ARTEMISININ CONFERENCE 2013
NAIROBI, KENYA, 14–16TH JANUARY

INTRODUCTION

Recent conferences, particularly in Madagascar, 2010 and Vietnam, 2011, have stressed the need to increase artemisinin supplies to meet increasing ACT and other treatment orders, and for greater clarity and timeliness of ACT forecasts. In 2012, with increased Artemisia plantings and good weather conditions during the growing season, the global production of artemisinin increased considerably and is predicted to be sufficient to meet the most optimistic ACT forecasts for 2012/13. However, there has been considerable uncertainty throughout 2012 as to the future of AMFm and therefore the earlier demand for a clear and timely ACT forecast has not been met. Without a clear indication of the 'market', API/ACT manufacturers cannot plan their production and therefore provide timely artemisinin orders for the extractors. Although some clarity on the future of AMFm has resulted from the Global Fund board meeting in November 2012, the position of AMFm, beyond 2013, is still unclear and with the increase in artemisinin production, artemisinin prices have recently fallen to below production cost. Even with the introduction of semi-synthetic artemisinin, if this situation continues, there is a very real fear that production in 2013/14 will be much lower and we will again be entering a period of "boom and bust" - the last thing that the sector needs. If artemisinin prices, for ACTs, continue to be below production costs and clear, realistic, ACT forecasts for 2013/14 are not available, an additional fear is that artemisinin production will find its way into non-approved anti-malarial products, as producers are forced to find alternative markets.

The 2013 Artemisinin Conference in Nairobi, therefore comes at a critical time in order to:

- Clarify the market situation and ACT/artemisinin forecasts and in particular, the future of AMFm.
- Provide the latest information regarding artemisinin resistance.
- Update on the introduction of commercial quantities of semi-synthetic artemisinin and other synthetic compounds.
- Detail the latest information regarding high yielding Artemisia seeds, processing and analytical technologies.
- Discuss how to implement sustainable communication and market intelligence systems throughout the ACT/API/artemisinin sector, beyond 2013 e.g. through sector/industry supported country and global associations.

Acknowledgements
The conference was organised with the support of RBM, UNITAID, The Global Fund and WHO, with local assistance from Botanical Extracts EPZ Ltd.

The following report provides a summary of each presentation For further information and detail click on the presentation title and this will open the individual PowerPoint presentation.

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

View the 2013 **Conference Agenda.**

Link to Conference Group Photo.

Day 1 – Tuesday 15th January 2013

The conference was opened by Dr Willis Akhwale, Head of the Diseases Control and Prevention Departments of the Kenya Ministry of Health and Public Sanitation. In his **Opening Address** Dr Akhwale highlighted the fact that Kenya was one of the AMFm pilot countries in 2009 and in 2013 will require 24m ACT doses. Kenya is also a country which grows and produces Artemisia and artemisinin but, due to the stringent WHO prequalification standards, is precluded from local manufacturer of 'pre-qualified' ACTs. Dr Akhwale stressed that, post 2013, best use of the funds available must be made,

but that a range of answers is required which will include AMFm (or its successor), local manufacture of both of ACTs and raw materials (funds and technical support are required); synthetises and RDTs.

Following the opening of the conference, the **Keynote Address** was presented by Dr Nafo-Traoré, RBM Executive Director. Dr Nafo expressed her pleasure in being at the conference as she had been present at the first conference organised by WHO, in Arusha, in 2005. In particular she noted how the conference had matured in both size and quality and expertise since then and become an important platform for information sharing and consensus building for the global availability of quality assured ACTs.

Dr Nafo stressed the problems of aligning demand and supply in a market which is largely donor driven, the uncertainties of which make accurate ACT forecasting, over a minimum 2yrs period, very difficult. She also raised the concerns if artemisinin prices fall too low i.e. below a viable production price; the need to ensure the proper planning and introduction of semi-synthetic artemisinin in order to stabilise supply and prices and the fears regarding the resistance of the parasite to artemisinin.

In conclusion, Dr Nafo stated that we look forward in sharing the lessons learnt from AMFm's proven capacity to increase drug access through the private sector when The Global Fund integrate the AMFm into its regular process after 2013.

1) The Global Fund/AMFm – The Future

- Fabienne Jouberton – GFATM

AMFm Phase 1, was a "Test of Concept', using pre existing supply chains (public, private non-profit and private for-profit), operational in 9 pilots in 8 countries and consisted of three elements:

- Negotiation with ACT manufacturers.
- Buyer subsidy (co-payment).
- Supporting interventions to ensure ACT scale-up.

Up to Dec 2012, 239m treatments had been approved and 272m treatments delivered. Although Phase 1 was over 2½yrs, in practice all pilots had less than 12 months implementation of the full model.

Key findings of the Phase 1 evaluation included:

- In 6 of the 8 pilots, 1st line buyers responded rapidly, moving ACTs quickly and efficiently, with limited evidence of profiteering.
- Longer duration of all three elements of the AMFm model (manufacturer negotiations, co-payments and support mechanisms), correlated to improved performance.
- Several supporting interventions were critical:
  - Strong AMFm governance structure, including private sector.
  - Large scale mass media campaign.
  - Use of Recommended Retail Prices (RRPs).
  - Training of providers.
  - Regulatory measures e.g. tax waivers etc.
  - Access to, and scaling up of, RDTs important.

