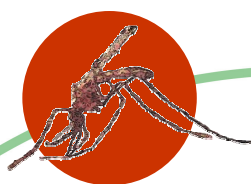




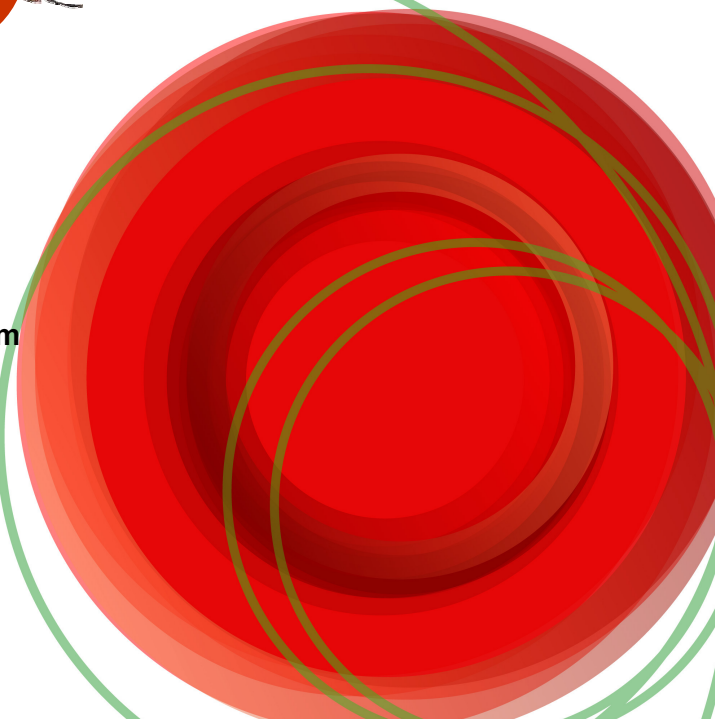
**World Health  
Organization**

**WHO informal consultation  
with manufacturers of artemisinin-  
based pharmaceutical products  
in use for the treatment of malaria**



**24 August 2007**

**Venue: Executive Board Room  
World Health Organization  
20, avenue Appia  
Geneva, Switzerland**



**© World Health Organization 2007**

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

## EXECUTIVE SUMMARY

The presence of oral artemisinin monotherapies in the market continues to represent a threat to the useful therapeutic life of these medicines, by encouraging the development of resistance. To contain that risk, WHO recommends the use of artemisinin-based combination therapies (ACTs) in order to ensure high cure rates of *Plasmodium falciparum* malaria and the withdrawal of oral artemisinin monotherapies from the market. These recommendations have been endorsed by all WHO Member States and are part of the malaria resolution WHA60.18, adopted by the 60th World Health Assembly in May 2007.

Recent findings at the Thai-Cambodia border, where several cases of ACT treatment failures have been documented (patients with prolonged parasite clearance time and/or without parasite clearance over 7 days), point to real risks of resistance development to artemisinin in areas where oral artemisinin monotherapies have been deployed on a large-scale. More efforts are needed to improve monitoring of ACT efficacy in all countries, to contain multi-drug resistance at the Thai-Cambodia border, and discontinue the use of artemisinin monotherapy.

The number of companies involved in the production and marketing of oral artemisinin monotherapies has been increasing progressively over the recent years. Up to 67 companies are known by WHO to manufacture oral artemisinin monotherapies. Additional 16 companies are manufacturing ACTs and not monotherapies. About 25 more companies are involved in the marketing of artemisinin pharmaceutical finished products. At least 94 oral artemisinin-based products are currently in the market, mostly in the private sector of endemic countries.

Out of the 74 countries with falciparum resistant malaria which adopted ACTs, 34 countries either did not register or are taking regulatory measures to withdraw the marketing authorization of oral artemisinin monotherapies, but 56.4% (44 out of 78) still allow the marketing of these products. Experience from Benin and Pakistan shows that the process of withdrawing the marketing authorization of these products require a transition period of 6–9 months, for manufacturers to minimize financial losses, to synchronise the withdrawal of these products with the deployment of ACTs in the public sector, and to prioritize registration of ACTs in line with the national treatment policy. Intensified WHO actions with NDRA of endemic countries are needed to limit the exploitation of niche markets created by companies phasing out monotherapies in compliance with WHO recommendations.

The overall market size for artemisinin-based treatments in 2007 is estimated at 150 million treatment courses, 20% of which in the private sector. The market and supply of artemisinin raw material is still unstable. Following the global shortage in 2004 and the consequent sharp increase in the price of artemisinin (from US\$ 230/kg in 2003 to US\$ 1100/kg in 2004–2005) there has been a major expansion of plantations and of artemisinin producers in China, Viet Nam and East Africa in 2006. The mismatch between increased offer and tempered demand for ACTs in the public sector (due to low approval rates in GFATM Rounds 5 and 6, and delayed disbursement and utilization of funds from Round 4) created a major reduction in the price of artemisinin (currently at US\$ 180/kg, below its production costs). There is growing concern that the withdrawal of farmers and artemisinin producers from this market will create a relative reduction of the artemisinin inventory and risk of shortages in 2008–2009. Only few manufacturers are establishing stockpiles of

artemisinin to prevent the effects of a possible shortage of raw materials, and the production of ACT will continue to depend from plant extraction.

The pre-qualification of artemisinin pharmaceutical products by WHO is hindered by the lack of "originator products" for most ACTs, i.e. medicines approved by stringent drug regulatory authorities against which generic companies are compared through bio-equivalence studies. Several ACT products are under evaluation, and the status of product assessment is available at <http://mednet3.who.int/prequal/>. Technical support to manufacturers is required to accelerate the pre-qualification of antimalarial medicines.

Differences exist in quality criteria for procurement of antimalarial medicines with international funds. The WHO/UNICEF joint tender list (available at: [www.who.int/malaria/pages/performance/antimalarialmedicines.html](http://www.who.int/malaria/pages/performance/antimalarialmedicines.html)) is different from the Global Fund to Fight Aids Tuberculosis and Malaria list (available at: [www.theglobalfund.org/pdf/guidelines/Compliance\\_list\\_MALARIA.pdf](http://www.theglobalfund.org/pdf/guidelines/Compliance_list_MALARIA.pdf)). However, a general trend is emerging for setting uniform quality criteria to guide procurement of medicines, and multiple agencies are requesting WHO to coordinate efforts in this direction.

At the meeting, seven new companies declared their willingness to stop marketing artemisinin monotherapies over a short period, increasing to 61.2% (41 out of 67) the proportion of companies willing to comply with WHO recommendations. WHO proposed to manufacturers present at the meeting to comply with a new "Code for Artemisinin Marketing Practices" (CAMP) based on the following elements:

- 1) phasing out oral artemisinin monotherapies and marketing medicines in line with the WHO Guidelines for the Treatment of Malaria;
- 2) manufacturing site is compliant with Good Manufacturing Practices, certified for the WHO Pre-qualification Programme or by a stringent drug regulatory authority;
- 3) no misuse of WHO name/logo for commercial purposes; and
- 4) reporting to WHO under confidential cover evidence of bad marketing practices, substandard or counterfeit products in the market.

All participating companies accepted to comply with the proposed code and to increase collaboration with WHO in providing the requested information.

---

# 1. Introduction

---

Artemisinin-based combination therapies (ACTs) continue to be the mainstay of treatment of uncomplicated falciparum malaria. For the next 8–10 years, no alternative medicines to the artemisinin derivatives able to offer similar high levels of therapeutic efficacy are expected to enter the market. For this reason, WHO has focussed its efforts not only to increase access to quality ACTs, but also to contain the risk of development of falciparum resistance, mostly created by the large-scale use of oral monotherapies for treatment of uncomplicated malaria.

In January 2006, WHO appealed to manufacturers to stop marketing oral artemisinin monotherapies and instead to promote quality ACTs in line with WHO policy ([www.who.int/mediacentre/news/releases/2006/pr02/en/index.html](http://www.who.int/mediacentre/news/releases/2006/pr02/en/index.html)). The position has been widely disseminated via WHO Offices, WHO briefings to staff and to representatives of national health authorities at regional and inter-country meetings. Major procurement and funding agencies and international suppliers have accepted WHO recommendation and agreed not to fund or procure oral artemisinin monotherapies.

In April 2006, the Global Malaria Programme of WHO provided a technical briefing to 25 pharmaceutical companies involved in the production and marketing of artemisinin monotherapies. Out of these, 15 declared their willingness to stop marketing artemisinin monotherapies over a short period of time, but 10 companies did not disclose their marketing plans for the future (meeting report available at: [www.who.int/malaria/docs/Meeting\\_briefing19April.pdf](http://www.who.int/malaria/docs/Meeting_briefing19April.pdf)). In addition, some countries, like China and Pakistan, have been visited by WHO delegations to address multiple domestic manufacturers involved in this sector. The evolving position of manufactures and of National Drug Regulatory Authorities (NDRA) of malaria endemic countries is monitored and displayed on the WHO Global Malaria Programme website front-page: <http://malaria.who.int/>.

