SUMMARY

Following the previous Artemisinin Conferences in Tanzania, Thailand, China, India and Madagascar, the 2011 Artemisinin Conference was held in Hanoi, Vietnam, a country which has been growing Artemisia annua and extracting artemisinin, for many years.

This year’s conference was entitled “Aligning Artemisinin and ACT Supplies”. This reflected the critical need, not only to achieve higher artemisinin production and more accurate and longer term ACT forecasting, but also to ensure closer coordination and planning between all sectors of the ‘supply chain’ i.e. from artemisinin producers through to the ACT manufacturers, the procurement and funding agencies, to serve the patients in need, in both the public and private sectors. The holding of the ‘Global Fund-ACT Manufacturers’ meeting on the day prior to the Artemisinin Conference (both held at the Sheraton Hotel, Hanoi), enabled the specific aspects related to the Global Fund to be discussed in detail by the ACT manufacturers, in the presence of representatives from the major international Agencies.

The 2011 Artemisinin Conference came at a time when the relation between artemisinin supply and demand for 2011 is very tight and whilst ACT requirements are increasing, especially following the successful introduction of the AMFm. Global Artemisia annua plantings in 2011 increased considerably compared with 2009 and also 2010, but poor weather during the growing season in China and during planting in Vietnam in 2011, resulted in reduced yields of up to 30% in these countries. The increasing demand for ACTs and the need for the industry to replenish its artemisinin inventories and API
buffer stocks (to meet the additional needs for 2011 and 2012), has contributed to artemisinin prices rising rapidly over the past year.

Extensive discussions were held and concerns voiced by the ACT manufacturers and artemisinin extractors, as to the need for longer term e.g. min 2yr, and more accurate ACT forecasts e.g. based on actual needs of the top 15 malaria endemic countries. Equally, concerns were raised as to the reasons for the very high prices of artemisinin now being reported and the potential increases of ACT prices reducing access to treatment in a financially constrained environment.

The conference also presented an update on the new technologies and programmes being introduced to increase productivity and efficiencies in both Artemisia production e.g. high yielding seeds, and artemisinin extraction and purification. The latest details on the introduction of semi-synthetic artemisinin was also presented and discussed.

**MAIN OBSERVATIONS AND RECOMMENDATIONS**

There is a need to:

1) Strengthen present global ACT forecasts (developed by the BCG led consortium funded by UNITAID) through the addition of a ‘rolling’ 2nd year forecast (i.e. presently to include 2013), focusing on 15 country generating the highest ACT demand and reflect quarterly trends in changes in demand.

2) Urgently assess the reasons for the present high prices quoted for artemisinin e.g. China leaf costs, production costs, API/ACT manufacturer re-stocking, market speculation.

3) Include all artemisinin demand in the global forecasts, i.e. as well as for approved ACT needs, include actual demand from all countries with major consumption of artemisinin based treatments e.g. India, re-stocking of artemisinin levels by API suppliers, extractors and intermediaries, and the needs of monotherapies and sub-standard ACTs not related to public sector requirements procured with international funds.

4) Report the decision on the future of AMFm and/or exit mechanism, as early as possible to enable adjustments in raw material supply and API/ACT manufacture planning - due to the average 14 month lead time from seeds planted to ACT production.

5) Clarify and regularly update supply/marketing plans, pricing and regulatory requirements of semi-synthetic artemisinin.

6) Provide regular update and support for introduction of high yielding Artemisia seeds and new processing technology.

7) Continue to provide financial support to the artemisinin extractors through the A2S2 project, promoting market intelligence dissemination and the establishment of an Artemisinin Sector Association.

**ACKNOWLEDGEMENTS:**

The conference was organised with the direct support of RBM, UNITAID and WHO, with local assistance from Vedic-Fanxipang Pharma. Appreciation is also given to Novartis and Sanofi-aventis for hosting dinners for the delegates outside the official programme of the conference.

The organisers wish to dedicate the 2011 Artemisinin Conference to our friend and colleague, Dr Ian Bathurst, who sadly and unexpectedly, died this year. He, together
with his colleagues from MMV, did much to further the cause for malaria treatment, including artemisinin development and in particular, the organisation of previous Artemisinin Conferences.

View the 2011 Conference Agenda

A review of the responses, received from the Feedback Forms, is shown in Annex 1 (attached).

Day 1 – Wednesday 2nd November 2011

The conference was opened by H.E. Vice Minister of Health for Vietnam, Dr Nguyen Thi Xuyen, who stressed the need for continuing research and development into new antimalarial treatments and highlighted the role Vietnam has played in the production and supply of artemisinin since it was identified as the primary compound for anti-malaria treatments.

Following the opening of the conference the Keynote Address was presented by Professor Tran Tinh Hien from the Centre for Tropical Medicine, Oxford University Clinical Research Unit Vietnam and provided An Update on Artemisinin Resistance. Professor Hien outlined the serious situation regarding the emergence of artemisinin resistance, based on the new WHO definition, in Asian countries (Cambodia, Viet Nam) but stressed that ACTs can still be used to treat most of patients with high cure rates. However, more research should be carried out to clarify the mechanisms of resistance, the determinants of its origin and spread, and the appropriate containment measures.

REPORTS ON RECENT MEETINGS CONCERNING ARTEMISININ SUPPLY AND ACT FORECASTING:

1) RBM-WHO Roundtable Meeting on ACT Supply – 8th Sept 2011:
   - Prashant Yadav, RBM-PSM Working Group

The meeting was organised following the sudden reported increase in demand for ACTs (to which the success of AMFm had contributed substantially) and the resulting, potential inability to supply both finished products and the required API and artemisinin.

