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# Evaluation of the quality of injectable ampicillin in the formal and informal circuit in the city of Yaoundé

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## Abstract

**Introduction**: The poor quality of medicines represents a threat to public health. However, the causes come from a variety of factors such as the use of an active ingredient of insufficient quality, inadequate manufacturing processes, or even unsuitable packaging, insufficient quality control measures. Thus, this study aims to assess the quality of injectable ampicillin in the formal and informal circuit in the city of Yaoundé.

**Methodology**: Thirty (30) batches of injectable ampicillin collected in the city of Yaoundé were the subject of an experimental study. The European and American Pharmacopoeia (USP) standards were used to assess pharmaco-technical and physicochemical compliance.

**Results**: According to the parameters including respect for the mass, the pH, the labeling and the dosage of the active ingredient were found non-compliant on 02 batches (7%), 01 batch (3%), 25 batches (83% ) and 01 lot (3%). However, of the 30 batches analyzed, 53% were non-compliant, including 13%, 3%, and 37% respectively from the private, public and informal sectors.

**Conclusion**: More than half of the batches of ampicillin injection analyzed in this study had corrupted qualities. Strict measures are necessary on the quality of badly needed drugs such as ampicillin from the first people in charge of drug control in the city of Yaoundé in order to improve the quality of treatment for pathologies.

**Keywords:** Ampicillin; Drug; Quality control; Conformity; Yaoundé

## 1. Introduction

The quality of medicines is one of the major concerns for both healthcare professionals and patients [1,2]. This is the control of a set of parameters and properties likely to ensure both patient safety and to bring the drug to a level of satisfactory requirements [3]. In addition, the guarantee of the quality of drugs is generally based on a set of analytical methods and in particular on the quality control which is carried out throughout the process, from manufacture to dispensation to the general public [4]. In principle, pharmacies are the place par excellence where quality medicines should be found. However, there are sometimes non-conformities [4]. Thus, Tchounga et al. (2021) in Cameroon, reported that up to 26.9% of drugs circulating in the country are of poor quality [5]. Other investigations have also

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reported poor quality drugs circulating in the cities of Yaoudé and Douala [6,7]. The case of antibiotics is more alarming because, not only do they appear on the list of the most accessible products on the illicit market, but in addition, the consequences of the consumption of non-compliant antibiotics have repercussions on the entire population, through different resistance mechanisms. Ampicillin being a broad spectrum antibiotic is widely used to treat respiratory tract infections, urinary tract infections, bacterial meningitis, salmonellosis and endocarditis [8,9]. It is also used in the treatment of streptococcal B infections in newborn babies [10, 11]. Therefore, it seems all the more important to check the compliance of drugs sold on the Cameroonian market, precisely in the city of Yaoundé and to assess the quality of these products from laboratory results. Thus, the interest of our study is to allow the pharmaceutical industries and the actors of the management of the drugs to be better informed on the questions related to the non-conformity of the drugs in particular the injectable ampicillin compared to the specifications. This would make it possible to use good manufacturing practices in order to limit the impacts generated.

## 2. Material and methods

### 2.1. Study frames and sampling

The study carried out was of an experimental type which took place from December 2018 to August 2019. The samples consisted of 30 batches of injectable ampicillin. These samples were collected randomly at the central and Mokolo markets, then in public hospitals and pharmacies in the city of Yaoundé. Thus, samples having ampicillin as the only active ingredient were taken into account and those having, in addition to ampicillin, another active ingredient were excluded. The technical platform of the National Laboratory for the Quality Control of Medicines and Expertise (LANACOME) in Yaoundé made it possible to carry out the experimental studies. Figure 1 illustrates a satellite photo of the geographical location of LANACOME.