In May 2007, the 60th World Health Assembly resolved to take strong action against oral monotherapies and approved the resolution WHA60.18, which:

- urges Member States to cease progressively the provision, in both the public and private sectors, of oral artemisinin monotherapies, to promote the use of artemisinin-combination therapies, and to implement policies that prohibit the production, marketing, distribution and the use of counterfeit antimalarial medicines;
- requests international organizations and financing bodies to adjust their policies so as progressively to cease to fund the provision and distribution of oral artemisinin monotherapies, and to join in campaigns to prohibit the production, marketing, distribution and use of counterfeit antimalarial medicines;

## 2. Objectives of the meeting

---

In order to review the progress made in implementing the WHO recommendations of phasing out oral artemisinin monotherapies and to agree on the way forwards, WHO convened an informal consultation (August 2007) with manufacturers, national health authorities of selected countries that made progress in the withdrawal of these medicines following WHO recommendations, international experts and WHO technical resource persons. The meeting had the following objectives:

1. To present to manufacturers the current evidence of risk for the development of resistance to artemisinin and its derivatives;
2. To review with manufacturers progress and challenges in reducing reliance on oral artemisinin mono-therapies for treatment of uncomplicated malaria;
3. To discuss with manufacturers the expected impact on the public sector market of new ACT funding initiatives;
4. To agree on mechanisms for self-regulation of artemisinin marketing practices and reporting system to WHO.

A total of 24 pharmaceutical companies were present, out of the 67 invited to the meeting. The topics presented and discussed at the meeting and the list of participants are provided in Annexes I and II.

## 3. Discussion points

---

The current product profile of ACTs requires improvements to simplify prescription and promote higher adherence to treatment: some ACTs have relatively complex regimens (twice daily for three days for artemether-lumefantrine) or are available mainly or exclusively as co-blistered products (artesunate in combination with amodiaquine, mefloquine or sulfadoxine-pyrimethamine). Current formulations have generally only 2 years shelf life. This, together with different age-specific course-of-therapy packaging, makes supply management of ACTs very difficult. Moreover, there are too few ACT paediatric formulations on the market or under development, and the co-administration of both ACT components in separate paediatric formulations (suspension, powder for dissolution, granulate in sachets) is suboptimal. There is a need for highly effective ACTs in fixed-dose combinations, with simplified dosage regimens, in stable formulations with appropriate packaging for large-scale use, as well as new paediatric formulations to facilitate administration to infants.

The market of artemisinin pharmaceutical products is very dynamic, with the number of generic companies active in this sector increasing every year. In particular the number of companies involved in the production and marketing of oral artemisinin monotherapies has increased from 17 companies identified in 2005, to 38 in 2006, up to the total of 67 companies known to WHO by August 2007. In addition, there are 16 companies involved in

manufacturing exclusively ACTs and 25 companies of uncertain status are involved in re-branding, re-packaging, re-selling products manufactured by other companies, without disclosing product information to the public. Overall, WHO has recorded and classified 94 oral artemisinin products, currently being sold for the treatment of uncomplicated malaria, mainly in the private sector of malaria endemic countries.

A major challenge for the implementation of the withdrawal of oral artemisinin monotherapies from the market has been the rapid occupation of the market by other manufacturing companies not following WHO recommendations. In unregulated settings, responsible manufacturers who are phasing out their monotherapies provide market opportunities to companies which may promote substandard products. Intensified support should be given to national drug regulatory authorities of malaria endemic countries to withdraw the marketing authorizations of all oral artemisinin monotherapies, withdraw/withhold licences for manufacturing and exports, establish national laws to prohibit imports, and to enforce strict control of borders for importation of medicines and promote active recall of the products already in the market. Measures should also be put in place at country level to mitigate the financial losses of manufacturers (domestic and international), importers and distributors, with agreed timeframes between private sector representatives and the national health authorities of the country concerned.

Increasingly high levels of funds are being mobilized for malaria control, and ACT procurement will be an important component of several new initiatives, including the GFATM Round 7, US PMI, World Bank and, more recently, UNITAID. A Global ACT Subsidy (recently renamed as "Affordable Medicine Facility for malaria") is under definition with increasing attention and support from international and bilateral development agencies as mechanism to ensure access to quality ACT at affordable prices in both the public and the private sectors. All these initiatives, however, and their potential high impact on the malaria burden is threatened by the risk of development of resistance to artemisinin and its derivatives, which is enhanced by the wide scale use of oral artemisinin monotherapies, and partially effective ACTs (e.g. ineffective companion medicine, sub-optimal dosage or substandard quality). The recent findings at the Thai-Cambodia border, where several cases of ACT treatment failures have been documented, point to real risks of development of artemisinin resistance in areas where oral artemisinin monotherapies and/or partially effective ACTs, have been deployed on a large-scale. Efforts to replace oral artemisinin monotherapies with highly effective ACTs need to be accelerated.

The overall market size for artemisinin-based treatments has been progressively expanded and, by 2007, it has reached an estimated 150 million treatment courses, 20% of which in the private sector. With increased mobilization of international funds, the size of the ACT market is expected to progressively expand in both the public and private sectors, and it will continue to be dependent on extraction from *Artemisia annua*, since bio-synthetic artemisinin or chemical analogues will not become available before 2011. The market of artemisinin raw material has undergone major price fluctuations over the last two years and present serious risks of supply shortages in the short term. In order to minimize supply shortages and to contain the risk that sub-standard quality artemisinin and API will be sourced at the critical time of supply shortages, international support needs to be mobilized soon for the creation of artemisinin safety stocks of high quality. Artemisinin offers the possibility of longer shelf life up to 4–5 years, through a process of re-crystallization, and its early establishment could serve the ACT production needs for multiple years.

The process of pre-qualification of artemisinin pharmaceutical products by WHO is the international reference standard to advice UN and international procurement agencies on

the procurement of quality medicines for HIV, tuberculosis and malaria. Differently from ARV medicines, the process of pre-qualification of ACTs is not satisfactory as only one fixed-dose combination ACT has met the required standards, i.e. artemether-lumefantrine supplied by Novartis Pharma. Acceleration of the review process, consistency in follow-up of technical questions raised by PQ programme, more opportunities for face-to-face meetings between manufactures and evaluators as well as intensified technical support to manufacturers are all required to increase the number of antimalarials which will be pre-qualified in the future.

In the absence of multiple pre-qualified products, two main systems are in use, i.e. the WHO/UNICEF joint Request for Proposals and the GFATM compliance list for single-source or limited source medicines (classified as "Ci"), supplemented by pre-shipment QC of samples ex-manufacturer. Over the recent months, multiple funding institutions and bilateral development agencies have expressed concerns regarding significant important differences in quality assessment criteria for antimalarial medicines in case of non-prequalified medicines. A general trend is emerging between multiple Agencies to agree on common quality criteria for the procurement of antimalarial medicines in the absence of pre-qualified products.

## **4. Position statements of pharmaceutical companies**

---

The short statements below summarize the position expressed by representatives of the companies participating to the meeting.

### Ajanta Pharma Limited

- After the WHO meeting with manufacturers in April 2006, the company stopped the manufacturing and marketing of oral artemisinin monotherapies after a period of 2–3 months, and since then it has been investing exclusively in the development of ACT fixed-dose combinations. More efforts should be directed by WHO to guide the national regulatory authorities to withhold manufacturing licences and export permits for these products, so that custom authorities will not allow the export of monotherapies to recipient countries.

### Alchem International Ltd

- The company is a supplier of active pharmaceutical ingredients, with investments in plantations of *Artemisia annua* and extraction facilities. The company will cooperate with WHO to inform all customers on the international commitment to withdraw oral artemisinin mono-therapies from the market.

### Aum Health Care

- The company is involved in the manufacturing and marketing of several artemisinin pharmaceutical products and is also a supplier of artemisinin. The company is committed to follow WHO recommendations and to implement the code for artemisinin marketing practices.

Cipla Limited

- The company has stopped the marketing of artemisinin monotherapies and is only supplying these products to selected MSF projects for use in combination therapies. The company is investing in a range of fixed-dose combinations, including of existing co-blistered ACTs, some of which are on the market and other under evaluation by the WHO pre-qualification programme. CIPLA, like all other responsible companies attending the consultation, shares WHO concerns over the marketing of artemisinin mono-therapies. WHO should work with national health authorities that issue licences for manufacturing of medicines in order to ensure that licences for manufacturing of oral artemisinin monotherapies are withdrawn/withhold. In countries with law enforcement mechanisms for the pharmaceutical sector, such as India, this will ensure that these medicines cannot be manufactured anymore. Manufacturing of these products would then become illegal and court action could be taken against these companies.

Dafra Pharma NV

- The company will give its full support to the WHO code of artemisinin marketing practices. The company has deployed several ACTs in the African market since five years already and has stopped the production of oral monotherapies for uncomplicated malaria. The company believes that co-blistered ACTs may contribute to increase the risk of development of resistance, and it has invested strongly in the development of new fixed-dose combinations (FDC) over the last years. Two new FDCs will be launched in 2008, namely artesunate+amodiaquine and artesunate+sulfamethoxypyrazine-pyrimethamine.

Denk Pharma GmbH & Co. KG

- The company stopped its production and marketing of oral artemisinin monotherapies after the WHO briefing in 2006, and concentrated its marketing and sales activities on its combination of artesunate+sulphamethoxypyrazine-pyrimethamine. The company faced difficulties in promoting this product because of the large use of oral artemisinin monotherapies by prescribers. WHO should have a more active role in educating and training prescribers and pharmacists in malaria endemic countries to move away from monotherapies and to adopt effective ACTs instead.

ETDZS Industry Ltd. Chongqing

- The company has been involved in the marketing of oral artemisinin monotherapies for almost 10 years, and since last year it has developed a new ACT, i.e. artemether soft capsule co-blistered with piperaquine. The company is also developing a new fixed-dose ACT therapy and work in progress.

