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# Pharmaceutical Quality of Selected Metronidazole and Ciprofloxacin Infusions Marketed in South Eastern Nigeria

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**Background:** Pharmaceutical products need to be of good quality and it is even more critical when it comes to life saving medicaments like infusions.

**Objective:** This research surveyed the quality fitness of some ciprofloxacin and metronidazole infusion samples marketed in South-eastern of Nigeria.

**Methods:** Using Official Compendial methods, microbiological quality, active pharmaceutical ingredients quantitation, pH and particle count tests were evaluated on eighty infusion bottles (from eight pharmaceutical companies) of each of the two drugs.

**Results:** Out of the sixteen brands tested, 2 metronidazole brands and 1 ciprofloxacin brand (representing 18.75% of the total 16 brands/makes) were contaminated while the remaining 13 brands (81.25%) were found sterile. The active pharmaceutical ingredients quantitative assay showed that all the brands of ciprofloxacin infusion were between the 95% and 105% limit of label claim while one metronidazole brand has <95–110% limit label claim. Six brands each of the two drugs evaluated fall below the acceptable pH range [ciprofloxacin (3.5–4.6) and metronidazole (4.8–5.2)], while the other two brands of both drugs passed the test. In the antibacterial study, *Pseudomonas aeruginosa* and *Escherichia coli* were susceptible to the ciprofloxacin (5 µg). However, *Salmonella typhi* recorded inhibition zone diameters within resistant and intermediate range. *Peptostreptococcus* spp was susceptible (at minimum inhibitory concentrations of 100 µg/mL) to all the brands of metronidazole, while none of the brands were effective on *Lactobacillus* spp. All the brands passed the test for particulate contamination. The particles size range was <10µm.

**Conclusion:** About eighty-one percent (81.25%) of the infusions have acceptable good microbiological quality. However, 18.75% that failed the tests is a concern knowing that these are lifesaving products.

**Keywords:** intravenous infusions, quality assessment, ciprofloxacin, metronidazole, quality medicines

## Introduction

The circulation of substandard medicines remains a serious problem in resource limited countries like Sub-Saharan Africa, where most of the drugs available are imported. Medicines sold in these markets are frequently found to have ingredients at concentrations that are too high or too low. Porous borders between the countries in the region facilitate the illicit importation of drugs and drugs piracy.<sup>1</sup>

According to a study by Atata et al<sup>2</sup> in Nigeria, out of 160 samples of intravenous fluids analyzed, 14 (8.75%) were microbiologically contaminated with 2 bacterial and 3 fungal isolates. As much as 58 (36.25%) were pyrogenic.

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These findings necessitated the importance of monitoring pharmaceutical quality of intravenous infusions. Free trade and globalization policies have led to an anarchical invasion of poor quality medicines into the markets of developing countries. Nigeria has the biggest medicines market in the ECOWAS region, where there are very high activities in cross-border and parallel trade in pharmaceuticals.<sup>1</sup>

Intravenous administration of fluids (drug and nutrition) is very common in hospitals.<sup>3</sup> Patients on hospital admission are normally administered intravenous (IV) fluids and electrolytes due to at least one of the 4Rs needs: Resuscitation, Routine maintenance, Replacement or Redistribution.<sup>4</sup> Studies had shown that as much as 80% of patients on hospital admission do receive one form of intravenous therapy or the other.<sup>3,5</sup> These important life-saving fluids have been reported as sources of life-threatening infections and in some cases have been incriminated as one of the strongest factors for morbidity and mortality associated with nosocomial infections in hospitals all over the world.<sup>3,6,7</sup> Globally, contaminated fluids were found to be the largest and most lethal known cause of outbreak of nosocomial infections.<sup>2,8-11</sup> Between October, 1970 and March, 1971, eight United States hospitals in seven states experienced 150 bacteremia caused by *Enterobacter cloacae*; there were nine deaths and all were associated with intravenous fluid therapy.<sup>9</sup> Nigeria is not an exception. Some deaths and disease conditions have been attributed to the use of these microbiologically unfit fluids.<sup>2,6</sup> Nigerian National Agency for Food, Drug Administration and Control (NAFDAC) has fought assiduously against the menace of unwholesome pharmaceutical products including infusions.<sup>2,12-14</sup>

The aim of this research, therefore, was to establish the quality fitness of some metronidazole and ciprofloxacin infusions marketed in South-east of Nigeria. Manufacture and distribution of quality pharmaceutical products are vital components of good health-care practice and will promote quality health-care delivery.

