# An Exploratory Medicine Quality Survey of Furosemide Tablets in Selected Pharmacies around Hospitals Providing Specialist Cardiovascular Care in Nigeria

**Orubu S.F. Ebiowei [1,2,3], Robert O. Faith[4], Amabebe Emmanuel[5]**

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria.

[2]Department of Biomedical Engineering, College of Engineering, Boston University, Boston, USA

[3]Institute for Health System Innovation & Policy, Boston University, Boston, USA

[4]Department of Biochemistry, College of Medicine, Niger Delta University, Bayelsa State, Nigeria

[5]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

Corresponding author: samuelorubu@lycos.com

How to cite this article:
Orubu, E.S.F, Robert, O.F, Amabebe, **E. An Exploratory Medicine Quality Survey of Furosemide Tablets in Selected Pharmacies around Hospitals Providing Specialist Cardiovascular Care in Nigeria.** NDJMS 2021; 3(3):66-73

**Received** 19th March 2021 | **Accepted** 11th June 2021 | **Published** xxxx xxxx

Abstract

***Introduction:*** *Poor-quality medicines remain a public health challenge in Nigeria, despite the efforts of the National Agency for Food and Drug Administration and Control (NAFDAC). The quality of medicines intended for use in children is not known, as there are no studies on this area. The pharmacological management of cardiovascular disease in children is also an understudied research area. The aim of this study was to explore the quality of furosemide tablets intended for the extemporaneous preparation (compounding) of children's cardiovascular medicine in Nigeria.*

***Methods:*** *The study used the mystery shopper approach to obtain samples of furosemide tablets from pharmacies purposively and conveniently selected in Bayelsa State, Lagos State and Abuja, Nigeria. Rationale for locations included states with public healthcare facilities providing paediatric cardiovascular care. At these locations, the major pharmacies within one-hour's drive from these facilities were surveyed. Furosemide samples were assessed for quality by packaging inspection using registration by NAFDAC and chemical analysis for potency using the British Pharmacopoeia (BP) specification for Percent Label Claim (PLC).*

*Samples that met the specified PLC of 95-105% were defined as being of quality, for compounding purposes.*

***Results:*** *The majority, 90% (9/10) of the four brands of furosemide tablets samples were not registered by NAFDAC. The PLC of all samples was 100.2 ± 1.6% (mean ± SD).*

***Conclusion:*** *Samples met official potency standards for quality (while other pharmacopoeial specifications were not checked), but the majority were not registered by NAFDAC. Regular multi-site post-marketing screening for medicine quality is needed in Nigeria.*

**KEYWORDS:** furosemide, cardiovascular medicines, children, Nigeria, quality

## Introduction

Poor-quality medicines are prevalent in Low- and Middle-Income Countries (LMICs). The World Health Organization (WHO)'s recent estimate of the global prevalence of poor-quality, or Substandard and Falsified (SF) medicines, is 10.5%, based mainly on studies from Africa.[1] Nigeria, the largest country in Africa, stands out as regulatory model to containing the public health challenge of SF medicines through the activities of its regulatory body, the National Agency for Food and Drug Administration and Control (NAFDAC).[2] However, this threat is ever present. In the wake of COVID-19, there has been increased incident of SF medicines including putative curative medicines and vaccines.[3]

Furosemide is a high-ceiling diuretic classified as an essential medicine. It is included in the WHO Essential Medicines Lists for Adults and Children with indications for oedema and heart failure for use from birth, emphasizing its clinical importance.[4]Cardiovascular diseases (CVDs), including heart failure, and other Non-Communicable Diseases (NCDs) account for 70% of global mortality, with an over representation from LMICs.[5] Cardiovascular diseases are also a significant burden in children. Global estimates of the incidence of CVDs in children is 8/1000 births, but may be higher in LMICs.[6] Medicines for CVDs are commonly compounded for young children less than 5 years old who usually cannot safely swallow conventional sized (8-10mm) tablets.[7] In Nigeria, furosemide constituted 15% (n=2845) of medicines compounded into oral liquids for children.[8] In Ghana, this rises to 31.2% (n=622).[9] Furosemide is also frequently compounded in Kenya.[10] These studies highlight the lack of suitable furosemide formulations for pediatric use in these countries, despite its public health significance.