Genix Pharma (Pvt) Ltd

- The company is complying with the WHO recommendations on oral artemisinin monotherapies in line with the regulatory measures taken by the national health authorities of Pakistan. The company has recently launched its fixed-dose combination of artemether-lumefantrine, and is developing new combinations as well.

Helix Pharma (Private) Ltd.

- The company appreciates WHO initiative to phase out oral artemisinin monotherapies but it raises concerns that there should still be a role for paediatric formulations of artemisinin monotherapies for infants until paediatric formulations of ACT will become available.

Holley-Cotec Pharmaceuticals Co., Ltd.

- Since the first launch of DHA-piperazine in Eastern Africa, in the second quarter of 2006, the company has been focussing on the marketing of ACTs, mainly in the private sector market. The company has also invested in pre-qualification, but the inclusion of DHA-PPQ in the list of antimalarial medicines to be pre-qualified is conditional to prior approval in the malaria treatment guidelines yet. The company appeals to WHO to accelerate the process of reviewing this product as part of the process for updating the *WHO Guidelines for the Treatment of Malaria*.

Holley Pharmaceuticals (Chongqing) Co. Ltd

- Holley Pharmaceutical as one of the major global suppliers of artemisinin raw materials is willing and ready to cooperate with finished product manufacturers, to ensure a stable supply of artemisinin at high quality and reasonable price.

Hovid Bhd

- The company has registered its oral artemisinin monotherapy in Malaysia after a long regulatory process, but, following WHO recommendations, it has not launched this product. The company is currently considering to investing in the development of a fixed-dose ACT.

Kunming Pharmaceuticals Corp.

- The company agrees with WHO on the promotion of ACTs and has made serious investments to replace its monotherapy with a new fixed-dose combination (artemisinin+naphthoquine phosphate tablets). At the same time the company continues to be a major suppliers of artemether active pharmaceutical ingredient to Novartis for the manufacturing of artemether-lumefantrine.

Lachifarma

- The company is manufacturing artemisinin pharmaceutical products since 2005, and is has no longer in its warehouse any monotherapy products in line with the recommendations of WHO.

Mepha Ltd.

- The company has complied from the beginning with WHO recommendations on oral monotherapies, and has stopped production and exporting. There are still few countries where products can be found but by the end of 2007, no products will be present in the market. The company is marketing an ACT (artesunate+mefloquine) which is partly subsidizing the losses incurred in phasing out the monotherapies. The company has products under review by the WHO pre-qualification

programme, including a fixed-dose ACT paediatric formulation, and it strongly recommends that WHO speeds up his process. WHO should also promote ACTs with simple dosage regimens (once daily) to enhance patient adherence to treatment.

#### Novartis

- The company has been manufacturing and marketing ACT fixed-dose combinations since more than 10 years and fully supports WHO to actively promote the withdrawal of monotherapies. More emphasis should be given in the promotion of ACT only as fixed-dose combinations, as the use of combination therapies in co-blisters is suboptimal to promote good adherence to treatment. WHO should also monitor that no compromise on quality standards is made, especially as the demand for increased supply will increase with the launch of global ACT subsidy.

#### Plethico Pharmaceuticals Limited

- The company is mainly investing in the private sector market. The company has invested in co-blistered ACT, but encountered problems in market penetration of its ACT products due to the prevalent prescribing practices in endemic countries and the widespread availability of artemisinin monotherapies from multiple manufacturers. The company considers that availability and access to ACTs has to be ensured before proceeding with actual withdrawal of all mono-therapies.

#### Remedica Ltd

- The company is committed to follow the WHO code of artemisinin marketing practices and the two products manufactured by this company will be only marketed in co-blisters with another effective antimalarial product.

#### Sanofi-Aventis

- The company has complied with WHO recommendations: it has stopped its promotion of artesunate monotherapy and replaced it with ACT, recently developed in a fixed dose combination with DNDi. In the private sector of malaria endemic countries the demand for oral monotherapies (chloroquine, artemisinin derivatives etc) is still high because these products are less expensive, more widely available, easier to use than ACTs, and limited efforts have been made so far for changing prescribing practices. The challenge for ACT manufacturers is to be competitive with oral monotherapies with lower prices and simple regimens. Manufacturers should invest not only in reducing prices but also in providing information services and training to prescribers and education of the patients on the benefits of treatment with ACTs.

#### Saokim Pharma

- The company continues to play a major role as supplier of artemisinin raw materials, both for domestic use and for export, and has started production of a fixed-dose combination of artesunate-amodiaquine. The ACT is in the process of registration in a few African countries, and the company is preparing the necessary documentation to submit to the WHO Pre-qualification programme.

Shanghai Fosun Pharmaceutical (Group) Co., Ltd

- The company, in line with WHO recommendations, have already stopped marketing and sales to mono-therapies since two years ago, and is currently investing on its two ACTs, i.e. artesunate+amodiaquine and artesunate+SP, as well as its artesunate injection in line with *WHO Guidelines for the Treatment of Malaria*.

Shelys Pharmaceuticals Ltd.

- The company has one factory in Kenya and one in Tanzania. Following the decision of the national drug regulatory in Tanzania the company has stopped producing oral artemisinin monotherapy in this country. In other countries where the Government or the Regulatory Authorities do not withdraw the marketing authorization for these products and do not prohibit the importations, even if single companies comply with WHO recommendations, other companies will be selling these products in the market. WHO should advice Regulatory Authorities of each country to stop marketing of all monotherapies, not only artemisinin-based, but also conventional antimalarial medicines.

Swiss Pharma Nigeria Ltd

- The company is one of the leading pharmaceutical manufacturers in Nigeria, involved in the manufacturing of anti-malarial medicines over the last 30 years. The company first introduced in the market its artemisinin monotherapies in 2004, but has then discontinued the production of monotherapies in line with WHO recommendations. If all manufacturing companies attending the WHO meeting also do the same, this will have a major impact in Nigeria as all these companies together represent a large share of the private sector market in this country. The company is also investing its marketing efforts in two ACTs combinations.

Zenufa Group of Companies

- The company has an important market share in the Democratic Republic of Congo and neighbouring countries in the Central African Region. Since two years, the company is marketing ACTs and it will commit to phase out the mono-therapies in the near future time.

## 5. Priority actions for WHO

---

1. WHO will promote a universal campaign to ensure access to highly effective ACTs for the treatment of uncomplicated malaria in the public and private sectors as well as in the community, based on the most cost-effective treatment selected according to the resistance profile of *P. falciparum* in the country.
2. WHO will develop a new system of ACT forecasting based on tracking of international funds allocated for procurement, actual disbursements to recipients, and expected orders according to funded procurement plans, taking into account the operational targets and the implementation capacity of the countries concerned.
3. WHO will invest in ACT market analysis, to improve the understanding of production capacity of manufacturers of finished pharmaceutical products, API suppliers, including extractors and derivatizers, and better understanding of dynamics affecting the agricultural sector and production of *Artemisia annua*.
4. WHO will explore with international partners and funding agencies the feasibility of establishment of buffer stocks of high quality artemisinin, in order to reduce the risks of shortages due to recent high price fluctuations that have discouraged a large proportion of raw material suppliers from this market.
5. WHO will expand the pre-qualification of manufacturers of active pharmaceutical ingredients (API) for ACTs, including extractors of artemisinin and suppliers of arteether, artemether, artesunate, and dihydroartemisinin (derivatizers), in order to ensure sourcing of quality API for ACT manufacturers.
6. WHO will consider multiple approaches to increase the pre-qualification of antimalarial medicines, including the following: i) additional training workshops & materials for NDRA's and manufacturers, ii) expanded pool of consultants providing on-site technical advice to manufacturers on pre-qualification requirements, iii) increased opportunities for face-to-face meetings between manufacturers and inspectors, and iv) pre-qualification of individual medicinal components for co-packaged ACT products, when only one meets the pre-qualification requirements.
7. WHO will support National Drug Regulatory Authorities to take necessary measures to withdraw the authorization of oral artemisinin monotherapies and will be fully supportive of even more stringent actions by the national health authorities, such as recall of these products from the market, once ACTs have become widely available and affordable to the people affected by malaria.
8. WHO will seek information from collaborating companies willing to share confidential evidence of poor marketing practices (i.e. marketing oral artemisinin monotherapies, ineffective antimalarial medicines not in line with the *WHO Guidelines for the Treatment of Malaria*, or misusing WHO name/logo for commercial purposes) as part of the implementation of the new code for artemisinin marketing practices (CAMP).
9. WHO will also collate, as part of the implementation of the new code for artemisinin marketing practices (CAMP), confidential information provided to

manufacturers on results of analysis of substandard artemisinin products, including poor stability data, as well as alert reports on counterfeit products. A pilot reporting system already developed by WPRO (Rapid Alert System, see <http://218.111.249.28/ras/default.asp>) will be considered for possible extension to serve global monitoring of antimalarial counterfeits.

10. WHO will accelerate the current system for reviewing new antimalarial medicines as part of the updating of the *Guidelines for the Treatment of Malaria*, and, in addition to the planned cycle of regular updates every two years, it will also consider convening ad-hoc expert reviews during the interim periods, and making the results of such reviews publicly available.
11. WHO will also promote high international quality standards for the procurement of artemisinin-derivatives by multiple international organizations involved in the supply of these medicines for use in disease endemic developing countries.