## Materials and Methods

### Media

Soybean Casein digest broth (SCDB) by Oxoid, USA; Fluid thioglycolate medium (FTM) manufactured by TM Media, India; Peptone water manufactured by TM Media, India; Mueller Hinton Agar by Oxoid, USA; Nutrient Agar by Oxoid, USA. All the media were prepared according to

the manufacturers' instructions and sterilized as per the manufacturers' guidelines.

### Equipment

Water-bath sonicator manufactured by PCI Analytics, India; Ultra Violet (UV) Spectrophotometer manufactured by Pharmacia Biotech, Sweden; Liquid particle counter by HACH ALTRA, USA; suction pump by Thomas Industries, USA; Vacuum flask by Thomas Industries, USA and Laminar Air Flow Cabinet by Krishna Scientific suppliers, India.

### Sample

Ciprofloxacin 200mg/100mL and metronidazole 500mg/100mL samples were collected from the five South-eastern states of Nigeria namely Abia, Anambra, Ebonyi, Enugu and Imo. They were purchased from the open drug markets in the area and pharmacy outlets. The brand names, manufacturers, marketers, license numbers, lot numbers, NAFDAC registration numbers, manufacturing date and expiry dates were recorded. The samples were eight brands each of ciprofloxacin and metronidazole infusions. The number of samples taken for each test was 1 (a 100 mL product) from each brand according to British Pharmacopeia 2017. However, for the pyrogen test, 10 bottles were sampled from 5 brands each of the drug products.

### Microbial Test Isolates

The microorganisms used in this study were five bacterial isolates namely: *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Peptostreptococcus* spp and *Lactobacillus* spp. Except for the *Pseudomonas aeruginosa* and *Escherichia coli* (which were typed cultures), other microorganisms were clinical isolates previously purified, standardized to McFarland and preserved in the Laboratory of the Department of Pharmaceutical Microbiology & Biotechnology, Nnamdi Azikiwe University, Awka, Nigeria.

### Microbiological Analysis

#### Sterility Test

Membrane filtration method<sup>15</sup> was used for the analysis. One hundred-milliliter bottles of each of the samples were collected, transferred to the quality control unit of the laboratory and cleaned with 70% ethanol solution. Twenty milliliters (20 mL) each of Soybean casein digest broth (SCDB) and Fluid thioglycolate medium (FTM) were respectively dispensed in test tubes, plugged with cotton wool and sterilized.

Nanometer reading of the working Laminar Flow Cabinet (Krishna Scientific suppliers, India) was set at 08–15 mm while the temperature was set at  $27 \pm 2$  °C. The vacuum pump connected to the manifold holder was switched on. A sterile 0.22  $\mu\text{m}$  (pore size) membrane filter was placed in its proper place in the manifold using sterile forceps. The membrane was made wet with 15 mL of 1% sterile peptone water. Each drug container/bottle was aseptically opened using a sterile scissors and the whole content (100mL) was aseptically transferred to the membrane filter for vacuum filtration. One membrane filter was used for one drug bottle. The filtration system was rinsed three times with 1% peptone water after each session to neutralize and wash the membrane. The vacuum was stopped and the membrane was carefully lifted with sterile forceps and cut into two. One half was placed in FTGM and the other half in SCDB, unplugging in front of a gas burner flame. They were appropriately labelled and incubated. The FTM was incubated at 35 °C while the SCDB was incubated at room temperature for fourteen days. The set-up was inspected daily for visible turbidity. The number of samples tested in each brand was 1 as each vial contains 100 mL. This is according to British Pharmacopoeia.<sup>15</sup>