However, there are knowledge gaps on the quality of furosemide in the supply chain, and of any potential impact of the use of SF furosemide in the management of CVDs in children. Most medicine quality studies in Nigeria focus on medicines for communicable diseases or antimicrobials – antibacterial and antimalarials. Previous studies on NCD medicines either do not include furosemide,[11,12] or are limited to one study site.[13]

The aim of this project, as part of a broader project on access to age-appropriate medicines for children,[8,14] was to investigate the quality of furosemide tablets in circulation in Nigeria with a focus on pharmacies in close proximity to public health facilities providing specialized

pediatric CVDs care. With the frequent stock-outs in public facilities, patients often obtain prescribed medicines from private pharmacies.

## Materials and Methods

The study was designed as a multi-site medicines quality survey using the mystery-shopper approach. Reporting followed the MEDQUARG guidelines.[15]. Researchers posed as mystery-shoppers. Locations were conveniently selected based on the presence of health facilities providing pediatric cardiovascular care

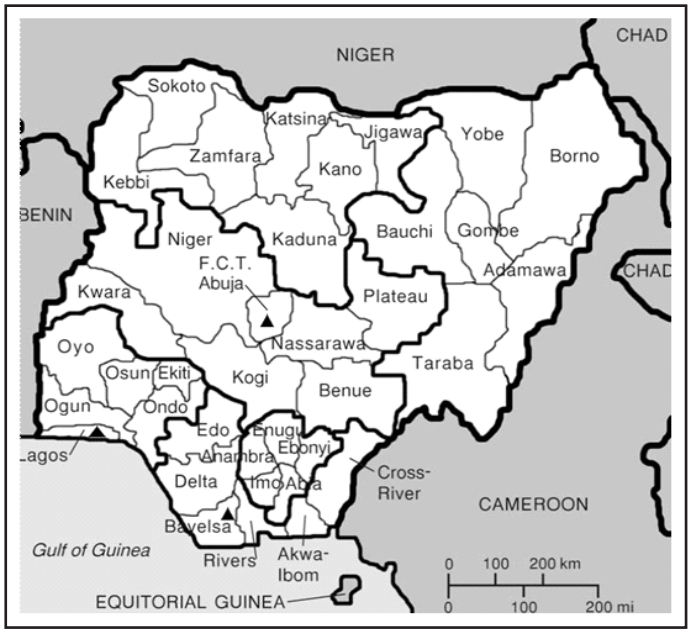


*Figure 1 Map of Nigeria showing survey locations identified by black triangles. The internal bold lines demarcate the six geo-political zones. [Modified from: https://www.nairaland.com/148185/6-geo-political-zones]*

and geographical dispersion, as previously described [14]. Three locations, out of 37 administrative units in Nigeria, were selected as: Bayelsa State, Lagos State, and the Federal Capital Territory (FCT). These are, respectively, in the South-South, South-West, and North-Central geo-political zones (Figure 1). Of these, Lagos and the FCT provide specialist pediatric cardiovascular care in public hospitals.[16] Bayelsa State, a peri-urban location without a specialized care facility at the time, was included as a "control" to account for any rural-urban effects. At these locations, private pharmacies were then purposively selected to include those within 10km from these public hospitals in the capitals of Lagos and the FCT, and the first tertiary hospital in Yenagoa – the capital of Bayelsa State. As this was designed as a rapid, exploratory study, sample size calculations were not performed. As with some other medicine quality audits, ethical approval was not sought [17]

Samples were collected using a "prescription" written out by the researchers, as is common in Nigeria (unreported data). Hospitals with a stock-out of medicines sometimes do this so that patients can obtain these medicines from private pharmacies. At each pharmacy, one pack of furosemide, of at least 20 tablets (to last three weeks, at a presumed dose of one 40mg tablet daily), constituting one sample, was requested over the counter. Samples were collected in December 2016 and analyzed in January 2017.

Data collected were: type (branded/generic); country of origin; NAFDAC's registration number; manufacturers' authentication technology, if any; expiry date; and batch number.

The quality of the samples was assessed using packaging inspection and potency assessments by UV-Vis spectroscopy at University College London.

Packaging inspection used the registration status by NAFDAC as a sign of quality. The presence or absence of a NAFDAC number indicates, respectively, licensing or non-licensing by NAFDAC. The manufacturer's seal of quality, hologram, or other mobile-authentication technology was also noted if present, as another indicator of quality.

