**Request for Proposal (RFP)**

**Manufacture of a low dose, child friendly formulation of primaquine for the radical treatment of malaria caused by *Plasmodium vivax*.**

**RFP Number:** MMV-2020-LDPQ

**Issue Date:** 8 January 2020

**Deadline for questions:** 30 January 2020

**Closing date:** 10 February 2020 15:00 CET

1. **Background**

***Plasmodium vivax* and radical cure of malaria**

Infection with *Plasmodium vivax* (*Pv*.) is estimated to have been responsible for between 5.9 million to 9.3 million cases of malaria worldwide in 2018[[1]](#footnote-2). *Pv*. is the predominant cause of malaria in most co-endemic countries i.e. those countries where both parasites, *Plasmodium falciparum* (*Pf*.) and *Pv*. - occur. While *Pv*. is geographically the most widely distributed form of malaria, over 70% of the disease burden is concentrated in 11 countries[[2]](#footnote-3). The main burden of disease is in children, with those less than 5 years of age being particularly vulnerable to recurrent infection and a cumulative risk of anaemia.

*Pv*. malaria can be more difficult to cure than *Pf*. malaria because it forms dormant liver stages (hypnozoites) that result in repeated attacks (relapses) of the acute form of the infection arising from a single infected mosquito bite. Patients require treatment with an effective drug regimen that clears both the blood and liver-stage infections, to prevent reactivation of the liver hypnozoites and subsequent relapses. The relapsing nature of the disease is a major contributor to individual morbidity and mortality, and to ongoing transmission. In co-endemic areas, malaria control programmes that do not include radical cure treatment for patients infected with *Pv*. cannot effectively reduce *Pv*. burden. Therefore, targeting this stage of the disease could reduce illness and dramatically curb or eliminate transmission.

**Public Healthcare Needs and the Market Gap**

8-aminoquinoline (8-AQ)-based drugs are the only class of drugs currently available that can kill *Pv*. hypnozoites, with primaquine (PQ) being the only widely available drug of that class. For preventing relapse in *Pv*.malaria the WHO guidelines recommend a 14-day course of PQ in all transmission settings[[3]](#footnote-4).

In addition to its role in radical cure of *Pv*. malaria, PQ can also be used to help reduce the transmission of Pf. malaria in low-transmission settings via its gametocytocidal activity - i.e. killing the sexual stages (gametocytes) of the parasite. This application is recognised by the WHO, in particular in those areas threatened by artemisinin-resistance and in areas implementing elimination programmes[[4]](#footnote-5).

The main burden of malaria is in young children and yet there is no suitable i.e. dispersible,and taste-masked - quality approved paediatric formulation available. (To date there are only two products that have SRA/WHO Prequalification: a 7.5mg film-coated tablet manufactured by Remedica and a 15mg hard tablet manufactured by Sanofi.) Therefore, the current practise is for hard tablets to be crushed for administration to children. Reliance on the adult formulation may result in inaccurate paediatric dosing, which in turn may result in a higher risk of adverse events and lower efficacy in preventing *Pv*. recurrence. In addition, decreasing *Pf.* transmission will depend on achieving high rates of coverage of the PQ, that are similarly limited by the lack of a paediatric formulation suitable for use in young children.

To address this gap, the *“18th Invitation to Manufacturers of Antimalarial Medicines to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team: medicines”* (July 2019) was updated to include the following PQ tablet strengths and presentations summarised as follows:

* Primaquine base 2.5 mg tablets (preferably dispersible for paediatric use)
* Primaquine base 3.75 mg tablets (preferably dispersible for paediatric use)
* Primaquine base 5 mg tablets (scored) (preferably dispersible for paediatric use)
* Primaquine base 7.5 mg scored tablets (scored) (preferably dispersible for paediatric use)
* Primaquine base 15 mg tablets (scored)

MMV is seeking proposals from eligible manufacturers to develop dispersible, taste-masked paediatric formulations of PQ based on the EOI. The proposals should include comprehensive development plans and associated costs including that of formulation and analytical method development, stability studies, bioequivalent studies (due to the change in formulation) and submission of dossiers for WHO prequalification. We are particularly interested to receive your recommendations for the best way to develop and deliver the presentations (all or some).

We are interested to hear from a wide range of manufacturing companies including, but not limited to the following:

* Companies who may already be planning the development, manufacture and seek WHO pre-qualification of a child-friendly formulation of PQ
* Companies manufacturing PQ drug substance or drug product now or in the past but who have not, to date, considered the WHO pre-qualification process
* Companies with experience of taking other products through the WHO pre-qualification process, for example HIV medicines, and who are therefore familiar with the process.

All interested parties should have experience of developing and manufacturing quality[[5]](#footnote-6) pharmaceutical products and have experience of product introduction in malaria-endemic countries (even if not specifically malaria products). Responding parties (“Responders”) may be invited for further discussions regarding a possible collaboration.

