

## Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo

Magnus A. Atemnkeng, Katelijne De Cock and Jacqueline Plaizier-Vercammen

Department of Pharmaceutical Technology and Physical Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium

### Summary

**OBJECTIVES** Artemisinin-derivative drugs are widely used to treat *Plasmodium falciparum* malaria and very few studies have investigated the quality of these medicines in Africa. We analysed the active ingredient contents of artemisinin-derivative drugs marketed in Kenya and DR Congo.

**METHODS** We analysed tablets, capsules, dry suspensions and injections (IM) containing either artemether (AM), arteether (AE), artesunate (ARS) or dihydroartemisinin (DHA). The content of active ingredients and preservatives was determined quantitatively using validated HPLC-UV methods. All analyses were done according to European pharmacopoeia requirements.

**RESULTS** Labelled active ingredients were identified in all samples, however with varying dosages. Nine of the 24 drug samples analysed did not comply with the pharmacopoeial requirements of 95–105%: seven samples were underdosed and two were slightly overdosed. DHA was the active ingredient in 57% of the underdosed samples. AE injections had the lowest drug content (77%). Two-thirds of the dry powder suspensions were either substandard or fake. Tablets were up to 23% out of range. Unidentified peaks were observed on the chromatograms of AE IM injections and a DHA dry powder.

**CONCLUSIONS** Counterfeit or substandard artemisinin-derivative drugs are being sold in parts of Africa, presenting a potential route for resistance development in the future. Appropriate measures need to be taken to maintain proper and safe use of these medicines.

**keywords** antimalarials, artemisinin derivatives, quality control, counterfeit, reversed-phase HPLC

### Introduction

Malaria continues to be the number one killer disease in third world countries especially those in Africa south of the Sahara. According to the recent world malaria report (<http://www.rbm.who.int/wmr2005>) falciparum malaria alone accounts for more than 1 million deaths and causes death to about 18% of children less than 5 years old each year. In addition to the small number of drugs available or under development, the rising prevalence of multidrug-resistant falciparum malaria is also accountable for this surge (Price & Nosten 2001). The problem of counterfeit or poor quality antimalarials is well established in Africa and this might have contributed to the development of resistance by the cheap and hitherto effective chloroquine: when patients are exposed to subtherapeutic doses of a drug, resulting in low bioavailability, this will promote selection of resistance and treatment failure (Petalanda 1995; Maponga & Ondari 2003). Recently, Newton *et al.* (2006) reported the documented death of a 23-year-old man, owing to the administration of fake artesunate (ARS), in eastern Burma. Poor quality of drugs may not only be the result of low therapeutic doses but also inactive

ingredients, incorrect excipients, contamination or degradation. Because of the declining efficacy of the quinolones and the antifolates, attention has shifted towards novel agents such as the artemisinin derivatives, to which resistance has not yet been reported. These compounds are characterized by a short half-life and rapid mode of action against gametocytes, the sexual stages of the parasite that infect mosquitoes (Navaratman *et al.* 2000; Ridley 2002). In Africa, the unofficial drug sector is not limited to illegitimate ambulatory drug sellers or stall owners in the marketplace. It is not uncommon to find cheap and ineffective drug copies existing next to the original or generic brand in the same pharmacy, or supplied by the same wholesalers (Aka & Legris 2005). Many pharmacists break the law by dispensing prescription-only drugs over the counter or providing counterfeit replacements to patients with insufficient money to purchase the original. It is therefore very important to put in place measures against abusive use of artemisinin derivatives, to secure their long-term efficacy. The FDA website (<http://www.fda.gov/oc/initiatives/counterfeit/>) suggests that more than 50% of antimalarials in Africa are counterfeit. Fake antimalarials appear in all types of dosage forms. Cross-sectional surveys

reported counterfeit ARS tablets in Cambodia (Rozendaal 2001) and the greater Mekong Southeast Asia region (Newton *et al.* 2003). We have not come across a similar study that has been performed in Africa, where malaria is most prevalent. However, counterfeit Cotecxin was found in Tanzania (Anonymous 2001). In most parts of Africa, artemisinin derivatives are now common in the big cities and can easily be acquired without medical prescription.