Chemical assay of active ingredient content for potency was performed as contained in the British Pharmacopeia (BP) 2017.[18] Briefly, 20 tablets of furosemide per sample were weighed, crushed and aliquots containing 0.2g of furosemide dispersed in 0.1 M sodium hydroxide solution by shaking with a magnetic stirrer for 10 minutes. The suspension produced was filtered using a 0.45 µm syringe filter, diluted 1:20 with 0.1 M sodium hydroxide and assayed at 271 nm (Cary 100 UV-Vis spectrophotometer, Agilent, UK). Replicate measurements were made for samples with >20 tablets. Assay, per force, was not blinded to packaging. Absorbances were compared to the A (1%, 1 cm) value to obtain the amount of active ingredient in the sample. The Percentage Label Claim, PLC, was determined as: PLC = (Amount of active ingredient/label claim) x 100%

Data was de-identified. Data analysis for packaging inspection was by descriptive statistics (%). Medicine quality was defined by the chemical assay. Thus, medicines that met the BP quality standard in terms of the PLC, irrespective of the presence or absence of a NAFDAC number and/or authentication technology, were said to be of quality, if the PLC was between 95-105% of the labelled strength. Poor-quality medicines, by extension, were defined as those failing to meet the BP's specifications for potency.

**Results**

The pharmacies surveyed were licensed premises – owned or managed by pharmacists. All visited pharmacies had only one type (brand/generic form) of furosemide. None had the child-friendly formulation, with some pharmacists unaware that furosemide is also commercially available as a liquid form for children. All but one sample were in their original primary and secondary packaging.
In all, 10 samples were collected from 10 different pharmacies across the three study locations (Table 1).

Samples: Across locations, samples were four brands of furosemide 40mg tablet(Table 1). The most prevalent was the originator brand by Manufacturer A (50%, 5/10), followed by a generic by Manufacturer B (30%, 3/10).

Packaging inspection: All but the local brand (90%, 9/10) were not registered by NAFDAC (Table 1). None had an authentication technology on the packaging. Most of the samples were stated as either manufactured in Turkey (50%, 5/10) or the United Kingdom (40%, 4/10). One brand was stated as manufactured in India with a Nigerian license holder (10%, 1/10). None of the medicines were expired during collection or analysis.

Chemical analysis: All 10 furosemide samples met the BP's PLC specification, with a mean of 100.2±1.6% (Table 2).

*Table 1 Packaging assessment for quality of 10 furosemide 40mg tablet samples collected from select pharmacies in Lagos State, Bayelsa State and FCT in Nigeria (2016)*

| **NAFDAC No.** | No | No | No | No | No | No | Yes | No | No | No |
|---|---|---|---|---|---|---|---|---|---|---|
| **Brand/generic** | Generic | Brand | Brand | Brand | Brand | Generic | Generic | Generic | Generic | Brand |
| **Manufacturer** | A | B | B | B | B | A | C | D | A | B |
| **Country of origin** | UK | Turkey | Turkey | Turkey | Turkey | UK | India/Nigeria | UK | UK | Turkey |
| **Expiry date** | 5.2019 | 12.2017 | 10.2018 | 4.2019 | 5.2018 | 5.2019 | 11.2017 | 11.2017 | 10.2019 | 12.2017 |
| **Location** | Abuja | Abuja | Abuja | Abuja | Abuja | Yenagoa | Yenagoa | Lagos | Lagos | Lagos |

*Table 2 Potency of 10 furosemide 40mg tablet samples collected from select pharmacies in Lagos State, Bayelsa State and FCT in Nigeria (2016)*

| **Sample ID** | **1** | **2** | **6** | **10** | **13** | **24** | **25*** | **29** | **31** | **38** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sample weight (20 tablets), mg** | 3289.3 | 3258.1 | 3251.3 | 3220.1 | 3184 | 3308 | 4545.1 | 3274.9 | 3284.2 | 3253.5 |
| **Aliquot, mg** | 828.3 | 815.3 | 813 | 804.8 | 796.3 | 828.9 | 1137 | 819.1 | 823.9 | 815.4 |
| **Absorbance (271nm) #1** | 0.476 | 0.47 | 0.476 | 0.463 | 0.459 | 0.4848 | 0.48 | 0.465 | 0.464 | 0.465 |
| **Absorbance (271nm) #2[†]** | - | - | - | - | - | 0.483 | - | - | 0.465 | 0.466 |
| **Average of absorbance readings** | 0.476 | 0.47 | 0.476 | 0.463 | 0.459 | 0.4839 | 0.48 | 0.465 | 0.4645 | 0.4655 |
| **Sample content of furosemide[‡], mg** | 205 | 203 | 205 | 200 | 198 | 209 | 207 | 200 | 200 | 201 |
| **Percent Label Claim[3]** | **102** | **101** | **103** | **100** | **99** | **104** | **103** | **100** | **100** | **100** |
| **Inference** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** |

Notes:

*Sample dispensed into plastic envelopes. Details of manufacturer was requested. The researcher expressed concern about the sample being in a hospital pack and asked to see more details including NAFDAC registration.

