

Position paper on Financial Times article by Andrew Jack, March 30 2007

**“Corners are cut in order to bring drugs to Africa
Treatments against tropical diseases are being launched without western regulatory
scrutiny”**

The article raises several issues regarding ASAQ launch:

1. “Bypassing of stringent standards of developed world regulators”, and “getting quick approval in Morocco, based on relatively limited scientific data”
2. Issues with evaluation of drugs that are new formulations of existing medicines
3. Safety surveillance after the launch of medicines in the developing world.

The following points may be made in reply to these assertions:

Short Background

Artesunate (AS) plus amodiaquine (AQ) is one of the three WHO-recommended ACTs to treat uncomplicated *falciparum* malaria in Africa. Safe and rapidly acting, the combination of artesunate (AS) and amodiaquine (AQ) for malaria treatment in Africa is included in the latest WHO guidelines. Both AS and AQ are included in the WHO List of Essential Medicines, and the development of fixed-dose formulations is encouraged by the WHO.

The combination has been used by millions of patients during the last 3-4 years. AS+AQ has been adopted in national policies to treat uncomplicated malaria in 20 countries in Africa and in Indonesia. 11 additional countries in Africa, and also some districts in India could consider AS+AQ to treat uncomplicated malaria.

Since 2002, ASAQ has been developed as fixed-dose combination of AS and AQ by the FACT partners who have been supervised by of a group of experts and managed by the non-profit product development organization, DNDi, together with sanofi-aventis after 2004.

ASAQ has a simple dosing regimen which should improve adherence to prescribed regimens: 1 tablet per day for 3 days for infants and children, and 2 tablets once a day for 3 days for adolescents and adults.

The doses of ASAQ were carefully chosen based on study results recently published in the *WHO Bulletin* (Taylor et al. 2006). Demographic data from over 88,000 African children and adults, including malaria patients, were used to select four different presentations based on age and weight. These AS and AQ doses provide the smallest risks of over- and under-dosing.

ASAQ is available under the name Artesunate-Amodiaquine Winthrop® (ASAQ) for public markets, and under the brand name Coarsucam® for private markets.

1. “Bypassing of stringent standards of developed world regulators”, and “getting quick approval in Morocco, based on relatively limited scientific data”

DNDi and sanofi-aventis are not cutting any corners on drug quality, efficacy, or safety in the ASAQ registration strategy. Considering the background of the AS + AQ combination and the urgent need of patients in malaria endemic countries, sanofi-aventis, with the support of DNDi, chose to register in Morocco and in disease-endemic countries as well as to apply for WHO prequalification to allow qualified assessment experts to evaluate the quality,

safety and efficacy of the medicine. In making that choice, we reaffirmed our compliance with internationally recognised quality standards. Morocco is where this drug is manufactured, and it is customary to register a drug first in the country of manufacture. We reject the argument that “Western regulatory authorities” are the only ones that are qualified to address public health issues in the developing world.

Box 1: Q&A Concerning the Registration Strategy

Why did you register in Morocco?

Registration process started in Morocco in December 2005, and marketing authorization was granted on February 1, 2007.

→ Choice of Morocco as manufacturing country is consistent with sanofi-aventis approach to manufacture drugs “for the South” in the “South”

→ Co-blister of AS and AQ were already registered and manufactured in Morocco: thus local authorities know this drug combination well

→ Important financial investments have been made to ensure that the sanofi-aventis plant complies with worldwide sanofi-aventis quality standards, as well as those of multiple international pharmaceutical companies that contract this plant to manufacture their own drugs for the Moroccan market

→ Moroccan standards are in line with international standards:

- The National Drugs Control Laboratory is the reference lab for the French African network and is being accredited by the European network of National Drugs Control Laboratories
- Morocco is a WHO reference country for pharmacovigilance in Sub-Saharan Africa

Where is ASAQ registered today?

ASAQ was submitted for registration in 23 African countries and is already registered in 12 countries (Benin, Burkina Faso, Congo, Ivory Coast, Gabon, Guinea, Ghana, Mali, Mauritania, RDC, Togo and Zanzibar).

