

## Evaluation of the quality of oral pediatric antimalarials used for the treatment of uncomplicated malaria in Douala, Coastal Region (Cameroon)

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**Abstract:** The study conducted was to evaluate the quality of oral pediatric antimalarials drugs found in the formal and informal sectors of the city of Douala: particular case of syrups and suspensions of quinine and some powders for oral suspension of artemether-luméfanthrine. An analytical study was made on 100 samples selected at random sanitary formations, whole salers distributors and markets of illicit distribution found in the various districts of the city of Douala at which the takings were made. The labeling, the visual aspect, the pharmaco-technical parameters (pH, density, volume) and physic chemical parameters (identification, dosage and stability of actives ingredients) of the different samples were estimated. The results of the analyzes showed an global rate of non-compliance of 77%, the informal sector was the most represented with 92% of its samples non-compliant as compared to 62% in the formal sector. The pharmaco-technical non-compliance concerns the pH with 30%, then the density with 46.7% and the volume 46.7%. The physico-chemical non-compliance concerns the identification of the active substance with 2% and the dosage of active substances with 77%. As regard the stability of the reconstituted suspensions, the pH was stable during 14 days after the reconstitution whereas 22.7% of samples saw their concentration of artemether reduce more than 10% and 41.4% of samples for the lumefantrine. In view of all this, the WHO recommends instead the use of dispersible compressed forms for the treatment of simple malaria in children.

**Keywords:** antimalarial medicines, artemether, lumefantrine, oral fluid forms, quality

## INTRODUCTION

Malaria, a disease caused by parasites transmitted to humans by infested female Anopheles bites, remains today a disease with high morbidity in the world in general and in Cameroon in particular where it is endemic. According to the latest WHO estimates published in December 2016, 212 million cases of malaria and 429 000 deaths from this disease were counted in 2015 worldwide [1]. The WHO region of Africa bears a disproportionate share of the global burden with 2015, 90% of malaria cases and 92% of deaths from this disease recorded in this region [1]. In Cameroon, according to the report of the Ministry of Public Health at the commemoration of the 10th World Malaria Day on April 25, 2017, malaria remains an important public health problem through its impact on mortality and morbidity [2]. In 2016, out of 7,579,360 people consulted in health facilities, 1,790,550 cases of malaria were recorded, representing a morbidity of 23.6%. Of the 21,268 officially registered deaths, 2,637 were attributed to malaria, a rate of 12.4% [2]. The highest mortality is found in the population of children

under 5 due to their immunity being established with more than two thirds (70%) of deaths from malaria occurring in this age group [1]. One of the main causes of the spread of this disease, especially among children, is the use of poor quality drugs, as a poor quality antimalarial can not only negatively affect the health of the child but also undermine the credibility of health services by contributing to the development of plasmodium resistance to antimalarials [3]. Many antimalarial quality assessment studies in several African countries have shown a large number of non-compliance of these products in terms of their labeling, pharmaco-technical properties, presence or of the dosage of the principle [4-7].

Few studies aimed at evaluating the quality of antimalarials in Cameroon in the formal and informal sectors were found in 2004 and 2005. In 2004, a study investigating the quality of antimalarials in the illicit pharmaceutical sector which revealed that 38% of chloroquine, 74% of quinine and 12% of antifolate products did not have ingredient, or insufficient active

ingredient, or bad ingredient or ingredient (s) unknown [8]. In 2015, a study evaluating the pharmaco-technical properties of the tablets of antimalarial drugs of the legal market and the illicit market of Yaoundé showed that of the samples tested, 23.34% were non-compliant, of which 19.99% came from the illicit market Nga *et al.*, [9]. The present study was to evaluate the quality of pediatric oral anti-malarial forms (syrups, suspensions and powder for oral suspension), marketed in the city of Douala. The specific objectives were to determine pharmaco-technical parameters, and to estimate physico-chemical parameters of pediatric oral anti-malarial forms.

## MATERIALS AND METHODS

### Framework and period of the study

The study experimental was conducted during a period from December 2016 to June 2017. Sampling took place in the formal and informal sectors of the various districts of the city of Douala and analyzes in the Laboratory of GENEMARK SA.