Following an independent evaluation of the AMFm, the Global Fund Board in November 2012, recommended:

- Integration of lessons learnt from Phase 1 into the Global Fund grant management and financial processes.
- Transition of AMFm pilots into 2013 ensuring:
  - Access to ACTs not disrupted.
  - ACT and API markets not destabilised.
  - Countries are supported in the transition to the integrated model post 2013.
- Co-payment system maintained for private sector only.
- Supporting interventions maintained
- Funding request of $114m (historical) up to $154m.

Beyond 2013 – Integration:

- ACT co-payments no longer available through a separate funding mechanism i.e. as in AMFm Phase 1.
- All eligible countries can allocate funding from their core Global Fund grants to a private sector subsidy.

- The Global Fund secretariat will continue to negotiate prices and make direct payments to manufacturers (on behalf of the countries).
- Phase 2 – those countries presently reprogramming grants, Phase 2, or will have to wait for New Funding Model.
- Funding for post 2013 still to be determined.

2) Semi-Synthetic Artemisinin(SSA) – Progress Report

- Ponni Subbiah – OWH/PATH
- Wolfgang Laux – Sanofi

Semi-Synthetic Artemisinin project goals are to:

- Supply a complementary source of non-seasonal, high quality affordable artemisinin to supplement the current plant based artemisinin.
- Ensure SSA is available to all qualified derivative manufacturers.
- Contribute to stabilising the price of ACTs.

Project status update:

- 2012 - Process evaluation completed – test samples of SSA available.
- 2013 - Production goal 35 MT – for Sanofi use.
- 2104 – Production capacity 50-60MT.
- Cost estimate is $350 – $400/kg (not for profit price).
- Shelf life estimated to be 3-4yrs (as with natural artemisinin).
- Min lead-time for SSA production is 4 months, then available for derivitisation.

Main questions and discussions following the presentation and in the Break-Out Session included:

- 60MT SSA represents over 1/3rd of artemisinin needs, and if available in such as short time scale i.e. in 2014, many natural artemisinin producers feared that this could have a negative affect on overall supply, due to greatly reduced plantings in 2014 and natural producers going out of business.
- If the price is below $400/kg, SSA will undercut natural production cost. Natural producers also fear that the competition is unfair if SSA is marketed at a “not for profit price”.
- API manufacturers commented that regulatory issues i.e. the use of SSA in derivatives, could delay the uptake of SSA.
- It was requested that the Commercial Oversight Committee for the project should have independent or natural artemisinin producer representation, to ensure close cooperation and transparency, in order to ensure clear, transitional, introduction of SSA.

3) Semi-Synthetic Artemisinin – Regulatory Issues

- Valerie Faillat-Proux – Sanofi

Naturally produced artemisinin is considered a ‘starting material’ before being derivatised. However, WHO guidance concerning artemisinin as a ‘starting material’, excludes artemisinin produced using synthetic chemical processes or fermentation. The ‘starting material’ for SSA is considered to be the artemisinic acid and therefore the semi-synthetic artemisinin (SSA), is now classified as an ‘intermediate’. The master file has been submitted to WHO (October 2012) and is now pending peer review.

The data required to be submitted for registration, by the API manufacture, when incorporating an SSA includes:

- An API manufacturers amendment (APIMF) introducing the supplier of the semi-synthetic artemisinin as an API intermediate manufacturer.
- A copy of the ‘letter access’ allowing them to refer to the master file held for semi-synthetic artemisinin. Note: this file and an ‘open part of the master file’, will be available from Sanofi.
- A single set of harmonised specifications for the control of artemisinin (regardless of source) Note: this was stated as a possible ‘challenge’.
- Data verifying that the use of semi-synthetic artemisinin affords the target API of the same quality i.e. does not lead to the carry over of unacceptable impurity content.

4) Semi-Synthetic Artemisinin – Max Planck Institute
- Dirk Pohlmann – Max Planck / ArtemiFlow GmbH

ArtemiFlow GmbH was founded in November 2012 to commercialise the research into the production of semi-synthetic artemisinin, undertaken by the team lead by Dr Peter Seeburger at the Max Planck Institute of Colloids & Interfaces.

The Max Planck process uses a continuous flow photoreactor yielding up to 65% artemisinin before final purification. The prime objective of the programme is to add value to the present natural artemisinin producers by converting the dihydro-artemisinic acid (DHAA), which is present in the waste following the existing, solvent based, primary extraction process, into artemisinin. Alternatively the raw material could be provided from a biotech source.

The project is successfully running a 200g per day pilot plant and is now planning an industrial scale 1 tpa plant, which could be scaled up to 10tpa. Estimated cost of a prototype industrial plant is €1m.

ArtemiFlow GmbH has now:
- Defined funding.
- A business plan (currently being finalised).
- Identified clients.
- Identified a development company to build the industrial prototype.
- Estimated costs.

ArtemiFlow GmbH is now carrying out further trials to establish the DHAA content in different plant materials, grown in different regions.

5) Country Reports on 2012 – Artemisinin Production and Market Observations.

a) China – Christine Lin – PIDI Standard

Due to increased confidence (including higher prices), Artemisia plantings in China in 2012 were around 15,500ha, an increase of 70% on 2011. With good growing conditions 45,000MT of leaf has been collected (45% from wild plants), with high quality (5.5kg of Art/ha, compared with up to 4.5kg/ha in 2010 and 3.4kg/ha in 2011), but due to the high production and market uncertainty, at lower prices per MT than in 2011. The 15 main extractors in China have a total artemisinin production capacity of 230MT, but actual production in 2012 is estimated to be between 180-200MT.

Production in 2013 is very uncertain at present due to labour shortages, competition from other crops and currency devaluation, but above all due to the reductions in artemisinin prices, market uncertainties and the introduction of semi-synthetic artemisinin.

