



Briefing note

### **Investigation into compliance with quality specifications of artemisinin-based combination products procured during the pilot phase of the Affordable Medicines Facility – malaria**

The Affordable Medicines Facility – malaria (AMFm) is an innovative financing mechanism designed to expand access to artemisinin-based combination therapy (ACT) products, currently the most effective treatment for malaria. It is hosted and managed by the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). AMFm Phase 1 is being implemented through 9 pilots in 8 countries: Cambodia; Ghana; Kenya; Madagascar; Niger; Nigeria; Tanzania (including Zanzibar); and Uganda. The pilot phase has been running since 2009 and is scheduled for completion at the end 2012.<sup>1</sup>

All of the products made available through AMFm must be WHO prequalified or approved by a stringent regulatory authority. In procuring products that have already been evaluated and found to comply with quality standards, the Global Fund/AMFm maximizes the likelihood that those products are quality-assured. The Global Fund/AMFm also stipulates that products for AMFm undergo pre-shipment testing. Its testing policy is based on application of a risk-based approach to determine which products and batches should be tested before shipment. The batches to be tested are selected randomly by an independent, WHO prequalified quality control laboratory (QCL) contracted by the Global Fund, based on the procurement list provided by the manufacturer. The sampling is performed by an independent sampling agent who sends the samples to the QCL. The manufacturer selects neither the batches nor the samples to be tested. Products are tested according to all their specifications, including active pharmaceutical ingredient (API) content, impurities, uniformity of mass of individual tablets, and dissolution/disintegration.<sup>2</sup> The results of pre-shipment testing are made publicly available.<sup>3</sup>

In short, the Global Fund/AMFm operates a two-step process to ensure that the quality of medicines procured is sustained: pre-procurement and (following procurement) pre-shipment.

#### **Quality of some Global Fund/AMFm products questioned**

However, in July and November 2012 Bate and co-workers published articles<sup>4,5</sup> regarding medicines

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<sup>1</sup> AMFm receives key financial support from the Bill & Melinda Gates Foundation and the United Kingdom Department for International Development, and technical support from members of the Roll Back Malaria Partnership. For further information about AMFm go to : <http://www.theglobalfund.org/en/activities/amfm/>

<sup>2</sup> Initially, in view of the scale up of ACT production, and up until September 2011, 10% of batches were subject to pre-shipment testing. Since none failed to comply with specifications, the Global Fund/AMFm thereafter decided that testing of 5% of batches would be both cost-effective and sufficient for quality assurance purposes.

<sup>3</sup> [http://www.theglobalfund.org/documents/psm/coas/PSM\\_CoAs\\_List\\_en/](http://www.theglobalfund.org/documents/psm/coas/PSM_CoAs_List_en/)

<sup>4</sup> Bate R, et al. (2012). Subsidizing artemisinin-based combination therapies: a preliminary investigation of the Affordable Medicines Facility — malaria. *Research and Reports in Tropical Medicine*. 2012 July, (3):63–68. Available at: <http://www.dovepress.com/subsidizing-artemisinin-based-combination-therapies-a-preliminary-inve-peer-reviewed-article-RRTM>.



quality. In the July 2012 article<sup>4</sup> the authors state that the quality of some ACT products supplied via AMFm to participating countries, and thereafter bought from private pharmacies in Ghana, Nigeria and Togo in May 2011, contained less than 75% of the declared artemisinin component content. They express concern about distribution of ACTs that lacked sufficient API and conclude that, given their consistent finding of a low artemisinin component content, the occurrence of sub-standard medicines was probably not random. They suggest that the reason for systematic low content was due to “undetected manufacturing practices” such that all the sub-standard ACT products tested were found to have insufficient API, and none too much.

In the November 2012 article,<sup>5</sup> the authors suggest that, in view of ACT testing results (including those presented in the earlier article<sup>4</sup>) that demonstrate quality failure, donors should systematically test every batch of medicines that they buy.

### **Action taken by WHO-PQP to evaluate the quality of AMFm medicines tested**

Each of the products referred to in the July 2012 article had been prequalified by WHO. The WHO Prequalification of Medicines Programme (WHO-PQP) immediately initiated an investigation into the quality of the alleged sub-standard medicines.

At WHO-PQP’s request, the authors provided details about the batches that had been tested. These details included product names, batch numbers and manufacturer information. In summary, 12 batches of ACT tablets from 5 different manufacturers were suspected to contain less than 75% of the artemisinin-derived API. It should be noted that 3 of the 12 “suspect” batches had already been independently sampled and tested before shipment by Global Fund/AMFm (as described above) and found to be compliant with specifications, and the testing results published.

WHO-PQP reviewed all potential causes of the alleged quality failure, such as failure to comply with Good Manufacturing Practice (GMP), degradation during transportation and/or storage, and criminal falsification. It also considered whether laboratory errors could have been made during the testing organized by Bate and co-workers of the samples they had collected.