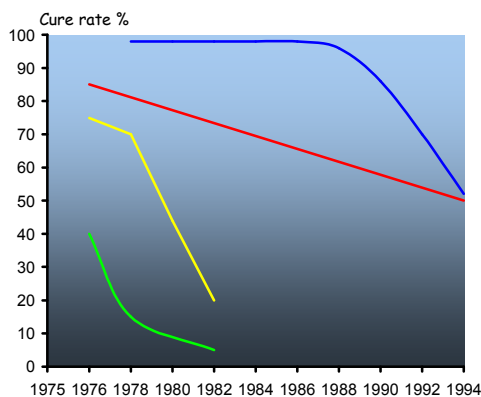
## ANNEX I

### WHO briefing sessions

#### 1. The risk of resistance to artemisinin derivatives (Dr Pascal Ringwald)

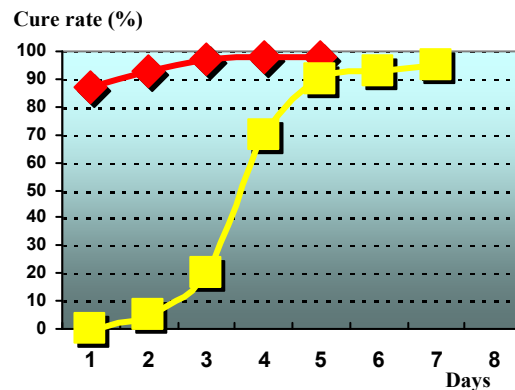
*P. falciparum* has shown the development of resistance towards all antimalarial medicines when used as monotherapy: time periods vary from 12 years (chloroquine), to 5 years (mefloquine), to 1 year (proguanil) up to even less than 1 year (sulfadoxine-pyrimethamine, atovaquone). Experience in Thailand with successive drug regimens of monotherapy drugs has shown substantial decreases in cure rates as shown in figure 1.1.

**Figure 1.1. Cure rates (%) of different antimalarials over time in Thailand**



Mefloquine (blue), quinine (red), sulfadoxine-pyrimethamine (yellow), chloroquine (green)

**Figure 1.2. Cure rates (%) of AS + MQ and AS monotherapy over days of treatment**



Artesunate + mefloquine (red), artesunate (yellow)

As already proven with other diseases like e.g. tuberculosis, the deployment of combination therapy can be used to face the resistance challenge. High-degree synergies or the combination of rapidly acting drugs with compounds having longer half-life that will destroy the residual parasite may enhance efficacy and delay resistance, as the probability that the parasites are resistant to both drugs decreases and *de novo* selection is less likely. Used as monotherapy, artesunate, after a 3-day administration, will lead to a very poor cure rate; a cure rate > 90% is reached after 7 days. When administered as combination over 3 days, a cure rate > 95% will be reached. This clear advantage of combination therapy compared to monotherapy can be seen in figure 1.2. Due to rapid improvement of symptoms, compliance to the full 7-day treatment needed to completely eliminate the parasite is very low.

There is evidence of the risk of development of resistance to artemisinin derivatives. In rodent malaria, resistance to both artemisinin and artemether has been obtained after several passages in *P. yoelii* and *P. berghei*, though this resistance was reversible after the removal of drug pressure. In *P. chabaudi chabaudi* resistance has been induced, but the candidate gene mutation remains unknown. In vitro, cross sensitivity as well as synergies

among artemisinin and amino-alcohols have been demonstrated. *P. falciparum* resistance to artemisinin is unstable, but there is rapid recurrence after re-exposure to drug pressure. Studies in China have documented changes to artesunate in vitro susceptibility of *P. falciparum* in the Yunnan Province; the 50% inhibitory concentration (IC<sub>50</sub>) and minimal inhibitory concentration in 1999 were 3.3 and 2 times greater than in 1988. Due to massive cross-border migration from the Yunnan Province to Myanmar, Lao PDR and Viet Nam, drug resistance could rapidly spread within these countries of South-East Asia.

Several cases of treatment failure in Cambodia and Thailand were seen, either without parasite clearance over seven days or late failure with reduced in vitro susceptibility to artemisinin derivatives, with both ACTs or artesunate monotherapy treatment.

Currently, ACTs are the most effective treatment for falciparum malaria. As first warnings of resistance development, e.g. from the Thai-Cambodian border, are detected, continuous monitoring of efficacy is indispensable. Ideal combinations shall deploy partner drugs with unrelated modes of action and which are not available as monotherapies. In addition, artemisinin-based monotherapies should be banned from the market.

## **2. WHO appeal to reduce reliance on oral artemisinin monotherapy (Dr Andrea Bosman, Silvia Schwarte)**

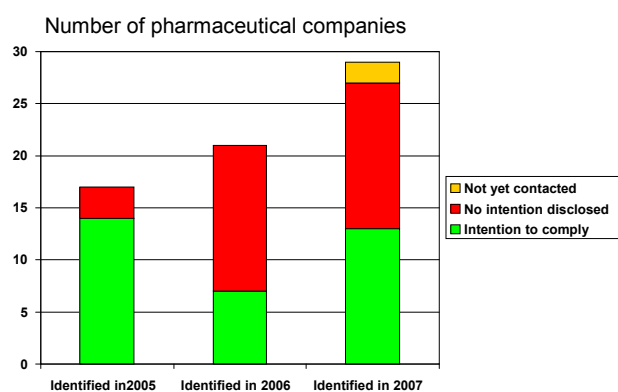
Since January 2006, when WHO appealed to manufacturers to stop marketing oral artemisinin monotherapies and to promote instead quality ACTs in line with WHO policy ([www.who.int/mediacentre/news/releases/2006/pr02/en](http://www.who.int/mediacentre/news/releases/2006/pr02/en)), the following important measures have been taken:

- The position has been widely disseminated via WHO Offices, WHO briefings to staff and to representatives of national health authorities at regional and inter-country meetings. *WHO Technical Briefing on Malaria Treatment Guidelines and Artemisinin Monotherapies*, 19 April 2006.
- Meetings with funding and procurement agencies have succeeded in convincing the procurement and funding agencies (GFATM, UNICEF, USPMI, the World Bank,) and international suppliers (IDA Foundation) not to fund or procure oral artemisinin monotherapies.
- In April 2006, the WHO Global Malaria Programme provided a technical briefing to 25 pharmaceutical companies involved in the production and marketing of artemisinin monotherapies. Out of these, 15 declared their willingness to stop marketing artemisinin monotherapies over a short period of time, but 10 companies did not disclose their marketing plans for the future ([www.who.int/malaria/docs/Meeting\\_briefing19April.pdf](http://www.who.int/malaria/docs/Meeting_briefing19April.pdf)).
- All WHO Member States have endorsed the malaria resolution WHA60.18, adopted by the 60th World Health Assembly in May 2007, recommending the use of artemisinin-based combination therapies, the progressive withdrawal of oral artemisinin monotherapies, and removal of counterfeits ([www.who.int/gb/ebwha/pdf\\_files/WHA60/A60\\_R18-en.pdf](http://www.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf)).
- All information regarding the position of manufacturers and National Drug Regulatory Authorities (NDRA) of malaria endemic countries in relation to oral

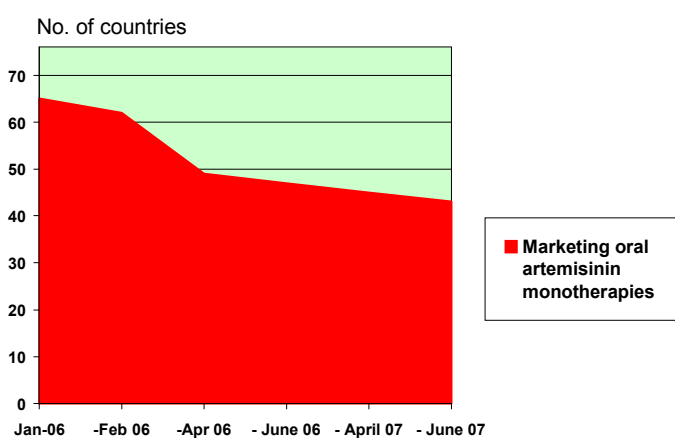
artemisinin monotherapies is available on the WHO Global Malaria Programme website (<http://malaria.who.int/>).

The number of companies involved in the production and marketing of oral artemisinin monotherapies has been progressively increasing over the recent years: 17 companies were identified in 2005, additional 21 were identified in 2006, up to a total of 67 manufacturing companies known to WHO by August 2007 (see Fig. 2.1, below)

**Figure 2.1 Manufacturers of oral artemisinin monotherapies and compliance with WHO**



**Figure 2.2 Countries marketing oral artemisinin monotherapies over time**



Additional 16 companies are manufacturing exclusively ACTs and 25 more companies of uncertain status are involved in the marketing of artemisinin pharmaceutical finished products. WHO has recorded and classified 94 oral artemisinin-based products, currently being sold for the treatment of uncomplicated malaria in the private sector of malaria endemic countries.

Out of the 78 countries with falciparum resistant malaria which need to adopt ACTs, 34 countries either did not register or are taking regulatory measures to withdraw the marketing authorization of oral artemisinin monotherapies, but 44 out of 78 (56.4%) still allow the marketing of these products.