### Selection criteria

The inclusion criteria included oral liquid antimalarial forms including quinine syrup and suspensions and powders for oral suspension of artemether-lumefantrine and were excluded antimalarials with other active ingredients and other pharmaceutical presentations.

### Sampling

Sampling consisted of randomly selecting health facilities, wholesale distributors and illicit distribution markets found in the various districts of the city of Douala, from which 30, 20 and 50 samples were taken respectively, i.e a total of 50 samples in the formal sector and 50 samples in the informal sector (15 quinine syrups and 35 powders for oral suspension of artemether-lumefantrine in each sector), the various samples taken were placed in boxes to be sent to the laboratory for analysis.

### Pharmaco-technical parameters

#### Analysis of samples

#### Common tests of all samples

#### Labeling

The control of labeling was based on the determination of the conformity of pharmaceutical preparations with the labeling standards specified in the B.P.F. The following statements on the container label will be verified [10]: the name of the medicine; the names of the active ingredients; the names of the excipients; PA dosage; the pharmaceutical form; the lot number assigned by the manufacturer; the expiry date and date of manufacture; the conditions of conservation; the name and address of the manufacturer or person responsible for placing the product on the market. And especially for the powders for oral suspensions must find: the mention granule or powder for suspension;

instructions on how to reconstitute the suspension and the amount of liquid to be used; the storage conditions and the half-life of the reconstituted preparation.

Standard: the label is compliant if none of the elements mentioned above are missing.

### Visual examination

The visual inspection of the syrups made it possible to be reassured of the clarity of these and a total absence of any precipitate. A change in color or darkening of liquid preparations for oral use might thus indicate chemical degradation or microbial contamination.

### Analysis of powders for oral suspension of artemether-lumefantrine

#### Identification by CCM

The methodology used included several steps : stationary phase: silica gel R6 as the coating substance; mobile phase: a mixture of 40 volumes of petroleum ether R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R; apply separately to the plate 10 µl of each of the two following solutions in acetone R. For solution (A) stir a quantity of the powder containing about 10 mg of artemether for 5 min with 10 mL, filter and use the filtrate clear. For solution (B) use 1 mg of artemether RS and a proportional amount of RS lumefantrine per mL. After removing the plate from the chromatographic chamber, dry with a stream of fresh air; place the chromatographic plate in the chamber and close; wait for the solvent to migrate to 3/4 of the length of the plate (approximately 15 min); remove the plate, mark the front of the solvent and allow to dry; examine the chromatogram under ultraviolet light (254 nm). The main task obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B (identifying lumefantrine); spray the plate with sulfuric acid/methanol, heat the plate for 10 min at 140 °C; Examine the chromatogram in daylight. The main task obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B (artemether identifier); a weak spot due to the presence of lumefantrine may also be visible [10]. After revealing the spots, the following plates were obtained: the frontal ratio:  $R_f = d/D$  ( $R_f$ : frontal ratio,  $d$ : distance traveled by the spot,  $D$ : distance traveled by the solvent); the Standard (the  $R_f$  value of the reference solution corresponds to that of the standard solution).

### Determination by visible UV spectrophotometry

#### Determination of artemether

The process was based on the preparation of a solution of artemether in methanol, followed by hydrolysis with concentrated HCL to obtain the decomposition product, an  $\alpha$ ,  $\beta$ -unsaturated ketone [11].

The dosage of the artemether was as follows: preparation of a standard artemether solution in

methanol: a standard solution of artemether was prepared by weighing and dissolving with precision 20 mg of pure artemether powder in 20 mL of methanol to obtain a concentration of 1000 µg/mL of solution; preparation of the calibration curve: from the stock solution, different aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 mL were transferred into a series of 10 mL volumetric flasks and the volume was filled to the mark with methanol to obtain serial dilutions of the concentrations 20, 40, 60, 80, 100 and 120 µg/mL. 1 mL of each solution was removed and transferred to a series of test tubes and 1 mL of concentrated HCL acid added to each test tube and capped. The solutions were allowed to stand for 30 min and their respective absorbances were determined at 260 nm. An absorbance curve with respect to the corresponding concentration gave the calibration curve; for the