Christine Lin stressed that, “it only takes 3 months to destroy the confidence in cultivation, but 3 years to rebuild it”.

b) Vietnam – Bui Minh Ut – Cat Khanh Co Ltd.

Production in Vietnam in 2012 increased to 2,600ha (double 2011 plantings) due to increasing prices. Around 8,000MT were harvested and with higher efficiencies than in 2011 (3.3 – 3.8kg/MT), artemisinin production was between 23-26MT. However, because the Vietnam harvest starts one month before China, Chinese buyers competed for leaves, resulting in prices rising from $900/MT to $1,600MT. Other production costs have also risen steeply with power and solvent costs increasing and banking reform leading to extractors having difficulty raising working loans and, if obtained, they are at high interest rates. There has also been no investment in high yielding seeds.

With artemisinin prices falling, buyers demanding 90 days credit and with no clear market information (AMFm) in 2012, some extractors have had to sell at below cost price. This cannot continue. For 2013 it is forecast that Vietnam production may only be a half of 2012 levels, due to the low prices, lack of market information and the introduction of semi-synthetic artemisinin – at what price? If artemisinin production in Vietnam is to stabilise, policies need to be urgently introduced which will give the growers confidence in the market and with prices viable for both the producer and buyer.

c) **Madagascar** – Charles Giblain, Bionnex

Bionnex contract around 10,000 growers i.e. circa 2,000ha, plus 300ha of their own production. Leaf yield in 2011 averaged 1.13MT/ha at an average artemisinin content of 1.1% (aim is to reach 1.4% average).

Planned production is:
2013 – 2160MT dry leaf, 16MT artemisinin
2014 – 3,300MT dry leaf, 25MT artemisinin
2015 – 4,000MT dry leaf, 30MT artemisinin

Seeds used are largely high yielding varieties from Mediplant and NIAB, with trials from CNAP. Bionexx is also establishing it own varieties. The new artemisinin extraction plant, using HFC technology, will be fully operational from March 2013.

Bionnex claim to be able to closely control the whole production process from planting through to processing and is positive about the short to medium term future, as long as the market is clearly defined and artemisinin prices are stable at around 400$/kg.

d) **East Africa** – Patrick Henfrey – Botanical Extracts, Kenya

Botanical Extracts cooperates closely with Afro-Alpine in Uganda and the presentation covers both extractors.

The combined capacity of both production units is 25MT of artemisinin per year. However in 2012 the total production was less than 5MT because of:

- Increasing competition from other high priced commodity crops.
- Disappointing results from contract suppliers.
- Unusual rainfall patterns.
- Third parties buying BE crops – this has never happened before.

In 2013 the target is to produce 14MT by restructuring the raw material production chain to:

- Offer higher prices to compete against higher food prices.
- Expand directly controlled production.
- Better auditing of crops close to harvest and leaf security, to prevent fraud.

In the medium term BE is confident that it has in place the management, raw material and processing technology to provide consistent supplies of high quality artemisinin. However, for the medium to long term, if BE and other extractors are the invest and continue production there needs to be:

- Greater stability and clarity concerning demand and pricing.
- Greater coordination of supply and demand to prevent oversupply and low prices.
- Urgent clarification on Semi-Synthetic Artemisinin progress/policy.
- Need to diversify global artemisinin production.

6) Panel Discussions between ACT/API Manufacturers and Procurement Representatives

a) Building ACTs Forecasts - René Cazetien - Sanofi

The presentation outlined the steps which a manufacturer has to take in approaching and supplying the ACT market; considering the Decision Factors that have to be made at Global and Manufacturing level, and the Supply Chain Management challenges.

Decision Factors in building an ACT forecast:

- At a Global Level:
  - Demand (Effectiveness and safety of ACT; Simplicity of treatment; IEC).
  - Orders (Funding available; capacity of distribution).
  - Malaria Intervention (Diagnosis (RDTs); Bed Nets; IRS; Vaccines).
- At Manufacturer Level:

- Market Dynamic (Competition; Starting material pries; National malaria guidelines; New anti-malarial drugs).
- Industrial (Capacity; GMP; Prequalification)
- Supply Chain (Shelf life; Procurement mechanism; Cycle of production).

Supply Chain Management and Support:
This is a major issue and a well managed system is required, comprising Quantification; Product Management; Supply Planning; Acceptability; Consumption and Follow Up.

The presentation ended with comments regarding the present situation and problems being encountered in the supply chain:

- Ignorance of the different stages of the supply chain cycle.
- Independence of the different services and lack of communication between them.
- Difficulty in getting reliable forecasts, leading to stock outs and decreasing frequency of patients visiting health centres.
- Employees motivation.
- Training problems.

b) IPCA – Murali Sarma

The presentation detailed IPCA's programme as a major supplier of anti-malarial treatments, noting that between July 2010 – Dec 2012 the company provided 77% of AL manufacturers orders (based on orders uploaded onto the Global Fund website). Average malaria treatment cost is $1.5-1.7 per treatment.

In order to improve the supply of treatments, IPCA, based on their experience, request that the following areas are urgently addressed:

- Greater clarity of funding and the future of AMFm (private sector orders).
- Quick approvals of AMFm orders.
- Advance orders which will help suppliers in the procurement of raw materials/APIs, production planning etc.
- On time payment.
- Two year ACT forecast, from one agency source.
- Price stability of artemisinin.