A series of important challenges remain in the implementation of WHO appeal to reduce reliance on oral artemisinin monotherapies, including the following:

- There is still a significant number of companies that do not respond to WHO communications, and most of "non-responders" market oral artemisinin monotherapies or are involved in re-branding, re-packaging, re-selling products manufactured by other companies, without disclosing product information to the public.
- In the majority of malaria endemic countries, the pharmaceutical sector is poorly regulated and many products are registered without a stringent regulatory review of the quality, safety and efficacy. Moreover, several countries have limited mechanisms to control their borders and illegal importation of medicines is widespread.
- There is still limited availability of ACT in both the public sector, due to limited and slow disbursements of international financial to procure these medicines, and limited penetration of ACTs in the private sector, due to the very high and unaffordable prices for the large majority of the population.
- There are new manufacturing companies entering the artemisinin market every year, especially generic companies manufacturing of sub-standard products which are exploiting "niche market" left open by companies complying to WHO recommendations.
- Information on marketing practices for antimalarial medicines in endemic countries is highly fragmented and there is a need for collecting and comparing multiple sources of information to ensure reliable monitoring of progress in this area.

### **3. The experience of Benin in the withdrawal of oral artemisinin monotherapies (Professor Dorothee Kinde-Gazard)**

Malaria is a major public health problem in Benin, representing 41% of all reported diseases, and the main cause for outpatient visits and hospital admissions. Annual incidence in all age groups is 122.9‰ (infants: 425‰; children from 1–4 years old: 216‰) and the case fatality rate of severe malaria lies above 15%. In the period from 1998–2002 failures to chloroquine treatment were documented and the national malaria treatment guideline recommends treatment of:

- uncomplicated malaria with artemether-lumefantrine or artesunate-amodiaquine;
- severe malaria with quinine; and
- pre-referral treatment of severe malaria with artesunate suppositories or artemether injections.

To obtain the withdrawal of oral artemisinin monotherapies, a consensus meeting was organized on 14 March 2006, inviting participants of the National Malaria Control Programme (NMCP), the MoH Direction of Pharmacy and Medicine, WHO, the medical and pharmacist associations and representatives of the private pharmaceutical sector, suppliers and wholesalers. The objective of this meeting was to give an overview about all antimalarial medicines available in the private sector and to define a process for the progressive withdrawal of these drugs from the market. During the meeting, challenges regarding ACT availability, supply, access, coverage and use as well as price levels were identified. The need for a transitional period, giving all involved parties the chance to adopt the new regulation, as well as the need for information and training campaigns for drug

sellers were stressed. The NMCP, during the transitional period, should promote the co-blistering or co-administration of artemisinin derivatives with other effective antimalarials as long as fixed-dose combinations are not yet available to the public sector on a large scale.

Currently, ACTs in public sector health facilities cover only four out of the 12 health departments (Mono, Couffo, Zou, Collines); in addition, in the health departments of Mono and Couffo, ACTs are used in pilot projects at community level. Artemisinin monotherapies are still widely available in private pharmacies. The main problem in Benin is to ensure availability of and access to ACTs on a large scale before the withdrawal of monotherapies on the market. Sustainable financial mechanisms, cooperating closely with key partners as e.g. GFATM, World Bank, WHO, UNICEF, USPMI and others, should be established to guarantee the uninterrupted supply of ACTs at affordable prices.

#### **4. Strategies to contain the use of oral artemisinin monotherapies in Pakistan (Dr Faisal Mansoor)**

Malaria, after acute respiratory infections (ARI), represents the second priority disease in Pakistan. Malaria incidence is highest in the Western parts of the country (more than 3.5 Annual Parasite Index (API)), whereas the Eastern parts are less affected (less than 0.5 API). As a tendency, overall parasite incidence slightly decreased during the period of 2004–2006, with seasonal increase of *Plasmodium falciparum* in the months of July until December and a clear peak in September.

Due to wide spread clinical diagnosis and marginal use of RDTs and microscopy, the majority of malaria treatments was administered to non-malaria fevers. In 2004, a huge discrepancy between the number of confirmed malaria cases (approx. 128,000) and the number of probable malaria cases (more than 8 million detected by community health workers and peripheral health facilities) was detected. As a result, of the large over-consumption of antimalarial medicines it is estimated, that nearly half of the Pakistani population takes antimalarial medicines each year.

The last drug resistance monitoring survey, conducted in 2004, showed high levels of failure rates against chloroquine, amodiaquine and in one place also against sulfadoxine-pyrimethamine. These alarming results induced a change of the national malaria drug policy in 2005, but the ACTs are not yet being deployed in the public sector.

A series of steps have been undertaken to withdraw the marketing authorization of oral artemisinin-based monotherapies in Pakistan:

- The Directorate of Malaria Control (MC) requested the national drug regulation authority (NDRA) on 28 December 2006 (with reminder on 13 January 2007) to ban the production and use of artemisinin-based monotherapies. The National Drug Controller on 16 April 2007 informed the national pharmaceutical companies about its plans to convene a meeting to discuss the ban.
- Representatives of 14 pharmaceutical companies producing monotherapies attended the meeting on 5 May 2007. During the meeting the important role of the pharmaceutical industry as partner – not competitor – of the MoH was recognized and a transitional period to phase out monotherapies as well as the need for an accelerated registration process of ACTs was agreed.

- An ad-hoc group was formed with representatives from MC, NDRA and the pharmaceutical sector. Key decisions taken during the meeting of this group on 28 May 2007 comprised: i) halting of monotherapy production within a six months period (1 June 2007–30 November 2007); ii) as of 31 March 2008, no monotherapies, but only ACTs will be available on the market; iii) grant transitional phase to manufacturer's to adopt new regulations (e.g. allowing the use of premixed combination raw material until the availability of stable combinations); iv) fast track registration of ACTs.
- The Federal Ministry of Health Drug regulatory Board, which ratified these decision points, posted them on the internet on 8 August 2007 ([www.dcomohgov.pk](http://www.dcomohgov.pk)).

The halting of production and use of monotherapies was an integral part of the policy changes made in Pakistan. At the same time, malaria diagnosis, even at most peripheral level, will be encouraged by: i) the establishment of new microscopy centres and strengthening existing ones; ii) the adoption and use of RDTs; iii) capacity building of microscopists and lab technicians; iv) the development of a Quality Assurance System for malaria microscopy and RDTs; and v) strengthening of federal and provincial reference labs. Likewise, as part of the introduction of the new National Treatment Guidelines, case management is improved by: i) adoption of ACT (artesunate+sulfadoxine-pyrimethamine which is not produced in the country) and the decentralization of procurement; ii) the development of training guidelines and the improvement of skills of care providers; and iii) the involvement of private and corporate sectors.

Despite the promising steps taken in Pakistan, there are still several challenges ahead. Compliance to the regulatory decisions should be carefully monitored and the Essential Drug List should be updated at all levels, with inclusion of ACTs because this is the basis for procurement of medicines by provincial health authorities. The use of antimalarial drugs in the private sector and the extension of diagnostic facilities to remote health facilities are necessary. Sustainable availability of ACTs at all first level care facilities must be ensured and the adherence to Good Manufacturing Practice by all manufacturers for guaranteeing minimum quality standards of medicines is indispensable.

## **5. Factors affecting the public sector market for ACTs** **(Jacques Pillay)**

Public sector market. Currently, 70 out of 78 countries in need have adopted ACTs in their treatment policies, among them, 45 are deploying ACTs mainly due to a general lag time of 12 to 24 months between the country's ACT adoption and the implementation. All new antimalarial products expected until the year 2011 are ACTs.

Procurement. Table 5.1. shows that procurement of ACTs for the public sector on a global level was relatively low in 2001 and 2002. It started to increase slightly in 2003 (1.3 million Tx) and 2004 (3.6 million Tx). However, the total need of artemether-lumefantrine in 2004 could not be satisfied, mainly due to inadequate supply of artemisinin in relation to increasing demand. In 2005, a strong increase in the procurement of ACTs was noticeable, that nearly quadrupled in 2006. Estimates for 2007 are expected to sum up to a total of approx. 124 million treatment courses.

**Table 5.1. ACT procurement from 2001 to 2007**

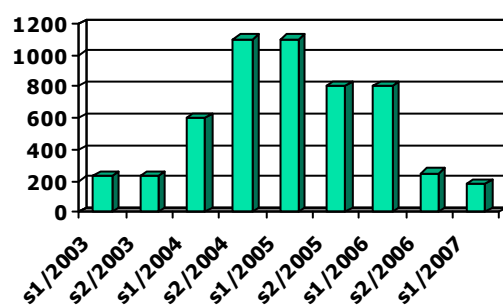
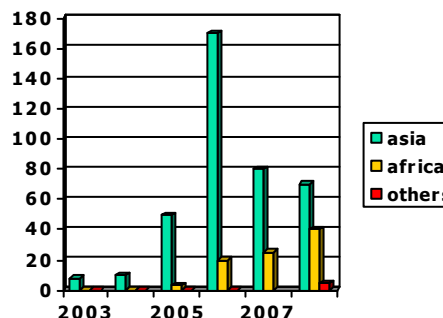
	2001	2002	2003	2004	2005	2006	2007f
AS	155 800	39 120	1 682 600	1 540 200	5 617 800		
A/L	227 503	82 873	1 339 346	3 626 670	10 468 712	61 406 282	94 000 000
AS + AQ					10 048 719	14 446 246	20 000 000
AS + SP					2 298 000	6 671 212	10 500 000
AS + MQ						251 000	300 000
<b>Total ACTs</b>	<b>227 503</b>	<b>82 873</b>	<b>1 339 346</b>	<b>3 626 670</b>	<b>22 815 431</b>	<b>82 774 740</b>	<b>124 000 000</b>

(AS: artesunate; A/L: artemether/lumefantrine; AQ: amodiaquine; SP: sulfadoxine-pyrimethamine; MQ: mefloquine)

**Funding.** The public sector depends mainly on public financing: In 2006, the GFTAM covered approx. 85% of the overall ACT purchase. The remaining 15% were covered by other funding agencies, e.g. USPMI or the World Bank Booster Programme. The new funding initiative UNITAID might play a strategic role in the future: to date their allocated funds add up to US\$ 52 million and it has a strong interest in funding a global ACT subsidy (renamed in September 2007 to "Affordable Medicine Facility for malaria").