### Rabbit Pyrogen Test

Pyrogen test was evaluated using the Rabbit method. The test, based on the intravenous injection of sterile solutions, has been employed for many years and it is still valid for the quality control of parenteral preparations.<sup>16</sup> The test was carried out by following procedures in British Pharmacopoeia.<sup>15</sup> Three rabbits, each weighing 1.5 kg, were used for each product. Prior to the test, the animals were acclimatised for two days in pathogen-free environment where the test was carried out. The animals were handled following established guidelines<sup>17–19</sup> for care and use of animals for scientific research. The study was approved by the Proposal/Ethics Committee for animal studies in the Faculty of Pharmaceutical Sciences of Nnamdi Azikiwe University, Awka. Approval Number: FPhS/AEC/Vol.1.003

Before the injection of the product, initial temperature of each rabbit was determined and recorded. The ciprofloxacin samples were appropriately diluted with pyrogen-free isotonic sodium chloride solution. The products were then slowly injected into the marginal vein of the ear of each rabbit. The temperature of each injected rabbit was taken at 30 min intervals for a period of 3 h. The maximum temperature of each rabbit is the highest temperature recorded

for the rabbit in 3 h after injection. The difference between the initial temperature and the maximum temperature of each rabbit is taken as its response. Where this difference was negative, the result was considered as zero response.

## Quantitative Assay

### Metronidazole and Ciprofloxacin Intravenous Infusion Analytical Procedure

#### Preparation of the Standard Solution

UV Spectrophotometer Method in British Pharmacopoeia<sup>15</sup> was used. Briefly, Step 1: A 500 mg of metronidazole powder was weighed into a 50 mL volumetric flask, 20 mL of 0.1M HCl was added and sonicated for five minutes. The volume was made up with 0.1 M HCl and re-sonicated for five minutes. Step 2: A 10 mL volume of the resulting solution was transferred into a 100 mL volumetric flask, 60 mL of 0.1 M HCl was added and sonicated for five minutes and volume made up and sonicated again for five minutes. Step 3: From the resulting solution, 10 mL was taken into another 100 mL volumetric flask, 60 mL of 0.1 M HCl was added and sonicated for five minutes, the volume was made up and the content sonicated again for five minutes. Step 4: From the resulting solution, 10 mL was taken into another 100 mL volumetric flask and sonicated for five minutes; the volume was made up with 0.1M HCl and sonicated for five minutes to give the studied solution which has a concentration of 0.01 mg/mL. The final concentration was 0.01 mg/mL.

500 mg → 50 mL → 10 mL → 100 mL 10 mL → 100 mL 10 mL 100 mL

The Metronidazole powder (reference standard) was manufactured by Sigma Aldrich, a subsidiary of Merck USA.

## Sample Preparation

Step 1: A 10 mL volume of each brand of the metronidazole sample was transferred into 100 mL volumetric flask, 50 mL of 0.1 M HCl was added and sonicated for five minutes; the volume was made up with 0.1 M HCl and the content re-sonicated for five minutes. Step 2: 10 mL of resulting solution was transferred into 100 mL volumetric flask; 60 mL of 0.1 M HCl was added and sonicated for five minutes. The volume was made up with 0.1 M HCl and sonicated for five minutes. Step 3: Next, 20 mL was taken from the resulting solution into 100 mL volumetric flask, 60 mL of 0.1 M HCl was added and sonicated for five minutes, the volume was made up and sonicated for five minutes to give the studied solution.

10 mL → 100 mL → 10 mL 100 mL → 20 mL 100 mL

## Blank: 0.1 M HCl

The absorbance was measured at 277 nm as per SOP on UV-Vis spectrophotometer operation and calibration.

## Ciprofloxacin I.V. Infusion Analytical

### Procedure

#### Standard Solution Preparation

Step 1: A 200 mg quantity of ciprofloxacin was accurately weighed into 100 mL volumetric flask, 50 mL of 0.1M HCl was added and sonicated for five minutes, the volume was made up with 0.1 M HCl and sonicated for five minutes. Step 2: A 2 mL quantity was taken from the resulting solution into 50 mL volumetric flask; 30 mL 0.1M HCl was added and sonicated for five minutes, the volume was made up with 0.1 M HCl and sonicated for five minutes. Step 3: Another 2 mL was taken from the resultant solution into 50 mL volumetric flask, 30 mL of 0.1M HCl was added and sonicated for five minutes, the volume was made up with 0.1M HCl. The final concentration was 0.0032 mg/mL.