Specifically the Objectives of the Roundtable were to:
- Better understand the ACT demand and supply situation, based upon best available and unbiased information.
- Improve communications among all stakeholders in the ACT supply chain.
- Discuss additional ACT needs arising from any possible emergency or epidemic situations (as is anticipated in the Horn of Africa).
- Agree on a co-ordinated plan of action to address any supply challenges.

It was reported that the original forecasts showed that ACT demand for 2011 was between 287-310m treatments, manufacturing capacity (over a 12 month period) was 320-395m treatments and artemisinin supply equivalent to 250-290, treatments. This shows an approximate balance in supply and demand over the year. However, it was emphasised that this tight balance could create ACT shortages on a country-by-country basis.
The Key Recommendations from the meeting were to:

- Maintain open communication between all major stakeholders in the supply chain.
- Improve forecasting and communication of forecasts to ensure all stakeholders are making decisions on the best information possible.
- Improve systems to increase the flexibility in the supply chain to ensure that ACT supplies reach the countries and places where the need is greatest.
- Gather real-time supply and demand data that will help identify countries where supply may not meet demand (under the leadership of WHO GMP).
- Wider access to and use of diagnostic testing and reduced use of ACTs for non-malarial fevers.

Key Recommendations - Long term

- Analyze the role of buffer stocks of ACTs and APIs to meet sudden emergencies and ensure market stability.
- Explore the technical, legal, and economic feasibility of ACT manufacturers’ request for binding forecasts of ACT demand.

2) Global Fund – ACT Manufacturers Meeting – 1st November, 2011:

- Sophie Logez, The Global Fund

The meeting was held the day before the Artemisinin Conference, at the Sheraton, Hanoi, and therefore the findings from the meeting could then be presented and discussed by the wider audience at the Artemisinin Conference.

The main Objectives of the Global Fund Meeting were to:

- Provide an update on Global Fund policies and processes on procurement and supply management
  - Policies, Quality assurance
  - Procurement information: price and quality
  - Market shaping strategy and Voluntary Pooled Procurement
  - AMFm overview
- Dialogue with manufacturers
  - Feedback
  - Procurement challenges

Historically, the Global Fund has:

- Approved total malaria grants of $6.1 billion (84 planned countries), between 2002-2011 – rounds 1-10
- 28% of malaria grants were for treatment (2009 data)
- Number of treatments delivered were:
  - 2009: 80-90m treatments
  - 2010: 85-105m treatments
  - 2011: 90-105 treatments (estimate)
  - 2012/13: 10m+ treatments/yr (planned estimate)
- In 2010/11, 73% of treatments were Artemether-Lumefantrine, 21% Artesunate-Amodiaquine and 6% other treatments.
The main questions asked and discussed, following the presentation and in the subsequent Break-Out Session, included:

- Plans to respond to stock-outs through a financial and/or physical buffer stock.
- Voluntary Pooled Procurement (VPP) – need to identify necessary policy changes to fully implement VPP.
- With future budget uncertainties and rising raw material and ACT costs, there is an urgent need to fully respond and review these issues in order to ensure a sustainable supply of treatments.
- The future of AMFm needs urgent clarification i.e. before end of 2012.
- Information such as budgets spent and available and global ACT forecasts for Global Fund should be clearly shown on the Global Fund website, as it is currently done for AMFm.

3) UNITAID Consultative Forum – Malaria Recommendations:
   - Johannes Ambachew - UNITAID

The main objectives of the UNITAID Consultative Forum were to:

- Summarize the challenges in malaria that were identified during the “UNITAID Partner Day”.
- Explore the different opportunities in the global health landscape, market and product interventions.
- Identify those opportunities in the malaria arena (prevention, diagnosis and treatment) that fit with UNITAID’s mandate.

Following discussions the overall challenges identified for malaria were:

- Forecasting demand - better country data for treatment and diagnosis.
- Funding sources for products identified & sustainable.
- Engaging manufacturers of ACTs through (partially) binding commitments (orders placed, LTAs).
- Availability and quality of RDTs improved and monitored.
- Recognition of integrated approach to prevention (LLINs), diagnosis (RDTs) and treatment (ACTs).

The actions recommended by the UNITAID stakeholder forum include the following:

- Prevention: Incentives (challenge grants) for improved LLIN products.
- Diagnosis: Bundling RDTs and ACTs to promote rational ACT use.
- Treatment: accelerate market access for new essential products (paediatric formulations and injectable artesunate for severe malaria).

ACT DEMAND FORECASTING:
- Mathieu Lamiaux – Boston Consulting Group (BCG)

The consortium originated from recommendations from the 2009 Artemisinin Conference and the work of the AMFm Ad Hoc Committee, which requested a global demand forecast to understand the impact of the AMFm, superseding the several groups which produced forecasts with differing methods and conflicting results in the past. The BCG consortium includes BCG, CHAI and MIT-Zaragoza, which work together to produce a single quarterly forecast of global ACT demand. UNITAID finances and manages the
The presentation outlined the wide range of sources from which data is acquired, including intermediary sources i.e. programmes funded primarily by international donors for the public sector and consumer, First Line Buyers (FLB) and order approvals in the private sector.