Quality evaluation studies are primarily important to provide information on the drug content and second, to identify the cause (if any) of the poor quality, especially in the field. Thus simple, rapid and inexpensive assays are necessary to easily set up an on-site quality control unit before large-scale quality evaluation can be performed by a reference laboratory (Green *et al.* 2001; Basco 2004).

In this study, we analysed the quality of artemisinin derivatives bought in two endemic African countries: Kenya and the Democratic Republic of Congo. We tested the different dosage forms on the market and also a semi-industrial (pilot) batch of an artemether (AM) dry suspension.

## Materials and methods

### HPLC instrumentation

A Merck-Hitachi HPLC system consisting of a LaChrom L-7100 pump connected to an L-7400 UV detector and a D-7500 integrator (Merck-Hitachi Ltd, Tokyo, Japan) were used. For AM, arteether (AE) and dihydroartemisinin (DHA) analyses, a Nucleosil 120–4 C<sub>18</sub> column, 125 mm long by 4 mm (i.d.) and 5 µm particle size from Macherey-Nagel, Düren, Germany was employed. Separation of ARS was achieved on a LichroCart 250–4, LiChrospher 100, RP-18 column (5 µm, particle size) from Merck, Darmstadt, Germany. The following mobile phase compositions were prepared to elute the different components: AM: Acetonitrile:water:KH<sub>2</sub>PO<sub>4</sub> (0.05 M, pH 5.0) buffer (480:100:320, v/v/v) DHA: Acetonitrile:water:KH<sub>2</sub>PO<sub>4</sub> (0.05 M, pH 5.0) buffer (480:600:500, v/v/v) AE: Acetonitrile:water:KH<sub>2</sub>PO<sub>4</sub> (0.05 M, pH 5.0) buffer (500:100:320, v/v/v) ARS: Acetonitrile:KH<sub>2</sub>PO<sub>4</sub> (0.05 M, pH 5.0) buffer (600:500, v/v).

Detection of these analytes was set at 215 nm. In any DHA dry suspension that used a combination of methylparaben (MP) and propylparaben (PP) as preservative, the mobile phase was adjusted to separate all four components ( $\alpha$ -DHA,  $\beta$ -DHA, MP and PP). For each analysis, a constant flow speed of 1.0 ml/min was maintained and injections were done with a 20-µl Rheodyne® loop. The column was flushed between analysis with a

methanol:water (50:50, v/v) solvent mixture and ambient temperature conditions were maintained throughout the experiments.

### Sample collection

All drugs analysed in this study were obtained randomly from the main pharmacies within Nairobi in Kenya and Bukavu in DR Congo in 2004. Samples were purchased anonymously by local nationals based on their availability in the pharmacies and maintained in the original package as supplied by the manufacturer. All tablets were packaged in blister packs. The packaging was examined for any features of illegal prints. Further checks to distinguish the genuine drugs from the fake were not performed. From each sample the origin, labelled dose, type of preservative (if present), registration status and shelf-life of the active drug were noted. An Artenam® semi-industrial batch dry powder suspension containing AM (180 mg/60 ml) was added to the study. All analyses were performed before the expiry dates of the product. Table 1 presents a summary of the drugs analysed.

AM, AE, ARS and DHA reference standards were kindly provided by Arenco Pharmaceutica, Geel, Belgium. MP and PP were obtained from Federa, Brussels, Belgium.

### Sample analysis

The tablets were weighed, crushed and dissolved in the appropriate solvent as its corresponding standard solution except for the Artemos® ( $\beta$ -AM) softgel capsules which uses soya oil as vehicle. The latter was treated for analysis by dissolving the content of each capsule in a 4:1 (v/v) methanol:dichloromethane solvent mixture.

Powder in each bottle was weighed and for the DHA dry suspensions, exactly 200 ml of methanol:water (80:20, v/v) mixture was added to eliminate the influence of the unknown matrix and powder volume in the analysis. We employed this solvent mixture in order to use the content of the same bottle to analyse both the active drug and the preservative. For the AM dry powders, exactly 200 ml of pure methanol was added. The bottles were mixed, ultrasonicated and their contents centrifuged at 3000 rpm ( $g = 1512$ ) for 15 min. The supernatant was injected without further dilution into the chromatograph. After addition of water to the dry powder, the stability of the actives was also followed for 7 days.

