or liability to the potential service provider.
- Withdraw this RFP at any time before or after the submission of bids without any advance notice, explanation or reasons.
- Modify the evaluation procedure described in this RFP.
- Accept a proposal other than the lowest one.

- Award a contract on the basis of initial proposals received without discussions for best and final offers.
- Award all services to only one supplier or allocate them to different suppliers as DND*i* considers necessary.

f) Late submission proposals are subject to rejection.

g) DND*i* reserves the right to request additional data, information, discussions or presentations to support proposals. All bidders must be available to discuss details of their proposal during the RFP process.

h) All offers should be submitted in electronic format.

i) The proposed timelines below indicate the process DND*i* intends to follow. If there are changes to this timelines, DND*i* will notify you in writing.

2.2. Timelines

Process steps	**Responsible party**	**Timelines**
Launch RFP	DND*i*	21st Nov 2016
Send back the Intent to Participate letter	Service Provider	28th Nov 2016
Full Technical Package disclosed to participants	DND*i*	1st Dec 2016
Q&A sent to DND*i*	Service Provider	8th Dec 2016
DND*i* responses to Q&A	DND*i*	15th Dec 2016
Reception of proposals	Service Provider	6th Jan 2017
Bidder Preselection notification*	DND*i*	20th Jan 2017
Bid defense meetings	DND*i*	27th Jan 2017
Project award	DND*i*	6th Feb 2017
Project Start (Drug Substance)	Service Provider	1st March 2017
Project Start (Drug Product)	Service Provider	1st March 2017

2.3. RFP processes and contact information

2.3.1. Instructions

All bidders may request further clarifications regarding this RFP by addressing their questions in writing to the dedicated key contacts identified below. These questions should be submitted to DND*i* at the date mentioned in the section 2.2 Timelines of the RFP.

In order to maintain a fair bidding process, questions related to this RFP will only be answered in a document shared with all the bidders on the date indicated in section 2.2. Timelines of the RFP.

To submit your questions, please use the form attached as Annex 2.

2.3.2. Confirmation of Intent

Please transmit your intent to participate by using and signing the document attached in Annex 1. To notably ensure equal treatment of all bidders, the terms of this document are not open to negotiation.
Each bidder is required to provide DND*i* with a written confirmation of intent or decline to participate by the date as indicated in the section 2.2.
Confirmations of intent should be sent by email to Christophine Marty-Moreau (contacts details below).

Questions types	**Contact person**	**Title**	**Contact information**
Contractual & Technical aspects	Christophine MARTY MOREAU	Procurement Manager	15 Chemin Louis Dunant 1202 Geneva Switzerland Phone:+41 22 906 92 61 Email: cmarty@dndi.org

2.4.Format and content of the proposal

Responses to this RFP must be in English and should contain the following information:

- A cover letter including:
  - Name and address of the service provider
  - Name, title, phone number and email address of the person authorized to commit the service provider contractually
  - Name, title, phone number and email address of the person to be contacted in regards of the content of the proposal, if different from above
  - Signature of this letter done by a duly authorized representative of the company
  - Acceptance of the consultation principles

- A technical proposal
  - Detailed proposal explaining how your company approach will enable DND*i* team to meet project timelines, deliverables and ensure quality results.

- A financial proposal
  - Budget template for drug substance (Annex 3a) and drug product (Annex 3b) to be completed

- API Quality Questionnaire and Drug Product Manufacturing (IMP) Quality Questionnaire completed

- High-level comments on the DND*i* template for Pharmaceutical Development Services Agreement

- Administrative information
  - Business Company information: directors and officers, creation date, corporate headquarters, locations, business turnover of the past three years (global and in the field of service provided), headcounts (global and in the field of service provided), general services provided, customer's reference, pricing strategy for NGOs.
  - Any other relevant information enabling DND*i* to assess the opportunity of contracting with your company

2.5. Conflict of Interest

The Company shall disclose any actual or potential conflicts of interest in the Intent to Participate letter.

3. DND*i* OVERVIEW

3.1. Mission & objectives

Neglected tropical diseases continue to cause significant morbidity and mortality in the developing world. Yet, of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden.

Founded in 2003 to address the needs of patients with the most neglected diseases, DND*i* is a collaborative, patient's needs driven, not for profit drug R&D organization.

Acting in the public interest, DND*i* bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DND*i*'s primary focus has been the development of drugs for the most neglected diseases, such as Human African Trypanosomiasis (HAT, or sleeping sickness), visceral leishmaniasis (kala-azar), and Chagas disease, while considering engagement in R&D

projects for other neglected diseases to address unmet needs that others are unable or unwilling to address.