**Demand for artemisinin-based pharmaceuticals.** ACTs remain a small share of the total antimalarial market. In 2006 the total volume of demand was estimated at 546 million treatments, of which 140 million treatment courses went to the public (ACTs: 82–90 million) and 406 million to the private sector (ACTs: 8–10 million; artemisinin-based monotherapies: 25 million).

**Prices, offer, demand.** Following the global shortage of Coartem® in 2004 and the consequent sharp increase in the price of artemisinin (from US\$ 230/kg in 2003 to US\$ 1,100/kg in 2004–2005) there has been a major expansion of plantations (e.g. Nigeria, Ghana, East Africa and Madagascar) and of artemisinin producers in China (10 producers in 2004, more than 80 in 2006), Viet Nam (3 producers in 2004, 20 in 2006) and East Africa in 2006 (Fig. 5.2.). The mismatch between increased offer and tempered demand for ACTs in the public sector (to which also the low approval rates in GFATM rounds 5 and 6 have contributed), created a major reduction in the price of artemisinin (currently at US\$ 180/kg, below the production costs). The consequent withdrawal of farmers and artemisinin producers from this market will create a reduction of the artemisinin inventory for 2007, with high risk of ACT shortages in 2008–2009.

**Figure 5.1. Artemisinin prices (US\$/kg) over time****Figure 5.2. Estimate of artemisinin dry leaves production (metric tonnes)**

Cost drivers. The price of artemisinin is influenced by many different factors. To make cultivation of the *Artemisia annua* plant still profitable for growers, prices for dry leaves should not go beyond certain levels. Likewise, the content of artemisinin substance in the leaves may vary due to agronomic factors, and it is also affected by storage. Artemisinin costs for extraction from the dry leaves as well as its purification require investments from the manufacturers in facilities and equipment. Processes should be efficient to guarantee yield and a high level of quality.

The future. The extraction from *Artemisia annua* plants will remain during the next years; before 2011, at the earliest, no new sources of artemisinin for ACTs are expected. Results of the studies on high yield seeds are not expected before 2010. Investment in new extraction processes should be required, as the efficiency and safety of current extraction is not satisfactory with the present conditions. Overstock and low prices in 2007 may lead to further withdrawals from producers and thus the risk of a new shortage in the two coming years. The implementation of high quality artemisinin safety stocks is needed. Prequalification, not only on the production but also on the API producers' level, should be strengthened to guarantee good quality and fair competition between the producers. To minimize financial risks, reliable forecasts before the planting season, covering two years, are needed, to allow ACTs producers to contract with upstream.

New products. Up to 2006, only artemether-lumefantrine and other co-blistered ACTs were available; in 2008 several new fixed-dose combinations will appear in the market: The Drugs for Neglected Disease Initiative (DNDi) is developing artesunate-amodiaquine and artesunate-mefloquine combinations and the Medicines for Malaria Venture (MMV) is developing pyronaridine-artesunate, chlorproguanil-dapsone-artesunate (CDA), and dihydro-artemisinin-piperaquine (results likely in the period from end 2007 till the beginning of 2009). By 2008–2009, fixed-dose combinations (artesunate-naphthoquine, artesunate-piperaquine) are also expected to be available in the market at internationally recognized regulatory standards.

## **6. WHO prequalification of antimalarial medicines (Dr Lembit Rågo)**

The 5<sup>th</sup> invitation to manufacturers of antimalarial medicines to submit their Expression of Interest (EOI) was launched in June 2007 and it includes a wider range of drugs, specifying recommended dosage forms and strengths:

- Artemisinin-based fixed dose combination or co-blistered oral formulations for adults:
  - artemether + lumefantrine (tablet 20 mg + 120 mg);
  - artesunate + amodiaquine (tablet 50 mg + 153 mg (200 mg));
  - artesunate + mefloquine (tablet 50 mg + 250 mg);
  - artesunate + sulfadoxine/pyrimethamine (tablet 50 mg + 500 mg + 25 mg).
- Artemisinin-based fixed dose combination or co-blistered oral paediatric formulations:
  - artesunate + amodiaquine;
  - artesunate + mefloquine;
  - artesunate + sulphadoxine-pyrimethamine.

- Artemisinin-based single ingredient formulations:  
artemether (oily injection 80 mg/ml; 80 mg/ml);  
artesunate (powder for injection 60 mg (vial));  
artesunate (suppositories 50 mg; 100 mg; 200 mg; 400 mg);  
artesunate (tablet 50 mg; 100 mg).
- Other antimalarial medicines:  
amodiaquine (tablet 153 mg (200 mg));  
mefloquine (tablet 250 mg);  
sulphadoxine + pyrimethamine (tablet 500 mg + 25 mg).

Since 2003, there are several pre-qualified antimalarial products available: two artesunate 50 mg tablets, artemether-lumefantrine 20/120 mg tablets and artemotil 50 mg/ml and 150 mg/ml for injection. (One week after the meeting, three further pre-qualified products were added to the list: artesunate 50 mg tablets, amodiaquine 150 film-coated tablets and artesunate + amodiaquine 50 mg + 150 mg tablets.)

In addition, as of mid 2007, there are several combinations in the pre-qualification pipeline: artesunate-amodiaquine (fixed dose combination (FDC) tablets), artesunate + sulfamethoxypyrazine/pyrimethamine (CoB tablets), artemether-lumefantrine (generic FDC tablet), artesunate+mefloquine (tablets in CoB, paediatric FDC pellet formulation), artesunate (injectable) and artemether (injectable).

All above information regarding the Pre-qualification Programme can be found on the internet: <http://mednet3.who.int/prequal/>. Since a few months, to increase transparency, the status of product dossiers under assessment in the WHO Pre-qualification Programme can be derived from this web page.

The absence of originator products is a challenge to the pre-qualification of artemisinin-based antimalarial pharmaceuticals, as generic companies do not dispose of the reference standards, approved by stringent drug regulatory authorities, to prove bio-equivalence of their products against. The most common problems seen during the pre-qualification process of antimalarial medicines are challenges in GMP (both for finished dosage forms as well as API), quality of data in the dossier (above all on specifications, stability data, etc.) and poor information on clinical and safety data related to the manufactured product. However, if all the required documentation is properly elaborated and submitted, pre-qualification of antimalarial products could be realized in an estimated three-month period.

## **7. WHO/UNICEF procurement of ACTs** *(Dr Ahmed Bellah)*

WHO/UNICEF joint procurement of ACTs was initiated in 2003. At present, the list of available antimalarial products for WHO/UNICEF procurement comprises:

- Artemether-lumefantrine (Novartis);
- Artesunate + amodiaquine (Guilin, Ipca, Strides);
- Artesunate + sulfadoxine-pyrimethamine (Guilin, Ipca);
- Artesunate + mefloquine (Mepha);

- Artemether injectable forms (Dafra, Strides);
- Artesunate injectable forms (Guilin);
- Artesunate rectal preparations (Mepha).

Currently, WHO and UNICEF are preparing a joint Request for Proposal (RFP-DAN-2007-500332) for the procurement of ACTs in 2008. Acceptable products have to meet a set of criteria:

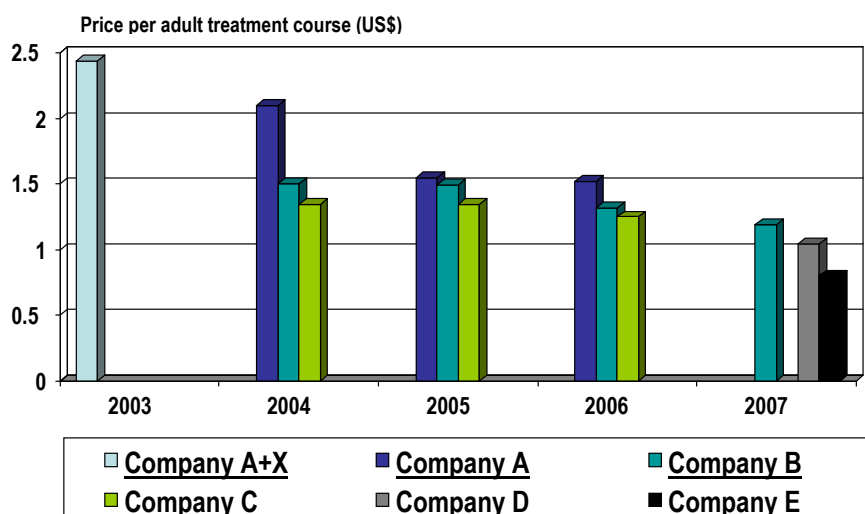
- Compliance with *WHO Guidelines for the Treatment of Malaria* (i. e. product selection, dosage, treatment regimens, strength formulation, therapeutic indication);
- GMP compliance certified by WHO or stringent drug regulatory authority;
- Evaluation of the Interagency Pharmaceutical Product Questionnaire and support documentation submitted by the supplier on the following:
  1. registration information,
  2. regulatory (licensing) situation,
  3. finished product specifications and compliance with international
  4. pharmacopoeial standards,
  5. stability testing data (both accelerated and real time studies in Zone IV),
  6. labelling information,
  7. active pharmaceutical ingredient (API) characteristics and certification.