determination of artemether/lumefantrine powder samples for oral suspension, each sample was weighed and the weights recorded. A quantity of powder equivalent to 45 mg of artemether of each sample was weighed. This was transferred to a 100 mL volumetric flask containing about 30 mL of methanol. The volume was completed to the mark with methanol and stirred for 10 min. The solution was filtered through Whatman N° 41 filter paper. From the filtrate, 1 mL was transferred to a 10 mL volumetric flask and made up to the mark with methanol to give a concentration of 45 µg /mL. An amount (1 mL) of the solution was transferred to a test tube and 1 mL of concentrated hydrochloric acid was added and allowed to stand for 30 min. The absorbance of the contents of each test tube was measured at 260 nm (Table-1).

**Table-1: Calibration of artemether**

Etalon	Concentration (µg/mL)	Absorbance ( $\lambda = 260$ nm)
S1	20	0.064
S2	40	0.120
S3	60	0.180
S4	80	0.236
S5	100	0.292
S6	120	0.348

**Determination of lumefantrine**

The dosage of lumefantrine was as follows: preparation of the stock solution: 100 mg of pure drug were weighed and transferred to a 100 mL volumetric flask, 50 mL of methanol was added to the flask, dissolved and subjected to an application to the ultrasound for 15 min, the volume was supplemented with methanol. The concentration obtained was 1000 µg/ml; preparation of the calibration curve: prepare aliquots by diluting the stock solution with methanol so as to obtain concentrations of 8; 10; 12; 14 and 16

µg/mL. The absorbance of its solutions was measured at 234 nm [12]; Preparation of the sample solution: weigh a powder of artemether-lumefantrine for suspension equivalent to 50 mg of lumefantrine and transferred to a 100 mL volumetric flask then add about 20 mL of methanol and submit the mixture to an ultrasound for 15 min to completely dissolve the drugs, the volume was added with methanol and filtered through filter paper. A dilution was made so as to obtain a solution dosed at 50 µg/mL. The absorbance of the content of this volumetric flask was measured at 234 nm (Table-2).

**Table-2: Calibration of lumefantrine**

Etalon	Concentration (µg/mL)	Absorbance ( $\lambda = 234$ nm)
S1	16	0.062
S2	14	0.056
S3	12	0.046
S4	10	0.036
S5	8	0.030

**Physico-chemical stability study**

The physicochemical stability study was carried out only for artemether-lumefantrine suspensions by UV spectrophotometry and by measuring the pH of the samples on days 1, 3, 5, 7 and 14 [11]. With regard to chemical stability the analyzes were made as follows: preparation of a standard artemether suspension: weigh 180 mg of standard artemether powder and 1080 mg of standard powder of lumefantrine and transfer them to a clean mortar and dried. Then weigh and add 600 mg of microcrystalline cellulose (as suspending agent), carefully mix the

powders. Add about 30 mL of water and mix gently and transfer to a previously calibrated 60 mL bottle. The mortar was rinsed with water and the water transferred into the bottle and the volume was completed with more water up to the mark; repair of different samples of artemether-lumefantrine suspensions: each of the suspension powders samples were reconstituted with water according to the instructions on the label. After opening the bottle (breaking the seal), drinking water was added and carefully brought to the mark indicating a level of 60 mL. After adding the water, the mixture was vigorously shaken until all the powder has

disappeared from the bottom and a suspension has formed. ; Protocol for stability studies: 2 mL of each sample of suspensions and the standard artemether-lumefantrine suspension prepared were measured and dissolved in methanol and stirred for 10 min. These were transferred to 100 mL volumetric flasks and the volumes were supplemented with methanol and stirred for 10 min. The solutions were filtered through Whatman N° 41 filter paper. With particular reference to the artemether, from each of the filtrates, 1 mL was transferred to a test tube and 1 mL of concentrated HCL acid was added, then plugged and allowed to stand for 30 min. The absorbances of each solution were measured at 260 nm for artemether and 234 nm for lumefantrine. The remaining suspensions were stored in a closet at room temperature and the test was repeated at days 1, 3, 5, 7, 10 and 14. The various concentrations obtained from these following days were compared to the concentrations obtained immediately after reconstitution to check the stability of the suspensions after a period of 14 days.

Standard: when the solution loses 10% or more of its initial concentration it was said not stable.

