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Substandard Medicines in Nigeria: Case Study of Four Commonly Used Medicines Using HPLC Analysis

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Abstract

Counterfeit, invariably substandard medicines pose huge safety concerns both in developed and developing countries, much worse in the latter. It carries huge morbidity and, in some cases, fatal mortality burden. This study used HPLC to determine percentage purity levels in four commonly used medicines in Nigeria namely, Adrenaline, Furosemide, Ceftriaxone and Ciprofloxacin. The study aims to scrutinize and analyze the purity composition of these above drugs purchased from different sources to address the safety and efficacy of common medicines patients use in Nigeria. Previous studies on revealed a wide range of doses of active pharmaceutical ingredients from 0% to >200% of the labelled dose, with industry standard set at 98% to 100%. This study revealed a percentage purity of 152% to 225% with the Adrenaline samples; Ceftriaxone samples, being the purest of the four samples, had 94.3% to 101% purity. The Ciprofloxacin samples had a percentage purity of 84% to 98%, while the Furosemide samples were 55.1% to 75.5% pure implying that industry quality control standards were not adhered to strictly.

The implications of the higher concentrations of active ingredients in the Adrenaline samples analyzed could be adverse effects such as arrhythmias, while that of the lower concentration of Frusemide samples could be therapeutic failure.

Keywords: Counterfeit medicines; HPLC; NAFDAC; Nigeria; Developing nations

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Introduction

Safety alerts concerning counterfeits of medicines are a perennial global issue. Counterfeit medicines sales and use are quite common globally [1]. They range from products devoid of Active Pharmaceutical Ingredients (APIs), to products with a high number of other unneeded active molecules that can invariably harm or make treatment ineffective. Causes are numerous, these include greed by the counterfeiters, poor individual nations' medicines legislation control, the parallel unregulated import chain, political instability across Western Africa and corruption present in many countries. Figures are difficult to estimate, however a global increase in the seizures of counterfeit medicines has nevertheless been observed in the last couple of years [2]. Increasing awareness of the population of this menace of huge public health significance is one of the goals of engaging in this study. Counterfeiting is worse in the food supplement industry. As there is very lax control, but of more concern is its extension to anti-cancer medicines, antivirals, antimicrobials and other life-saving medicines.

The World Health Organization (WHO) defines counterfeit drugs as "drugs that have been deliberately or fraudulently mislabeled with respect to identity and/or source" [3]. In 2017 WHO added a warning concerning the exact composition of the drug ("deliberately or fraudulently misrepresent their identity, composition or source) [4]. The products could contain incorrect ingredients, may misstate the amount of the active ingredients, or are manufactured under circumstances that lack quality control. Counterfeit drugs in Nigeria include preparations without active ingredients, toxic preparations, expired drugs that are relabeled, drugs issued without complete manufacturing information and drugs that are unregistered with the National Agency for Food and Drug Administration and Control [5]. The current estimate suggests that 10% to

50% of prescription drugs sold worldwide are counterfeit, fake or contaminated, and in parts of Africa and Asia, the figures exceed 50% [1,6].

Causes and effects of counterfeit medicines

For decades, Nigeria has faced an overwhelming counterfeit medicines problem. A study by the National Agency for Food and Drug Administration and Control, Nigeria found that nearly 41 percent of pharmaceuticals in the country were counterfeit, and 70 percent were unregistered [5]. Fake drugs otherwise called counterfeit medicines ideally should be unfit for human and animal use as they pose huge health concerns. Drug counterfeiting is a growing danger and not only in developing countries where it can account for up to 40% of the market. Counterfeiting is easy to detect, investigate and quantify to put measures in place to curb its menace. Counterfeiting occurs throughout the world, although there are claims it is common in Nigeria due to ineffective enforcement of existing law, non-professional businessmen in the pharmaceutical retail industry, high cost of genuine drugs, greed, ignorance and corruption, illegal medicines importation and chaotic drug distribution network [7].