200 mg → 100 mL → 2 mL → 50 mL

The ciprofloxacin reference standard was manufactured by Sigma Aldrich, a subsidiary of Merck USA.

### Sample Preparation

Ten milliliters of metronidazole sample was transferred into 100 mL volumetric flask. Fifty milliliters of 0.1 M HCl was added and sonicated for 5 min. The volume was made up to 100mL with 0.1 M HCl and re-sonicated for five minutes. Ten milliliters of resulting solution was transferred into another 100 mL volumetric flask and 60 mL of 0.1 M HCl added and sonicated for five minutes. The volume was made up to 100mL with another 0.1 M HCl followed by re-sonication for five minutes. Then, 20 mL was taken from the resulting solution into another 100 mL volumetric flask and 60 mL of 0.1 M HCl added and sonicated for five minutes. The volume was also made up to 100mL and sonicated finally for five minutes. Tests were carried in triplicates.

For the ciprofloxacin, 2 mL of each sample was taken into 50 mL volumetric flask and 25 mL of 0.1 M HCl was added and sonicated for five minutes. The volume was made up to 50mL with 0.1 M HCl and re-sonicated for five minutes. From the resultant solution, 2 mL was taken into another 50 mL volumetric flask and 30 mL of 0.1 M HCl added and sonicated for five minutes. The volume was made up to 50mL with 0.1 M HCl and re-sonicated for five minutes. Tests were carried in triplicates.

Blank was 0.1 M HCl. The absorbance of both the standard and sample was measured at 277–278 nm as per standard operating procedure on UV-Vis spectrophotometer operation and calibration.

The calculations on how the standard preparations were used to obtain the concentration of the drugs in the samples tested are contained in the [supplementary materials 1](#) and [2](#).

$$\% \text{Label Claim} = \frac{(5)(A)(W)(P)}{(B)} \quad \text{For metronidazole}$$

While for ciprofloxacin

$$\% \text{Assay w/v} = \frac{(2)(A)(W)(P)}{(B)}$$

where A = Average absorbance of sample, B = Average absorbance of standard, W = Weight of standard, P = Potency of standard = 101.0 for Metronidazole = 99.6% Ciprofloxacin

## Particle Count Using Liquid Particle Counter System

The test for particulate contamination of the samples was done according to the International Pharmacopoeia.<sup>20</sup> For parenteral infusion containing 100 mL or less, the preparations complies with the test if the average number of particles present in the unit tested does not exceed 6000 per container (cumulative particle size ≤10 μm) and does not exceed 600 per container (cumulative particle size ≤25 μm). Here, size criterion was used to judge if a product as passed or failed. Briefly, the contents of the samples were carefully mixed by slowly inverting the container 20 times successively. Gas bubbles were eliminated by allowing mixture to stand for 2 minutes. A magnetic stirrer was dropped in 100 mL beaker. The sample was poured into and placed under the needle pointer of the counter and the machine is started. The principle is that the needle sucks the liquid and passes it through the laser light inside; any particle that obstructs the light is counted and displayed on the screen. After each count, the system was flushed with 70% isopropyl alcohol to prevent crystals from blocking the discharge pipe. Tests were carried in triplicates.

## Hydrogen Index (pH) Analysis

A Hydrogen Index analysis was undertaken according to The United States Pharmacopoeial Convention<sup>21</sup> using a pH meter (model = PHS-3C and accuracy = 0.05). The sample was poured in a nestler tube. A pH electrode connected to



the pH meter was rinsed with distilled water, cleaned with tissue and inserted into the sample. The pH meter was turned on and the reading was taken on the viewing screen. The acceptable pH range for metronidazole IV is 4.8–5.2, while that of ciprofloxacin IV is 3.5–4.6. However, for concentrated infusions, the pH range is between 3.3 and 3.9.<sup>21</sup>

## Antibacterial Evaluation of the Test Samples

The antimicrobial assay for ciprofloxacin samples was carried out using the agar well-diffusion assay as described by Waltrich et al,<sup>22</sup> against *Salmonella typhi*, *Pseudomonas aeruginosa* (ATCC 27853), and *Escherichia coli* (ATCC 25922) while agar dilution method as described by Okore<sup>23</sup> was used to test for the antibacterial potency of the metronidazole samples against *Peptostreptococcus* spp and *Lactobacillus* spp.