The new tender will also include as new element the submission of the Product Dossier to the WHO Prequalification programme.

Review of the documentation submitted by suppliers is effected by a WHO Team consisting of GMP, QSM and Procurement Services. The recommendations of the team are presented to the respective Contract Review Committee for endorsement. On behalf of each Organization Letters of Long Term Agreement (LTA) will be issued to the selected suppliers and the products will then be indicated on the RBM website respectively in the Organization's WebBuy Catalogue (product list available on: [www.who.int/malaria/pages/performance/antimalarialmedicines](http://www.who.int/malaria/pages/performance_antimalarialmedicines)). This WHO/UNICEF-approved list of ACTs is used as reference list to guide procurement by other entities such as the World Bank, USPMI.

The market effect of tenders can be illustrated by the example of artesunate + amodiaquine (Graph 7.1.). Over the past five consecutive WHO/UNICEF tenders a substantial reduction in prices has been obtained for this combination. In 2003, when no co-blistered product was available on the market, the total price for the two components was at US\$ 2.44/treatment course. The prices for the co-blistered products started at a range of US\$ 2.10–1.35 in 2004 and went down to US\$ 1.52–1.25 in 2006. In 2007, two companies did not respond to the WHO/UNICEF tender, but two new companies responded. Prices currently range between US\$ 1.19–0.80 per adult treatment course; compared to the lowest price valid in 2005, this represents a price reduction of 20%.

**Graph 7.1 – AS + AQ price reduction over five consecutive WHO/UNICEF tenders (price per adult treatment course (in US\$) from 2003 to 2007)**



## 8. The Global Fund: Quality Assurance Policy for Pharmaceutical Products (Dr Joëlle Dauviaud)

Being a financial institution, about 49% of grant funds of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) are for medicines' and health products' procurement. Though the GFATM is not a procurement agency, it elaborates procurement policies for quality assured medicines and health products. It is the Principal Recipient's (PR) responsibility to ensure adherence to GFATM quality assurance and quality control requirements.

The Global Fund's Quality Assurance Policy considers i) multi-source pharmaceutical products (off-patent products with standards available in the public domain like e.g. International Pharmacopoeia, the British Pharmacopoeia or the United States Pharmacopoeia) and ii) single- and limited-source pharmaceutical products (standards are not publicly available in an International Pharmacopoeia and the products tend to be available from only one or a limited number of manufacturers). Single- and limited source products are classified based on pre-qualification-, GMP- and registration-status by stringent regulatory authorities: option A, B, Ci and Cii.

- A-classified product: WHO Pre-qualification;
- B-classified product: stringent NDRA approval;
- Ci-classified product: GMP certificate issued by a stringent NRA or WHO Pre-qualification letter certifying the compliance of the manufacturing site with WHO GMP requirements and proof of dossier submission to either WHO pre-qualification programme or to NDRA for registration;
- Cii-classified product: GMP certificate issued by a stringent NRA or WHO certifying.

Most of the antimalarial medicines are considered to be single-source or limited source products belonging to category Ci. GFATM financed procurement of limited- and single-source products should be as follows: as a first choice, Options A or B-products should be procured, if two or more products in the same category are available. Second Option is Ci and third Option could be Cii products. Procurement under option Ci or Cii, however, is supposed to be time-limited and recipients shall revert to options A or B as soon as two or more suppliers become available.

The GFATM is currently introducing a new system for compulsory quality control testing. This system is based on sampling at the manufacturing sites and testing in registered qualified laboratories. Conditions and procedures of testing vary depending on the source respectively classification of the product (Table 8.1.); for Ci and Cii classified products pre-shipment testing by the SGS Laboratory (Belgium) is mandatory.

**Table 8.1. The GFATM quality control project of pharmaceutical products**

Quality control test	Multi-source pharmaceutical product and single- and limited-source products complying with Option A or B	Single- and limited-source products complying with Option C (Ci and Cii)
Responsibility	PR or sub-recipient, cost may be included in the GFATM grant budget	GFATM Secretariat, paid by GFATM secretariat
Condition	In accordance with Good Procurement Practice	1. Notification submission by PR to GFATM 2. No Objection by GFATM
When	After receipt of drugs at country level	Before any shipment of drugs to the country
Frequency	At random	Mandatory for all Purchase order (PO)
Laboratory	To be selected by PR, WHO pre-qualified laboratory or recognized NCL when possible	SGS Laboratory (Belgium) contracted by GFATM
Technical procedures	To be defined by the PR and selected laboratory	Listed in SGS-GFATM contract (see in FAQ)
All details in FAQ: <a href="http://www.theglobalfund.org/pdf/guidelines/QCTestingPharmaceuticalProducts.pdf">http://www.theglobalfund.org/pdf/guidelines/QCTestingPharmaceuticalProducts.pdf</a>		

## 9. Introduction of WHO's planned next steps to progressively cease the marketing of oral artemisinin monotherapies (Dr Andrea Bosman)

The phasing out of oral artemisinin monotherapies has taken a long period of time even by those manufacturers that declared intentions to comply with WHO recommendations in April 2006. Several reports have been received by WHO documenting that these products were still largely on the market in many African countries as of January and February 2007. Because of the nature of the private sector market where products are sold through multiple importers, wholesalers and distributors, without national laws which prohibit imports and active programmes for product recall, it takes time for the progressive removal of the products from the market once the manufacturing and marketing have been suspended.

Many companies make inappropriate use of WHO name and logo for commercial purposes, often printing on the secondary packaging or promotional materials (pamphlets, posters, bill-boards, etc.) statements as "recommended by WHO", often accompanied by the display of the WHO logo/emblem. The use of the WHO name and emblem is governed by the resolution WHA1.133, approved by the First World Health Assembly, which resolved that the name and emblem of the Organization cannot be used without authorization by the

Director-General, especially when a possible use is considered for commercial purposes. Most Member States of WHO have specific legislation to protect the name and emblem of the Organization. The Director-General generally refuses permission of using WHO name and/or emblem if there appears to be a possibility such use might imply WHO support of commercial interests.

In addition, there are specific *WHO Guidelines on Interaction with Commercial Enterprises*, which on paragraph 48 state that:

*WHO's name and emblem are recognized symbols of integrity and of assurance to the public. No commercial enterprise shall be authorized to use WHO's name or emblem for the promotion, advertisement or marketing of its products or services. Use of the name or emblem in all other circumstances involving commercial enterprises or trade associations representing commercial enterprises must always be cleared with the Office of the Legal Counsel, in particular when the name or emblem is to be used in conjunction with other names or logos to indicate joint work or ownership.*

The artemisinin-based pharmaceutical products on the market in malaria endemic countries show significant heterogeneity of quality, with several products not meeting international quality standards (drug content, stability, preservative efficacy, degradation products, etc.). Counterfeits of artesunate, artemether, dihydroartemisinin, and more recently of dihydroartemisinin-piperaquine, have been detected in South-East Asia and in several countries of Africa. Increasing number of scientific papers are being published to report on quality control survey of products in the market, as well as reports on counterfeits, including communications through the general media. Most of the evidence on products not meeting quality standards and presence of counterfeits is not in the public domain, but it is generally available to individual manufacturers who, on a regular basis, evaluate the quality of competitor products in the market and validate/monitor claims of counterfeits/substandard of their own products.

The efforts on the international community to phase out oral monotherapies will not succeed without the collaboration of responsible pharmaceutical companies. Over the last year several manufacturers have already reported to WHO, under confidential cover, useful information on problematic marketing practices and laboratory analysis results for artemisinin pharmaceutical products. The Global Malaria Programme of WHO proposes to companies present at the meeting to agree on a "Code for Artemisinin Marketing Practices" (CAMP), based on the following elements:

1. Phasing out oral artemisinin monotherapies and marketing medicines in line with the *WHO Guidelines for the Treatment of Malaria* (2006);
2. Manufacturing site compliant with Good Manufacturing Practices, certified by the WHO or a stringent drug regulatory authority;
3. No misuse of WHO name/logo for commercial purposes; and
4. Reporting to WHO under confidential cover evidence of bad marketing practices, substandard or counterfeit products in the market.

Reports to WHO must be in writing (fax or e-mail) and include the following:

- Identity of the **reporter**, with fax or e-mail address for correspondence (the identity of the reporter will be kept confidential by WHO)
- Identity of **the company** which is alleged in breach of the CAMP and the name of any product or **products** which are specifically involved
- Specific reference to the source of the **advertisement/activity/test** and copy of the material in question provided to WHO
- **Date of the event**, allegedly in breach with the CAMP
- **Summary** of the findings

Reports to WHO in relation to CAMP, should be addressed under confidential cover to: Director WHO Global Malaria Programme, attn. GMP/SCM Unit, Av. Appia 20, 1211 Geneva, Switzerland, Fax: +41 22 791 4824, e-mail: [schwartes@who.int](mailto:schwartes@who.int). Within 30 days from receipt of the report and documentation, WHO/GMP will investigate the case with the company in question, asking what action has been/will be taken to remedy the matter. WHO will make available the information collected on status of implementation of the CAMP, through its website ([www.who.int/malaria](http://www.who.int/malaria)), the printed media, and annual progress reports to be shared at meetings with manufacturers.