Statistics by the European Commission reported India as the main culprit of counterfeiting, India accounts for 75% of counterfeit medicines distributed worldwide [8]. Therefore, it does not come as a surprise that most of the counterfeit medicines in Nigeria originate from India [9]. To put this huge public health menace in perspective NAFDAC states that Nigeria is the one of the world's largest markets for fake and counterfeit medicines among developing nations of the world though progress being made in the war against counterfeiting medicines, as NAFDAC reported reduction in counterfeit medicines, from 40% in 2001 to 16.7% in 2005 [10]. Particularly notorious for counterfeiting in Nigeria are antimalarials. 64% of antimalarial medicines circulating in Nigeria as at 2011 were reported to be substandard [11]. It was estimated in the year 2013 that more than 120,000 Africans are killed by fake malaria drugs among children younger than 5 years in 39 countries in sub-Saharan Africa [12]. WHO stated in 2017 that 1 out every 10 of drugs and pharmaceutical products sold in developing countries are faked and counterfeit [13]. India and China are the major suppliers of fake and counterfeit medicines globally [7]. About 42% of all the antimalarial medicines sold in most pharmaceutical stores, clinics and hospitals in sub-Sahara Africa are fake [13].

Studies revealed that millions of counterfeit PDE5 inhibitors are seized annually forming the bulk of all counterfeit pharmaceutical product seizures. An estimated 2.5 million men in Europe are believed to be exposed to illicit sildenafil (Viagra) [14]. A wide range of doses of active pharmaceutical ingredients (from 0% to >200% of labelled dose) has been documented in the analysis of the contents of counterfeit PDE5Is. Contaminants (including talcum powder, commercial paint and printer ink) and other excipients ingredients that are potentially dangerous. Only 10.1% of samples were within 10% of the labelled tablet strength in one study [14]. Forty-four to 90% of counterfeit medicines are estimated to be sold over the internet where 67% of these purchased medications on the internet were for ED [15].

In the developing world, antimalarials, antimicrobials, diuretics, and analgesics are particularly counterfeited owing to the huge demand to treat the most prevalent tropical diseases which are malaria, infections and pain as the other prevalent condition requiring medications etc. (reference). Therefore, we ran an HPLC analysis of APIs in four common medicines used in Nigeria at the Yarmouck University, Irbid Pharmaceutical Laboratory in Jordan between January and February 2022. The four medications analyzed are Adrenaline, Ceftriaxone, Ciprofloxacin and Furosemide.

Furosemide is a diuretic. It is used to treat cardiovascular and renal disorders such as high blood pressure, heart failure, renal failure etc. Ceftriaxone is a cephalosporin antibiotic that is used to treat bacterial infections, including severe or life-threatening forms such as *E. coli* septicemia, pneumonia, and meningitis etc. Ciprofloxacin is a broad-spectrum antibiotic belonging to the class fluoroquinolones. It is used to treat a variety of infections, especially respiratory, urinary tract and gastrointestinal, sexually transmitted infections etc., while synthetic Adrenaline is used management of severe allergic reaction: Anaphylaxis, cardiac arrest, and securing hemostasis in superficial bleeding. The inhaled form can be used to manage severe croup infection. Adrenaline is normally produced by the small organs located on upper pole of the kidneys called adrenal glands and by a small number of neurons in the medulla oblongata. It is pivotal in human fight-or-flight response by increasing blood flow to muscles, increasing cardiac output through its action on the SA node, [16]. It also exerts a pupil dilation response, and increases blood sugar level [17,18].

Methods used to detect fake medicines

Mass Spectrometry (MS): Accurately measures the mass of different molecules within a sample. It can be used to identify molecules in a mixture such as API and other labelled excipients, detect impurities in a sample and quantify them. This is through ionization, acceleration, deflection and detection.

High performance liquid chromatography (HPLC): Most times a gradient reversed-phase HPLC method is developed and validated for the analysis of related substances in a medicine of choice using an appropriate column with a validated flow rate and detection at specific validated wavelength. It would also involve the use of a mobile phase component with pH adjusted to validated levels. The limit of detection and limit of quantitation are predetermined at specific sample concentrations.

Material and Methods

HPLC analysis of APIs in Adrenaline, Ceftriaxone, Ciprofloxacin and Furosemide were conducted at the faculty of pharmacy at Yarmouk University in Jordan between January and June 2022.

For each of these medications analyzed, samples were gotten from Nigeria from either Roadside Pharmacy Stores (RS), Reputable Pharmacy Stores (R) and Tertiary Hospital Pharmacies (TH). The rationale of this separation was to have a wide range of sources, bearing in mind that tertiary hospitals and reputable pharmacies were more likely than roadside pharmacy stores to have qualified pharmacists who are likely to follow institutionalized measures to mitigate the procurement of substandard medications.