#### Quinine analysis

##### Density measurement

The measure provided reassurance that our liquid preparations for oral use was not be subject to microbial contamination.

The density measurement was done using the formula  $D = \rho \text{ syrup} / \rho \text{ water}$  with:  $\rho \text{ water} = 1 \text{ g/cm}^3$ ;  $\rho \text{ syrup} = \text{mass syrup} / \text{volume syrup}$ .

Standard: to be considered compliant, the density must be between 1.16 and 1.24.

##### Measurement of pH

The pH measurement was done using a pH meter that works as follows: put 50 mL of the buffer solution, pH 4.0 into a beaker; insert the electrodes into the buffer solution; turn the pH meter switch to the auto position and note the reading; adjust the switch to read pH 4.0; repeat this procedure with the pH 7.0 solution; measure about 50 mL of sample in a beaker and immerse the electrodes in the solution; measure the pH of the solution by turning on the pHmeter and record the reading; after the measurements rinse the electrodes with distilled water.

Standard: the pH of quinine bichlorhydrate syrup should be between 2 and 4; the pH of the quinine sulfate suspension should be between 7.5 and 8 [13].

##### Measurement of volume

The volume of quinine syrups and suspensions was measured using a graduated 250 mL test tube. The

volume was said to conform, when it is equal to the volume displayed on the label  $\pm 5 \text{ mL}$ .

##### Identification by UV fluorescence

Identification was by UV fluorescence of a solution of quinine in sulfuric acid (1 g in 0.1M H<sub>2</sub>SO<sub>4</sub>) with the appearance of a blue fluorescence.

##### Determination of the quinine

Quinine dihydrochloride and quinine sulfate were assayed by titrimetry, which consists in dissolving 10 mL of the test sample in 20 mL of ethanol, then titrating with 0.1 N NaOH until the pink turn of the sample. Phenophthalein was used as a colored indicator.

Note that 1 mL of NaOH corresponded to 19.87 mg of quinine bichlorhydrate; quinine base = 81.63% quinine bichlorhydrate; the standards were between 90 and 110% for quinine base.

## RESULTS AND DISCUSSION

### RESULTS

#### Pharmaco-technical parameters

##### Labeling, pH, Density and volume

Of the 100 samples analyzed 75 had non-compliant labeling, i.e a pourcentage of 75%. pH measurement was made only on samples of quinine syrup and quinine suspension. Of the 30 samples analyzed 9 had a lower pH than normal, i.e a 30% percentage. Density measurement was made only on samples of quinine syrup and suspension. Of the 30 analyzed samples 14 were non-compliant from the point of view of density, i.e a percentage of 46.7%. Volume measurement was also done only for the quinine samples. Of the 30 samples of quinine, 14 had a volume below the standard, i.e a percentage of 46.7%.

##### Identification of active ingredients

Of the 100 samples analyzed, only 2 contained no active ingredients, i.e a percentage of non-compliance of 2% with, among others, 1 sample out of 30 for quinine (3.3%) and 1 sample out of 70 for the artemether-lumefantrine (1.4%).

#### Quality-sourcing and quality-manufacturer correlation

##### Evaluation of sampling sites

After analyzing the samples from the various sampling sites, the street counters found recorded the highest rate of non-compliance with 92%. It should be noted that poor results, although less important, were also obtained for health centers and wholesaler-dispatchers, which recorded respectively 63.3% and 60%.

##### Evaluation of sampling sectors

The results showed that the informal sector recorded a very high rate of non-compliance with 92%

compared to 62% of non-compliance in the formal sector.

#### Evaluation of manufacturers

The results of the evaluation of the samples according to the manufacturers show that the laboratories J of English origin, G of Chinese origin, H of Chinese origin and X of Indian origin have the most non-compliance with 100%.

#### Physico-chemical stability of reconstituted artemether-lumefantrine suspensions

The pH of the various reconstituted suspensions is stable over the days until 14 days after reconstitution.

For the chemical stability, of the 70 samples analyzed, 16 saw their artemether concentrations decreased by more than 10% and thus were not stable, a percentage of 22.9% and 29 saw their lumefantrine concentrations decreased by more than 10%.