The primary objective of DND*i* is to deliver a total of 11 to 13 new treatments by 2018 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, and specific filarial infections and to establish a strong R&D portfolio that addresses patient needs. Expanding upon R&D networks built on South-South and North-South collaborations, DND*i* aims to bring medical innovation to neglected patients by developing field-adapted treatments.

In doing this, DND*i* has two further objectives:

- Use and strengthen existing capacities in disease-endemic countries via project implementation
- Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility.

For more information, please visit DND*i* website: www.dndi.org

4. SCOPE OF WORK

4.1. Drug Substance

Oxfendazole is registered only for veterinary use currently and a drug substance monograph is available in the European Pharmacopoeia. "Veterinary grade" oxfendazole drug substance is available commercially from a number of GMP suppliers, as is its synthetic precursor (fenbendazole). Within the proposal, service providers should evaluate three options for supply of drug substance suitable for human clinical trials:

a. Procure and use veterinary grade drug substance "as is" for clinical trials
b. Procure and then purify (e.g. recrystallize) veterinary grade drug substance under GMP conditions
c. Procure fenbendazole and convert to oxfendazole under GMP conditions

Please note that:

- *Phase I clinical trials will be performed in EU or USA, Phase II trials in Africa.*
- *Initial formulation development studies may utilise veterinary grade drug substance "as is" in order to accelerate timelines, i.e. Work Packages 1 and 2 may proceed in parallel.*

The drug substance proposal should cover performance of the activities in the following work package:

Work Package 1 – drug substance development and manufacture

- Procurement of veterinary grade oxfendazole drug substance for initial formulation development activities.
- Procurement of veterinary grade oxfendazole drug substance (or fenbendazole precursor) and process development according to the option selected from a-c above.
- Sourcing of oxfendazole and impurity reference standards (e.g. from LGC or Sigma-Aldrich).
- Establishment of key Ph. Eur analytical methods and validation suitable for early stage clinical trials.
- Manufacture of drug substance development batch (2 kg) according to the option selected from a-c above, for formulation development and stability use.
- 36-month stability studies under ICH conditions on development batch to establish an appropriate drug substance retest period.
- GMP manufacture of drug substance (5 kg) for clinical drug product manufacture.
- Quality control testing.

DND*i* will provide a technical package to participating service providers containing further information about oxfendazole drug substance, including supplier details, physico-chemical and safety data. Please note in particular:

- Oxfendazole drug substance should be protected from light
- In animal studies, very high doses of oxfendazole produced teratogenicity and embryotoxicity. However at doses of 10 mg/kg or less, oxfendazole was not teratogenic or embryotoxic in rats, mice, sheep or cattle.
- A permissible exposure limit of 0.35 mg/m^3 (8 h TWA) was established previously by a commercial manufacturer.

4.2. Drug Product

Veterinary products containing oxfendazole are used to target gastrointestinal and respiratory endoparasites such as roundworms and tapeworms. Commercial products include oral pastes, suspensions, tablets, drenches and feed additives. Oxfendazole is characterised by low aqueous solubility (< 5 □g/mL), therefore formulation approaches targeting increased bioavailability may be needed for treatment of filarial infections in humans.

DND*i* is requesting the CDMO to carry out formulation development, GMP manufacturing and stability studies to enable Phase I single and multiple ascending dose studies. FIH studies conducted by an independent research group targeted single oral doses in the range 0.3 - 30 mg/kg using a veterinary oral suspension product, corresponding to a total dose of 21 – 2100 mg for a 70 kg adult. Drug product

development should therefore focus on flexible, enabling formulations that allow exploration of a wide dose range in Phase I. Solution or suspension formulations, or a combination of these, may be considered to cover the dose range. Formulations suitable for extemporaneous manufacture would be attractive, especially for lower doses.

In addition to a lead formulation approach, the CDMO should propose options to develop alternative formulations for use in the event of poor bioavailability. Consideration should also be given to relative bioavailability studies in a suitable species (e.g. dog) to rank prototype formulations.

The formulation development program should also guide the design of a suitable solid oral formulation for Phase I/II clinical trials.

The drug product proposal should cover performance of the activities in the following work packages:

Work Package 2 - Phase I enabling formulation (solution and/or suspension):

- Preformulation studies
- Development and evaluation of prototype enabling Phase I formulations, leading to identification of a lead and back-up formulation.
- *OPTIONAL ACTIVITY: Relative bioavailability study of up to four formulations in dogs.*
- Adaptation of key Ph. Eur/USP analytical methods (e.g. assay and related substances) and validation suitable for early stage clinical trials.
- Manufacture and packaging of development batches (2000 units maximum) of the lead formulation, two dose strengths/drug loadings and one matching placebo (batch size may be decreased according to the eventual dosage form nominated).
- Formal stability studies under ICH conditions on development batches for 36 months.
- GMP manufacture, packaging and labelling of clinical batches (2000 units maximum), two dose strengths/drug loadings and one matching placebo.
- *OPTIONAL ACTIVITY: Formal stability studies under ICH conditions on clinical batches for 36 months.*
- Quality control testing.
- QP certification.
- Distribution to clinical sites as directed by DND*i*.