For the Emal<sup>TM</sup> IM injections, the tips were cut open and the content transferred into separate 50-ml volumetric flasks. To completely empty the content, serial rinsing with isopropanol was done and the solution raised to the mark with the same solvent. Isopropanol was the most suitable

**Table 1** Summary of formulations tested with the percentage of drug content

Brand name/manufacture	Dosage form	Country bought	Registration status	Active compound/claimed dose	Percent found
Artenam <sup>®</sup> , Arenco Pharmaceutica, Belgium	Tablet	Kenya	Registered	Artemether, 50 mg	100.0
Cosunate <sup>®</sup> , Cosmos Ltd, Kenya	Tablet	Kenya	Registered	Artesunate, 50 mg	101.2
Gsunate Forte <sup>®</sup> , GVS Labs, India	Tablet	Kenya	Registered	Artesunate, 100 mg	88.5
Malarthem <sup>®</sup> , NIC Pharma, India	Tablet	Kenya	Registered	Artemether, 50 mg	100.0
Plasmotrim <sup>®</sup> 200, Mepha Ltd, Switzerland	Tablet	Kenya	Registered	Artesunate, 200 mg	100.0
Zysunate <sup>®</sup> , Cadila Healthcare Ltd, India	Tablet	Kenya	Registered	Artesunate, 50 mg	101.0
Arinate <sup>®</sup> , Dafra Pharma, Belgium	Tablet	DR Congo	Unknown	Artesunate, 100 mg	100.5
Artesaph <sup>®</sup> , Saphire sprl, Belgium	Tablet	DR Congo	Unknown	Artemether, 50 mg	100.6
Salaxin <sup>®</sup> , Saphire sprl, Belgium	Tablet	DR Congo	Unknown	Dihydroartemisinin, 60 mg	87.8
Saphnate <sup>®</sup> , Saphire sprl, Belgium	Tablet	DR Congo	Unknown	Artesunate, 100 mg	98.9
Alaxin <sup>®</sup> , GVS Labs, India	Tablet	Kenya	Registered	Dihydroartemisinin, 60 mg	107.8
Armax-200 <sup>®</sup> , London United Exports Ltd, England	Tablet	DR Congo	Unknown	Artesunate, 200 mg	99.0
Artesunate tablets, Guilin Pharm. Works, China	Tablet	DR Congo	Unknown	Artesunate, 50 mg	99.0
Gvither <sup>®</sup> , GVS Labs, India	Dry powder, 100 ml	Kenya	Registered	Artemether, 300 mg	88.2
Artenam, Arenco (semi-industrial batch), Belgium	Dry powder, 60 ml	–	–	Artemether, 180 mg	100.3
Santecxin <sup>®</sup> , Shsj, China	Dry powder, 80 ml	Kenya	Registered	Dihydroartemisinin, 160 mg	78.0
Alaxin <sup>®</sup> , GVS Labs, India	Dry powder, 80 ml	Kenya	Registered	Dihydroartemisinin, 160 mg	81.0
Artesiane <sup>®</sup> , Dafra Pharma, Belgium	Dry powder, 100 ml	Kenya	Registered	Artemether, 300 mg	100.0
Artexin <sup>®</sup> , Sphinx Pharma, Kenya	Dry powder, 80 ml	Kenya	Registered	Dihydroartemisinin, 160 mg	110.0
Cotecxin <sup>®</sup> , Jiaying Nanhu Pharma, China	Dry powder, 80 ml	Kenya	Registered	Dihydroartemisinin, 160 mg	94.1
Artenam <sup>®</sup> IM Paediatric, Arenco, Belgium	Injection, 2 ml	Kenya	Registered	Artemether, 40 mg	100.2
Artenam <sup>®</sup> IM Adult, Arenco, Belgium	Injection, 1 ml	Kenya	Registered	Artemether, 100 mg	100.6
EMAL <sup>TM</sup> Inj., Themis Medicare, India	Injection, 2 ml	Kenya	Registered	$\alpha$ - $\beta$ Arteether, 150 mg	77.0
Artemos <sup>TM</sup> , ETDZS Co., China	Softgel capsule	DR Congo	Unknown	Artemether, 40 mg	99.3

