EMPIRICAL QUALITY EVALUATION OF COMMON BRANDS OF CEFTRIAXONE SODIUM INJECTION MARKETED IN THE NORTHERN REGION OF NIGERIA

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ABSTRACT

Information related to the quality of ceftriaxone (CF) sold in northern Nigeria is limited. Therefore, we aimed to evaluate the quality of different brands of CF sodium injections marketed in Kano State of Nigeria. Thirteen different brands of CF sodium for injection (three samples per brand) were obtained from patent medicines vendors (PMVs), pharmacies and a government drug store in Kano State of Nigeria. The quality of these brands was assessed using physicochemical quality-control tests (colour, appearance, labelling, pH, weight uniformity and percentage of content). The results obtained from these tests were checked for compliance with the standards specified in British Pharmacopoeia 2009 (BP 2009) and the United States Pharmacopeia 2016 (USP 2016). All 13 (100%) brands were registered with the National Agency for Food and Drug Administration and Control (NAFDAC). The samples were brands imported from other countries and passed tests for colour and pH. However, 1 of the 13 samples did not pass the labelling inspection and only 4 (30.8%) brands were found to fulfil the requirements for physical appearance. Twelve (92.3%) of the 13 evaluated brands were found to have an acceptable percentage of content within a range of 95%–105% based on BP 2009 standards. The tested brands of CF sodium injection being marketed in Kano State of Nigeria were found to have variable compliance regarding the BP 2009 and USP 2016 specifications. Therefore, there is a need for relevant regulatory agencies to embark on more post-marketing surveillance to ensure the quality of medicines in Nigeria.

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INTRODUCTION

The menace of substandard and falsified medicines is a universal problem, particularly in low-and-middle-income countries (Newton, Green and Fernández 2010; Almuzaini, Choonara and Sammons 2013). According to the World Health Organization (WHO), medicines that fail to meet either quality standards, specifications or both are considered 'substandard' (WHO 2017a). Similarly, falsified medicines are products deliberately and fraudulently mislabelled concerning their identity and source (Aminu *et al.* 2017; European Commission 2020).

The proliferation of substandard and falsified medicines is a serious public health concern and has consequences for both patients and global health (WHO 2017a). According to recent data released by the European Commission, customs agents confiscated almost 40 million counterfeit pharmaceuticals in 2015, with a value of €650 million (Świeczkowski *et al.* 2021). As of 2020, an estimated monetary value of USD200 billion is being lost annually due to the counterfeiting of medicines (Millar 2020). Alarmingly, 42% of global cases of substandard and falsified drugs were linked to Africa (WHO 2017b; Millar 2020). This proliferation led to various consequences such as increased drug resistance and treatment failure and adversely posed a financial burden on both patients and governments (Kelesidis and Falagas 2015; Ozawa *et al.* 2018).

In Nigeria, despite the efforts of the National Agency for Food and Drug Administration and Control (NAFDAC), the proliferation of substandard and falsified medicines continues to rise (Aminu and Gwarzo 2017; Aminu *et al.* 2020). The economic burden of substandard and falsified medicine is reportedly more prominent in northern Nigeria as compared to the southern part, especially in antimalarial medicines due to the higher population in the northern region with a corresponding higher malaria transmission rate, which poses a greater risk of the disease (Beargie *et al.* 2019). Kano State is the largest state in northern Nigeria, and it is the place where the famous open-drug market (Sabon Gari) is located. Most people, patent medicine vendors (PMVs) and some pharmacies from the region relied on this market as a source of drugs, possibly due to relatively cheaper costs. To date, despite the enforcement activities by regulatory agencies such as NAFDAC, substandard and fake medicines are finding their way to the market. This problem could lead to numerous adverse drug-related events to the patients and consequently, add more burden to the weak healthcare system of the country. Thus, making Kano State a suitable setting for this study.