The issue of this RFP and submission of RFP responses by Responders does not represent a commitment of either party to enter into discussions or any collaboration. However, by submitting a response to MMV, Responders indicate that they are interested to enter discussions for a possible collaboration with MMV. MMV reserves the right to enter into collaboration discussions and a resulting collaboration(s) with one or multiple parties, with no parties, or to cancel this RFP at its sole discretion.

1. **About MMV**

MMV is a not-for-profit public-private partnership and was established as a foundation in Switzerland in 1999. MMV’s mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating the delivery of new, effective and affordable antimalarial medicines. MMV’s vision is a world in which these innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria and help to ultimately eradicate this terrible disease. In partnership with pharmaceutical companies and research institutions worldwide, MMV has supported the development, approval and uptake of 13 new treatments for malaria and has over fifty other drug discovery and development projects. MMV works closely with its partners and provides disease-specific and development expertise in addition to financial support in return for certain commitments such as pricing and supply of product in the public sector.

1. **Summary of Project Scope**

MMV is currently in the process of securing donor funding for this project that will enable us to expedite the entry of at least one or more WHO-prequalified child-friendly versions of PQ, currently a major missing gap in the therapeutic armamentarium. Conditional upon the success of our fund-raising activities, MMV support will be available for the following activities:

* Development of taste-masked, dispersible tablet formulations of PQ tablets with a focus on the three lowest strengths (2.5mg, 3.75mg and 5 mg) for submission to WHO Prequalification for evaluation
* Support to ensure GMP audit-readiness of manufacturing facility (if required)

*Packaging:* Blister pack containing 14 tablets

*Stability*: Climatic Zone IVb in order to safeguard product quality throughout its entire intended shelf-life, stability studies under the conditions defined for Climatic Zones IVb should be performed and the data submitted, i.e. the shelf-life should be established based on complete long-term data at 30ºC ±2ºC/75% RH ±5% RH[[6]](#footnote-7).

Development and manufacturing must comply with ICH[[7]](#footnote-8) standards.

1. **Instructions to interested parties**

4.1 Submission of RFP responses

1. All RFP responses, including the completed forms (Annex), should be submitted in English and in the format of a PDF or WORD document, and should be signed by an authorized representative of the Responder.
2. RFP responses should be submitted via e-mail with the subject line *Request for information (RFP) - MMV-2020-LDPQ* toDr. Joan Herbert at [herbertj@mmv.org](mailto:herbertj@mmv.org). with copy to Dr. Anya Ramalho, [ramalhoa@mmv.org](mailto:ramalhoa@mmv.org)
3. RFP responses received after the stipulated closing date shall be invalid.
   1. Questions and answers
4. Questions should be addressed to Dr. Joan Herbert in writing at [herbertj@mmv.org](mailto:herbertj@mmv.org). with copy to Dr. Anya Ramalho, [ramalhoa@mmv.org](mailto:ramalhoa@mmv.org), by the stipulated deadline for questions. Questions and answers will be published on [the](http://deliver.jsi.com) MMV website [www.mmv.org](http://www.mmv.org), and responders should check the website regularly for updates.
5. Telephone requests cannot be honoured.

4.3 Eligibility

This RFP process is open to companies who manufacture medicines at a manufacturing site that is compliant with WHO GMP as confirmed by a favourable inspection conducted recently by either an SRA, WHO or another entity acceptable to MMV (However see footnote on p. 4).

4.4 Costs of preparing documents

All costs associated with preparing and submitting a response to this RFP will be borne by the Responder.

4.5 Confidentiality

Information which the Responder considers to be proprietary should be clearly marked as such. All such information will be treated as confidential and used for MMV internal purposes only.

4.6 Disclosure

Information relating to the examination, clarification, and evaluation of responses shall not be disclosed to Responders or any other persons not officially concerned with such process.

1. **Minimum information requirements**

Responders should provide the following information at a minimum:

1. Project Proposal comprising the following:

* Development plan with a thorough outline of proposed activities and the staff expected for completion of work
* Gantt Chart showing development timelines
* Areas of support needed and Budget

1. Completed forms A, B, C (Annex)
2. Company information
   1. Audited annual financial statements and reports for the past 3 fiscal years;
   2. A recent organigram/organizational chart, including the title and names of key employees;
   3. The resumes/CV of the management team.
3. Additional information about your current level of activity, interest and expertise in the development of PQ tablets that is not otherwise provided (form D).

We encourage Responders to provide additional information as relevant. For example, for those companies that have not previously considered WHO pre-qualification of PQ finished product or API, or companies striving to achieve international GMP compliance, please provide information on your plans for achieving GMP compliance and, where appropriate, the status of review for WHO pre-qualification of another product or your development plan for doing so.