The main conclusions and observations presented were:

- Latest ACT forecast is 287m treatments for 2011 and 295m for 2012 (global consumer demand).
- AMFm Phase 1 countries driving global growth in demand (>60% of global demand).
- Forecast indicates greatest demand for child doses (61%) and AL formulation.
- Recent trends show private sector FLB demand outstripping modeled consumer demand and AMFm deliveries, but following the recent introduction (since August 2011) of “levers” by AMFm secretariat, the trends are stabilizing.
- If order approvals resume at the peak levels observed in April-June, FLB orders for delivery in 2011 could reach 111m treatments and a total 2011 ACT demand of 310m treatments, even under more stringent AMFm order approvals.
- Growing FLB demand contributes to a backlog of deliveries.

Key Recommendations:

- Urgent need for 2013 ACT forecast to identify artemisinin and other API requirements i.e. Artemisia planting end 2011/1st qr. 2012.
- ACT manufacturers request quarterly forecasts based on top 15 malaria endemic countries. Also incorporate variance in order needs e.g. additional variations within the year on a quarterly basis.
- Clarity that artemisinin needs will exceed that for quality ACTs procured with international funds i.e. for other treatments (monotherapies and substandard ACTs), and manufacturer’s needs for buffer/safety stocks.

AFFORDABLE MEDICINES FACILITY Malaria (AMFm) - INTERIM REPORT AND NEXT STEPS:

- Emmanuel Nfor, AMFm/Global Fund

The AMFm is a 24-month multi-country pilot project for the co-financing of ACTs to:

- Sharply reduce retail prices of ACTs in the private sector
- Widely increase access to ACTs in the private, public and non profit sectors
- Delay the emergence of resistance by replacing oral artemisinin-based monotherapies in the pilot countries.

It was reported that by August 2011, in six pilot countries, the percentage of outlets surveyed having AMFm ACTs of “any type” (among the 16 pre-qualified product presentations supplied through this initiative) was between 73% and 100% in the formal private sector and between 27% and 86% in the informal private sector. Prices have fallen dramatically with median prices for AMFm treatments (adult AL treatment course, 20/120mg tablets), across the six countries, being $1.01 compared with $8.13 for the originator branded products and $5.93 for the lowest priced generic (CHAI survey, August 2011).
As of the end of October 2011, total approved ACT orders through the AMFm, since the start in July 2010, were:

- Public – 61.1m
- Private for-profit - 114.2m
- Private not-for-profit – 1.6m

Total = 176.9m

In July 2011 the AMFm Secretariat adjusted its order approval policy by introducing a series of drivers for future order approval (for full list see presentation):

- Conserving co-payment fund
- Closing the gap between approved orders and deliveries
- Promoting the supply of pediatric formulations and pack sizes
- Improving manufacturer performance (in terms of ratio of actual to planned deliveries by a particular date)

An independent evaluation of the AMFm is now being undertaken with all end-line data collection to be completed by January 2012. A decision on whether to Continue, Modify or Terminate the project will then be taken by the Global Fund Board Meeting in November 2012.

Key Findings:

- General feedback from the conference delegates was that the AMFm has been successful and must be continued.
- For continuity, the decision on the future of the AMFm should be made as soon as possible and cannot wait until the Board Meeting in November 2012. If the AMFm is not to continue there needs to be a structured exit mechanism announced well in advance.
- The approval of the orders and ordering schedules, need to be closely integrated into the BCG-led global forecasting programme. This should also incorporate, wherever possible, specific monthly or quarterly variances, predicted in line with changes in order placements and approvals by the AMFm secretariat.
- In addition to the approved orders country by country, the AMFm website should also show the remaining funds available for the approval of pending and additional orders.

**ARTEMISININ SUPPLY, COSTING AND PRICING:**
Jacques Pilloy, RBM/A2S2

The presentation detailed the problems in planning artemisinin production in relation to ACT needs, given the wide range of different ACT forecasts from 2009 to 2011. Through the unified forecasting programme, coordinated by BCG, this has now been significantly improved for 2012, however, longer term forecasts are still required to enable accurate Artemisia plantings and artemisinin production. The prediction for 2012 is that the supply of artemisinin in the order of around 160MT, is considered adequate to meet ACT demand, without considering the volumes required to replenish stocks. The availability of semi-synthetic artemisinin from 2013 will help to ensure sufficient artemisinin supplies but natural artemisinin will still be the main source of production, with around 160MT needed from the 2012 crop, to meet the 2013 ACT production.
The price of artemisinin increased sharply during the 2\textsuperscript{nd} half of 2011, with prices quoted at around $750/kg. The causes of this rise are reportedly due to high dry leaf prices in China (and Vietnam), increased use of low quality wild leaves, higher manufacturing costs, strong demand (restocking) and US$/Yuan exchange rate changes. However, it is also believed that there is presently considerable price speculation and with increasing availability of artemisinin i.e. from the Chinese crop, prices are expected fall over the next months.

**Key Recommendations:**

- 2013 artemisinin demand will have to be met from natural sources and still provide the majority of supply for 2014.
- There is a need to increase production from plantations, end 2011/beginning 2012, particularly in China, to replace poor quality artemisinin supply collected from wild plants.
- In order to bring back prices to a fair level, there needs to be increased artemisinin production above the market needs and mechanisms to contain price speculation.
- Improved production processes are needed and the promotion of high yield seeds.
- Continue to improve links and communication between all parties in the supply chain, especially longer term contracts between ACT/API manufacturers and artemisinin producers.