After completion of registration in Africa, ASAQ registration will be considered in selected Asian and Latin American countries, based on local recommendations and resistance patterns.

Why did you not consider registration by the US FDA or the European EMEA?

Regulatory assessments of risk and benefit apply primarily to the population of the regulatory authority’s country. Malaria kills 3000 children each day, with few of those preventable deaths occurring in Europe or North America.

ASAQ is not intended for use in American or European travellers, who are rightly the first priority for American and European regulatory authorities. Filing for registration in the US or in Europe is not excluded, but the current focus is on malaria-endemic countries.

Artesunate is the most widely used artemisinin derivative in the world, yet for the US FDA and the EMEA, it is still a New Chemical Entity, whereas it is not for the WHO. Amodiaquine is registered in many European countries (eg. France).

The WHO prequalification process has been chosen based on WHO’s ample regulatory documentation on artesunate and on amodiaquine: Arsumax® (the sanofi-aventis artesunate) is already WHO prequalified. Also, Arsucam® (the sanofi-aventis artesunate-amodiaquine co-blister) was submitted for WHO prequalification; work on this file was suspended to focus on ASAQ in line with WHO recommendations to develop co-formulations.

The WHO prequalification process was chosen over the EMEA "Article 58" procedure because the latter has never been used for assessing a combination of compounds which were not already licensed in Europe, and is purely a consultative scientific process.

Where are you with WHO prequalification of ASAQ?

ASAQ has entered the WHO prequalification process. The prequalification dossier was submitted to the WHO on February 23, 2007 and was formally referenced on March 12, under the following numbers:

artesunate/amodiaquine 25/67.5 mg, bilayer tablet (dossier number MA 56)

artesunate/amodiaquine 50/135 mg, bilayer tablet (dossier number MA 57)

artesunate/amodiaquine 100/270 mg, bilayer tablet (dossier number MA 58)

As part of the prequalification process, WHO has proposed a plant inspection in Morocco to be carried out on June 11-13, 2007.

What about quality assessments?

A GMP inspection of the s-a production site in Morocco has been carried out by international GMP experts appointed by Médecins Sans Frontières last January 30, 2007, without any "critical" findings. The final report will be communicated to UNICEF/WHO.

What about ASAQ on the WHO model list of essential medicines?

An application will be filed for ASAQ to be included in the next review session, in July 2007, which will be focused on essential medicines for children.

2. Evaluation of drugs that are new formulations of existing medicines

The regulatory dossiers that were submitted to Morocco, the African malaria-endemic countries, and the WHO prequalification process, strictly comply with these institutions' respective regulatory requirements. We have answered questions from Moroccan and some sub-Saharan African regulatory authorities. We are awaiting feedback from the WHO and are ready to answer their queries.

Box 2: Key Elements of the Registration File Submitted to the WHO for Prequalification of the Fixed-Dose Combination (FDC) of ASAQ

- 1) A full "Quality package" (former CMC file) in ICH format and with ICH compatible information. Extensive work on stability and packaging and also on potential degradation products. This data has been strengthened by sanofi-aventis in their file from industrial batches.
- 2) A pre-clinical safety package testing of the drug substances used for the new FDC. DNDi's approach was "the well-established" use argument for presenting the minimal package based mainly on genotoxicity. Sanofi-aventis has performed a series of 47 additional studies (including safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive and development toxicity on artesunate on amodiaquine and on the combination).
- 3) The following elements were available as information from the start of the FACT program and are available in the clinical file:
 - The initial multi-centre study performed by TDR (with supplies of artesunate from Sanofi) in Africa demonstrating the therapeutic benefit of using the combination of artesunate (AS) with amodiaquine (AQ) versus AQ alone (*published*).
 - A pharmacokinetic study performed by TDR (with supplies of artesunate by

Sanofi) comparing the kinetics of AS, AQ, and AS+AQ in volunteers, showing the absence of clinically significant Pharmacokinetic interactions between the two drugs.