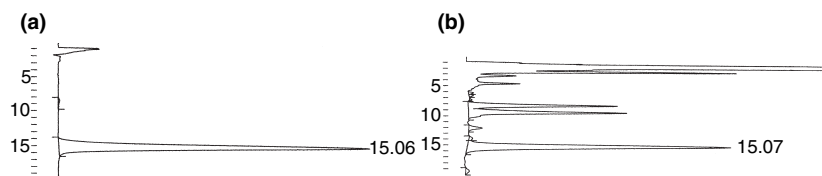
solvent in which *Arachis* oil (vehicle) was miscible. *Arachis* oil was not miscible with methanol, acetonitrile or dichloromethane. For the Artenam<sup>®</sup> IM injections, samples were dissolved in methanol, in which Miglyol<sup>®</sup> oil (vehicle) is soluble. All analyses were done in triplicate and the results presented are the mean of the three determinations. Standard solutions were accurately prepared to check the recovery of the actives.

## Results

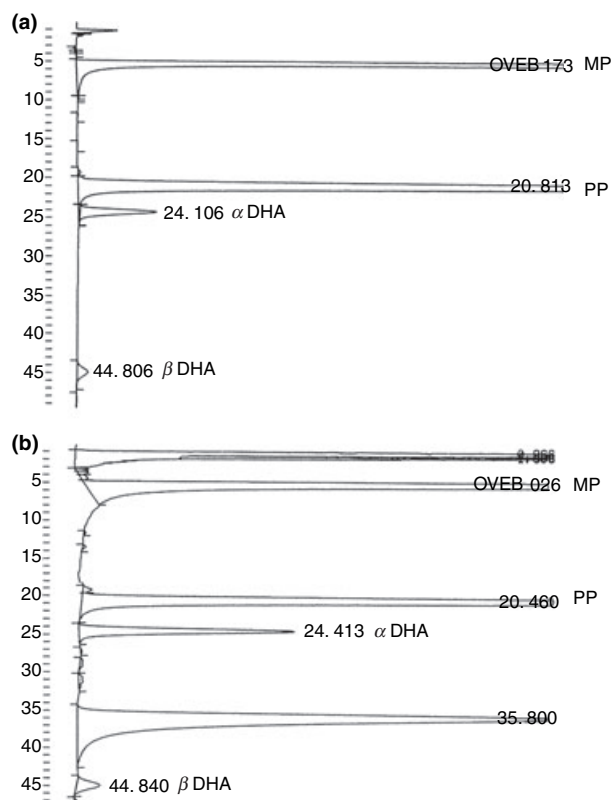
### Drug content in the dosage forms

Of the seven dry powders only Artenam<sup>®</sup> (AM 180 mg/60 ml) and Artesiane<sup>®</sup> (AM 300 mg/100 ml) indicated the excipient composition including the preservative used on the insert and/or container-closure system. Before use each dry powder was thoroughly shaken to free the powder, but in the Alaxin<sup>®</sup> bottle particles stuck together. No break-point was indicated on the IM AE ampoules (EMAL<sup>®</sup>; Themis Medicare, India). All packaging was examined before and after chemical analysis and there was no physical evidence that the medicines were counterfeit.

A total of 24 drugs were analysed (Table 1). Only 15 (62.5%) met the Ph. Eur. content requirements of 95–105% of active drug substance. No mislabelling was observed as all batches contained at least the claimed active ingredient though in varying amounts. Seven batches were underdosed while two batches were slightly overdosed containing respectively 107.8% and 110.0% of the claimed dose. Fifty-seven per cent (4/7) of the underdosed drugs were because of DHA samples alone; all but one AM formulation did not meet the requirements. AE IM injections contained only 77% of the labelled dose making it the drug with the lowest content. HPLC-UV analysis showed several unidentified peaks on the chromatograms of both the AE IM injections and Alaxin<sup>®</sup> dry suspension powder (Figures 1 and 2). To verify if these peaks were members of the artemisinin family, separate injections of AM, DHA, ARS and artemisinin were performed on the HPLC systems of AE and DHA. The results did not attribute the unidentified peaks to the tested artemisinin derivatives. Eighty-six per cent of the underdosed drugs were manufactured in China and India; one overdosed dry suspension was manufactured in Kenya (Table 1). A set of drugs manufactured by Saphire Lifesciences<sup>®</sup> sprl in