The quality control testing of marketed essential medicines is crucial, especially in developing countries like Nigeria, where fake and substandard medicines still form an integral part of the drug supply chain (Aminu and Gwarzo 2017; Aminu *et al.* 2017). It is a firm requirement that generic brands meet the specifications for quality stipulated by the official monographs for every standard pharmaceutical product (Da Silva Ferreira *et al.* 2020). Failure to fulfil such specifications (especially for parenteral preparations) renders the products poor quality. Quality control evaluation checks for parenteral preparations include content uniformity, clarity of reconstituted solutions, crystallinity, extractable volume, particulate matter in injections, bacterial endotoxin test, sterility test, pyrogen test, pH, packaging test, specific optical rotation and water determination (British Pharmacopoeia Commission 2009; Deshmukh *et al.* 2015; United States Pharmacopeia 2016).

Ceftriaxone (CF) is a third-generation broad-spectrum antibacterial agent with proven efficacy against many bacterial strains (Sweetman 2009; Aléssio *et al.* 2017; Hossein Abadi *et al.* 2021). Its tolerability, good pharmacokinetic and safety profile make CF an antimicrobial of choice in emergency and inpatient care (Kaliamoorthy *et al.* 2012; Zeng *et al.* 2017; Hossein Abadi *et al.* 2021). In Nigeria, generic brands of CF sodium are cheaper than the innovator brand (Sotade, Idowu and Adegoke 2017). A survey conducted by the Federal Ministry of Health (Nigeria) in conjunction with WHO indicated the cost ratio of an innovator brand to the lowest-priced generic equivalent of CF injection is 200% (WHO 2006).

The proliferation of numerous brands of CF sodium injections in the Nigerian market poses a risk for the rise of substandard and falsified products in circulation (Sotade, Idowu and Adegoke 2017). This problem, if left unchecked, could increase the portfolio of substandard and falsified products and their associated ill consequences. Despite being a cheap option, several studies have shown that many generic brands of CF injection failed quality standard tests (Akasha *et al.* 2014; Arnet *et al.* 2015; Sotade, Idowu and Adegoke 2017). In one study, the generic samples of CF manufactured in East Asia (China, India, Indonesia) in comparison with the Rocephin® innovator brand failed to meet pharmaceutical quality standards in at least three tests, including sterility, purity and physical characteristics (Arnet *et al.* 2015). Two studies conducted in southern Nigeria indicated that generic brands of CF sodium injections in the markets are pharmaceutically equivalent to the innovator brand; and conform to the British Pharmacopoeia 2009 (BP 2009) specifications (Okorie, Abayomi and Onyinyechi 2016; Sotade, Idowu and Adegoke 2017). Based on our knowledge of the available literature, there is no study on the quality of CF sodium injection marketed in northern Nigeria, particularly Kano State. Therefore, this research aims to investigate whether the common brands of CF sodium injection being sold in Kano State (north-western region of Nigeria) meet the standard specifications of the BP 2009 and the United States Pharmacopeias 2016 (USP 2016) requirements as claimed by the manufacturers.

MATERIAL AND METHODS

Materials

We investigated the quality of 13 different brands (three samples for each brand) of CF sodium for injection (1,000 mg/vial). These samples were randomly selected and coded as CF1–CF13 (Table 1). All samples were procured from wholesale pharmacies, retail pharmacies, PMVs and the Kano State Drug and Medical Consumable Supply Agency located in Kano, the north-western region of Nigeria. We ensured that the products (vials) were within their shelf-life at the time of this study and were stored in a powdered form below 25°C, protected from light. A BP 2009 reference standard of the CF sodium powder was purchased from Zayo-Sigma Chemicals Ltd. Jos, Nigeria. Distilled water was produced in-house using the All-glass UL, SZ–96 water distiller (Chincan, Hangzhou, China). Methylene blue was obtained from Zayo-Sigma Chemicals Ltd. Jos, Nigeria. All other chemicals used in the present study were of analytical grade.

Methods

The following analyses were conducted in this study: assessment of the physical state and the colour of dry powder and the reconstituted solution; uniformity of weight; vial closure integrity; pH determination; labelling inspection and determination of the concentration of the samples using a calibration curve. The analyses were performed as described by official books (British Pharmacopoeia 2009; United States Pharmacopeia 2016) and previous studies (Arnet *et al.* 2015; Jambulingam *et al.* 2015; Okorie, Abayomi and Onyinyechi 2016; Aléssio *et al*. 2017; Sotade, Idowu and Adegoke 2017; Trindade and Salgado 2018). The details for each test are described below.