This system of self-regulation of marketing practices and voluntary reporting to WHO is expected to increase the capacity of monitoring pharmaceutical practices in endemic countries and to better enforce the phasing out of these products by the national drug regulatory authorities. All companies present at the meeting accepted to comply with the code and to increase collaboration with WHO in providing the requested information.

## ANNEX II

### *List of participating companies*

#### **AJANTA PHARMA LTD**

Ajanta House  
Charkop, Kandivli (W)  
Mumbai 400 067  
INDIA

*Representative:*

Mr Mani KURIAKOSE,  
Senior General Manager

#### **ALCHEM INTERNATIONAL LTD**

25/2, Mathura Road, Village Kaili  
Ballabgarh, Haryana -121 004  
INDIA

*Representatives:*

Ms Kavita KHANNA,  
Sr. Vice President-Marketing  
& Business Development  
Mr Bharat MEHTA, Vice President  
Mr Raman MEHTA

#### **AUM HEALTH+CARE**

B-29/4, D.S. Ramesh Nagar  
New Delhi-110015  
INDIA

*Representatives:*

Mr Umeysh BHASIN, C.E.O.  
Ms Shalini BHASIN

#### **CIPLA LTD**

Mumbai Central  
Mumbai 400 008  
INDIA

*Representatives*

Mr Shailesh PEDNEKAR, Exports  
Mr William F. HADDAD

#### **DAFRA PHARMA**

Slachthuisstraat 30/7  
2300 Turnhout  
BELGIUM

*Representatives:*

Mrs Caroline JANSEN, Consultant  
Mr Bruno JANSEN, CEO  
Dr FH JANSEN  
Mr Edwin MINCKE, Export Manager

#### **DENK PHARMA GmbH & Co. KG**

Prinzregentenstr. 79  
81675 Muenchen  
GERMANY

*Representative:*

Mr Frank ZIMMERMANN,  
International Sales Manager

#### **ETDZS INDUSTRY LTD. CHONGQING**

A2 Jingxin Garden, Golden Burg,  
23 Huayi Rd, Yubei Dist.  
Chongqing  
CHINA

*Representative:*

Mr Zhimin YIN, General Manager

#### **GENIX PHARMA (Pvt) Ltd**

44,45-B  
Korangi Creek Road  
Karachi - 75190  
PAKISTAN

*Representative:*

Mr Ch. Muhammad ISRAR SHARIF,  
Managing Director

**HELIX PHARMA (Private) Ltd.**

Hakimsons House  
A-56, S.I.T.E.,  
Manghopir Road,  
Karachi 75700  
PAKISTAN

*Representative:*

Mr Naveed Nawazish ALI HAKIM,  
Managing Director

**BEIJING HOLLEY-COTEC PHARMACEUTICALS CO., LTD.**

Room 1602, Full Tower  
No. 9 Dong San Huan Zhong Road  
Chaoyang District  
Beijing 100020  
CHINA

*Representative:*

Mr Claude FAURANT,  
Senior Vice President

**HOLLEY PHARMACEUTICALS (Chongqing) Co. Ltd**

12/F, 76 Jianxin Road North  
Jiangbei District  
Chongqing 400020  
CHINA

*Representative:*

Mr Charles LU, President

**HOVID Bhd.**

121 Jalan Tunku Abdul Rahman  
30010 Ipoh, Perak  
MALAYSIA

*Representative:*

Ms Ming-Chui YEW,  
Business Development Manager

**KUNMING PHARMACEUTICAL Corp.**

No. 166 Keyi Road  
Kunming 650 106  
CHINA

*Representatives:*

Mr Li YONGQIANG, President  
Mr Xu SHUGUANG, Vice President of  
Institute for Drug Research & Develpt  
Ms Yu ZELIN,  
Director International Trade  
Mr Yang SHANGHUA,  
Sales Manager, International Trade

**LACHIFARMA**

S.S. 16 Zona Industriale  
Zollino (LE)  
ITALY

*Representative:*

Dr Gianluca FASIELLO,  
Quality Assurance

**MEPHA Ltd.**

Dornacherstrasse 114  
P.O. Box 445  
4147 Aesch BL  
SWITZERLAND

*Representative:*

Dr Dieter MEPIEL,  
International Product Manager Malaria

**NOVARTIS**

Lichtstrasse 35  
4002 Basel  
SWITZERLAND

*Representative:*

Mr Hans RIETVELD,  
Director Global Access & Marketing  
Malaria Initiatives

**PLETHICO PHARMACEUTICALS Ltd**

1st Floor, Crimpage Corporation  
Plot No.57, Street No.17  
MIDC, Andheri (East)  
Mumbai 400 093  
INDIA

*Representative:*

Mr K.R. KRISHNAN,  
Assistant Vice President

**REMEDICA Ltd**

Limassol Industrial Estate  
Aharnon St.,  
P.O.Box 51706  
3508 Limassol  
CYPRUS

*Representatives:*

Mr Charalambos PATTIHIS,  
Group Managing Director  
Mr Emilios SAVVIDES,  
Managing Director

**SANOFI-AVENTIS**

74-82, avenue Raspail  
94255 Gentilly Cedex  
FRANCE

*Representatives:*

Associate Vice-President,  
Medical Access to Medicines  
Mr René CAZETIEN, Director,  
Sales Operations Access to Medicines

**SAOKIM PHARMA**

Quang Minh Industrial Park  
Me Linh dist., Vinh Phuc Pro.  
VIET NAM

*Representatives:*

Mr Duong NGOC VAN,  
Vice General Director  
Prof. Achille BENAKIS, Consultant

**SHANGHAI FOSUN PHARMACEUTICAL (Group) Co., Ltd**

No. 2 East Fuxing Road  
Shanghai 200010  
CHINA

*Representative:*

Dr FENG Xiaojie,  
Director Global Cooperation

**SHELYS PHARMACEUTICALS Ltd**

Sumaria Group (T) Ltd  
Sumaria House, Band Street  
P.O. Box 3016  
Dar es Salaam  
UNITED REP. TANZANIA

*Representative:*

Mr Dipen SHAH, Executive Director

**SWISS PHARMA NIGERIA Ltd**

5, Dopemu Road, Agege  
P.O. Box 463, Ikeja, Lagos State  
NIGERIA

*Representatives:*

Mr Abbas S. SAMBO,  
Pharmaceutical Director  
Mr Mopa E. ESUGA, Pharma Technical  
Operations & Manufacturing Manager  
Mrs Monica U. AGU,  
Quality Manager/Supt Pharmacist

**ZENUFA GROUP OF COMPANIES**

B.P. 15110, Kin 1, No.3  
Avenue des entrepôts, Kingbwa  
Kinshasa  
DEMOCRATIC REP. OF CONGO

*Representative:*

Mr Satnam Singh ALAG,  
Director General

## ***Invited speakers***

### **Ms Joëlle DAVIAUD**

Technical officer Pharmaceutical QA  
The Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM)  
Chemin Blandonnet 6-8, 1214 Vernier, Geneva  
SWITZERLAND

### **Dr Dorothée KINDE-GAZARD**

Professeur Agrégé de Parasitologie (et ancien ministre de la Santé du Bénin)  
Faculté des Sciences de la Santé  
Université d'Abomey Calavi  
Cotonou  
BENIN

### **Dr Faisal MANSOOR**

Director  
Directorate of Malaria Control  
Ministry of Health  
Islamabad  
PAKISTAN

### **Mr Jacques PILLOY**

Office Technique d'Etudes et de Coopération Internationale (OTECI)  
Artepal Project Manager  
Paris  
FRANCE

## ***Observers***

### **Ms Bianca KAMPS**

UNICEF Supply Division  
Copenhagen  
DENMARK

### **Ms Atieno OJOO**

UNICEF Supply Division  
Copenhagen  
DENMARK

### **Dr François SUGNAUX**

Société AFRIQUE DÉVELOPPEMENT  
Dakar  
SENEGAL

### **Dr Jan VAN ERPS**

Roll Back Malaria Partnership Secretariat (RBM)  
Geneva  
SWITZERLAND

## ***World Health Organization Secretariat***

**Mr Paul-A. ACRIVIADIS**, Coordinator Contract and Procurement Services (CPS)

**Dr Ahmed BELLAH**, Procurement Officer, Drugs and Biological Procurement (DBP)

**Dr Andrea BOSMAN\***, Medical Officer GMP/Case Management and Research (CMR)

**Dr Arata KOCHI**, Director, Global Malaria Programme (GMP)

**Dr Jacob KUMARESAN**, Special Adviser to Dir/GMP and Coordinator SCM

**Dr Hiroki NAKATANI**, Assistant Director-General for HIV/AIDS, Tuberculosis and Malaria

**Dr Peter OLUMESE**, Medical Officer/Scientist GMP/CMR

**Dr Lembit RAGO**, Coordinator Quality Assurance and Safety: Medicines (QSM)

**Dr Pascal RINGWALD**, Medical Officer GMP/CMR

**Ms Silvia SCHWARTE**, Technical Officer GMP/SCM

**Dr Sergio SPINACI**, Associate Director, Global Malaria Programme

**Dr Amor TOUMI**, Technical Officer, Medicines Regulatory Support (MRS)

*\* Secretary of the meeting*