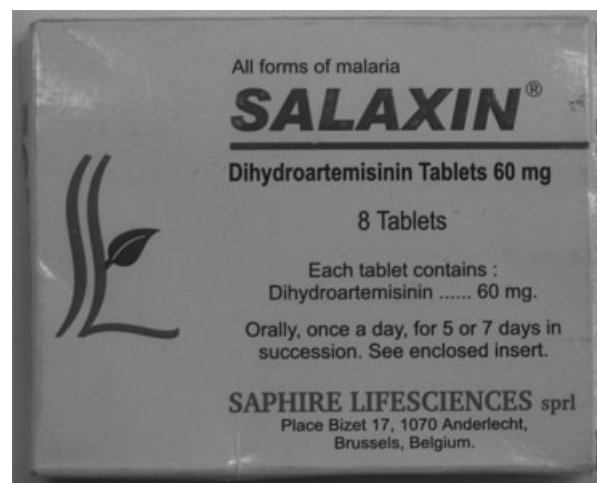
**Figure 1** HPLC chromatograms of: (a) standard (arteether) and (b) sample (EMAL<sup>®</sup> IM injection) solutions.



**Figure 2** HPLC chromatograms of: (a) standard (methylparaben, propylparaben,  $\alpha$ - and  $\beta$ -dihydroartemisinin, respectively) and (b) sample (Alaxin<sup>®</sup> dry suspension) solutions.

Belgium (Artesaph<sup>®</sup>, Saphnate<sup>®</sup> and Salaxin<sup>®</sup>) were all counterfeit as this company did not exist at the address mentioned on the packaging (Figure 3). This was confirmed by the Ministry of Health in Belgium. We verified the registration status of the drugs bought in Kenya ( $n = 16$ ) and all brands were registered by the Kenya Drug Regulatory Agency. It was not possible to obtain a similar reply from the Congo Health authorities. Of the registered medicines in Kenya, only 50% qualified for the content requirement.

Ten of 13 (77%) tablet formulations met the Ph. Eur. requirements, whereas 71% (5/7) of the dry suspension



**Figure 3** Picture of counterfeit dihydroartemisinin showing fake manufacturing company and address.

**Table 2** Percentage of formulations that met the requirements of the European Pharmacopoeia

Form	<i>n</i>	Percent conformed
Tablets	13	77
Dry suspensions	7	29
Injections	3	67
Registered drugs	16	50

powders were substandard. Two of the three injection ampoules conformed to the standards and both were from the same manufacturer (Arenco Pharmaceutica, Belgium). These results are summarized in Table 2. In the reconstituted suspensions the content of the actives did not deviate from the corresponding dry powder amount and remained constant throughout the 7-day storage period. This was valid for both AM and DHA.

## Discussion

Great hopes rest on artemisinin compounds as the best alternative drugs for the treatment against falciparum malaria. As these medicines gain widespread application,

uncontrolled use may follow. Therefore, effective ways have to be developed to maintain the efficacy of the long-lasting effects of artemisinin derivatives. In addition to propagating artemisinin combination therapy, marketed therapeutic dosage forms should be checked frequently. Normally this is the duty of regulatory authorities in the countries where the drug is registered. However, routine analysis of marketed drugs by control laboratories and independent groups is desirable, to alert patients and health professionals as early as possible. Exposure of parasites to underdosed drugs creates an easy route to selective resistance (White 1992). Several studies in Africa have investigated counterfeit drugs (Hogerzeil *et al.* 1992; Abdi *et al.* 1995; Taylor *et al.* 2001). In poor economies, people tend to buy cheap drugs without knowing whether they are genuine or fake. This may be especially common in case of the expensive artemisinin compounds.