4) New additional clinical studies:

- A Pharmacokinetic/Tolerance/ECG study in 24 healthy volunteers comparing the new fixed dose formulation and the separate drugs administered at the recommended dose. There were no unexpected results in the tolerance/ECG part. Peak blood levels were attained more rapidly with the FDC. The blood levels of parent drug and metabolites were similar for the separate and fixed-dose combinations. There was a tendency for less variability with the FDC compared to the separate drugs. A full ICH type report is available (*to be published*).
- The field study in 750 patients in Burkina Faso (age of 6 months to 5 years), with 28-day follow-up, demonstrated the statistical non-inferiority of the FDC compared to the two drugs given separately. Rapid curative action (reductions in fever and parasitaemia) was observed. No unknown side effects were observed and from a clinical point of view the FDC was tolerated as well as the two drugs given separately. A full ICH-type report is available (*to be published*).
- A meta-analysis of 30 studies (18 African countries) involving AS+AQ versus single components or other combinations has been performed and oral presentations of the data made at the ASTMH in Atlanta (Olliaro et al, 2006). In more than 5000 patients the advantage of the AS+AQ combination versus single component and the similar efficacy compared to other ACT when PCR corrected data were demonstrated (*submitted for publication*).
- This meta-analysis includes a study of 3500 patients started in 1999 in Casamance region (Senegal) to assess effectiveness and tolerance with combined-free drugs and co-blisters. Long follow-up showed no development of resistance and safety of the combination (*to be published*).

5) Another important study was started by sanofi-aventis in 2006:

- A multi-centre study comparing Coartem (considered by the MHRA as the "gold standard") and ASAQ in about 1000 patients including adults. *This study, for which the clinical part is concluded, also compares ASAQ once versus twice a day. First results submitted for presentation at the European Congress on Tropical Medicine and International Health, Amsterdam, 24-28 May, 2007.*

3. Safety surveillance after the launch of medicines in the developing world

Sanofi-aventis and DNDi are acutely aware of the importance of monitoring the safety and efficacy of newly launched drugs in "real life" conditions, in order to detect issues that could not be identified during clinical development studies. This is a particular challenge in sub-Saharan Africa, where many countries do not have operative pharmacovigilance systems. To address this challenge, sanofi-aventis and DNDi are preparing a comprehensive post-marketing surveillance programme of studies of effectiveness and safety in the field so that high-quality clinical data on ASAQ is collected through sentinel sites in Africa. A meeting with experts is scheduled in May 2007, to finalize these plans.

Box 3 - Preliminary Plan of Pharmacovigilance Studies

The objective of this programme is to provide good-quality data through a variety of study designs and epidemiological settings. Through this plan, data will be collected from several thousands of treated patients, with the aim of addressing specific issues such as safety and efficacy after repeated ASAQ administration and in special populations (pregnant women, HIV positive patients), etc. The following studies are being considered:

- Comparative randomized clinical trials. These provide good-quality comparative data, but they involve relatively few patients. Three such studies are about to be launched, comparing ASAQ with other ACTs, in Benin, Cameroon and a multinational study.
- Cohort studies. 2 groups, each of 200 randomized patients, will be followed over several years after receiving either ASAQ or a comparator during each malaria attack. This follow-up will enable the impact of renewed ACT administration on efficacy and tolerability to be evaluated. Two such studies are under preparation in Senegal (adults and children) and Uganda (children).
- Large-scale tolerability study: a comparative study, focused on short-term safety data collection of several thousands of patients, is under preparation.
- Implementation side-studies: the aim is to collect pharmacovigilance data in selected countries that have implemented ASAQ in their national programs, for all patients treated in a community health centre. Additionally, efficacy, clinical and biological tolerability data will be collected on some of the randomized patients. Several countries and sites could be considered for such studies. Final decision is dependent on countries' choice of ACT.

Addition opportunities for data collection through a variety of channels will be considered: networks of private physicians, selected pharmacists and "antimalarial integrated action programs" set up in collaboration with national malaria control programs and NGOs (4 such programs are under way or being prepared).