Adrenaline

Formulations: Three commercial formulations were examined. All were solutions for injection of claimed concentration as follows: Adrenaline R 1 mg/ml, Adrenaline RS 1 mg/ml, Adrenaline TH 0.5 mg/ml.

Chromatographic conditions: The samples were separated at ambient temperature, using the C18 column. The UV detector was set at 280 nm, the injection volume at 20 uL and the flow rate at 1

ml/min.

The mobile phase was a mixture of Methanol and ultra-pure water (50:50% v/v respectively). pH was adjusted by adding Phosphoric acid to obtain a value around 3.

Standard solutions preparation: Six standard solutions of adrenaline reference were prepared with ultra-pure water, started with an initial concentration of 3.1 mg/ml, followed by two-fold serial dilution to give the final concentrations of 3.1, 1.55, 0.775, 0.3875, 0.19375 and 0.096875 mg/ml.

Samples preparation: 1 ml was directly taken of each drug and injected in HPLC vials without any dilution.

Ceftriaxone

Test Samples preparation: Four commercial formulations were examined; all of them were powder for reconstitution. Mesporin TH, Bazreal TH, Ceftriaxone NCPC RS and Rocephin R.

A certain amount of each formulation was weighed and dissolved in 30 ml ultra-pure water to give the appropriate concentrations.

Mesporin TH = 240 ug/ml

Bazreal TH = 243.33 ug/ml

Ceftriaxone NCPC RS = 240 ug/ml

Rocephin R = 240 ug/ml

Standard solutions preparation: Six standard solutions were prepared with ultra-pure water, starting with an initial concentration of 300 ug/ml (0.3 mg weighed and dissolved in 10 ml ultra-pure water), followed by two-fold serial dilution to give the final concentrations of 300, 150, 75, 37.5, 18.75, 9.375 ug/ml.

Chromatographic conditions: The samples were separated at ambient temperature, using the C18 column. The UV detector was set at 240 nm, the injection volume at 20 uL and the flow rate at 1 ml/min.

The mobile phase was a mixture of Acetonitrile, Methanol and 0.1M Phosphate buffer (1:1:2% v/v respectively).

Ciprofloxacin

Samples preparation: Four commercial formulations of different dosage forms were examined; 3 of them (Hanbet R, Rebocip RS, Ciprotab IV R) were intravenous solutions and 1 (Ciprotab Tab TH) was in form of tablet.

Intravenous formulations were of claimed concentration 2 mg/ml. 1 ml was transferred and diluted with ultra-pure water three times by half to give a final concentration of 0.25 mg/ml (to ensure that the test sample concentration fell towards the center of the standard range).

For tablet dosage form, 3 tablets were crushed into powder and remixed together. Three measurements of weight were taken (2.7, 3.0, 1.3 mg) and each was dissolved in 10 ml ultra-pure water to give a final concentration of 0.27, 0.30, 0.13 mg/ml respectively.

Chromatographic conditions: The analyte was separated at ambient temperature, using the C18 column. The UV detector was set at 300 nm, the injection volume at 20 uL and the flow rate at 1 ml/min.

The mobile phase was a mixture of Acetonitrile and 0.1M Phosphate buffer (30:70% v/v respectively). pH was adjusted by adding Phosphoric acid to obtain a value around 2.

Standard solutions preparation: Six standard solutions were prepared with ultra-pure water, starting with an initial concentration of 2 mg/ml, followed by two-fold serial dilution to give the final concentrations of 2, 1, 0.5, 0.25, 0.125, 0.0625 mg/ml.

Furosemide

Samples preparation: Five commercial formulations were examined; all of them were solutions for injection of claimed concentration as follows:

Rotexmedica TH 20 mg/ml

Rotexmedica RS 20 mg/ml

Petamide RS 20 mg/ml

Rotexmedica R 20 mg/ml

Petamide R 20 mg/ml

0.5 ml was transferred and diluted with 10 ml ACN (total volume =10.5 ml) to give a final concentration of 0.952 mg/ml.