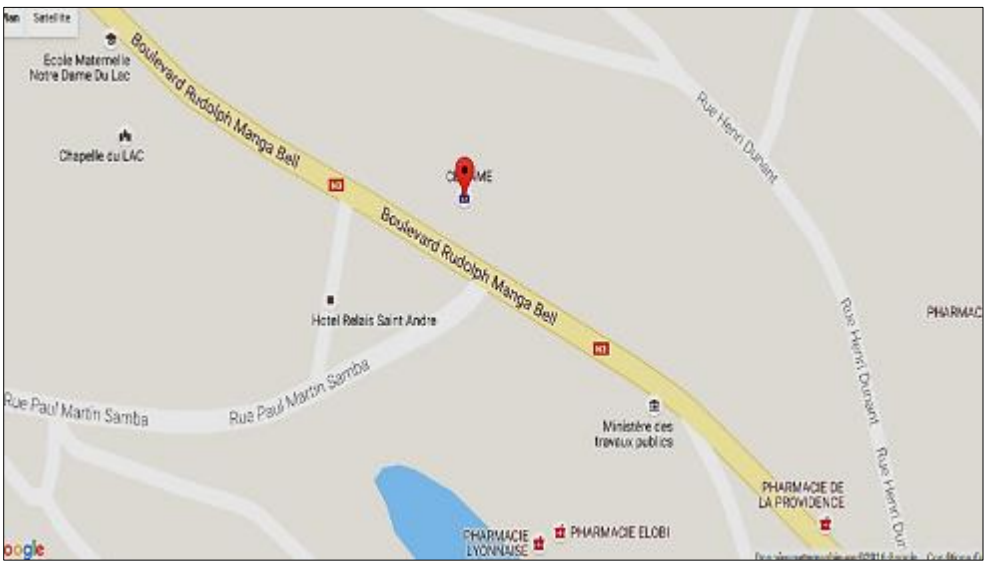


**Figure 1** LANACOME location

### 2.2. Sample analysis techniques

*2.2.1. Pharmaco-technical tests on sample batches*

The pharmaco-technical tests were oriented towards the labeling, visualization and mass controls of the sample batches. Indeed, the evaluation of the quality of packaging labeling has been adapted to the protocol of [3]. This consisted of checking the name of the drug, international common name, quantity of active ingredient in the bottle, method of use and route of administration, batch number assigned by the manufacturer, date of manufacture and expiry date, special conditions storage or precautions to be taken during handling, presence of the statement "do not leave within the reach of children", classification in terms of delivery of the drug, leaflet in two languages, French and English, name and address of the manufacturer or person responsible for marketing. As for the visual checks, they were carried out on 10 vials chosen at random from each batch. The assessment focused on the presence or absence of foreign particles in the powder or solution, on the "granular or crystalline" aspects of the powder, on the coloring of the powder or solution and on the "homogeneous and clear" phase. The quality of the mass was assessed according to the recommendations of

the European Pharmacopoeia 6th Edition. This consisted first of individually weighing 20 full bottles sampled in such a way and determining the average mass. Then, the bottles were emptied and cleaned with methanol, then weighed again. In the end, a difference between the average masses of the full and empty bottles made it possible to determine the average mass of the contents of the 20 bottles and to calculate the tolerable deviations. Thus, the mass of a batch was deemed uniform, if the individual mass of at most 2 of the 20 vials can deviate from the average mass by a percentage greater than 10%, if the average mass is more than 40 mg.

*2.2.2. Physico-chemical tests of injectable ampicillin*

The pH and the active ingredient were the quality control parameters of the ampicillin injection samples collected. Indeed, the quality of the pH of the samples was evaluated according to the normative recommendations of the American Pharmacopoeia [1]. This consisted of preparing a test suspension of 10.0 mg/ml of ampicillin with $CO_2$-free water. Thus, the pH was measured within 10 minutes after preparation and the values found to be compliant were those between 8.0 and 10.0. As for the dosage of the active ingredient of ampicillin, it was carried out according to the normative recommendations of the American Pharmacopoeia (USP 40 NF-35). Thus the identification of the active ingredient was carried out by comparing the retention times of the peak obtained with the substance analyzed and the peak obtained with standard ampicillin. This last activity was carried out with the "Agilent technology 1260 infinity" HPLC and the spectra were generated by the "CHEMSTATION" software.

Solutions used in HPLC analysis

- Preparing the buffer solution

A mass of 13.6 g of monobasic potassium phosphate monohydrate (KH2PO4, 1H2O) was dissolved in a volume of 100 ml in a volumetric flask with water. Table 1 shows the composition of the mobile phase.

