BREAK-OUT SESSIONS
Comments & Questions

The following points were raised during the break-out sessions and in discussion after the presentations. Note: the consensus of the main comments and recommendations on future activities, are included in the Introduction/Summary.

AGRICULTURE, PLANT PRODUCTION

- FAO involvement in Good Agricultural Practice (GAP) for Artemisia: FAO has not expressed interest, and the *Artemisia annua* crop is not seen as a priority.
- Artemisia growing is not seen by donors as a part of the public health issue, resulting, therefore, in a lack of funds.
- Cultivation and extraction in East Africa has reached high levels of quality and documentation.
- Good quality seeds give good quality plants. Keeping seeds from high-yielding plants does not guarantee a good yield.
- Adaptation or selection for individual growing conditions is important.
- Need to harvest before flowering and keep all the leaves including the 'dead' ones is important to maximise yields.
- Farmers need to be closely linked to the extractors. India has a system of recognised (A1) growers. In Vietnam certain regions with known yields are paid directly by weight. In Brazil and Africa, below an agreed percentage yield is discarded and above an agreed percentage is paid a bonus.
- Most successful (profitable) relationships develop from close grower/extractor relationships through extension programs involving a) seed supply b) nursery development c) plant breeding programmes d) Fertilisers e.g. NPK fertilizer in Fe rich soils e) causes of flowering f) the advantage of cuttings g) harvest, drying (effect of sun/heat) and collection (all the leaf material).
- Post-harvest science is lacking - effects of long term storage: some leaves appear to lose 50% of artemisinin in 12 months, others can keep the crop (with just 10% artemisinin loss) for 3 years. Effect of water content, temperature, light etc.
- Raw material sampling and handling recommendations needed - leaf content may not be same as extractability. Post-harvest and post-extraction conversions need to be studied.
- More information needed (Growers Manual - Best Practices)) on growing conditions, drying conditions and storage conditions.
- Has any one published a manual for growing artemisinin i.e. seeds - what is the best way to grow them, when do you plant out, what is the optimum spacing what is the best fertilizer to use? What is the best watering schedule, temperature, and sunlight? What to look for in replanting, taking cuttings, harvesting and how to optimise stem to leaf ratios.
- The GAP report needs to be strengthened and supported.
- Local adaptation of seed needed - what are the parameters?
- What is the right time for harvest and the best conditions for drying?
- What causes stress and does this increase or decrease the artemisinin content?

EXTRACTION, PROCESSING & TESTING

- Extraction methods: Relating to pure artemisinin (without further derivitisation) - if used as API, the extraction method needs to be qualified, i.e., GMP levels - current extraction methods and standards might not meet stringent criteria.
- Other examples in the food industry show, that improvements of production/ processing might be more sustainable over older, cheaper technology i.e. efficiency, safety etc, whereas cost issues should only be part of the assessment.

- New extraction technologies: need to show increase in efficiency, improve solvent loss and lower costs over existing methods. It can take up to 1 1/2 yrs to develop the required protocols to satisfy buyers.
- $scCO_2$ can co-purify artemisinic acid, and could therefore benefit the extraction process.
- WHO has assisted African producers to reach GMP levels - efforts ongoing but needs more funds (from EU).
- Coordination needed between national and WHO initiatives to implement GMP in developing countries.
- Need standardized labs with standard protocols and independently certified labs.
- Need reference labs either government- or state-run or certified.
- Need, as soon as possible, reference standards at all levels.
- Need to upgrade the monograph and more information on tests being used by purchasers.
- Primary extraction needs, how much is thrown away, solvent toxicology effect safe practices, effect of other solvents used with hexane.
- Precursors such as Dihydro-artemisinic acid and artemisinic acid – what is the effect on storage?
- Real shelf-life data, what derivatives are needed, DHA, artesunate, arteether artemisinin?
- We still don't have an accurate picture of how much we are getting out of the plants and we have no reliable assays to determine this. This is important when trying to stay competitive.
- Quality problems in API especially in determining impurities, what are the pharmaceutical companies really testing for and what tests do they use?
- Studies from four different sources showed differences in impurity profile. How much of a problem is this?
- Do we need 99+% purity - the last 1% can easily double the price. Is it really necessary given that derivitisation still has to occur?
- FDA suggests a maximum of 2% impurity together with the characterisation of the major impurities. Why change the accepted pharmaceutical standards?
- Residual solvents can be a problem and some methods to remove them cause product degradation.
- Yield from the plant is extremely important, not only to growers in determining what they get paid but also to extractors to determine their extraction yields. It would also speed up optimisation of growing and extraction.
- What is the best water content for storage?
- Need for a rapid test of artemisinin levels for farmers.
- In field testing not a priority, unless linked to extractability and payment.