**GLOBAL ARTEMISININ PRODUCTION REPORTS:**

**CHINA** – Christine Lin, PIDI Standard

It was reported that although artemisinin investment/production in China increased in 2011 compared with 2009 and 2010, and farmer confidence increased, there were many challenges in 2011 including shortages of manpower, competition from other crops, extreme climate changes and competition between extractors for dry leaf (not all extractors invested sufficiently in Artemisia cultivation).

This situation resulted in high leaf prices due to insufficient leaf quantities; low leaf quality due to harvesting leaf early and a high percentage of wild leaves (average artemisinin yield, from 1MT of leaf, has reportedly dropped from 3.5-4.0kg in 2009 down to 3.3-3.5kg in 2011) and a disordered market (not enough leaf cultivation leading to high competition amongst extractors, panic buying and illegal practices). Chinese artemisinin production in 2011 is estimated to be 132 – 140MT.

For 2012 it is expected that the cultivation area will expand but farmers fear that oversupply will lead to a fall in prices. Costs of production are expected to continue to rise (in line with other cost increases in China) and quality may also continue to fall if crops are not allowed to reach maturity and/or there are still large volumes of wild leaf harvested compared to limited investment in plantations.

**VIETNAM** – Bui Minh Ut, Cat Khanh Co.

Artemisia cultivated area in 2011 in Vietnam was reported to be 1,500ha, producing 4,000 MT of dried leaves which, at 4.0kgs/MT and less than 50% processing efficiency, resulted in a total 12-13MT of artemisinin. Leaf prices, due largely to competition (including from China), rose to between $1,000 – 2,000/MT. Note: An additional 5-6MT was also produced from other, new production sources in Vietnam in 2011.
Although the cultivation area increased in 2011, there was no investment in new seeds; extractors in Viet Nam are facing increased competition from Chinese buyers; collection agencies increased prices to extractors and limited coordination and investment between the growers and extractors. Processing technology was also poor, leading to low efficiencies; high processing costs; poor working standards and safety procedures and high borrowing rates (22-24% on local loans). It was also reported that many extractors were not good at marketing their products, partly due to poor language skills and limited direct contact with buyers, leading to a reliance on middle-men and Chinese traders, which also resulted in poor transparency and traceability.

Although it is expected that the cultivation area will increase for 2012, in order for production to improve in Vietnam it was reported that there is a need for new technology and seeds, low costs loans e.g. through A2S2 and greater market linkage with buyers.

**MADAGASCAR** – Charles Giblain, BIONEXX

Bionexx is the sole artemisinin producer in Madagascar and since it started in 2005 it now has over 9,000 out-growers in four regions, a 650ha farm (2010) and three agricultural R&D centres.

In 2011 Bionexx produced 1,000MT of leaf with expansion planned to 1,800MT in 2012, 2,700MT in 2013 and 3,300MT in 2014. Artemisinin production will be 15MT in 2012 (90% committed), 30MT in 2013 (40% committed) and 35MT in 2014 (45% committed).

Madagascar, through Bionexx, is now an established producer of artemisinin with experience with high yielding Artemisia varieties, advanced processing technology and experienced and trained out-growers and own Artemisia production facilities.

**EAST AFRICA** – Patrick Henfrey, Botanical Extracts EPZ Ltd, Kenya

Botanical Extracts EPZ Ltd (BE) in Kenya and AfroAlpine Ltd in Uganda are presently the only artemisinin producers in East Africa. It is planned that artemisinin production in 2012 from both companies will total 15-18MT.

Although Artemisia is a relatively new crop in the region, considerable development has been undertaken with new higher yielding Artemisia varieties and the introduction of a modern artemisinin processing facility (BE). It is therefore believed that East Africa can be a significant contributor to the ACT supply chain, with artemisinin production reaching 30MT by 2013.

The main concerns include the need to insure against drought through irrigated production and limited access to affordable finance e.g. need support as offered through A2S2. Equally all producers need to have regular access to forecasted prices and increased clarity concerning the introduction of semi-synthetic artemisinin and other relevant products and initiatives (including vaccines) which could affect future ACT needs.
ACT AND API PANEL DISCUSSION:
A one hour ‘panel’ discussion was held to discuss and review the 1st mornings presentations. The panel consisted of representatives from ACT manufacturers, donors and procurement agencies. The outcomes of, and recommendations from, these discussions are included in the PROPOSALS FOR ACTION (see below).

TECHNICAL DEVELOPMENTS:

**HIGH YIELDING ARTEMISIA TRIALS** – Xavier Simmonet, Mediplant, Switzerland

Mediplant has 20 years of experience developing Artemisia varieties, cultural/post harvest practices and analytical techniques. They have developed varieties now being widely used in East Africa/Madagascar and are an important partner in the CNAP, York project to develop higher yielding Artemisia varieties.

Mediplant are presently undertaking agronomic trials, both in Switzerland and Madagascar on planting densities (using varieties from CNAP, Mediplant and NIAB), dynamic trials and on direct sowing v’s nurseries. The results have yet to be collated but once available (early 2012) they will be circulated to the artemisinin sector.

**HIGH YIELDING ARTEMISIA VARIETIES** – Dianna Bowles, CNAP, York and Bert van der Feltz, East-West Seeds.

Since 2009 the CNAP, University of York research project has been using the latest genetic and analytical technologies to improve the artemisinin content and yield, of *Artemisia Annua*. Since 2010 over 100 CNAP hybrids have been trialed in 7 different geographical areas (6 countries) with data on second generation hybrids also now becoming available. This has identified a number of ‘front runners’, which will enable different varieties to be recommended for specific growing regions/conditions.