#### DISCUSSION

A similar study conducted by Mbadinga [4] on amodiaquine syrups showed that in 16 samples, 12 had a lower pH than normal, which is 75%. There is a relationship between pH and action of the active ingredient, and different stability studies conducted by manufacturers have shown that neither time nor temperature has an impact on pH [14].

The percentage of labeling was closed to that of Danzabe [15], who worked on the evaluation of the quality of amoxicillin 500 mg generic tablet of formal and informal circuit of the city of Yaoundé, and obtained a percentage 64%; but moves away from those of Djim-Madjim [7] and Nga *et al.*, [9], which obtained percentages of non-compliance of 38.5% and 24.1% respectively. A lack of labeling is evidence of non-compliance with good manufacturing practices, which may lead to poor compliance with risks of intoxication, deterioration of the dosage form or even lack of product traceability.

In galenic form, a decrease in the density of simple syrup means bacterial development.

Volume non conformity gives patients incorrect dosage of the drug

Similar studies have been carried out: a study conducted in Cameroon in 2004 investigating the quality of antimalarials in the illicit pharmaceutical sector revealed that 74% of quinine and 12% had no ingredient, or insufficient active ingredient, or bad ingredient or unknown ingredient(s) [8]; similarly one conducted in three African countries showed that 1 sample of quinine out of 39 or 2.6% did not have the indicated active ingredient; another conducted by

Mbadinga [4] showed that 1 sample out of 24 quinine did not contain any active principle, i.e 4.2%; also a study on the pharmaco-technical evaluation of artemether-lumefantrine tablets showed that 10% absence of active ingredient [9]. This serious anomaly can lead to therapeutic failures or even cases of intoxication.

These abnormalities constitute dangers for the health of the patient. Under-dosages can lead to therapeutic failures as well as the risk of drug resistance. Overdosage can cause very dangerous toxic effects with examples of cinchonism occurring with high doses of quinine.

The 92% of non-compliance can be explained by the poor conservation of drugs by street vendors.

Other studies have shown similar results about evaluation of sampling sector, notably that of Danzabe [15], who obtained 93% of non-compliance in the informal sector against 57% of non-compliance in the formal sector and that of Nga *et al.*, [16]. The informal sector recorded 24.84% of non-compliance compared with 13.08% in the formal sector.

Kouanang [17, found that China and Morocco were the countries with the most non-compliance with respectively 25% and 10%. Danzabe [15], found India to be the country with the highest non-compliance at 18.14%.

This result was also obtained by André Sawa *et al.*, [14], who evaluated the stability of reconstituted suspensions of the artemether-lumefantrine based antimalarial drug combination with different types of water [14]. Indeed, neither the weather nor the temperature has an impact on the pH.

This result is similar to that obtained by the WHO, which recommends using this galenic form as little as possible because of their instability [18].

These results show that the oral liquid antimalarials marketed in the city of Douala are for the most part of poor quality this can be explained either by a non compliance with the good manufacturing practices by the various laboratories, or by a poor conservation of the drugs wholesalers, health centers or street vendors. It is with this in mind that in order to reduce the prevalence of children suffering from malaria from a point of view of poor quality medicines, the WHO has issued a guideline urging countries to use as little as possible oral liquid forms (syrups, suspensions and powders for oral suspensions) for the treatment of uncomplicated malaria in children, mainly because of the inherent instability of these products and the inaccuracy of the assay. Also the lack of stability is even more significant when we know that many patients

take only part of their treatment to be able to use the rest later despite the rapid degradation of the active ingredient.

## CONCLUSION

The general objective of the study was to evaluate the quality of liquid oral forms of antimalarials marketed in the city of Douala. The results showed a global rate of non-compliance of 77%, the informal sector being the most represented with 92% of its nonconforming samples versus 62% in the formal sector. The pharmaco-technical non conformities noted only for quinine samples are pH with 30%, density with 46.7% and volume with 46.7% and physicochemical non conformities were the identification of the active principle with 2%, and the dosage of active ingredients, with 77%. It should also be noted that 75% of the samples had non compliant labeling and that the suspension forms recorded the highest number of non compliances, with a percentage of 100%. In view of all this, the WHO recommends instead the use of dispersible compressed forms for the treatment of simple malaria in children.

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