Suggestions to help improve supply:

- Sharing VPP orders between approved suppliers to cut lead times, mitigate risk of non delivery etc.
- Regional warehouses to stock anti-malarial formulations i.e. as with HIV.
- Global donors to help stabilise artemisinin prices.

c) ACT Funding and Forecasting - Mariatou Tala Jallow – Global Fund/VPP

VPP presently accounts for 40% of all Global Fund grants. Confirmed orders from June 2009 – Dec 2012 totalled $1.03 billion, with $400m forecast for 2013.

Dr Tala's presentation outlined how the Global Fund can best leverage its purchasing power to improve market outcomes and impact. In particular she emphasised the following areas:

- Improve VPP Mechanism (Pooling volumes; Improved forecasting; Reducing funding volatility).
- Strengthen secretariat's capacity for strategic market shaping (Chief Procurement Officer has been appointed; Procurement structure reorganised)
- Establish rapid response mechanism (Physical stockpile and cash to better manage stock outs)
- Management and use of health product information system (2-stage process – 1) Manual consolidation of PSM plan 2012 – 2014 and 2) IT tool for PSM plan management; monitoring of procurement activities and automating VPP process).

In order to ensure future Funding and Forecasting emphasis needs to be placed on:

- New Funding Mechanisms, which will provide sustainability and predictability.
- Pharmaceutical Management Systems - improve forecasting mechanism and procurement forecasting.
- New/Improved Procurement Strategies – improved VPP mechanism.

e) UNICEF – Suvi Rautio

- UNICEF programmes support key interventions to fight malaria (prevention, diagnosis and treatment).
- Together with WHO, UNICEF continues to strive for the replacement of oral monotherapies with ACTs.
- Continued focus on quality assurance and fit-for-purpose.
- Procurement services provider for recipients of GFATM, UNITAID and other funding.

UNICEF provides procurement services to 25-30 countries annually and in 2012 purchased over 30m ACT treatments.

UNICEF's ACT procurement strategy includes:

- Joint WHO-UNICEF tendering process.
- Multiple framework agreements (LTAs) established to ensure flexibility and availability.
- Allocation of orders: secondary competition.
- Screening of requisitions based against treatment guidelines.
- Regular sharing of forecasts with LTA holders.

7) ACT Demand Forecast

- Aaron Woolsey – CHAI (on behalf of the Boston Consulting Group)

The ACT Forecasting Consortium consists of BCG, CHAI and MIT-Zaragoza, who work together to produce a single quarterly forecast of global QAACT demand. The consortium is funded through UNITAID.

Market Analysis and Projections:

- Rapid growth in ACT demand in 2011 (287m) and 2012 (289m) due largely to AMFm.
- Growth in 2012 slowed as subsidised market reached steady state (Ph1 countries).
- Forecast for 2013 is 251m treatments assuming AMFm fully financed but reduction in donor commitments through public channels.
- ACT supply through public channels represents 62% of global market.

2014 Predictions:

- Impact of the new GF/AMFm model in 2014 is still to be determined. Based on the present funds agreed only an estimated 142m treatments will be available in 2014, but could be up to 260m if the funding gap is bridged.
- New funding model is unlikely to affect demand up to 4th qr of 2014, after which the impact is unclear.
- The huge fiscal challengers faced by other funders makes the situation unclear for 2014 and beyond.
- Any fall in funding and therefore treatment availability, is inconsistent with the epidemiological demand.
- The Forecasting Consortium believe that the funding gap could be (at least partly) bridged through continued subsidizing through the private sector, GF transition monies and new donors.

Additional comments during questions:

- It is recognised that without firm donor commitments for the necessary funds, it is impossible for the Forecasting Consortium to provide accurate forecasts.
- Without these forecasts it is impossible for the supply chain and ACT manufacturers to plans and organise the necessary production.
- Without the timely supply of raw materials and ACTs, the market will suffer from delays and stock outs leading to increased suffering of patients.
- The donor community must recognise this situation and urgently act to prevent it becoming a reality.

8) Artemisinin Supply, Costing and Pricing

Jacques Pilloy – A2S2/AEDES (with Malcolm Cutler & Ben Smith – A2S2)

Artemisinin Production in 2012:

- Due to high prices at the end of 2011, extractors sharply increased plantings in 2012
- Climatic conditions were good in most areas, leading to increased Artemisia leaf production.
- Whilst the potential artemisinin production in 2012 could be over 250MT, in practice it is likely to be less, as it was reported that China may not process all the Artemisia grown due to the falling prices and uncertain market.
- Cross border buying of leaves and selling of crude artemisinin to other producers, makes it difficult to accurately assess production.
- The first trial samples of semi-synthetic artemisinin became available.

Artemisinin Demand in 2013:

- Whilst the Forecasting Consortium predicted a demand for 286m treatments in 2012, the figures received from the manufacturers indicate that actual sales of pre qualified ACTs was around 330m i.e. 150MT of artemisinin requirement. This is also as predicted for 2013 if full funding is obtained.
- Rebuilding ACT and API manufacturer inventories – 10-20MT artemisinin.
- Other non-qualified uses, injectables etc – 20-30MT of artemisinin.
- Global artemisinin demand for 2013 is therefore likely to be between 180-200MT.

Artemisinin Demand for 2014:
Until firm ACT forecasts i.e. funding, is available it is impossible to predict artemisinin needs at this point of time!