CNAP has recently partnered with East-West Seed, based in Thailand, to produce and market the new varieties. Seed production of the selected hybrids is now being scaled up and bulk seeds of the first generation hybrids will be available from mid 2012. Bulk seed of the second generation hybrids will be available from mid 2014.

**Key Observations on the High Yielding Seeds:**
- It was reported, through the presentations, that commercial trials of the high yielding seeds from CNAP and Mediplant are showing increased artemisinin percentage and dry leaf yields, as are the NIAB, UK seed which are now in commercial production (through reports from growers). However, much has still to be learnt with regard to achieving consistent results and assessing optimum flowering timing i.e. harvest, in different climatic locations.
- Yield potential is closely linked to field management standards.
- Extractors/farmers, particularly in China and Vietnam, largely use their own seed (which is effectively free) and therefore it is essential that examples of the cost/yield benefits of the new varieties are demonstrated as soon as possible e.g. through producer and user trials, to ensure full understanding of the benefits of these new varieties.
ARTEMISININ PRODUCTION TECHNOLOGY:

REVIEW OF ARTEMISININ PURIFICATION TECHNOLOGY – Parag Shah, Elysian Life Sciences (ELS), India.

ELS are cultivating Artemisia and processing artemisinin in Vietnam and East Africa. Therefore, prior to his presentation on purification technologies Parag Shah outlined his experience and observations as to the necessary ‘field practices’ needed to first ensure good leaf yield and quality. These included the choice of production location, use of high quality seed, understanding of seasons and climatic effects and the need for good soil preparation, plant husbandry and post harvest practices.

Whilst the primary extraction of the crude artemisinin from the dry leaves is well understood and most extractors use very similar technology, apart from different solvents, the purification of the crude extract can differ greatly. The presentation compared the traditional process (as used in Vietnam) with the adsorption process, using silica gel (as largely used in China) and the chromatographic process (also using silica gel). No observations were made concerning HFC or other technologies as this was covered in a later presentation.

The main findings presented were that the yield of artemisinin per 1MT of leaf, (at 1% artemisinin content) from the three processes were:

- Traditional process – 4.0kg to 5.0kg
- Adsorbant process – 6.0kg – 6.5kg
- Chromatographic process – 7.5kg – 8.0kg

Further advantages of the chromatographic process included the use of less solvent, faster processing and less resulting impurities e.g. artemisitene and 9-epi artemisinin.

PURIFICATION OF ARTEMISININ WITH HFC 134a – Bhupinder Khambay, Kamtech Technologies Ltd (KTL), UK and Colin Hill, Extraction Technology Developments Ltd (ETDL), UK.

HFC 134a is widely used in refrigerant/air conditioning systems (domestic, commercial and automotive) and for medical purposes e.g. propellant in inhalants. Its properties as an efficient solvent have been known for many years, including its use in the extraction of essential oils. In 2006 a study was commissioned by MMV to explore new solvents for artemisinin and this work resulted in further laboratory trials, by KTL, in 2007/8 and the subsequent scale up to kg scale i.e. commercial application in 2010/11 by KTL and ETDL. Further collaboration is now being undertaken with commercial partners. With the present, urgent, need to improve the efficiency of artemisinin purification the emphasis to date has been on using HFC 134a to purify the crude extract. However, HFC 134a has also been proven as an efficient solvent in extracting artemisinin from the dry Artemisia leaves i.e. primary extraction and therefore with additional development could be applied the whole extraction/purification process.

The advantages of using HFC technology for artemisinin purification were presented as including:

- Fast extraction time
• High recovery rate from the primary extract of >85%
• Low solvent losses (HFC solvent cost is higher than other solvents e.g. hexane)
• Highly flexible i.e. can easily be scaled up.
• Low cost compared with other purification technologies e.g. @ US$400,000 (2 x 500litre extraction vessels, able to isolate >250kgs artemisinin per day.

**DERIVITISATION OF ARTEMISININ** - Alexei Lapkin, University of Warwick, UK

Dr Lapkin has been involved in the research into artemisinin extraction/purification since managing the MMV sponsored “Review of Artemisinin Extraction Technologies” project in 1996. He has subsequently undertaken research into HPLC analytical protocols for artemisinin and into new solvents for artemisinin extraction and purification. Currently the group at Warwick University are:

• Identifying co-metabolites which reduce the yield and purity of crystals from artemisinin and MS analysis which can clearly identify 9-epi artemisinin in the raw extract (with the present HPLC method 9-epi, an impurity, is masked from analysis when using the recommended HPLC protocols).
• Researching new derivatisation technology for the conversion of artemisinin into DHA and tandem conversion of artemisinin into artesunate and arteether in an integrated flow process (covered by patent application). Demonstration units are being developed and Dr Lapkin is now looking for an industrial partner to develop an industrial scale artemisinin derivatisation process under flow conditions.

**KEY POINTS FROM DAY 1** – for further discussions at the Break Out Sessions – Antony Ellman, Conference Rapporteur

**SEMI-SYNTHETIC ARTEMISININ PROGRESS REPORT** – Tue Nguyen, One World Health and Michel Arnoux, Sanofi Chimie, France

The work funded through the Gates Foundation and undertaken by One World Health, Amyris, the University of California, Berkeley and Sanofi, to develop a process to produce semi-synthetic artemisinin, has been regularly presented at previous Artemisinin Conferences.

The Goals for the project are to:
• Create a complementary source of non-seasonal, high-quality and affordable artemisinin to supplement the current plant-derived supply.
• Ensure semi-synthetic artemisinin is available to all qualified derivative manufacturers.
• Contribute to stabilizing the price of ACTs to benefit patients and donors.