**Table 1** Composition of the mobile phase

| Reagents | Acetonitrile | Water | 1M potassium monobasic phosphate | 1N Acetic acid |
|---|---|---|---|---|
| Volume | 80 mL | 909 mL | 10 mL | 1 mL |

- Preparation of thinner

The diluent was a suspension consisting of water (989 ml), monobasic potassium phosphate (1M, 10 ml) and 1N acetic acid (1 ml).

- Preparation of the standard solution

This involved preparing 1 mg/ml of Ampicillin Chemical Reference Substance (CRS) in the diluent and shaking. This solution was used promptly after preparation.

- Preparation of system compliance solution

This solution was obtained by weighing caffeine powder to obtain a concentration of 0.12 mg/ml of caffeine in the standard solution.

- Preparation of the solution to be examined

A suspension of ampicillin at a concentration of 1mg/ml in the diluent of each sample was prepared to be injected into the circuit of the automaton.

HPLC chromatographic conditions

The high-performance liquid chromatograph equipped with a UV detector, reading at a wavelength of 254 nm, the analytical column of 30-cm length for a diameter of 4mm with a particle size of 5-10 µm, the flow rate at 2 ml/min and the injection volume at 20 µl.

The performance conditions of the system are checked by the Resolution which must not be less than 2.0 between caffeine and ampicillin, the symmetry factor must not be less than 1.4 with the standard solution. The capacity factor must not be less than 2.5 with the standard solution and the Coefficient of variation must not be more than 2.0% with

the standard solution. Calculate the percentage content of ampicillin (C16H19N3O4S) labeled on the vial with an acceptance criterion of 90.0 – 115.0%.

### 2.3. Statistical analysis of data

Input: Microsoft Excel 2013. The Phi test was used to identify associations between variables. Reduced deviation test: score of the binomial distribution used to compare the proportions (conformities). The significance threshold was set at 0.05. The overall quality index was calculated using the weighted average of the quality index of each parameter

## 3. Results

### 3.1. Breakdown of samples by business sector

The samples were collected from structures in the informal, public and private sectors. Figure 2 illustrates the distribution of the samples collected by business sector.

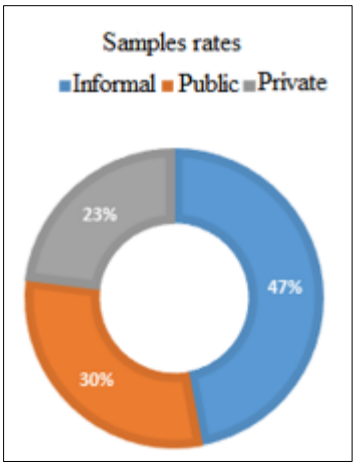


**Figure 2** Breakdown of samples by business sector

### 3.2. Batch analysis

*3.2.1. Pharmaco-technical tests*

The control of the labeling of the samples showed that 71.00% of the sample batches from the informal sector were non-compliant against (57.00%) and (11.00%) respectively from the private and public sectors. In addition, the visual assessment of the sample batches showed compliance rates of 100.00% for each sector. As for the evaluation of the uniformity of the mass, the compliance rate varied from one sector to another. Figure 3 presents the results of the assessment of the uniformity of the mass of the samples.

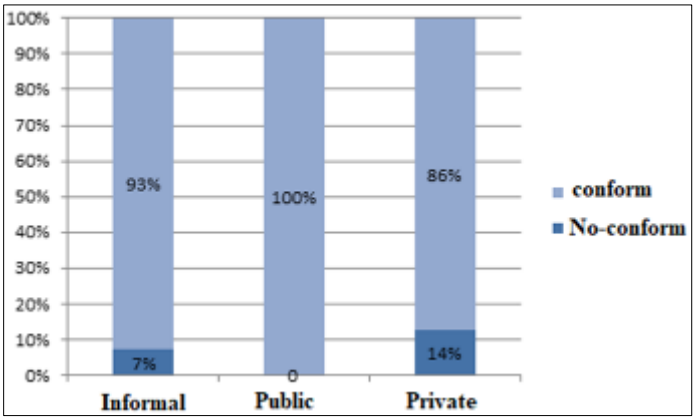


**Figure 3** Compliance by mass uniformity (Axe Y= compliance rate)

*3.2.2. Physicochemical tests*

The batches of samples collected from agents in the informal, private and public sectors showed pH non-compliance rates of 7.00%, 0% and 00% respectively. As for the sample identification test, it showed that all sample batches were compliant. In addition, the 30 sample batches were assessed for active ingredient content. Figure 4 shows an illustration of the spectra of the active ingredient identity of the samples and the ampicillin standard.