MARKETING

- Acceptable, sustainable price for Artemisinin (rapid assessment from participants at the conference initiated by the Clinton Foundation): approx $250-275 minimum, up to $300 per kilo.
- Global subsidy: still only a proposal, not approved and the financial resources have not yet been provided. Suppliers should not dramatically ramp up capacities based on these preliminary discussions.
- Global fund: What does it do and how do its decisions affect growers and extractors. Can countries freely decide on allocation of funds between anti-malarial strategies? Countries need to specify the budget allocation between transmission control methods and making drugs available (this has to be specified in the countries' proposition, and is reviewed by the Technical Review Panel, which assesses the quality and suitability for funding, of the proposition). Transfer of money for procurement will be accelerated in revised policies.
- National Malaria Control Programs (NMCPs) procure treatments according to their national treatment guidelines, WHO makes recommendations according to

resistance profile, information is transparent and available through website. Global Fund should procure pre-qualified (PQ) products. UN agencies cannot procure non-PQ medications if there are PQ alternatives.

- Better prediction on needs from not just public market but also the private market.
- Prices came down due to competition and over supply. Buying from China and Vietnam has two distinct segments, contracts which are predictable both in quantities and prices (which leads to predictable quality) and a short tern spot market which is has unpredictable prices quality and supply.
- From a suppliers point of view it is difficult to predict what to do, complicated by unknown stability (shelf-life) of the plants and the extract.
- Forecasting in the public sector is easier. More work needs to be done in the private sector - maybe an ACT subsidy will help forecasting.
- Is it possible to have a guarantee minimum price, for the plants, for artemisinin, for the derivatives?
- Artemisia should be treated as a small specialized market and not a commodity.

REGULATORY & OTHER COMMENTS

- Has a study been done on a pre-purchase plan and an artemisinin bank? What is the economics of this idea?
- Artemisia bank: Not the WHO preferred way. Who would take the risk to implement an Artemisia bank?
    - China - since Artemisia is a politically strategic crop? Would it create a state-run market economy? Previous examples for state- run production planning are very negative. It is risky to be dependent on a single geographic region (for production). In previous years diversification has been promoted.
    - World Bank as an initiator and keeper of an artemisinin bank? - Unlikely, because this is not the mandate of the World Bank.
- Artemisia as a catalyst to develop African capacities to grow, extract, purify and manufacture plant-based medications: In 1999 a DFID-funded pilot study to investigate African-based artemisinin production and a subsequent Technoserve study in 2004, showed the potential for African production. There is a strong political emphasis to develop capacities, especially if there is local value added within the supply chain, i.e. through to derivitisation and local ACT manufacture.
- Need for bibliography, web page, including new methods, growers, extractors and drug producers.
- Other uses of Artemisia/artemisinin – needs research.
- Accelerate the WHO prequalification (PQ) process, provide resources for PQ training, mock inspections, clarity on API and Bioequivalence.
- What is the correct way for generic manufacturers to seek regulatory approval? Equivalency and safety is the usual way but the bio-equivalency and stability are additional problems for ACTs.
- What support is available, for the farmers, extractors, derivatisers, and pharma companies? This should be made transparent.