It was reported that the project is now in an advanced phase of development with:
• Process development and industrial scale up completed using current capabilities.
• Construction and finalization of final facility on-going.
• Technical transfer to final manufacturing site on-going.

The time lines for the introduction of the final product and planned quantities are:
• Material from the semi-industrial project is now available for testing by potential customers
• Mid 2012 – validation batches around 2.5MT
• End 2012 – 10MT
• 2013 – 40 to 45MT
• From 2014 – 50 to 60MT per year

With regard to pricing Sanofi made assurances that the costs of the semi-synthetic artemisinin will be based on commercial production costs and although not finalized, is expected to be around $400-450/kg – as previously quoted.

**Key Recommendations:**

• ‘Natural’ artemisinin producers are concerned as to how the price will be derived and requested assurances, possibly independently assessed, that it is based on commercial cost practice.

• In order that the natural artemisinin sector can accurately plan future production, it was requested that Sanofi regularly update and disseminate information on actual production plans, dates and also prices i.e. not just at the annual Artemisinin Conference.

• Semi-synthetic artemisinin is seen as a positive initiative to stabilize artemisinin supplies, but in order to ensure future stability throughout the artemisinin sector, its introduction must be handled openly and information be provided so that the natural artemisinin sector can plan accordingly.

**ASSURED ARTEMISININ SUPPLY SYSTEM (A2S2)** - Jan van Duijn, A2S2/i+solutions

A2S2 was introduced in July 2009, following recommendations from the Artemisinin Conference in 2008, to support the artemisinin sector in meeting the increased ACT demand following the introduction of the AMFm and increased procurement through Global Fund grants. The A2S2 programme involved:

• The introduction of an $8m revolving loan facility to help extractors finance additional artemisinin supply (up to 40 Tons over 2yrs) to approved API/ACT manufacturers.

• Support for the development of longer term contracts between artemisinin extractors and API/ACT manufacturers.

• Increase communication and dissemination of market intelligence throughout the sector.

• Close collaboration on the artemisinin requirements with the ACT forecasting consortium.

• Regular updates and dissemination of artemisinin prices and production costs.

After 2yrs A2S2 has:

• Agreed contracts for 36MT of additional, artemisinin (through four extractors) - close to meeting its target of 40 MT for the first Phase of A2S2.

• Helped introduce and develop longer term supply contracts between 4 specific extractors and API/ACT manufacturers. Based on the experience of these contracts it is believed that other longer term contracts have been entered into without the support of A2S2.

• Through visits and contacts with all major artemisinin extractors, API/ACT manufacturers and coordination with the BCG, ACT Forecasting Group, has been able to regularly disseminate market intelligence and other relevant information through the A2S2 website, newsletter and e-mail/telephone contact.

• Identified and regularly disseminated global artemisinin production costs and price information.
A2S2 has recently submitted proposals for an extension of the programme which would continue the extractor loan programme (based on repayments from the 1st project loans); maintain regular visits to and discussions with, extractors and API/ACT manufacturers and increased market intelligence dissemination through more regular e-mail contact, quarterly newsletter and a dedicated website. In addition, following extensive discussions throughout the industry/sector, it is proposed to introduce a Technical Support/Coordination Programme and an Artemisinin Association.

Key Recommendations:
- The work by A2S2 was supported by the extractors and API/ACT manufacturers at the conference, but it was requested that the loan application process be clearer and that the market intelligence gathered by the A2S2 technical experts be disseminated more regularly.
- Support wider global production of Artemisia/artemisinin, to minimise production problems e.g. climatic.
- With rising artemisinin production costs, the need for unbiased and expert advice on new technical initiatives e.g. high yielding seeds and artemisinin processing, to improve efficiencies, is urgently needed and therefore the A2S2 technical support/coordination programme would be welcome.
- There was considerable support for the introduction of both a global Artemisinin Association and also Artemisinin Associations at country level, which could help to raise the overall business standards of the local extractors, through code of best practices/accreditation scheme.

BREAK OUT SESSIONS:

Two, three hour, break out sessions were organised:
1) Stabilising Artemisinin/API/ACT Supply.
2) Technical Issues and Developments

The sessions enabled delegates to discuss, in detail, the main subjects raised by the presentations and/or concerns affecting the artemisinin and API/ACT manufacturing and supply sector i.e. as presented during the 1st days panel session.

Presentations of the Conclusions and Key Findings of the Break Out Sessions:
**Stabilising Artemisinin, API and ACT Supply** – Jan van Erps
**Technical Issues and Developments** – Antony Ellman & Bhupinder Khambay

The outcome of these discussions is also shown in the PROPOSALS FOR ACTION, at the end of this report.

During the break-out sessions it was arranged for three additional presentations to be given on the technical aspects of *Artemisia annua* production and the work undertaken to consider “Artemisinin as a Starting Material”:

**Trials of Artemisia annua with Mycorrhizal Fungi** - Prof Ajit Varma, Amity University, Uttah Pradesh, India

Prof Varma first discovered Piriformospora indica, in 1992, in the Thar desert in Western India. *P. Indica* is a newly described cultivable endophyte that colonizes roots. Inoculation with the fungus and application of fungal culture filtrate, has been shown to
promote plant growth and biomass production.