Artemisinin Prices:
From 2007 to the 3rd qr 2011 artemisinin prices had varied between $200 - $400 (av of $300), which has been low but until costs production recently started to increase dramatically were above production cost. However, in 2011 prices started to increase due to the poor harvests and increasing market needs with prices reportedly reaching over $900 towards the end of 2011 (due in part to reports of a sudden increase in demand for ACTs and some buyers paying high prices to secure supply). This encouraged increased Artemisia production in 2012 (especially in China), resulting in prices gradually falling in 2012 to around $400/kg. However, with low and unclear demand, largely due to the uncertainties over the future of AMFm, some extractors have had to sell at any price, and prices at the end of 2012 and in the 1st qr of 2013, fell to around $360/kg, which is below many extractors production costs. With increased confidence in the market, it was reported at the conference that prices are now increasing slightly.

The Future:
Without long term funding commitment for ACT purchase and thereby clear and consistent market forecasts, which allow realistic production planning, it is very difficult to stabilise artemisinin prices. The imminent introduction of large volumes of semi-synthetic artemisinin, without careful coordination, could also exacerbate this problem. It is therefore essential that these factors are addressed if we are to have sustainable supplies of artemisinin in the future (from all sources), at a viable price for both extractors and buyers.

9) Update on the Status of Artemisinin Resistance

Andrea Bosman – WHO (on behalf of Pascal Ringwold)

To date artemisinin resistance is still centred on the Thai – Cambodia (Mekong) and Thai – Burma borders, but there have also been reports recently from Vietnam. The WHO working definition of resistance is:

- Suspected Resistance: “more than 10% of parasites detectable on day 3 after ACT treatment”.
- Confirmed Resistance: “presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence of parasites after day 7, within 28/42 days, after treatment with an oral artemisinin-based monotherapy”.

According to this definition there has yet to be any recorded resistance to ACTs in Africa.

There is also indication of mutations in the companion drugs. Whilst As/Mq is still working DHA/Pq is seen to be failing. It is also worrying that Quinine is also not working in these areas.

Slide 18 of the presentation details the GPARC recommended action for containment of the resistance with Tier 111 action including Good Control; More Routine Monitoring and Elimination of Monotherapies and Poor Quality Drugs.

10) Synriam – Arteroiane/Piperaquine Combination

- Sanjukta Bhuttacharyya – Ranbaxy Laboratories, India

Ranbaxy's goal was to produce a fixed dose anti malarial combination with a low propensity for development of resistance; to have convenient dosing i.e. once daily for 3 days, and be affordable.

Synriam was developed between 2003 – 2007 with the support of MMV, but following their withdrawal form the project following poor clinical trial results, assistance was provided through the Dept. Of Science & Technology of the Government of India.

Arteriane is a totally synthetic trioxolane, fast acting (clears parasites in 3 days) and inexpensive oral drug and is combined with Pieraquine, which is also inexpensive and has proven effectiveness (stays active for 3 weeks).

Synriam has been approved by the Drugs Controller General (India) and has been available for malarial treatment in India since April 2012. Price per treatment is $2.30 with cost of production of $1.50. It is now undergoing Phase 11 and 111 trials in a range of African countries and Ranbaxy expect it to be registered in these countries from May/June 2013.

11) Assured Artemisinin Supply Scheme (A2S2)

- Malcolm Cutler & A2S2 Team (Jacques Pilloy, Ben Smith, Koert Jansen)

A2S2 was introduced in June 2009, funded and supported by UNITAID, in order to support the production of artemisinin to meet the short/medium term demands of the Global Fund/additional AMFm. Phase 1 of the project ran through to May 2012, followed by a 12 month extension which will finish at the end of May 2013.

Phase 1 of the project included two components:

- Market and Technical Intelligence i.e. accessing production and market data through visits and regular contact with extractors, API/ACT manufacturers etc and dissemination of that information through meetings these meetings, RBMPSM work groups, A2S2 website/Newsletters and at the annual Artemisinin Conference.
- Pre-finance Facility for Extractors which, through a tripartite contract between the extractor, API/ACT buyer and Triodos Bank, enabled the extractor to access low cost loans (with no further guarantees), to pre-pay Artemisia purchase and for artemisinin extraction.
  Results: Four contracts were approved (China, Vietnam, Madagascar, East Africa) for 35MT of artemisinin, but the actual projected total will be around 25MT due to problems with production (poor climatic conditions) and last minute changes in finance regulations (in China). In addition to these contracts, A2S2 worked extensively to help create long term contracts between extractors and their buyers to replace 'last minute' spot buying. This allowed extractors to better plan their production and help to stabilise prices. It is estimated that a further 9MT of artemisinin were contracted, on this basis, with A2S2 support (no finance involved).

Phase 2 of the project has included:

- Whilst the loan facility was terminated at the end of Phase 1, Triodos Bank is actively looking to source alternative sources of finance to support extractors. Two of the potential investor organisations were present at the Artemisinin Conference in Nairobi.
- Market and Technical Intelligence programme continues as in Phase 1 including visits to extractors and API/ACT manufacturers.
- Assessing how the A2S2 services can be continued following the end of Phase 2, in particular investigating and planning the introduction of an 'industry' lead Sector Association and support to develop affiliated in-country associations e.g. in China.

Note: At the Artemisinin Conference there was considerable support for the formation of an industry association and agreement that its development should be initiated through A2S2, with links to the RBM PSM Working Group.