WHO-PQP requested 4 of the 5 manufacturers whose products were suspected of being sub-standard to investigate the complaint received about their product and to inform PQP within 30 days of the progress of their investigation. (With respect to the fifth manufacturer, please see below.)

GMP requires manufacturers to keep sufficient retention samples of products, for provision to regulators upon request, and in particular to facilitate investigation of product complaints. The manufacturers were therefore requested to analyse these retention samples as part of their investigation, and, in the case of quality failure, to identify its root cause, and to inform WHO-PQP what corrective action and preventive action they would be taking to prevent recurrence.

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<sup>5</sup> Bate R & Hess K. (2012) The role of pre-shipment batch testing in ensuring good medicine quality. *MWJ*. 2012 November, Vol 3(12):1–4. Available at: <http://www.malariaworld.org/mwj/2012/research-role-pre-shipment-batch-testing-ensuring-good-medicine-quality>



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In parallel, WHO-PQP initiated a risk-based inspection plan, targeting some of the concerned manufacturing sites, with a special focus on on-site investigations, with a view to elucidating any issues that might contribute to the lack of quality alleged by Bate and his co-workers. As a routine inspection of the manufacturing site of the 5th manufacturer had already been scheduled and announced, it was decided not to disclose information regarding the complaint to the manufacturer before the inspection took place. Thus the complaint investigation was not announced before the inspection and the manufacturer had no time to prepare for it in advance.

WHO-PQP requested that Bate and co-workers make available to it any remaining samples of the “suspect” batches. These were very limited in number, but nevertheless, one or two tablets from each of the 5 suspect samples were provided. These samples will be analysed at a prequalified QCL that has proven expertise in analysing ACTs.

### **Outcomes and results obtained to date**

Four manufacturers provided detailed reports of their investigations to WHO-PQP. Retained samples of the alleged defective batches had been tested by their quality assurance departments, according to their routine validated analytical procedures, as approved in the product dossiers submitted to and approved by WHO-PQP. All of the results obtained to date indicate that the retention samples of the allegedly defective batches fully meet their approved regulatory shelf-life specifications. In every case, the retention samples of the batches which were alleged to contain less than 75% of the artemisinin component, contained more than 90% of declared content.

The investigation reports also included review of: the relevant manufacturing documentation; annual product quality reviews (including trends of on-going stability); product distribution; and of the validation of the manufacturing and testing processes required by WHO GMP. No problems were found.

During the inspection of the 5<sup>th</sup> manufacturer, retention samples of batches of artesunate/amodiaquine tablets that had been described as sub-potent by Bate and co-workers were subjected to unannounced sampling by the WHO-PQP inspectors. Samples were taken from the company's retention store and tested in the manufacturer's QCL. These actions, including the preparation of the samples and their analyses, were witnessed by the inspectors. Additionally, samples of one of the batches were collected and sent for analyses to a WHO-prequalified QCL. The results of this independent testing are awaited.

In summary:

- the results of pre-shipment testing organized by the Global Fund/AMFm for 3 of the 12 suspect batches indicate that the 3 products concerned complied with specifications before they were dispatched to the recipient countries
- all of the results obtained to date from the manufacturers concerning their investigations indicate that the retention samples of the concerned batches held at the manufacturing site fully met their registered regulatory specifications.



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These results do not support the recommendation that pre-shipment testing of all donor-funded medicines would be an effective use of donor funds.

However, WHO-PQP will carry out yet further investigation focusing on products collected at field level.

### **Ongoing survey of GF/AMFm products in the field**

In collaboration with AMFm, that provided the list of buyers who had received the suspect batches, WHO-PQP has collected samples at two points:

- after delivery of the products by the manufacturer to the country of destination but before distribution, in order to verify the quality of the product as supplied by the manufacturer
- after storage of the products for some time in pharmacies, in order to verify the quality of the products when they are received by patients.

The survey involves three of the countries — Ghana, Nigeria and Uganda — to which products are being supplied via AMFm during its pilot phase. Bates and co-workers reported sub-standard products in Ghana and Nigeria. Uganda, was selected for purposes of comparison. The national medicines regulatory authorities of these countries are closely cooperating with WHO-PQP on the survey.

Importantly, the collected samples will be tested at a WHO-PQP prequalified laboratory (which is also a WHO Collaborating Centre, with extensive experience of testing of antimalarials). This laboratory is also responsible for independent repeat testing the of samples supplied by Bates and his co-workers.

The survey will contribute to quality monitoring of WHO-prequalified medicines and will be used also to assess the storage conditions to which medicines supplied via the AMFm are subject. The results are expected to assist responsible authorities in the countries surveyed, as well as the Global Fund, to adopt any necessary action. The report from the survey will be made publicly available.

### **Contacts for further information:**

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