[†]Duplicate measurements of absorbance were made only where sample size was more than 20 tablets.

[‡]Rounded to the nearest integer/whole number.

## Discussion

This assessment, the first of such multi-site investigations, for furosemide in Nigeria provides information on the quality of furosemide in selected pharmacies around healthcare facilities providing specialized cardiovascular care for children.

All furosemide samples were compliant with official potency specifications. In this, our results differ from the findings of a multi-state survey conducted in 10 African countries (excluding Nigeria) assessing the quality of several cardiovascular medicines in circulation that found a mean SF furosemide prevalence of 12.5%.[19] They also differ from a localized study in Port Harcourt, Nigeria, that found that one out of five registered brands of furosemide did not comply with official (US Pharmacopeial) standard, which, with an allowed range of 90-110 PLC, is slightly different from the BP standard used here.[13] Our findings were similar with the results from a survey in Ethiopia, with respect to assay of active ingredient, which found five brands of furosemide to be of quality [20] Nevertheless, together, these studies indicate the need for continuous post-marketing surveillance of the quality of medicines in circulation in Nigeria.

This relatively simple official (BP, 2017) UV-Vis method could be used for the routine screening of procured furosemide tablets before compounding in hospitals in Nigeria, possibly integrated into a proposed 3-level medicine quality assurance protocol.[21]

The majority (90%, 9/10) of the samples were not registered. This very high proportion of medicines unlicensed by NAFDAC is surprising. Medicine quality surveys from Nigeria report much lower proportions of unlicensed chloroquine (25%, 5/20), metformin (13%, 2/15), quinine (33%, 6/18), with NAFDAC reporting 68% in 2001 [22–25]. In the past, the absence of a NAFDAC registration number was a sign not to buy a product from a medicine outlet or pharmacy during the *"Operation Shine Your Eyes"* campaign to eliminate SF medicines in Nigeria [2]. There is the need to strengthen regulatory inspections at ports of entry and for more regular post-marketing surveillance activities to ensure that all medicines in the supply chain in Nigeria are licensed by NAFDAC. This would need substantial investment in capacity building and strong political will.

One limitation of these findings, considering the complex medicine supply chain in Nigeria is that they may not be generalizable. However, the specialized nature of furosemide use in children means that they are more likely to be purchased in pharmacies in close proximity to the healthcare facilities providing specialist cardiovascular medicines such as the ones surveyed, where these specialist hospitals experience stock-outs. Also, it is to be noted that dissolution studies, an important quality specification for medicines meant to be swallowed intact, were not conducted in this study as these medicines are usually compounded, or crushed and dispersed in a liquid for administration to young children – obviating the need for dissolution testing as a sign of quality.

## Conclusion

The majority of furosemide in circulation among selected pharmacies close to locations providing specialized cardiovascular care for children met official potency standards for quality, though other pharmacopoeial specifications were not checked, but they were not registered by NAFDAC. There is an urgent need to secure the supply chains, include more frequent

regulatory inspections and routine post-marketing screening for medicine quality in Nigeria.

**Acknowledgement:** Prof. Catherine Tuleu, Department of Pharmaceutics, University College London (UCL), School of Pharmacy, UK. for the Visiting Scientist position granted to ESFO for this research.