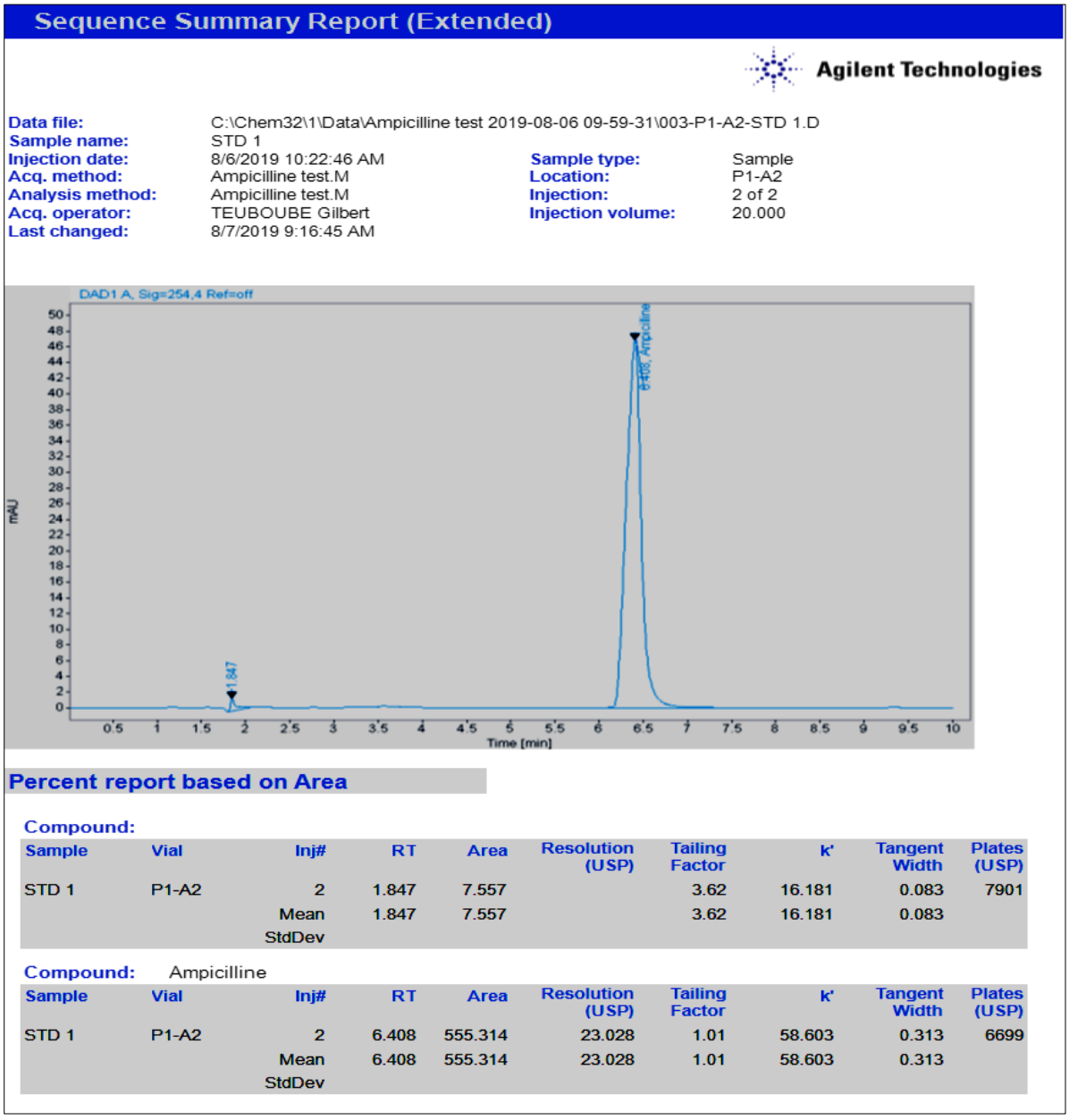


**Figure 4A** Detection spectrum of the active ingredient of ampicillin with the standard

The retention time of the ampicillin molecule was recorded as 6.383 min. The quality control of the active ingredient of the ampicillin molecule of the samples revealed 7.00% of non-compliance of the samples collected in the informal sector against 00% of the structures of the private sector and as many from the public sector.

However, on all the criteria for evaluating the quality of the 30 sample batches collected, sample non-compliance rates were 79%, 57% and 11% respectively from the informal, formal private and formal public sectors. . Notwithstanding, sample quality corruption was observed in at least one lot from each country of origin.