12) High Yielding Artemisia Varieties and Production Methods

A) High Yielding Density Trials – Xavier Simonnet, Mediplant

Mediplant have recently undertaken a series of trials to identify the effects of planting density, environment and plant age on artemisinin content. The trials were undertaken in Switzerland and Madagascar, with four varieties – CNAP 1, CNAP5, NIAB 1062 and Apollon. Four representative trails were done on 1) Density (5 different) and Dynamic (eight different harvest times). All analysis was undertaken at CNAP, York University, UK. The results of thes trials were:

1) Density Trials:
   - Different densities had a significant effect on dry leaf yield and artemisinin concentration, at both locations.
   - In Madagascar artemisinin yield was significantly higher at 20 – 50,000 then 5-10,000 plants/ha.
   - In Switzerland artemisinin yield at 50,000 plants/ha than at any other density.
   - Amongst others, the above shows that density must be adopted to the duration of the growing period.

2) Dynamic Trials:
   - Harvest time has a significant effect on dry leaf yield and artemisinin concentration/yield.
   - Results were found to be location specific.
   - No trails were undertaken on the extraction of precursors to yield per ha, but this would be an interesting e.g. against the age of the plant e.g. for AA and DHAA.

Conclusions:
- Field management plays a major role in artemisinin yield (as important as varieties).
- Planting density and date of harvest had a significant effect on dry leaf yield and artemisinin concentration/yield.
- Results were found to be location specific.
- Field management must be adapted to: the environment; plant density/intensification; interaction between cultivation methods; variety.

Only if all these factors are considered can optimum artemisinin yield be achieved and thereby competiveness of the crop improved.

B) F1 Hybrid Update – Wendy Lawley, CNAP, University of York

Of the four 1st Generation Hybrids introduced in 2011/12, only one (Hyb1209r) is continuing in production as the other three have been replaced by 2nd generation hybrids.

The four hybrids therefore considered to be promising are:
- Hyb1209r – Shennong – Suitable for: China, Kenya, Uganda
- Hyb1252r – Jewel – Suitable for: China, Madagascar, Kenya, Uganda
- Hyb8001r – Zenith – Suitable for: China, Uganda, Madagascar
- Hyb8003r – Verdant – Suitable for: India

Max yields for these hybrids range from(see presentation for detailed figs):
- Artemisinin concentration: 1.08 – 1.52%
- Dry leaf yield: 2,908 - 4,488kg/ha
- Artemisinin content: 28.6 – 54.5kg/ha

Seed samples for all varieties are now available through CNAP or East-West Seeds.

Discussions following the presentation centred on the fact that some users had not been fully consulted on what varieties were suitable for their needs and also on the price of the seeds through East-West

Seeds (it is understood that these issues have been further discussed and resolved at a later time, at the conference).

C) HFC134a Artemisinin Purification and Comments on Proposed Changes to Specifications for Artemisinin as an API and a Starting Material

- Bhupinder Khambay – Kamtach Ltd

HFC134a Artemisinin Purification:

In 2009/10, based on the earlier work under the MMV Artemisinin programme, scale up of artemisinin purification with HFC134a was carried out by Kamtech and ETDL, UK. This work has now been expanded with Kamtech working closely with Bionexx, Madagascar, where commercial scale production is now being introduced and with IPCA, India, where small scale 'commercial' trials have been undertaken in 2012. The detailed result of the work with these companies is considered commercially confidential, but it was reported that 'excellent progress has been made'.

Proposed changes in artemisinin specifications:

Over the past two conferences, in Madagascar and Vietnam, there has been extensive discussion regarding artemisinin as a Starting Material. Some national bodies have interpreted the regulations to suggest that artemisinin is an API and therefore has to be produced under GMP conditions. If this were the case no artemisinin extractor would be able to continue production and any investments would cause costs and therefore artemisinin prices, to soar. Following extensive work by WHO QC Dept. this anomaly has now been corrected and artemisinin can now be considered as a starting material. However, at the same time, the allowable levels of certain impurities have seemingly been increased, in the draft recommendations circulated by WHO (on artemisinin as a starting material), but the reasons behind these changes have not been clearly explained.

The main changes noted in the draft recommendations for artemisinin as a starting material are:

- An allowable increase in artemisitene from 0.08% in 2010 to 0.15% in 2011 and 0.2% in 2012.
- Total impurities have been reduced from 5 to 3.

The latest changes in artemisinin as an API include:

- A ten fold allowable increase in artemisitene.
- 1.2 times allowable increase in 9-eptART.

The presentation then asked what were the key factors in relaxing these specifications and is their compelling evidence to justify key levels of impurity? Some evidence was presented, as included in a paper Stringham et al in 2011:

- Specifications should be based on historical results.
- Use of indirect evidence to postulate fate of impurities.
- Given the difficulties in synthesising impurities, they cannot be used in routine analysis of artemisinin.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations also realized that the monograph on Artemisinin in *The International Pharmacopoeia* (for Artemisinin used as an API) would benefit from an update, partly due to:

- The Artemisinin API monograph was lacking a transparency list,
- It had turned out that it was not possible to establish a common reference substance with one assigned content that was suitable for both assay methods described in the Artemisinin API monograph.

In order to answer these questions the presenter asked for:

- Definitive work on the fate of pure artemisitene and 9-epiART under API synthesis conditions.
- Indication that levels of impurity effect yields of API.
- Availability of reference impurities (now available).
- Access to relevant information – i.e. circulation of information, for discussion, direct to industry members affected.

Break Out Sessions:

Two Break Out Sessions were organised:

1) ACT and Artemisinin Demand and Supply Planning:

The issues discussed included:

- ACT manufacturer forecasts.
- ACT demand and the 2013-14 forecast.
- Perceived risks in 2014.
- Consequences of the forecasts on RDT/ACT demand.
- Artemisinin supply to meet ACT demand.
- Approaches to stabilise the artemisinin market.
- Semi-synthetic artemisinin and market impact.
- AMFm transition period (2013) – levers.
- Expected funds for ACT procurement in 2014 and beyond and impact on mortality die to funding cuts.