In trials undertaken by Prof Varma, the use of inoculant from P. Indica has more than doubled the fresh weight gain of crops such as maize, tobacco and parsley and has shown a 2.5 weight gain in Artemisia annua, also resulting in more dark green and less brown i.e. senescent, leaves.

Patents have been taken out on the use of P. Indica on Artemisia annua and Prof Varma now wishes to work with an industrial partner on commercial trials.

**Bioengineered Artemisia annua L Variety with Higher Artemisinin Content** – Prof M Z Abdin, Jamia Hamdard University, New Delhi, India

Prof Abdin initially outlined the production of artemisinin in India and that the artemisinin yield and dry leaf weight, per ha, was lower than the global average.

Prof Abdin then presented the work his team is undertaking, using transgenic technology, to increase the artemisinin content of A. annua. In the trials transgene integration and copy number were assessed by PCR and Southern hybridization, which confirmed the stable integration of multiple copies of the transgene in 7 different transgenic lines of A. annua. The leaf tissue of three of the A. annua transgenic lines was shown to possess significantly higher HMGR activity compared with wild-type controls, and this activity was associated exclusively with microsomal membranes. The artemisinin content of one of the transgenic lines showed an increase of 38.9% artemisinin content compared with non transgenic plants.

Further trials and field work are currently now ongoing.

**QUALITY REQUIREMENTS FOR ARTEMISININ AS A STARTING MATERIAL IN THE PRODUCTION OF ANTIMALARIAL API's** – Dr Herbert Schmidt, WHO

Following the recommendations of the 2009 Artemisinin Conference in Mumbai, a working group was established to develop draft technical specifications for artemisinin as starting material. While there are still few antimalarials on the market with artemisinin API (notably artemisinin suppositories and the FDC artemisinin-naphtoquine), for most antimalarial medicines artemisinin is derivatised before final drug formulation and for these compounds, it should be classified as a starting material. The working group developed a draft paper, which was submitted for consideration to the ‘45th WHO Expert Committee on specification for pharmaceutical preparations’ held in October 2010.

In agreement with WHO Secretariat of the Expert Committee, the draft paper was also discussed in detail during the break-out session of the Conference in Madagascar. The outcome of the review was then submitted to the WHO Expert Committee before the 18th October 2010.

Specific concerns were raised at the conference regarding the content, levels and attribution of peaks of the related substances i.e. impurities, resulting in recommended changes in the draft document on technical specifications for artemisinin as starting material.
Since the Madagascar Artemisinin Conference, concerns have still been raised by some technical experts and artemisinin extractors with regard to the impurity content and levels contained in the revised document and therefore the 2011 Artemisinin Conference provide an opportunity for Dr Schmidt to give a detailed overview of the work undertaken and for all concerned parties to meet and discuss the issues.

**Key Recommendations:**
- It is essential that any discussions regarding the pharmacopeia should not in any way delay the agreement on artemisinin as a starting material.
- Understanding and agreement was reached on the issues regarding impurities.
- Concerns were voiced that the circulation of the draft, revised documentation did not include industry experts who have clear understanding and knowledge of the issues involved - or the documents were not seen until after the deadlines for comments.

### PROPOSALS FOR ACTION:

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<tr>
<th>SHORT TERM Artemisinin Prices and Supply Issues</th>
<th>RECOMMENDATION</th>
<th>ACTION</th>
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| 1) Urgently confirm reported high artemisinin prices and assess reasons.  
2) Continue to monitor reported artemisinin shortages.  
3) Validate the information reported at the Conference of large volumes of artemisinin imported every year for use in manufacturing anti-malarial treatments in India | 1-3)  
- Verify, asap, artemisinin spot prices, especially leaf prices being reported in China.  
- Confirm, as closely as possible, figures reported at the Conference on actual plantation hectares in China (2011 and ha possible in 2012), as opposed to wild leaf harvest.  
- Investigate available stocks of artemisinin (also in the form of API & ACTs) with extractors/manufacturers – and replenishment plans for 2012, including import figures for use in anti-malarial treatments for India. | A2S2 |

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<th>SHORT TERM ACT and artemisinin Forecasts</th>
<th>RECOMMENDATION</th>
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| 1) Urgent need for development and publication of detailed 2013 ACT global forecasts to enable raw material supply chain planning.  
2) Include needs for other key API e.g. lumefantrine, in the global forecasts.  
3) The AMFm (after 2012) is a key determinant of major recent changes in ACT demand. | 1) Publication of 2013 inclusive ACT global forecast with description of quarterly split in demand and focus on top 15 malaria endemic countries, accounting for 95% of ACT demand.  
2) Expand present forecasts to include non-artemisinin APIs.  
3) Clarification and regular communication on 2012 and 2013 expected approval rates of ACT orders from | 1) BCG ACT forecasting consortium  
3) AMFm |
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| Other Anti-Malarial Treatments | 1) Semi-Synthetic Artemisinin - need for clearer and more regular communication on pricing, introduction dates, supply/marketing plans.  
2) Need for regular update on the new synthetic antimalarial medicines (e.g. OZ compounds), malaria vaccines and large-scale introduction of RDTs and LLINs with potential for high level impact on ACTs | 1) Regular updates on the progress with timelines, regulatory requirements, quantities and pricing, with possible price oversight by independent panel including representatives from natural artemisinin producers.  
2) Dissemination of correct information through a central communication source. | 1) Sanofi / One World Health  
2) A2S2/RBM-PSMG |
|                |        |         |
| Technical Issues | 1) High Yielding Artemisia Varieties - need for regular update on introduction timing, cost and yield data.  
2) Urgent need to promote more efficient purification technologies and analytical procedures.  
3) Need to develop register of 'approved' extractors. | 1) Advise and assess CNAP & Mediplant Artemisia seeds introduction plans and ensure NIAB high yielding seed experience is not lost.  
Monitor other new Artemisia production initiatives e.g. fungal inoculant.  
2) Inform and demonstrate new technologies and their cost/yield implications, especially to low efficiency artemisinin extractors  
3) Explore feasibility of programme e.g. with inputs from API/ACT manufacturers, to approve extractors e.g. through 'best practices'/accreditation scheme. | A2S2  
Proposed Artemisinin Association (country level) |
| **MEDIUM TERM** |        |         |
| Artemisinin Production | 1) Need for an "Artemisinin Sector Association", both Globally and in individual Countries, particularly in China and Vietnam.  
2) Identify and support national financial institutions to support artemisinin extractors and growers.  
3) Continue to support diversified sourcing of artemisinin, via production in other 'lower cost' regions e.g. Africa.  
4) Assess possible introduction of a central API/ACT 'bank'. | 1) Development of a global Association with in-country counterparts (already included in A2S2 request to UNITAID for project extension 2012-2013).  
2) Promote diversified sourcing of artemisinin through multiple global initiatives | 1-3) A2S2  
4) RBM – PSMWG |
ANNEX 1:

