Request for Proposal

Pharmaceutical Development (Drug Product) for Trichuriasis candidate Oxantel Pamoate

Dated: July 2020
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1. PURPOSE
Oxantel pamoate is a veterinary anthelmintic drug introduced on the market in 1974. Oxantel pamoate has been shown to be efficacious in human clinical trials for Trichuriasis. Due to possible resistance to currently available drugs, DNDi and its partners are interested in developing this as an alternative treatment for Trichuriasis. In order to supply Phase I clinical trials, DNDi is now sourcing a Contract Development and Manufacturing Organisation (CDMO) for formulation development and GMP manufacturing of clinical product and placebo.

2. RFP INSTRUCTIONS

2.1. General information
a) DNDi invites you as a Service Provider to submit a proposal covering the formulation development & GMP drug product manufacturing operations for clinical supplies and also covering all the associated 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 return the Intent to Participate letter.

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

e) DNDi 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 another proposal than the lowest priced 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 according to what DNDi will consider necessary.

f) Late submission proposals are subject to rejection.
g) DNDi reserves the right to request additional data, information, discussions or presentations to support their proposal. All bidders must be available to discuss details of their proposal during the RFP process.

h) All offers should be submitted in an electronic format.

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

### 2.2. Timelines

<table>
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<tr>
<th>Process steps</th>
<th>Responsible party</th>
<th>Timelines</th>
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<tbody>
<tr>
<td>Open bidding process</td>
<td>DNDi</td>
<td>10 July 2020</td>
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<td>Intent to participate letter</td>
<td>Service Provider</td>
<td>24 July 2020</td>
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<tr>
<td>Questions sent to DNDi</td>
<td>Service Provider</td>
<td>24 July 2020</td>
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<td>DNDi responses to questions</td>
<td>DNDi</td>
<td>3 August 2020</td>
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<tr>
<td>Reception of proposals</td>
<td>Service Provider</td>
<td>13 August 2020</td>
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<tr>
<td>Bid defence meeting (TBD)</td>
<td>DNDi</td>
<td>Week of 24 August 2020</td>
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<tr>
<td>Project award</td>
<td>DNDi</td>
<td>31 August 2020</td>
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<td>Project Start</td>
<td>Service Provider</td>
<td>October 2020</td>
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<tr>
<td>Formulation and analytical development (+ stability study)</td>
<td>Service Provider</td>
<td>November 2020 to January 2021</td>
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<td>Technical batch manufacturing</td>
<td>Service Provider</td>
<td>February 2021</td>
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<td>Clinical Manufacturing completed</td>
<td>Service Provider</td>
<td>May 2021</td>
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<td>Clinical batches release</td>
<td>Service Provider</td>
<td>July 2021</td>
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<tr>
<td>Start of study</td>
<td>DNDi</td>
<td>November 2022</td>
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</tbody>
</table>

### 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 DNDi at the date mentioned in the section 2.2 Timelines of the RFP.

In order to keep 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 forward your intent to participate by using and signing the document attached in Annex 1 with no mark-up.

Each bidder is required to provide DNDi 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 Olivier Degodet and questions should be sent to Delphine Launay (contacts details below).

<table>
<thead>
<tr>
<th>Questions types</th>
<th>Contact person</th>
<th>Title</th>
<th>Contact information</th>
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</thead>
<tbody>
<tr>
<td>Business / Procurement</td>
<td>Olivier DEGODET</td>
<td>Senior Procurement Manager</td>
<td>15 Chemin Louis Dunant 1202 Geneva Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: +41 22 555 19 11 Email: <a href="mailto:odegodet@dndi.org">odegodet@dndi.org</a></td>
</tr>
<tr>
<td>Technical aspects</td>
<td>Delphine LAUNAY</td>
<td>Senior Pharmaceutical Development Manager</td>
<td>15 Chemin Louis Dunant 1202 Geneva Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: +41 22 906 92 30 Email: <a href="mailto:dlaunay@dndi.org">dlaunay@dndi.org</a></td>
</tr>
</tbody>
</table>

2.4. Format and content of the proposal

Responses to this RFP must be in English and should contain the following standard 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 contractually the service provider.
  - 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 DNDi team to meet project timelines, deliverables and ensure quality results.

- A financial proposal
  - Detailed cost breakdowns for each work package or activities including key individual hourly rates, positions, and time allocated.
• Completed Drug Product Manufacturing (IMP) and Packaging Quality Questionnaires

• Administrative information
  o 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.
  o Any other relevant information enabling DNDi to assess the opportunity of contracting with your company.

• High-level comments on the DNDi template for Pharmaceutical Development Services Agreement. This should include a list of issues or challenges that your company would consider as being major concerns and imperatively require negotiation, together with a brief explanation.

2.5. Compliance

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

3. DNDi OVERVIEW

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

Acting in the public interest, DNDi 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.

DNDi’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 patients (e.g. malaria, paediatric HIV, filarial infections) and development of diagnostics and/or vaccines to address unmet needs that others are unable or unwilling to address.
The primary objective of DNDi is to deliver 16 to 18 new treatments by 2023 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, filarial diseases, mycetoma, and hepatitis C, 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, DNDi aims to bring medical innovation to neglected patients by developing field-adapted treatments.