Although the sample size in this study was small, it gives an indication about the availability of counterfeit artemisinins in Africa. The high proportion of out-of-range antimalarials (up to 37.5%) suggests that appropriate measures to check drug manufacture or importation are inefficient or absent. The reason why most of the sub-therapeutic dosage drugs were manufactured in India and China may be because of the laxity of Indian and Chinese regulatory bodies in checking exported medicines. In most countries, including industrialized economies, regulatory data are mainly available on drugs meant for local consumption, leaving exported medicines uncontrolled.

Importing low-income countries may not have the resources to evaluate all medicines that come in through different entry routes. Corruption may lead to drug companies being given sales licences without undergoing all the documented regulatory check procedures. In Kenya, where all the drugs analysed had an official sales licence, half were substandard. Hence, there was no clear correlation between registration and drug quality. Possible reasons for the poor quality here are probably poor manufacturing practice, poor storage conditions or insufficient quality assurance.

In most African nations, people have developed confidence in products developed abroad especially in Europe and the United States. Unscrupulous individuals seize this opportunity to produce illicit drugs and label them as manufactured in a European country or the United States – as we found with the three Sapphire Lifesciences products bought in Congo supposedly manufactured in Belgium.

We did not check whether the poor quality drugs were from a genuine or fake firm. The packaging alone gave no indication of a drug's genuineness. Adequate information concerning the dose, frequency of intake and adverse events was given in most inserts. Thus the container-closure system alone is not sufficient to determine drug

quality. Chemical analysis procedures are essential to check drug quality.

Generally, there are more counterfeit tablets on the market than other dosage forms because of their ready availability and low price. However, in this study the proportion of sub-standard dry powders was higher than that for the tablets; 71% and 23%, respectively.

Two drugs (IM AE injection and Alaxin® DHA dry powder) showed several extra peaks on their chromatograms. In artemisinin-derivative compounds such as  $\beta$ -AM, known impurities resulting from artemisinin, DHA and  $\alpha$ -AM may be present as these are intermediate products of synthesis process. The International Pharmacopoeia (2003) allows the content of the related substances to be 0.25%. None of the samples contained such known impurities. These unknown peaks may either be because of the excipients in the dry powder or, for the AE ampoules, to the *Arachis* oil used as vehicle. Additionally, these may be degradation products as both drugs were underdosed (81.0% and 77.0%, respectively). Several factors could be responsible for the degradation. Hogerzeil *et al.* (1992) found that extreme temperatures and high relative humidity could reduce drug content by up to 6%; some samples of ergometrine contained less than 80% of the stated amount. The low concentrations of active ingredients and the unidentified peaks could also result from poor storage conditions. Guilin ARS, which we tested in this study, has been counterfeited on an enormous scale in Asia (Dondorp *et al.* 2004).

Glass vials for injection drugs have to indicate a breakpoint at which the vial can easily be split open. Poorly manufactured vials may not only lead to inadequate dosing because of spillage but may also be a security concern to the administering staff. Intravenous ARS, which is likely to become important in the treatment of severe malaria, was not tested in this study.

The dry suspensions are particularly important as they are specifically made for children (although the dose can also be adapted to an adult patient). This is a very vulnerable age group; therefore, more precaution is necessary in formulating medicines for these patients. The powder particles have to freely disperse. If they stick or cake, as we observed in some samples, their reconstitution in water may be incomplete, resulting in incorrect doses.

This study also portrays the ambiguity surrounding the terms counterfeit and sub-standard drugs (Shakoor *et al.* 1997). Two of the three products from the fake company conformed to the content requirements. Several of the registered drugs were underdosed. Substandard compounds have the potential to do as much harm as counterfeit drugs or even more.

This work was performed on a small number of samples and needs further larger-scale surveys to determine the true extent of artemisinin derivatives' availability and quality in Africa. In addition, other quality attributes like uniformity of mass, disintegration time and dissolution rates of the tablets have to be studied. For the dry suspensions, the content and also the efficacy of the preservatives are essential, as these medicines are normally made for a vulnerable paediatric population. This will be studied in the near future.