2) Artemisia/SSA and Artemisinin Technical Issues:

- Semi-synthetic introduction, pricing and regulation.
- High yielding Artemisia varieties.
- Field cultivation issues.
- Extraction, Purification and Derivitisation issues.
- Impurity and regulatory issues for SSA and artemisinin as a Starting Material.

Note: for further details on the discussions, please access the web link to the Break Out Presentations and also view the following 'Major Conference Findings and Recommendations".

FIELD VISIT - Thursday 17th January

The field visit was made to an Artemisia plantation near Naivasha, 80km NW of Nairobi (1,550m altitude). This is a joint collaboration between Elysian Life Sciences, India and Botanical Extracts EPZ Ltd, Kenya. The plantation is 80ha, all under a single central pivot and divided into 16, 5ha blocks. Crop cycle is approximately 6 months, planting to harvest and replanting, with planting/harvesting, on average, one block a week.

CONFERENCE MAJOR FINDINGS AND RECOMMENDATIONS

1) Need for clarity into availability of funds for ACT procurement (for private and public sector distribution), resulting in realistic ACT forecasts 2014-2106:

In order to plan for the sustainable production of artemisinin, APIs and ACTs (also RDTs), it is essential that the actual level of available funds to purchase ACTs (and RDTs), in 2014-2016, is confirmed and clarified as soon as possible. Without this information, regardless of whether the ACTs are to be delivered through private or public channels, manufacturers cannot plan their production, and the uncertainties concerning ACT supply and the lack of stability in the artemisinin market will continue.

Only when this level of clarity on available funds is provided, can accurate and detailed ACT forecasts be developed by the ACT Forecasting Consortium, enabling artemisinin extractors to more accurately plan their production, so as to achieve stable artemisinin prices. This level of clarity will also enable the artemisinin supply chain to better adapt to the introduction of semi-synthetic artemisinin, again leading to more sustainable supply and price stability.

Without timely confirmation of available funds and the resulting ACT forecasts for 2014-2016, it is feared that Artemisia plantings and thereby artemisinin production, could be seriously reduced in 2013/2014 (as well as expansion of semi-synthetic artemisinin availability) leading, again, to artemisinin shortages and price instability.

The conference urges all donor organisations involved in providing funds for ACT purchase to understand the seriousness of the present situation where, without timely forecasts, Artemisia growers, through to the ACT manufacturers, are unable to plan their production. Given the long lead times for the production of ACTs, without timely forecasting, drug stock outs are unavoidable (natural artemisinin has a lead time of around 6 months and the semi-synthetic artemisinin is reported to have a lead time of up to 4 months, both plus time for API/ACT production and distribution).

Any global stock out of prequalified ACTs could result in the 'market vacuum' being filled by non approved ACTs and monotherapies.

2) Need to confirm mechanisms for defining how Global Fund monies will be proportioned between the private and public sectors, and funding for ACT procurement, post 2013:

It is reported that the introduction of AMFm has resulted in greater security and improved production planning for ACT manufacturers and their supply chain partners. However, this situation is now seriously threatened due to the delay in identifying exactly how co-payment funds for ACT distribution through the subsidised private sector will be proportioned post 2013. There is therefore an urgent need to clarify how, post 2013, the Global Fund monies available to purchase ACTs (and RDTs) will be proportioned, by the receiving countries, to ensure that the private sector demand for ACTs, is maintained and adequate time allowed so that manufacturers can plan production and enable efficient, timely, distribution.

During the break out sessions the conference stressed the need to:

- Urgently work to identify alternative and sustainable funds for ACT and RDT purchase i.e. beyond 2013.
- Undertake a literature review on the impact of stock outs due to lack of funds.
- Increase information on countries actual needs and levels of funding required, as well as private sector requirements/quantification, in-country.
- Work to identify realistic ACT demand to create a stable market and the project requirements to 2016 and beyond.

3) Need to stabilise the artemisinin market:

Following increased Artemisia plantings at the beginning of 2012 (especially in China) and good climatic conditions during the growing period, the potential availability of artemisinin (if all Artemisia leaves are purchased and processed), will more than meet the forecasted ACT demand for 2013. With a small surplus, prices would normally stabilise, as excess production will replace previously used stocks, however, with the uncertainties during 2012 over the future of the AMFm, and the need for some extractors to sell 'at any price' e.g. to meet borrowing and other costs, artemisinin prices have recently fallen to below production cost (although increasing confidence in the 2013 'market' is reportedly resulting in prices now slightly increasing). If firm funding levels and ACT forecasts for 2014, are not clarified by March, Artemisia plantings could be seriously reduced in 2013/2014, leading again to artemisinin shortages and price instability (the reports that large volumes of semi-synthetic artemisinin could be available in 2014, may also add to the decision by extractors to plant even less natural artemisinin in 2013/14).

In order to stabilise the artemisinin market, the conference proposed:

a) The urgent need to confirm funds available for ACT purchase and thereby the production of accurate and detailed ACT forecasts for 2014-2016.
b) Investigation into the introduction of a global Artemisinin Sector Association which would:
    - Create greater communication and decision making between all levels of the Artemisia – ACT supply chain on a regular basis e.g. incorporating the role presently played by A2S2 and Artemisinin Conference.
    - Assist the development and coordination of country/regional associations in China, Vietnam and other production regions.
    - Help introduce Accreditation/Codes of Practice e.g. contractual agreements, socially responsible practices etc, to extractors which would be recognised (in purchase contacts) by API/ACT buyers.
    - Maintain and develop Market Intelligence and Technical Information gathering and dissemination.