**Conflict of Interest:** None

**Funding:** This research received no funding.

**References**

1. WHO. WHO Global Surveillance and Moonitoring System for Substandard and Falsified Medical Products [Internet]. 2017 [cited 2019 Dec 25]. Available from: https://apps.who.int/iris/bitstream/handle/10665/326708/9789241513425-eng.pdf?ua=1
2. Makgetla I. Innovations for Successful Societies. Oral history program: Governance Traps, Interview no H1. 2009;1-8.
3. Muanya C, Onyenucheya A. NAFDAC raises alarm over fake COVID-19 vaccine in Nigeria. The Guardian Nigeria News - Nigeria and World News [Internet]. 2021[cited 2021 Jan 29]; Available from: https://guardian.ng/news/nafdac-raises-alarm-over-fake-covid-19-vaccine-in-nigeria/
4. WHO. WHO Model List of Essential Medicines for Children - 7th list, 2019 [Internet]. 2019 [cited 2021 Feb 11]. Available from: https://www.who.int/publications-detail-redirect/WHOMVPEMPIAU201907
5. WHO. Non communicable diseases [Internet]. 2020. [cited 2020 Dec 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
6. Zühlke L, Mirabel M, Marijon E. Congenital heart disease and rheumatic heart disease in Africa: recent advances and current priorities. Heart 2013;99(21):155461.
7. Bowles A, Keane J, Ernest T, Clapham D, Tuleu C. Specific aspects of gastro-intestinal transit in children for drug delivery design. Int J Pharm 2010;395(12):3743.
8. Orubu ESF, Okwelogu C, Opanuga O, Nunn T, Tuleu C. Access to age-appropriate essential medicines: a retrospective survey of compounding of medicines for children in hospitals in Nigeria and implications for policy development. Health Policy Plan 2016;32(2):22535.
9. Ankrah DNA, Turkson JT, Boateng EB, Amegavie FTT, Bruce E. Insufficient access to oral paediatric medicines in Ghana: A descriptive study. BMC Health Serv Res 2016;16(1):15.
10. Bilakhia NA, Tirop LJ, Menge TB, Kuria KAM. A retrospective study of oral medications compounded for pediatric patients at Kenyatta National Hospital. East Cent Afr J Pharm Sci2014;17(3):649.
11. Ndichu ET, Ohiri K, Sekoni O, Makinde O, Schulman K. Evaluating the quality of antihypertensive drugs in Lagos State, Nigeria. Musinguzi G, editor. PLOS ONE2019;14(2):e0211567.
12. Redfern J, Kaur H, Adedoyin RA, Ofori S, Anchala R, Vamadevan AS, et al. Equivalence in Active Pharmaceutical Ingredient of Generic Antihypertensive Medicines Available in Nigeria (EQUIMEDS): A Case for Further Surveillance. Glob Heart 2019;14(3):327.
13. Chinaka CN, Nwachukwu N. Comparative in vitro quality assessment of five brands of furosemide tablets marketed in Port Harcourt, Nigeria. Niger J

Pharm Res 2017;13(2):97104.
14. Orubu ESF, Robert FO, Samuel M, Megbule D. Access to essential cardiovascular medicines for children: a pilot study of availability, price and affordability in Nigeria. Health Policy Plan 2019;34(3):iii20iii26.
15. Newton PN, Lee SJ, Goodman C, Fernández FM, Yeung S, Phanouvong S, et al. Guidelines for Field Surveys of the Quality of Medicines: A Proposal. PLoS Med 2009;6(3):e1000052.
16. Ekure E, Sadoh W, Bode-Thomas F, Orogade A, Animasahun A, Ogunkunle O, et al. Audit of availability and distribution of paediatric cardiology services and facilities in Nigeria. Cardiovasc J Afr 2017;28(1):549.
17. Anyakora C, Oni Y, Ezedinachi U, Adekoya A, Ali I, Nwachukwu C, et al. Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits. BMC Pregnancy Childbirth2018;18(1):44.
18. British Pharmacopoeia Commission. British pharmacopoeia: Furosemide. Vol. 1. London, United Kingdom: TSO2020.
19. Antignac M, Diop BI, Do B, NGuetta R, Toure IA, Zabsonre P, et al. Quality Assessment of 7 Cardiovascular Drugs in 10 Sub-Saharan Countries: The SEVEN Study. JAMA Cardiol 2017;2(2):223.
20. Abebe S, Ketema G, Kassahun H. In vitro Comparative Quality Assessment of Different Brands of Furosemide Tablets Marketed in Northwest Ethiopia. Drug Des Devel Ther 2020;14:511928.
21. Pribluda VS, Barojas A, Coignez V, Bradby S, Dijiba Y, El-Hadri L, et al. The Three-Level Approach: A Framework for Ensuring Medicines Quality in Limited-Resource Countries. Pharmaceut Reg Affairs 2014;3:117.
22. Mukhtar MD, Bashir M, Arzai AH. Comparative in-vitro studies on antiplasmodial quality of some Nigerian and foreign brands of chloroquine oral formulations marketed in kano. Afr J Biotechnol 2006;5(24):2464-68.
23. Okhuelegbe ES, Dennis ICA, Amara IM. Pharmaceutical quality assessment of brands of metformin hydrochloride tablets available in south-east nigeria. Afr J Pharm Res Dev 2020;12(3):333-341.
24. Nnamdi JA, Arhewoh IM, Okhamafe AO, Enato EFO. Evaluation of the Pharmaceutical Quality of Some Quinine Preparations Sold in Nigeria. Med Princ Pract2009;18(3):1937.
25. Akunyili D. The challenges faced by NAFDAC in the national regulatory process as it relates to essential drugs for prevention of maternal and newborn deaths in Nigeria. Trop J Obstet Gynaecol 2010;27(1):817.