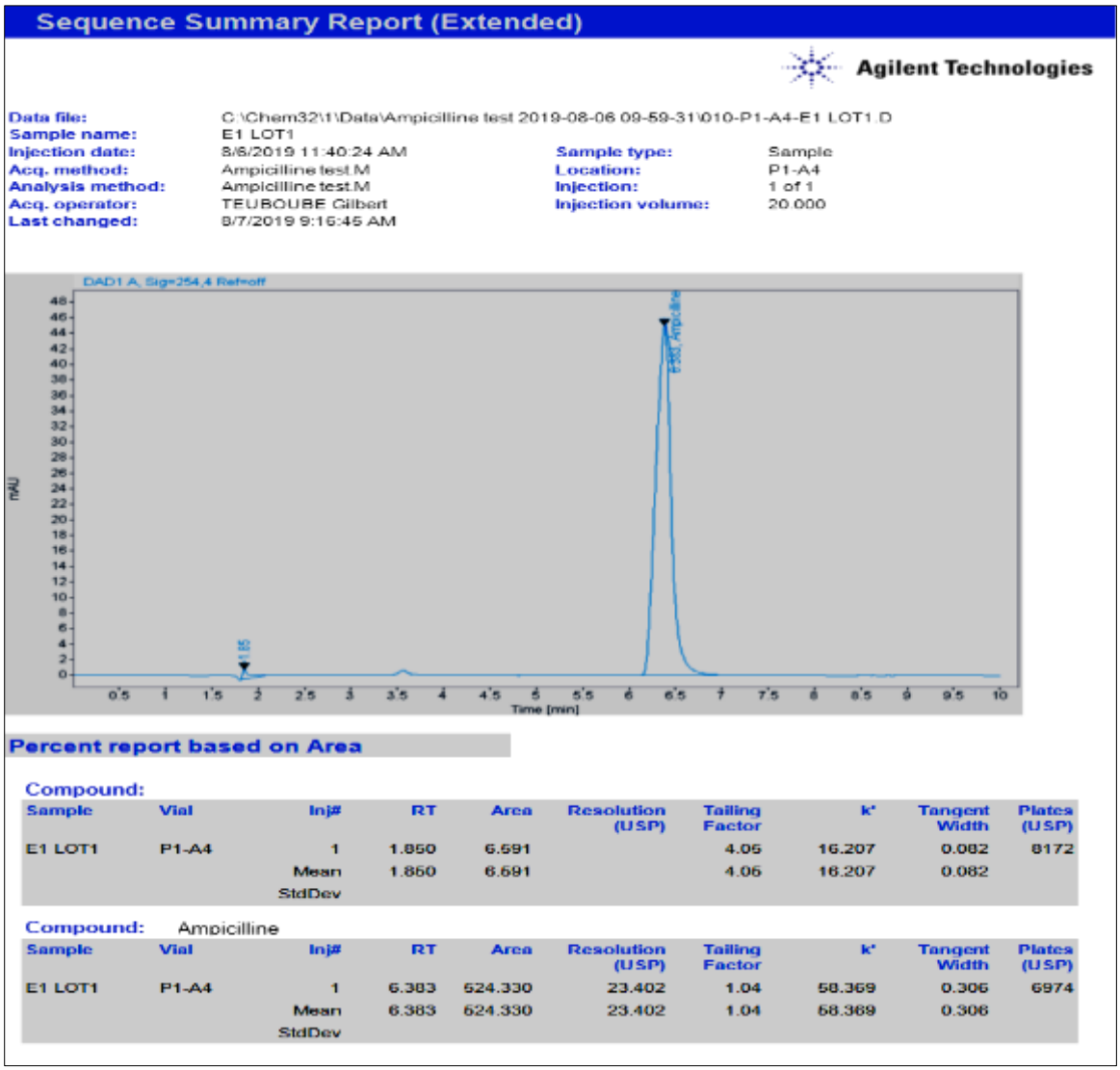


**Figure 4B** Detection spectrum of the active ingredient of ampicillin with sample from batch 1

**Figure 4 (A and B)** Detection spectrum of the active ingredient of ampicillin

## 4. Discussions

The mass uniformity test of the 30 sample batches in this study showed non-conformities of the sample batches collected from private sector and informal sector units with respective rates of 14% and 7% against 0% of the public sector. Several other authors had reported the mass irregularity in the batches of drugs analyzed during their investigations [7, 12]. Indeed, the corruption in the mass uniformity of drug batches would be due to a poor distribution of the active ingredient in the drugs [7, 13, 14]. This could lead to overdoses of certain drug batches and underdoses in others. Thus, this investigation reveals an under-dosage of 7% of the batches of injectable ampicillin samples from the informal sector compared to 0% from the formal sectors (private and public). However, Nnanga et al. (2016) in Cameroon reported drug batch underdosing rates of 33%, 86% and 79% respectively collected from the private, public and informal sectors [7]. A poor dosage of the active ingredient of the drug, especially antibiotics such as ampicillin, could promote a proliferation of target germs despite good prescription from doctors and compliance with the patient's intake. In addition, 71% of the 14 sample batches collected from informal units had labeling defects against 57% and 11% respectively from the private formal sector (7 batches) and the public formal sector (9 batches). Other investigations had reported tricks in the labeling of drug batches. The non-compliance of batch labeling would be due to non-compliance with good manufacturing practices, which can lead to poor compliance, product traceability problems and even poisoning [4, 12, 15]. However, pH non-compliances were observed in batches from the informal sector, the rate of which was 7%. This problem of pH non-compliance had also been reported by other [16, 17, 18, 19].