Standard solutions preparation: Six standard solutions were prepared with ACN, starting with an initial concentration of 3 mg/ml, followed by two-fold serial dilution to give the final concentrations of 3, 1.5, 0.75, 0.375, 0.1875, 0.09375 mg/ml.

Chromatographic conditions: The analyte was separated at ambient temperature, using the C18 column. The UV detector was set at 280 nm, the injection volume at 10 uL and the flow rate at 1 ml/min.

The mobile phase was a mixture of Acetonitrile and 0.1M Phosphate buffer (60:40% v/v respectively). pH was adjusted by adding Phosphoric acid to obtain a value around 3.

Results

Adrenaline

Figure 1 represents the standard curve of adrenaline and Table 1 represents the theoretical and actual calculated concentrations of adrenaline of three commercial products in Nigeria.

Ceftriaxone

Figure 2 represents the standard curve of ceftriaxone and Table 2 represents the theoretical and actual calculated concentrations of Ceftriaxone in eight commercial products in Nigeria.

Ciprofloxacin

Figure 3 represents the standard curve of ciprofloxacin and Table 3 represents the theoretical and actual calculated concentrations of ciprofloxacin in 4 commercial formulations of different dosage forms in Nigeria.

Furosemide

Figure 4 represents the standard curve of furosemide and Table 4 represents the theoretical and actual calculated concentrations of furosemide in five commercial formulations in Nigeria.

Discussion

As a snapshot, the study revealed that the percentage purity of Adrenaline samples studied ranged from 152% to 225% with the roadside and reputable pharmacy addition having the highest

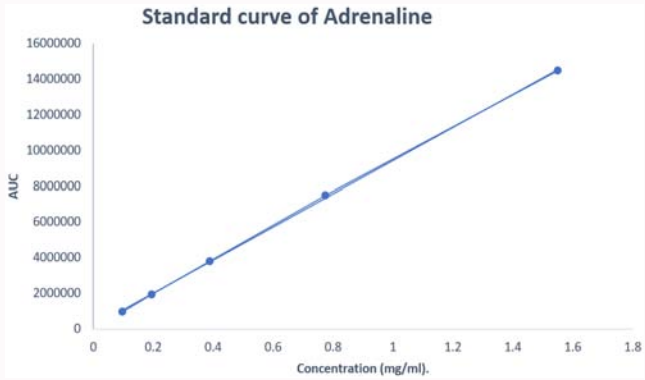

Figure 1: Standard curve of adrenaline.

Table 1: Claimed labelled concentrations and actual calculated concentrations of three commercial adrenaline products.

Product	Claimed labelled concentration (mg/ml)	Actual calculated concentration (mg/ml)	Percentage purity (%)
Adrenaline RS	1	2.25 ± 0.23	225 (± 23)
Adrenaline R	1	2.23 ± 0.23	223 (23)
Adrenaline TH	0.5	1.52 ± 0.17	152(17)

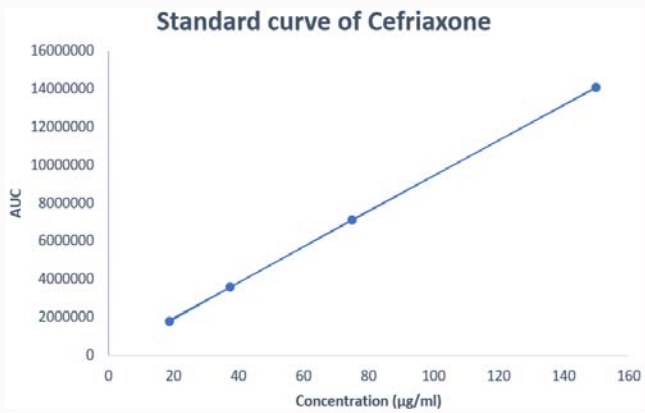

Figure 2: Standard curve of Ceftriaxone.

Table 2: Claimed labelled concentrations and actual calculated concentrations of 8 commercial ceftriaxone products.