Please note GMP manufacturing and long-term stability studies in Work Package 2 may not be required if extemporaneous preparation of some Phase I dosage forms is feasible.

Work Package 3 - solid oral dosage form for Phase I/II clinical trials:

- Additional preformulation studies relevant to solid oral dosage forms
- Development and evaluation of prototype tablet/capsule formulations, leading to identification of a lead and back-up solid oral formulation.
- *OPTIONAL ACTIVITY: Relative bioavailability study of up to four formulations in dogs.*
- Adaptation of key Ph. Eur/USP analytical methods (assay and related substances), method development (e.g. dissolution) and validation suitable for early stage clinical trials.
- Manufacture and packaging of development batches (2000 units maximum) of the lead formulation, two dose strengths/drug loadings and one matching placebo.
- Formal stability studies under ICH conditions on development batches for 36 months. Note stability studies for Phase II clinical trials should include climatic zone IVb long term conditions (30°C/75%RH).
- GMP manufacture, packaging and labelling of clinical batches (2000 units maximum), two dose strengths/drug loadings and one matching placebo.
- *OPTIONAL ACTIVITY: Formal stability studies under ICH conditions on clinical batches for 36 months.*
- Quality control testing.
- QP certification.
- Distribution to clinical sites as directed by DND*i*.

Primary packaging, secondary packaging and clinical labelling may be provided by the service provider, or otherwise by a third party vendor determined by DNDi.

5. CRITERIA FOR SELECTING SERVICE PROVIDERS

The decision to award any contract as a result of this RFP process will be based on Service Providers' responses and any subsequent negotiations or discussions. The decision making process will consider the ability of each service provider to fulfil DND*i*'s requirements as outlined within this RFP and the cost of the offer.

Proposals will be assessed against the main following criteria but not limited to:

5.1. Technical criteria

- Facilities and license to perform the GMP manufacture
- Regulatory Inspection history and outcomes
- API Quality questionnaire & Drug Product Manufacturing (IMP) Quality Questionnaire

- Ability to apply appropriate process development and analytical activities suitable to support early stages of development (fit for purpose)

5.2. Capacity to deliver

- Reasonable timelines
- Project management capabilities
- Past experience with similar work
- Profile of staff involved (CVs)

5.3. Financial criteria

- Realistic costing of the proposal with NGO rates when possible

6. PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

6.1. Proposal requirements

Following the issuance of the RFP, all interested bidders are invited to submit a proposal which describes:

- General information of the company as described in section 2.4
- Technical information (CMC, Regulatory, Quality) for each part of the project. European guidelines to be followed.
- Budget with full details of your offer including fixed costs and Pass-Through Costs. We recommend the use of DND*i* template inserted as Annex 3.
- Project team involved
- List of tasks and responsibilities
- Project Gantt Chart

6.2. Major deliverables

6.2.1. Drug Substance

- Demonstration batch (2 kg) and cGMP batch (5 kg)
- Certificate of analysis for each batch manufactured (final API)
- BSE/TSE statements and GMP certificate
- Process development report (including manufacture of demonstration batch)
- Process safety assessment reports
- cGMP campaign report
- Master and executed batch records
- Analytical test procedures, methods validation protocols and reports
- Reference standards and analytical markers characterization report, as needed

- Forced degradation study report
- Specifications for API release
- ICH stability protocol, interim and final reports
- Biweekly updates on project progress
- Documentation suitable for IMPD submission

6.2.2. Drug Product

- Clinical batch supply
- Certificate of analysis and statement of cGMP compliance (per batch manufactured)
- TSE statements for excipients
- Formulation development reports
- Executed batch records for DP manufacturing
- Analytical test procedures, methods validation protocols and reports
- Specifications for DP release
- ICH stability protocol, interim and final reports
- Biweekly updates on project progress
- Documentation suitable for IMPD submission

6.3. Terms and Timelines

- All GMP services will be performed under a Quality Agreement
- Beginning of Services planned in March 2017
- Completion of the services (excluding stability studies): Work Package 1 (3Q 2017), Work Package 2 (3Q 2017), Work Package 3 (2Q 2018).

6.4. Additional information

After receiving their Intent to Participate letter, DND*i* will provide the bidders with the documentation listed below on both Drug Substance and Drug Product:

- Physical and chemical properties of the API
- Safety data for API
- API and Drug Product Manufacturing (IMP) Quality questionnaires to be filled and provided as part of the full proposal
- Pharmaceutical Development Services Agreement template for review and comments concomitantly with the full proposal

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form

Annex 3: Budget template