Physical State and Colour of Dry Powder and Reconstituted Solution

Colour of dry powder

To assess the colour content of the powders, we used a spatula, withdrew a small amount of dry powder from each vial, and then placed it on a flat surface with a white background. This procedure was repeated using a black background. The colour obtained was then compared with the standard colour of CF sodium injection (as described in the BP 2009 and USP 2016, respectively).

Physical appearance

For the solid-state form of the sample, a small amount of powder was placed on a slide and covered with a cover slide. The specimen was examined using an optical microscope (Leica DM750, Leica Microsystems, Germany) at 40× and 100× magnifications. The visual characteristics presented by each specimen were observed and recorded.

Colour and clarity of the reconstituted solution

An aqueous solution (1.20% w/v) of all samples, including the reference standard, was prepared in carbon dioxide-free water. The solutions were transferred into clean colourless test tubes. The solutions' colour and clarity were examined against a white and black background under sufficient illumination. The colour of the sample solutions was compared with that of the reference standard solution. Likewise, the possible presence of floating or sedimented particles was assessed according to the BP 2009 and USP 2016 standards.

Uniformity of Weight

All 13 samples in vials (with no labels or closures/caps attached) were individually weighed using an electronic balance (Mettler Analytical Balance, England). Subsequently, the samples were emptied, and vials were rinsed with water and ethanol and dried at 105°C for 1 h. The empty vials were then weighed at room temperature. The weight of the sample was determined by subtracting the weight of the empty vials from the weight of the vials containing the samples. Subsequently, each sample's mean weight (percentage deviation) was compared with the standards specified in the monographs (USP 2016 and BP 2009).

Vial Closure Integrity

Sealed vials containing the samples were immersed in a methylene blue dye bath and left for 30 min. Subsequently, the vials were removed, rinsed with tap water and dried on a bench. The samples were reconstituted to produce a 12% w/v solution, which was then visually examined to check for the presence of a blue colouration.

pH Determination

The pH value was determined using 12.0% w/v and 10.0% w/v aqueous solutions of each sample using a pH meter (PHS–3C, China). A value of 6.0–8.0 is considered acceptable based on the BP 2009 and USP 2016 specifications for standard CF sodium injection at 12.0% w/v and 10.0% w/v concentrations, respectively.

Labelling Inspection

Labelling information, including batch number, manufacturing date, expiry date, manufacturer's address, amount of active ingredient and NAFDAC registration number of both primary and secondary packages of all brand samples under investigation were thoroughly examined and recorded. The written information on the samples was compared with the BP 2009 and USP 2016 specifications for labelling of CF sodium for injection and general parenteral products.

Determination of Calibration Curve

Finely ground powder of the reference standard (CF sodium) equivalent to 10 mg was dissolved in distilled water in a volumetric flask. This process was conducted to obtain a standard stock solution of 1,000 µg/mL at room temperature. Aliquots of this standard stock solution were diluted with distilled water to produce concentrations of six solutions containing 2, 4, 6, 8, 10 and 12 µg/mL. The resultant solutions were scanned against blank (distilled water) at a maximum absorbance of 240 nm (previously determined), using an ultraviolet and visible (UV-Vis) spectrophotometer (Jenway 7315, Bibby Scientific Ltd, Staffordshire, United Kingdom). Generated data for three determinations are analysed and presented as mean ± standard deviation (SD). A calibration curve was produced by plotting the absorbance against the concentration of the drug.

Preparations of Sample Solutions of the Brands of Ceftriaxone Sodium

Each vial of the sample (1,000 mg of CF sodium) was reconstituted with 10 mL distilled water to produce 100,000 µg/mL concentrations. From this solution, 1 mL was withdrawn and transferred into a 100 mL volumetric flask and made up the volume with distilled water to yield 1,000 µ/mL. The final sample solution was produced by transferring 200 µL of the resultant solution into a 25 mL volumetric flask and adding distilled water up to the mark to yield 8 µg/mL concentrations. The samples were measured in triplicates at 240 nm. The concentrations of the samples were estimated from the previously plotted calibration curve.