Product	Claimed labelled concentration (gm/ml)	Actual calculated concentration (gm/ml)	Percentage purity (%) %
Mesporin TH	1	0.943 ± 0.11	94.3 ± 11.0
Bazreal TH	1	1.01 ± 0.12	101.0 ± 12.0
Ceftriaxone NCPC RS	1	0.98 ± 0.01	98.0 ± 1.0
Rocephin R	1	1.00 ± 0.08	100.0 ± 8.0

values (223% to 225%) while the tertiary hospital pharmacy had a percentage purity of 152% (Table 1). The antibiotic samples studied (Ceftriaxone) had percentage purity ranging between 94.3% to 101% (Table 2). Conversely, the Furosemide samples studied had low percentage purity (55.1% to 75.5%) with a roadside pharmacy brand having the least percentage (55.1%) while a product from the tertiary hospital had a percentage purity of 75.5% (Table 4).

It is imperative that all medications used in medical practice contain the actual concentrations of active ingredients specified by

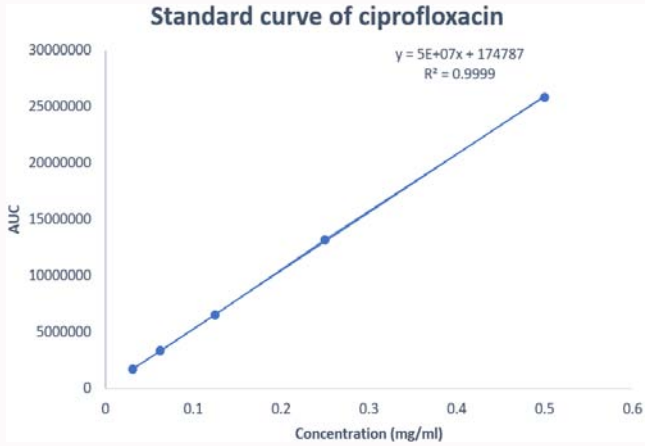

Figure 3: Standard curve of ciprofloxacin.

Table 3: Claimed labelled concentrations and actual calculated concentrations of four commercial ciprofloxacin products.

Product	Claimed concentration of the prepared solution (mg/ml)	Actual calculated concentration (mg/ml)	Percentage purity (%)
Rebocip RS IV	0.25	0.24 ± 0.23	96
Hanbet R IV	0.25	0.24 ± 0.23	96
Ciprotab R IV	0.25	0.23 ± 0.17	92
Ciprotab TH tab	0.13	0.11	84

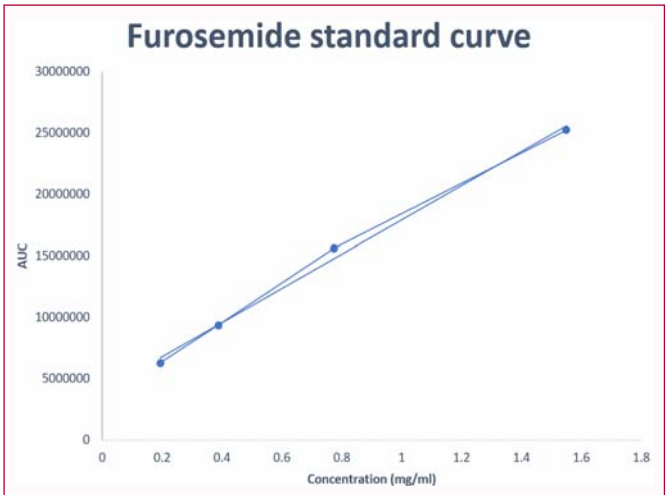

Figure 4: Standard curve of Furosemide.

Table 4: Claimed labelled concentrations and actual calculated concentrations of 5 commercial furosemide products.

Product	Claimed labelled concentration (mg/ml)	Actual calculated concentration (mg/ml)	Percentage purity (%)
Rotexmedica TH	20	15.10 ± 0.43	75.5 (± 2.2)
Rotexmedica RS	20	14.41 ± 0.15	72.1 ± (0.8)
Rotexmedica R	20	14.06 ± 1.09	70.3 ± (5.5)
Petamide RS	20	12.12 ± 3.17	55.1 ± (15.9)
Petamide R	20	14.48 ± 0.14	72.4 ± (0.7)

the manufacturers. When concentrations of medications significantly differ from that specified on the label, prescribers who prescribe even at appropriate dosages end up giving too much or too little of the

active ingredients with the attendant adverse effects and/or failure to achieve the therapeutic outcome.