- Provide regular monitoring of prices and web presentation.

c) Greater coordination of the introduction of semi-synthetic artemisinin to ensure total artemisinin supply i.e. from natural and semi-synthetic sources, is maintained.
d) Ensuring prices do not fall below production costs ($400-450/kg), but not to set price ceilings.
e) Revisit the potential for buffer stocks i.e. artemisinin, API, ACTs.

4) <u>Semi-synthetic artemisinin and market impact</u>:

The introduction of semi-synthetic artemisinin (SSA) and the role it can play in stabilising artemisinin supply and prices, has been the subject of much discussion over the past six Artemisinin Conferences. In order that the natural artemisinin producers can plan their long term production, the need to have accurate and timely information regarding the introduction time tables, tonnages and price of SSA, has been regularly requested. At the conference Sanofi stated that they would have 30MT of SSA available for their own API/ACT production in 2013 and had the capacity to produce 60MT in 2014. Price quoted was between $350 - $400/kg (although on API manufacturer stated that they had been quoted $450/kg).

The questions raised at the conference centred on the fact that such large volumes of SSA, being introduced over such a short period of time into a potentially reducing artemisinin market, could have a serious destabilising effect. Many natural producers are reliant on short term trade finance and continued investment into infrastructure, which could lead these investors to reconsider their support. If such a situation arose, the resulting closure of extractors could lead to a sharp and significant reduction in available artemisinin from the natural sector. Equally, concern was expressed that the semi-synthetic artemisinin is to be marketed on a not for profit basis, which could result in a price being below that of artemisinin from natural sources ($400-450/kg) as the existing extractors need to make a profit i.e. as is normal in commercial enterprises. <u>Whilst most conference delegates accepted that the availability of semi-synthetic artemisinin is now a reality, its uncoordinated introduction, instead of helping to stabilise the artemisinin market could, instead, potentially lead to its destabilisation i.e. future shortage of naturally produced artemisinin and price volatility.</u>

The conference therefore proposed:

1) There must be close coordination in the supply of artemisinin from both natural and semi-synthetic sources, with open and regular discussion and dissemination of information on volumes, timing and prices to ensure both coordinated and sustainable supply.
2) Clarification of the role of the Commercial Oversight Committee. It was requested that there is representation on the Committee (or through another body) by an independent person/organisation and/or from the natural artemisinin production sector, in order to ensure transparency and information flow.
3) Need for clarification as to how the Sanofi SSA will be made available to other API/ACT manufacturers after 2013/14 i.e. will it be on a first come/first served basis, or proportioned out i.e. fair availability to all manufacturers.
4) SSA was originally developed with the objective of providing price stabilisation in the market, although with the higher tonnage now being forecast for 2014 i.e. around 33% of total artemisinin need, is this still the case? If to an agreed standard, this objective could still be achieved through the introduction of a well managed and financed buffer stock of SSA to be available during shortages of natural artemisinin.

5) <u>Artemisinin Technical Issues</u>:

a) <u>High Yielding Artemisia *Annua* Varieties</u>:
Updates on the development trails of High Yielding Varieties from CNAP, University of York, UK; Mediplant, Switzerland; and NIAB, UK, have been regularly presented over past conferences. However, since 2011 commercial sowing of high yielding varieties from Mediplant and NIAB has increased to a point where most Artemisia plantings in Madagascar and East Africa in 2012 were with these varieties. CNAP trials have also now resulted in varieties, bred for different climatic conditions, being available for commercial planting (through East-West Seeds).

Trials by Mediplant, using different planting densities, in different climatic/growing conditions, has shown that leaf yields can vary widely. It is therefore essential that care is taken to ensure the right planting density, as well as variety choice i.e. through location trials.

As well as the choice of seed variety, the conference stressed the need for good field management practices and water availability, if the full production potential of the seed/variety is to be achieved.

b) Changes in WHO Recommendations (draft) as Artemisinin as an API and Starting Material: Extensive discussions have been undertaken during recent Artemisinin Conferences concerning the status of artemisinin as a 'starting material', as opposed to being categorised as an API. The outcomes of these presentations and discussions has resulted in artemisinin now being able to be categorised as a starting material and therefore not be subject to the manufacturing constraints as an API e.g. not requiring GMP standards.

The initial draft proposal in 2011 for ART as starting material, recommended Artemisitene levels of 0.08% and 9-epiART (single impurity) of 1%, an increase of x 5.7 (from 0.014%) and x4 (from 0.25%) respectively over the WHO monograph for ART. Justification was based on "historical" lack of evidence for detrimental effects. In the 2012 draft, the allowable level of Artemisitene was increased to 0.2% (a further increase of x2.4) with a reduction in total allowable impurities from 5% to 3%.

In 2012, the draft recommendation for ART as an API, also proposed increased levels of Artemisitene (0.014% to 0.15%) and 9-apiART (0.25% to 0.3%) while keeping the same overall levels of impurities.

The questions asked by the presentation at the conference were:

- Why has the Artemisitene level been increased, particularly what is the scientific reason given that this change could affect the upstream derivatisation process?
- Why has this proposed change not been more widely circulated for discussion to the artemisinin/API producing industry. This was a request raised at the Artemisinin Conferences in Madagascar in 2010 and in Vietnam in 2011 and one which had been agreed to be actioned upon.

Malcolm Cutler March 2013