ETHICAL APPROVAL

The study protocol was reviewed and approved by the Kano State Drug and Medical Consumable Supply Agency.

RESULTS

Thirteen different brands of CF sodium for injection were randomly selected and included in the present study. The samples were obtained between November 2019 and December 2019 and, were analysed between January 2020 and July 2020. All samples were imported from other countries: India (n = 6), China (n = 6) and Switzerland (n = 1). All the brands contained NAFDAC registration numbers.

Colour, Appearance and Clarity of Dry Powder and Reconstituted Solution

The results of an inspection of dry powder of the tested brands of CF sodium are presented in Table 1. The colour test showed that all the dry powdered form of the samples was off-white, thus, complying with the official specification provided in BP 2009 and USP 2016. Also, the colour of the reconstituted solution for all samples was found to be pale yellow (Table 1). On careful visual inspection of each sample solution, it was observed that all solutions are clear and no undissolved or foreign matters were seen sedimented or floating in the aqueous solutions.

Sample CF1, CF2, CF4 and CF8 appeared to be crystalline powder under optical microscope observation as they exhibited regular elongated or rod-shaped particles with a three-dimensional arrangement. This result conforms with the BP 2009 and USP 2016 specifications that CF sodium powder should be crystalline in appearance. However, the specimens of the remaining samples appeared to be amorphous in appearance under the optical microscope due to their irregular and fairly random arrangement.

Mean Weight of Ceftriaxone Powder in Vial

The mean weight range of all tested brand samples was 1.092 g to 1.260 g, corresponding to 109.2% to 126.0% of product content (Table 1).

Labelling and Closure Integrity

The labelling inspection of the vials (primary label) and the packages (secondary label) showed that all the tested samples met the BP 2009 and USP 2016 specifications for labelling of CF sodium for injection (British Pharmacopoeia 2009; United States Pharmacopeia 2016), except sample CF7 which failed the labelling inspection. Additionally, all vials were tightly closed, passed the vial closure integrity test and stated the amount of CF sodium on their label, except sample CF7, which presented blurred labels that cannot be read clearly.

The pH of Reconstituted Solution

The result obtained from the pH test is presented in Table 1. The pH of various tested brands falls within the range of 6.05 to 7.50. Sample CF7 was found to have the lowest pH, while sample CF3 with the highest pH. The BP 2009 requires that the pH of a solution containing the equivalent of 12.0% w/v of CF sodium should be between 6.0 and 8.0 (British Pharmacopoeia 2009). Similarly, USP 2016 stipulates the pH of CF sodium to be between 6 and 8 in a solution (1 in 10) (United States Pharmacopeia, 2016). All the tested samples satisfied these requirements.

Table 1: Physical descriptions and pH of the samples investigated.

Sample code	Colour of dry powder	Colour of reconstituted solution	Powder appearance	pH ± SD, $n = 3$	Mean weight ± SD (g), $n = 3$	Labelling inspection
CF1	Off-white	Pale yellow	Crystalline	7.33 ± 0.01	1.16 ± 0.21	Conformed
CF2	Off-white	Pale yellow	Crystalline	7.01 ± 0.04	1.09 ± 0.02	Conformed
CF3	Off-white	Pale yellow	Amorphous	7.50 ± 0.12	1.17g ± 0.11	Conformed
CF4	Off-white	Pale yellow	Crystalline	6.88 ± 0.02	1.20 ± 0.06	Conformed
CF5	Off-white	Pale yellow	Amorphous	6.70 ± 0.00	1.26 ± 0.01	Conformed
CF6	Off-white	Pale yellow	Amorphous	6.87 ± 0.01	1.21 ± 0.00	Conformed
CF7	Off-white	Pale yellow	Amorphous	6.05 ± 0.20	1.16 ± 0.18	Blurred/Not Conformed
CF8	Off-white	Pale yellow	Crystalline	7.03 ± 0.01	1.19 ± 0.11	Conformed
CF9	Off-white	Pale yellow	Amorphous	7.01 ± 0.07	1.25 ± 0.02	Conformed
CF10	Off-white	Pale yellow	Amorphous	7.15 ± 0.01	1.12 ± 0.01	Conformed
CF11	Off-white	Pale yellow	Amorphous	7.22 ± 0.01	1.19 ± 0.21	Conformed
CF12	Off-white	Pale yellow	Amorphous	6.87 ± 0.14	1.10 ± 0.03	Conformed
CF13	Off-white	Pale yellow	Amorphous	6.99 ± 0.05	1.15 ± 0.10	Conformed