MMV reserves the right to request additional information from Responders either in writing or via teleconference (will be via invitation and dates to be advised, but currently anticipated to occur during February 2020.

**ANNEX: FORMS**

INFORMATION AND INSTRUCTIONS:

It is in your interest to answer these forms completely. All responses must be typed into this form in the spaces provided (please use the ‘Enter’/ ‘Return’ key to continue writing on the next line). The completed forms should be submitted to MMV electronically, preferably as a PDF document.

We encourage you to provide additional information as relevant, but only in supplemental pages.

**Form A: Response to Request for Proposal**

This form must be completed, signed and returned to MMV.

**DECLARATION**

We, the undersigned, having read the ***Request for Proposal (RFP) - MMV-2020-LDPQ*** submit our response, which includes the information requested in Section 5. We confirm that all the information provided is true.

We understand that issue of the RFP by MMV and submission of our response is not a commitment by either party to enter into any discussions or collaboration.

This RFP and any responses thereto shall be the property of MMV.

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| **Name of authorized representative:** |  |
| **Title:** |  |
| **Signature:** |  |
| **Date:** |  |
| **Company name:** |  |
| **Postal Address:** |  |
| **Telephone No.:** |  |
| **Email Address:** |  |

**Form B: Business Information**

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| **Company name** |  | | |
| **Legal entity/ ownership** |  | | |
| **Brief history and decription** |  | | |
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| **Revenue and staffing** | **2017** | **2018** | **2019** |
| **Revenue (USD)** |  |  |  |
| **Staffing (end year)** |  |  |  |
| **Number of staff (whole company)** |  |  |  |
| **Number of staff (R&D)** |  |  |  |
| **Number of staff (Quality)** |  |  |  |
| **Number of staff (Manufacturing)** |  |  |  |
| **Number of staff (Sales)** |  |  |  |

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| **Manufacturing sites and marketing and distribution capability** | |
| **Manufacturing sites (e.g. API and /or finished product)** |  |
| **Countries with registered offices – Sales & Regulatory capacity (Please list)** |  |
| **Countries where represented by local distributors (Please list)** |  |

**Form C: Product Information**

**Anti-malarial products and APIs, registered and in development**

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| **Product** | **Trade** | **Dosage** | **Shelf-life in** | **Annual** | **Regulatory approval** | | | **GMP regulatory inspection facility** | | | **Submitted to** |
|  | **name** | **form of FPP** | **climatic zone IVb** | **capacity** | **SRA** | **WHO PQ1** | **Country (Please list)** | **SRA** | **WHO PQ** | **Other (Please list)** | **WHO PQ for review (status)** |
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1 WHO prequalification

**Other finished pharmaceutical products (FPP) and APIs with SRA approval or WHO Prequalification**

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| **Product** | **Trade** | **Indication** | **Dosage** | **Shelf-life in** | **Annual** | **Regulatory approval** | | | **GMP regulatory inspection facility** | | | **Submitted to** |
|  | **name** |  | **form** | **climatic zone IVb** | **capacity** | **SRA** | **WHO PQ1** | **Country (Please list)** | **SRA** | **WHO PQ** | **Other (Please list)** | **WHO PQ for review (status)** |
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1 WHO prequalification

1. ,2World Malaria Report 2019, These 11 countries (Burkina Faso, Cameroon,

   the Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda and the United Republic of Tanzania). [↑](#footnote-ref-2)
2. [↑](#footnote-ref-3)
3. WHO Guidelines for the Treatment of Malaria, 3rd Edition. Recommends PQ for malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency). [↑](#footnote-ref-4)
4. The WHO Guidelines for the Treatment of Malaria, 3rd Edition. In low-transmission areas, administration of a single dose of 0.25 mg/kg primaquine with ACT to patients with Pf malaria (except pregnant women, infants aged <6 months and breastfeeding mothers of infants aged <6 months) to reduce transmission. Testing for G6PD deficiency is not required. The single dose of PQ is administered on the first day of ACT administration; the single low dose of 0.25 mg/kg is unlikely to cause clinically significant haemolysis even in patients with G6PD deficiency. [↑](#footnote-ref-5)
5. MMV has a preference to work with manufacturers who are fully compliant with GMP processes as confirmed by a recent inspection with a favourable outcome conducted either by a Stringent Regulatory Authority (SRA), the WHO or another entity that is acceptable to MMV. However, we recognize that developing capacity to manufacture medicines is important and that some companies are close to being able to prove their compliance with global industry standards and have invested in appropriate quality management systems. Manufacturing companies who can demonstrate their progress and commitment in compliance with GMP are also encouraged to respond to the RFP. [↑](#footnote-ref-6)
6. <https://extranet.who.int/prequal/sites/default/files/documents/27%20Stability%20requirements_March2016.pdf> [↑](#footnote-ref-7)
7. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [↑](#footnote-ref-8)