2011 ARTEMISININ CONFERENCE – HANOI, VIETNAM

FEEDBACK FORM COMMENTS

The Feed Back Forms were given to all delegates and although they were repeatedly asked to fill them in, only 13 forms were returned (confidentially). This is similar to previous years but, from the comments made, many delegates believe that they had already made their comments either from the ‘conference floor’ or privately, now or at previous conferences. These previous comments have been very positive and where possible, their suggestions have been incorporated.

Q1 – How did you find the registration process through the web-base system for the conference:
Good; Very good and easy; Simple and easy; Helpful and convenient and smooth were the main comments.
There were NO adverse criticism – but a suggestion that there should be an “an automatic confirmation (e-mail) would be a great addition”.

Q2 – How did you find the presentations and discussions during the conference:
Good presentations; Useful and informative; Discussions open, frank and transparent and allowed exchange of useful information and criticism; Good opportunity to have discussions with colleagues; Opportunities given to provide opinions and offer advice in the breakout sessions; Good to hear progress in areas discussed/raised in earlier conferences; Very relevant, particularly market issues; The ‘design’ of the conference i.e. as a discussion forum, allowed for different perspectives to be discussed.

Q3 – Were you satisfied with the conference venue, accommodation and facilities:
100% satisfied; Good hotel, well organised; Venue very comfortable. One delegate suggested that it should be nearer the city centre.

Q4 - Were the topics discussed in the sessions relevant. Please suggest alternative or additional topics:
All replies agreed that the topics were relevant.
Additional topics/comments included:

- How to stabilise artemisinin and ACT supplies and how to fund Vietnamese extractors and farmers through A2S2.
- It would be interesting to have a representative from a recipient country explaining the distribution of ACTs in that country.
- An Industry Association is a good, sustainable, proposal, if it can be achieved.
- More feedback on new developments regarding alternative therapies which would be ‘game changing’ for natural Artemisia.
- More agronomic guidelines/recommendations, production techniques, harvesting methods.
- Country specific data could be published by the ‘consortium’, including funding.
- Fair price for artemisinin (Note: was discussed at length).
• More discussions on artemisinin resistance and preventative measures (vector control) (Note: the Keynote Address was on artemisinin resistance).

Q5 – Do you believe it necessary to have a follow up conference next year or in 2 years time:

Next year: 12 delegates
2 years: 1 delegate

Where: SE Asia (Bangkok) or Kenya
When: July; Nov/Dec; before planting season – depends on conference location.

Q6 – Were the break-out sessions useful? How could they be improved:
All agreed that the break out sessions were useful, focused and helpful; Actions should be assigned and ownership recommended; Some delegates thought they were too general and smaller group discussions on specific topics, giving more detailed feedback reports, would be better; Some felt ‘same old questions’ with no answers; Higher participation needed with panels formed to answer questions; It would be useful to have an expert in the sessions i.e. no expert on the resistance issue (Note: unfortunately Prof Hain, who gave the Keynote Address on artemisinin resistance, could not stay for the break-out sessions).

Q7 – Are there any particular speakers you think we should invite:
Expert from Heidelberg University on artesunate as an anti-cancer compound; MMV presentation on their portfolio; Farmers; End users of ACT – governments, NGOs.

Q8 – Any other comments:
• More microphones would be helpful so not so long to wait to speak (only 2 this year Note: this is as per previous years)
• It will be important to hear any feedback from A2S2, RBM on the formation of a more formal association and its form.
• A good suggestion from UNITAID to use A2S2 newsletter to follow up on the conference.
• Good to also have the Global Fund meeting at the same time/venue.
• Less time on break out sessions, stick to timing but give a lot more time for questions after each speaker. Spread speakers out over 1½ day’s with break out in 2nd afternoon with 1hr report break.
• Voluntary field trip and extraction plant visit (day 3).
• 2 day meeting sufficient, good side meetings.
• Artemisinin and its derivatives (known and future) have other activities other than anti-malaria e.g. anti-cancer. If the conference title is to remain ‘Artemisinin’, then such facts would add value to prospective planning over the next 5yrs.
• Thank you very much for a good conference and organisation, keep it up.

M Cutler, FSC – Dec 2011