## Conclusions

The emergence of poor quality artemisinin-like compounds in parts of Africa is real. If resistance develops to these vital medicines, endemic countries might take an even deeper economic plunge because of malaria. We need more aggressive crime control measures, better control of paediatric medicine approval procedures and rapid field tests to distinguish genuine and fake drugs. We need to involve not only medical practitioners and regulatory agencies, but also custom officials, police, local council officials and village heads. People should regularly hear about the adverse effects of poor quality medicines, especially in local markets, within community associations or at village meetings. Above all, original drugs must be made affordable. If fraud is less profitable, the risk to patients is minimized.

## References

- Abdi YA, Rimoy G, Ericsson Ö, Alm C & Masele AY (1995) Quality of chloroquine preparations marketed in Dar es Salaam, Tanzania. *Lancet* **346**, 116.
- Aka E & Legris C (2005) Let the buyer beware. *BMJ (British Medical Journal)* **331**, 358.
- Anonymous (2001) Fake malaria drugs in Tanzania. *Marketletter* (Article no. 011655604).
- Basco LK (2004) Molecular epidemiology of malaria in Cameroon. XIX. Quality of antimalarial drugs used for self-medication. *American Journal of Tropical Medicine and Hygiene* **70**, 245–250.
- Dondorp AM, Newton PN, Mayxay M *et al.* (2004) Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Tropical Medicine and International Health* **9**, 1241–1246.
- Green MD, Mount DL & Wirtz RA (2001) Authentication of artemether, artesunate and dihydroartemisinin antimalarial tablets using a simple colorimetric method. *Tropical Medicine and International Health* **6**(12), 980–982.
- Hogerzeil HV, Battersby A, Srdanovic V & Stjernstrom NE (1992) Stability of essential drugs during shipment to the tropics. *BMJ (British Medical Journal)* **304**, 210–212.
- Maponga C & Ondari C (2003) *The quality of antimalarials. A study in selected African countries*. WHO/EDM/PAR.2003.4. Geneva: World Health Organisation.
- Navaratman V, Mansor SM, Sit NW, Grace J, Li Q & Oliaro P (2000) Pharmacokinetics of artemisinin-type compounds. *Clinical Pharmacokinetics* **39**(4), 254–270.
- Newton PN, Dondorp A, Green M, Mayxay M & White NJ (2003) Counterfeit artesunate antimalarials in southeast Asia. *Lancet* **362**, 169.
- Newton PN, McGready R, Fernandez F *et al.* (2006) Manslaughter by fake artesunate in Asia – will Africa be next? *Public Library of Science* **3**(6), 752–755.
- Petralanda I (1995) Quality of antimalarial drugs and resistance to *Plasmodium vivax* in Amazonian region. *Lancet* **345**, 1433.
- Ph. Eur. (2003) – European Pharmacopoeia IV (2003) *Published by the European Directorate for the Quality of Medicines for the Council of Europe*. Strasbourg CEDEX1, France.
- Price RN & Nosten F (2001) Drug resistant falciparum malaria: clinical consequences and strategies for prevention. *Drug resistance updates* **4**, 187–196.
- Ridley RG (2002) Medical need, scientific opportunity and the drive for antimalarial drugs. *Nature* **415**, 686–693.
- Rozendaal J (2001) Fake antimalaria drugs in Cambodia. *Lancet* **357**, 890.
- Shakoor O, Taylor RB & Behrens RH (1997) Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health* **2**(9), 839–845.
- Taylor RB, Shakoor O, Behrens RH *et al.* (2001) Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet* **357**, 1933–1936.
- The International Pharmacopoeia (2003) *Monographs for anti-malarial drugs*, 3rd Edn., Vol. 5. World Health Organisation, Geneva, pp. 185–234.
- White NJ (1992) Antimalarial drug resistance: the pace quickens. *Journal of Antimicrobial Chemotherapy* **30**, 571–585.
- <http://www.fda.gov/oc/initiatives/counterfeit/>.
- <http://www.rbm.who.int/wmr2005>.