pH is an indicator of drug stability [20,21]. However, its variation within a batch of drug of the same active ingredient would be a real peace of mind on the stability of the molecule whose metabolic properties would vary from one batch to another [22, 23]. During this investigation, sample batches from the informal sector showed the highest rate of non-compliance (79%), followed by the formal private (57%) and public (11%) sectors. Nnanga et al. (2016) also reported corruption in the quality of cotrimoxazole 480 mg sold in the city of Douala. In their study, it was found that the non-compliance of the sample batches concerned the public sector, the informal sector and the private sector had rates of 86%, 79% and 33% respectively. These poor workmanship, sometimes intentional, particularly in the official sectors, can be explained by the lack of monitoring of the quality of systematic and regular controls after the registration of the drug. In the informal sector, these non-conformities are largely explained by the fact that these drugs are mostly counterfeit.

## 5. Conclusion

Labeling and mass uniformity were the pharmaco-technical parameters found to be non-compliant. Among the physico-chemical parameters, the dosage of the active ingredient of the under-dosage type was the only parameter found to be non-compliant in the informal sector (7%). Of all the batches analyzed, 53% were declared non-compliant according to the different pharmacopoeias used. That is 13% in the private sector, 3% in the public sector and 37% in the informal sector. Our results show that non-compliance affects the private and public sectors as well as the informal sector. All these non-conformities expose the population to treatment failures, death, aggravation of the existing pathology, problems of treatment compliance and the appearance of bacterial resistance phenomena.

## Compliance with ethical standards

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At the National Laboratory for Quality Control of Medicines and Expertise. To all the staff of the Department of Galenic Pharmacy and Pharmaceutical Legislation of the Faculty of Medicine and Biomedical Sciences.

*Disclosure of conflict of interest*

No reported conflicts of interest.

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