In doing this, DNDi 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 DNDi website: www.dndi.org

4. SCOPE OF WORK

4.1. Drug Product

DNDi is requesting the CDMO a proposal to carry out formulation development, GMP manufacturing, packaging, labelling and appropriate stability studies for the Phase I clinical trial. A solid oral dosage form with one dose strength is envisaged, along with matching placebo. The final product is intended for paediatrics use (age range: 2 - 16 years). The dosage form and excipients used must therefore be suitable for administration to paediatric patients.

The compound is characterised by very poor aqueous solubility (< 1 mg/mL) and the mode of action does not require systemic exposure but local delivery to the large intestine. Therefore, there is no necessity for drug solubility enhancement in the formulation. The human efficacious dose was set to 20 mg/kg (of oxantel pamoate, not free base equivalent), for single dose treatments. Provision of the dose in a single unit is preferred. The regions most touched by Trichuriasis are Africa and South-East Asia. Due to how the medication distribution is envisaged, the formulation development activities should focus on oral dispersible tablets, dispersible tablets or chewable tablets.

A GMP batch of API, representative of the API manufacturing process, is available and can be transferred to the CDMO, therefore formulation development can be performed with lower risk of significant change in the physical and chemical properties of the API that will be used for the clinical manufacture.
The CDMO should be able to develop the formulation and manufacture of one or several technical batches by Q1 2021 to allow for availability of supportive stability data prior to manufacture of the GMP batch of drug product in Q2/Q3 2021.

4.1.1. List of activities to be performed

**Work Package 1: Polymorph screening (Optional)**

1.1. API Characterisation.
   1.1.1. Profile the provided reference material.
   1.1.2. Characterise (XRPD, optical and polarised light microscopy, DSC/TGA) and determine aqueous solubility (thermodynamic at 37°C) and stability.

1.2. Polymorph screening (up to ten solvent systems and up to four recrystallisation conditions).

1.3. Full characterisation of the most stable form.

**Work Package 2: Pre-formulation**

Chemical stability/compatibility will have to be evaluated by storage of the API alone, excipient alone, API/excipient combinations, prototype batch generation (up to three formulations) and short-term stability studies. Depending on the final API particle size, mild processing such as calibration (e.g. oscillating mill or equivalent) might be required prior to use.

2.1. Compatibility study with excipients of interest for the formulation development (up to 20 excipients).

2.2. Calibration study to assess the impact of mild processing of the API on its behaviour (e.g. flowability, dispersibility, density).

**Work Package 3: Solid oral formulation development for Phase I**

Three formulation options to supply the phase I clinical trial are considered in this request for proposal. Depending on the available technology and expertise, the CDMO may evaluate up to three options in parallel as a risk mitigation.

**Option 1:** Oral dispersible tablets with 250 mg dose.

**Option 2:** Dispersible tablets with 500 mg dose.

**Option 3:** Chewable tablets with 500 mg dose. Formulation development including the evaluation of the formulation options listed above. A lead formulation will be selected.

3.2. Manufacture of a development batch (max. 2000 units) of the lead formulation at one dose strength, one back-up formulation (same option or not) as well as placebo (for stability purposes).

3.3. Formal stability study on the development batch: three years, four storage conditions (one month: 50°C/75%RH, six months: 40°C/75%RH, long...
term: 30°C/75%RH with a contingency at 30°C/65%RH). Several formulations might be set down on stability as a risk mitigation.

Work Package 4: Analytical support for Phase I drug product
4.1. Assay and related substances method development and validation.
4.2. Dissolution method development and validation.

Work Package 5: Phase I drug product manufacture and packaging
5.1. GMP Manufacturing of clinical batch plus one matching placebo (max. 2000 units each)
5.2. Clinical packaging for Phase I
5.3. Quality assurance and QP services
5.4. Technical documentation support for preparation of clinical trial applications
5.5. Shipment to clinical site (Tanzania)
5.6. Clinical stability studies for the drug product and matching placebo: three years, two storage conditions (six months: 40°C/75%RH, long term: 30°C/75%RH with a contingency at 30°C/65%RH)

5. CRITERIA FOR SELECTING SERVICE PROVIDERS
The decision to award any contract under 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 DNDi’s requirements as outlined within this RFP as well as the global costing.

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
- Drug Product Manufacturing (IMP) and IMP packaging Quality Questionnaires
- Ability to apply appropriate process development and analytical activities suitable to support FIH requirements

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 and competitive costing of the proposal considering NGO budget constraints.

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.
   - Project team involved
   - List of tasks and responsibilities
   - Project Gantt Chart

6.2. Major deliverables
   - Clinical batches (active + placebo) supply
   - Certificate of analysis and statement of GMP compliance (per batch manufactured)
   - TSE statements for excipients
   - Formulation development report
   - Executed batch records for DP manufacturing
   - Analytical test procedures, methods validation protocols and reports
   - Specifications for DP release
   - ICH-compliant stability protocol, interim and final reports
   - Biweekly updates on project progress
   - Documentation suitable for IMPD/clinical trial applications

6.3. Terms and Timelines
   - All GMP services will be performed under a Quality Agreement
   - Beginning of Services planned in October 2020
   - Completion of the service (excluding ICH stability) by August 2021

6.4. Additional information
DNDi is including here attached in Annexes 3, 4a and 4b the following documentation:
   - Physical and chemical properties of the API
• Drug Product Manufacturing (IMP) and IMP packaging quality questionnaires

7. ANNEXES

Annex 1: Intent to Participate letter
Annex 2: Q & A Form
Annex 3: Technical Package
Annex 4a and 4b: Quality questionnaires