**Corresponding Author** Jacqueline Plaizier-Vercammen, Department of Pharmaceutical Technology and Physical Pharmacy, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium. Tel.: +32 24774598; Fax: +32 24774735; E-mail: jplaizie@vub.ac.be

**Contrôle de qualité des principes actifs d'antimalariques dérivés d'artémisinine au Kenya et en RDC**

**OBJECTIFS** Les médicaments dérivés d'artémisinine sont largement utilisés pour le traitement de malaria *Plasmodium falciparum* mais très peu d'études ont investigué la qualité de ces médicaments en Afrique. Nous avons analysé le contenu en principes actifs de médicaments dérivés d'artémisinine vendus au Kenya et en République Démocratique du Congo.

**MÉTHODES** Nous avons analysé les comprimés, les gélules, les suspensions sèches et les injectables contenant soit l'artémether, l'arteether, l'artesunate ou la dihydroartémisinine. La teneur en principe actifs et en conservateurs a été déterminée quantitativement par des méthodes HPLC-UV. Toutes les analyses ont été effectuées selon la Pharmacopée Européenne.

**RÉSULTATS** Les principes actifs mentionnés sur les étiquettes ont été identifiés dans tous les échantillons avec cependant des doses variables. Neuf échantillons sur les 24 analysés ne satisfaisaient pas aux exigences 95–105% de la Pharmacopée Européenne. Sept échantillons avaient une dose inférieure et deux échantillons étaient légèrement surdosés. La dihydroartémisinine était le principe actif dans 57% des échantillons sous dosés. Les injectables à l'arteether avaient la plus basse teneur en principe actif (77%). Deux tiers des suspensions sèches étaient soit en dessous du standard ou faux. Les comprimés étaient jusqu'à 23% en dehors des normes. Des pics non identifiés étaient observés sur les chromatogrammes des injectables à l'arteether et celui des poudres de dihydroartémisinine.

**CONCLUSIONS** Des contrefaçons ou des médicaments hors normes dérivés de l'artémisinine sont vendus dans certains endroits d'Afrique, représentant ainsi un moyen potentiel de développement de résistances pour de future. Des mesures appropriées sont nécessaires pour maintenir la bonne utilisation et la sûreté de ces médicaments.

**mots clés** Antimalariques, dérivés d'artémisinine, contrôle de qualité, contrefaçon, HPLC en phase inversée

**Control de calidad de ingredientes activos en antimaláricos derivados de la artemisinina dentro de Kenia y la República Democrática del Congo**

**OBJETIVOS** Los medicamentos derivados de la artemisinina son ampliamente utilizados para el tratamiento de la malaria por *Plasmodium falciparum* y se han realizado muy pocos estudios que investiguen la calidad de estos medicamentos en África. Hemos analizado el contenido de ingredientes activos en medicamentos derivados de la artemisinina comercializados en Kenia y la República Democrática del Congo.

**MÉTODOS** Hemos analizado comprimidos, cápsulas, suspensiones secas e inyecciones (IM) que contengan artemeter, arteeter, artesunate o dihidro-artemisinina. El contenido de los ingredientes activos y preservantes se determinó de forma cuantitativa utilizando métodos de HPLC-UV. Todos los análisis se realizaron de acuerdo con los requerimientos de la farmacopea europea.

**RESULTADOS** Los ingredientes activos presentes en la etiqueta se identificaron en todas las muestras, aunque con dosis variables. Nueve de las 24 muestras de medicamentos analizadas no cumplían con los requerimientos de la farmacopea en un 95–105%: 7 muestras estaban por debajo de la dosis y 2 un poco por encima. La dihidroartemisinina fue el ingrediente activo por debajo de la dosis en 57% de las muestras. Las inyecciones de arteeter tenían el contenido de medicamento más bajo (77%). Dos tercios de la suspensión de polvo seco estaba por debajo del estándar o se encontraba adulterada. Los comprimidos estaban fuera de rango en un 23%. Se observaron picos no identificados en los cromatogramas de inyecciones IM de arteeter y en polvo seco de dihidroartemisinina.

**CONCLUSIONES** En África se están vendiendo medicamentos derivados de la artemisinina adulterados o por debajo de los estándares, presentando una posible ruta de desarrollo de resistencias en el futuro. Deberían tomarse las medidas apropiadas para mantener un uso adecuado y seguro de estos medicamentos.

**palabras clave** Antimaláricos, derivados de la artemisinina, control de calidad, adulterados, HPLC fase revertida