Note: CF = ceftriaxone

Lamda Max (λ max), Calibration Curve, Linearity and Range

The reference standard of CF sodium solution showed maximum absorbance at 240 nm following a scan from 200 nm to 350 nm wavelength range. The constructed calibration curve was linear (Figure 1). The linearity obeyed Beer-Lambert law over the concentration range of 2 µg/mL to 12 µg/mL and a correlation coefficient (R^2) of 0.9989.

$y = 0.0683x - 0.0079$
$R^2 = 0.9989$
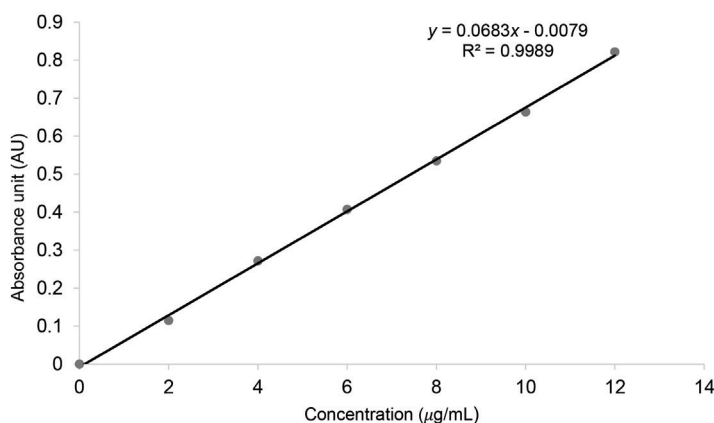
Figure 1: Standard calibration curve of CF sodium of the present study.

Drug Content

The percentage drug content of all the tested brands of CF sodium for injection is presented in Table 2. The concentration of CF sodium in each of the tested samples was determined through extrapolation from the Beer-Lambert plot previously constructed. The calculated concentration of all the prepared samples was 8 µg/mL, while the concentrations obtained in our analysis were between 7.60 µg/mL and 8.95 µg/mL. These values corresponded with percentage recoveries of between 95.0 ± 0.03 and 112.0 ± 0.04%, as shown in Table 2. Sample CF2 and CF10 had the minimum and maximum percentage of drug content, respectively.

Table 2: Basic information and drug content of the tested brands of ceftriaxone sodium injections.

Sample code	Source of brand	Country of manufacture	Manufacturing date	Expiry date	NAFDAC registration	Measured concentration ± SD (µg/mL)	%Recovery ± SD
CF1	DSA	India	09/2019	08/2021	Yes	7.83 ± 0.06	98.0 ± 0.06
CF2	DSA	India	02/2019	01/2021	Yes	7.60 ± 0.03	95.0 ± 0.03
CF3	Wholesale	China	03/2019	03/2022	Yes	8.38 ± 0.04	105.0 ± 0.04
CF4	Wholesale	China	09/2018	09//2021	Yes	8.08 ± 0.03	101.0 ± 0.03
CF5	DSA	Switzerland	10/2018	10/2021	Yes	8.39 ± 0.07	105.0 ± 0.07
CF6	PMV	China	03/2018	02/2021	Yes	7.99 ± 0.06	100.0 ± 0.06
CF7	PMV	India	02/2019	01/2022	Yes	7.73 ± 0.05	97.0 ± 0.05
CF8	Wholesale	India	04/2019	03/2022	Yes	7.77 ± 0.07	97.0 ± 0.07
CF9	DSA	India	02/2019	01/2021	Yes	8.18 ± 0.03	102.0 ± 0.03
CF10	DSA	China	01/2019	01/2022	Yes	8.95 ± 0.04	112.0 ± 0.04
CF11	DSA	China	11/2018	11/2021	Yes	8.43 ± 0.03	105.0 ± 0.03
CF12	Pharmacy	India	03/2019	02/2021	Yes	8.23 ± 0.05	103.0 ± 0.05
CF13	PMV	China	12/2018	12/2021	Yes	8.17 ± 0.00	102.0 ± 0.00