It was noted in this study that Adrenaline had actual concentrations that were significantly higher the that specified by the manufacturers. The implication of this would include the occurrence of adverse effects such as hypertension, tachycardia and dysrhythmias in patient [19]. The actual concentrations of the Furosemide samples assessed were conversely lower than that stated by the manufacturers with percentage purity ranging from 55.1% to 75.5%. Furosemide is used in the management of fluid retention resulting from cardiac failure, renal and hepatic disorders. Some of these conditions can be life threatening and giving lower dosages than required may spell doom for such patients who are usually quite critically ill.

On a positive note, Ceftriaxone had a percentage of purity that was relatively close to that claimed by the manufacturer. Ceftriaxone is a commonly prescribed antibiotic in many hospital settings in Nigeria; this finding, which though appears reassuring. It will however be important to subsequently analyze other commonly used antibiotic in future studies.

It is worthy of note that a high purity level within manufactured compounds is necessary to meet regulatory quality control standards, with 98% to 100% purity taken as the industry standard. Previous studies on counterfeit medicines revealed a wide range of doses of active pharmaceutical ingredients from 0% to >200% of the labelled dose [14]. This study however revealed a percentage purity of 152% to 225% with the Adrenaline samples, Ceftriaxone samples being the purest of the 4 samples had 94.3% to 101% purity. The Ciprofloxacin samples had a percentage purity of 84% to 96%, While the Furosemide samples were 55.1% to 75.5%. % pure implying that industry quality control standards were not adhered to strictly.

To combat the scourge of the spread of counterfeit medicines in West Africa, an innovative solutions like emergence of health start-ups that connects hospitals, and pharmacies with multinational and local drug manufactures is a welcome development. In Nigeria, drugs such as anti-malarial and antibiotics are sometimes sold in open-air markets, such start-up will put a spanner in the works of such practice. As well as putting patients at risk, counterfeit drugs are a constant bane for reputable pharmaceutical companies. Some pharmacists in Africa, for example, say that they are compelled to buy from the cheapest but not necessarily the safest suppliers to compete with illegal street traders.

A similar model that has seen success in both Kenya and Uganda, and should be considered across West African nations including Nigeria, is the direct selling method; this involves a micro-franchise model to provide much-needed medical items and medications at an affordable price. This structure allows an umbrella company to train and employ workers to sell often life-saving medications door-to-door at below market price. This is the method that created the "Avon Lady" which has shown success worldwide; direct selling micro-franchise operations provide a constant supply, low costs, and training for employees. Most importantly, they create a marketable brand and trustworthy products and might invariably fight the menace of counterfeit medicines sales in developing nations.

Nigeria is facing an uphill battle in combating the informal and counterfeit drug trade, as registration with NAFDAC adds to the cost of medicines, so invariably most regulated medicines have a high cost. Therefore, there is need for individual nations in the developing world to look and critically appraise their regulatory policy and cost, to bring down cost of essential medicines, make them affordable and reduce the menace of counterfeit medicines. If such policies are not put in place, end users will continue to seek out medicines sold on the black market, which can cause even more harm. If basic medical needs are met by these micro-franchises, then traditional healthcare facilities would be less burdened and patients who are in the most need of service will have greater access to these clinics. Adopting such direct selling model would invariably save the Nigerian government a great deal of money in enforcement, as the products would be sourced from the reliable manufacturers; as demand for counterfeit drugs decreases, so will the counterfeiters. However, whether this approach will not be compromised by illicit greedy individuals since it lacks regulatory control is worth critically evaluating before towing such line.

Conclusion

The pharmaceutical industry has a role to play in combating the menace of counterfeits medicines through enhanced cooperation between international bodies and improved partnerships with legitimate private supply chains to help reduce the issues of fake medicines in the developing world, Nigeria inclusive. In the long run, this would make medicines more accessible and cost-effective for everyone.

As standard practice when engaging in online purchases of medicines, end users of medicines can take safety precautions like looking out for spelling mistakes, mislabeled information, and unverifiable barcodes. After purchase the end user should examine the physical appearance of the pills (shape, size, color, non-uniform coloring of the drug) before use. If it seems different, it may indicate a fake drug. If there is no original product to compare, look out for features such as tampering, different packaging can also indicate that it may be counterfeit. Essentially, paying particular attention to the pill's appearance and packaging could be harmful or life-saving practice and should be routinely done to avoid falling prey of illicit fake medicine purchase and use in Nigeria.

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