Notes: CF = ceftriaxone; NAFDAC = National Agency for Food and Drug Administration and Control; DSA = Drug Supply Agency; PMV = Patent Medicine Vendor

DISCUSSION

We present the first study evaluating the quality of different brands of CF injections marketed in Kano State, the north-western region of Nigeria. The most populous state in the country where the largest open drug market is located. We found that all the analysed brands passed the quality test for colour and pH. Twelve (92.3%) of the samples met the official specifications for labelling inspection, while 4 (30.8%) had an acceptable appearance than standard specifications. Our findings also showed that 12 (92.3%) of the samples contained permissible percentage content of CF based on the BP 2009 standard. The outcomes of our study suggest that most of the brands of CF injections marketed in Kano State of Nigeria have variable quality based on BP 2009 and USP 2016 standards. Therefore, there is an urgent need for post-marketing surveillance by the NAFDAC to ensure quality control and subsequent safety of the general population.

The BP 2009 requirement for labelling is that each sealed container of CF sodium for injection must state the quantity equivalent to the amount of CF in it (British Pharmacopoeia 2009). Similarly, both BP 2009 and USP 2016 require the storage of the drug in an airtight container and protected from light (British Pharmacopoeia 2009; United States Pharmacopeia 2016). These requirements were met by all the tested brands of CF sodium for injection except for sample CF7, which presented a blurred label that cannot be read clearly. This lack of label clarity of CF7 could be associated with poor label printing during the product's packaging preparation.

Colour assessment for the vial content of CF sodium for injection is essential as it indicates decomposition when discolouration or the development of a new colour occurs. In a tropical climatic setting, extremes of sunlight, heat and humidity can catalyse the decomposition of chemical compounds such as drugs and their formulations (Sotade, Idowu and Adegoke 2017). Similarly, changes in physical states, i.e. from crystalline to amorphous and vice versa, of solid pharmaceutical products indicate a deterioration in the quality of that product. An adequately stored drug product will maintain its physical qualities such as colour, odour and crystalline or amorphous state. The present study showed that 9 out of the 13 evaluated brands had an amorphous appearance compared to the crystalline reference.

All the dry powder of the tested samples complied with the official specification for colour, which specified CF sodium powder for injection as white to yellowish-orange (British Pharmacopoeia 2009; United States Pharmacopeia 2016). Other researchers reported similar findings as they observed all the CF sodium they tested to be in an amorphous state and have a white or off-white colour appearance (Arnet *et al.* 2015). The BP 2009 stipulated that the solution of CF sodium for injection should be clear and not more intensely coloured than the reference standard solution (British Pharmacopoeia 2009). All the evaluated samples of the present study displayed a clear solution that was pale yellow in colour and freely soluble in water. Moreover, there was not much deviation in the colour of all samples from that of the reference standard, hence they satisfied both BP 2009 and USP 2016 specifications for clarity of reconstituted solution of CF sodium for injection. A clarity test is also an important visual assessment that provides information on the physical state of the formulations. It assists in the early detection of undissolved or foreign particles in parenteral preparations which have the potential consequences of obstructing capillaries in the body.

The pH analysis determines the acidity or alkalinity of a chemical substance. The pH of pharmaceutical products is a critical variable that serves as an essential indicator of their stability. It significantly influences partition coefficient, solubility, palatability and antimicrobial effectiveness for antimicrobial agents. Weakly acidic and basic drugs exhibit

better solubility when they get ionised. All the tested samples satisfied the BP 2009 and USP 2016 specifications for the pH of CF sodium for injection of 6.0–8.0 range.

The method used for the determination of drug content in the present study was simple and cost-effective. Distilled water was the only solvent used for the reconstitution and dilutions of all samples. The method obeyed Beer-Lambert law in the range of 2 μg/mL–12 μg/mL with a correlation coefficient (R^2) of 0.9989. This indicated excellent linearity of the method and compliance with the International Conference on Harmonisation (ICH) requirement for linearity of $R^2 \geq 0.995$ (International Conference on Harmonisation 2005).

For the CF sodium content, the USP 2016 stipulates that the product should contain CF sodium equivalent to not less than 90.0% and not more than 115.0% of the labelled amount of CF (United States Pharmacopeia 2016). The results of the present investigation revealed that the percentage recovery for the 13 samples was in the range of 95.0 ± 0.03%–112.0 ± 0.04% (Table 2); thus, all samples satisfied the USP 2016 requirement. On the other hand, BP 2009 requires the content of CF sodium to be in the range of 92.0%–108.0% of the labelled amount of CF (British Pharmacopoeia 2009). Among the 13 tested marketed brands, one sample (8%) has failed the BP 2009 specification for drug content. The failed sample was CF10 with a percentage recovery of 112.0 ± 0.04%, originating from China. This failure of the BP 2009 standard for drug content may lead to potential efficacy and safety issues such as an abnormal rise in blood concentration of such medicines and associated adverse health effects (Binagwaho *et al.* 2013; Newton *et al*. 2014). In a similar investigation conducted by a team of researchers in Southern Nigeria, one out of the seven samples tested (14.3%) was found to deviate from BP 2009 specification for percentage drug content (Okorie, Abayomi and Onyinyechi 2016). The researchers attributed the deviation to non-adherence to good manufacturing practices (Okorie, Abayomi and Onyinyechi 2016).

All the tested samples in this study have NAFDAC registration numbers. This finding indicated that they are all approved products by the drug regulatory agency charged with regulating and controlling medicines-related activities, including importation, exportation, manufacture and sales in Nigeria. Therefore, there is an urgent need for NAFDAC to step up its measures for screening and subsequent monitoring of medicines in the country's drug supply chain to ensure only medical products of standard quality are available within Nigeria's health system. This approach will assist in safeguarding the public from the potential dangers of substandard medicines.

PRACTICAL IMPLICATIONS AND FUTURE DIRECTIONS

The present study has the following practical implications. Firstly, our findings suggest the need for a stricter quality control evaluation of CF injections at the point of registration and during post-marketing surveillance in Nigeria. Secondly, there is a need for quality control of CF injections by drug stores states, wholesales (through third-party research laboratories) and healthcare facilities before stocking. Thirdly, there is a need for rational drug prescription, dispensing and use of quality brands of CF injections in clinical settings across the country.

LIMITATIONS/FUTURE DIRECTIONS

The present study has the following limitations. First, we utilised an optical microscope in the visual examination of the samples, thus unable to confirm the products' absolute crystallinity or amorphous state. Future studies should employ objective analyses such as differential

scanning calorimetry or X-ray powder diffraction, which are considered gold standard tests for the visual examination of medicinal products. Secondly, we observed that the mean equivalent weight of all the samples' content was higher than the claimed 1 g on the label. While the manufacturers did not provide the reasons for the weight variation, it is possible that the surplus could be due to sodium salt. Future studies should conduct the impurity test while assessing the quality of CF sodium injections to rule out impurities.

We assumed that other factors such as insufficient supply chain management system, high cost of quality medicines, inadequate implementation of existing drug laws and corruption might be responsible for the discrepancies in quality observed in this study. The literature suggests that porous borders, political and security instability, resulting in a high level of smuggling of pharmaceutical products into the region, could be potential reasons for the proliferation of poor-quality medicinal products in Nigeria (Akunyili 2006; WHO 2017b).

CONCLUSION

The present study revealed that the brands of CF sodium for injection available in the market in the northern region of Nigeria have variable compliance with the standard specifications of the BP 2009 and USP 2016. We found that all the analysed brands passed the quality test for colour and pH. Twelve (92.3%) of the samples met the official specifications for labelling inspection, while four (30.8%) had an acceptable appearance than standard specifications. Our findings also showed that 12 (92.3%) of the samples contained permissible percentage content of CF based on the BP 2009 standard. The outcomes of our study suggest that some of the brands of CF injections marketed in Kano State of Nigeria do not comply with the quality specifications of the BP 2009 and USP 2016 standards. Therefore, there is an urgent need for post-marketing surveillance by the NAFDAC to ensure quality control and subsequent reduction of substandard CF injection in Nigeria.

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