## Agar Well Diffusion Assay

The media, Mueller-Hinton agar, MHA (Oxoid, USA) were prepared and treated according to the manufacturer's specification. After sterilizing, the media was allowed to cool to 50 °C and later transferred into 90 mm sterile agar plates and left to set. The sterile MHA plates were inoculated with the test culture from each of the test suspensions, thereafter, 20 mL of the sterile molten agar cooled to 50 °C was added to the plate and was rocked clockwise and anti-clockwise to ensure even distribution of the test organism and uniformity of the inoculums. A sterile cork borer was used to make wells (6 mm in diameter) on the MHA plates. Aliquots of 60 mL of the stock concentration (5 µg/mL) were applied in each of the wells in the culture plates previously seeded with the test organisms. The cultures were incubated at 37 °C for 18–24 hrs. The antimicrobial potential was determined by measuring the zone of inhibition around each well (excluding the diameter of the well).

## Agar Well Dilution Assay

Stock solutions of 2 mg/mL equivalent of the various metronidazole products were prepared. Then, two-fold serial dilutions were made to get 1000, 500, 250, 125, 62.5, 31.3 and 15.6 µg/mL. Thereafter 10-fold dilutions of each of the concentration was made using 9 mL sterile molten Mueller-Hinton agar, MHA (Oxoid, USA) to get final concentrations of 200, 100, 50, 25, 12.5, 6.3, 3.1, 1.6 µg/mL then, this were allowed to solidify. The microbial inocula (*Peptostreptococcus*

spp and *Lactobacillus* spp) which have been standardized to 0.5 McFarland turbidity was streaked on the agar appropriately. The plates were incubated in an anaerobic jar for 24 hrs. After incubation the plates were examined for microbial growth by checking for growths using a plus sign (+) indicating growth while a negative sign (-) indicated no growth as shown in Table 1. Minimum inhibitory concentrations (MIC) were obtained from the results. The MIC is interpreted as the lowest concentration of the test samples that inhibited visible growth. Each experiment was performed in triplicate.

## Results

### Microbiological Analysis

We analysed eight brands of ciprofloxacin and eight brands of metronidazole infusions with each brand containing 10 sample bottles. Out of the sixteen brands tested, 2 metronidazole brands and 1 ciprofloxacin brand (representing 18.75% of the total 16 brands/makes) were contaminated microbiologically while the remaining 13 brands (81.25%) were found to be sterile (Table 1).

### Pyrogen Test

The result suggested probable contamination of the test samples. Two ciprofloxacin brands (three bottles per brand) and one metronidazole brand (4 bottles) were pyrogenic (Table 1).

### Quantification Assay of the Ciprofloxacin and Metronidazole Sample

Table 2 indicates the amount of ciprofloxacin and metronidazole molecules in each of the samples. All the brands of ciprofloxacin infusion (IV) tested were within the acceptable quality [acceptable range is 95–105% for ciprofloxacin infusion (IV)] for the active pharmaceutical ingredient. However, one brand of metronidazole infusion (IV) representing 12.5% failed while the remaining 7 (87.5%) passed the test. The acceptable range is 95–110% for metronidazole infusion (IV)

### Hydrogen Index (pH) Analysis of Samples

Table 3 shows the results of the ciprofloxacin and metronidazole infusion brands tested. The acceptable range for metronidazole and ciprofloxacin infusions is 4.8–5.2 and 3.5–4.6, respectively. The 8 brands of each drug were tested. Only two brands (25%) each of ciprofloxacin and metronidazole infusions passed while six brands (75%) in each category failed, showing acidity much higher than the acceptable range.

**Table 1** Microbiological Quality of the Metronidazole and Ciprofloxacin Samples

| Sterility Test |                                       |   |    |                             |   |    | Pyrogen Test |               |   |                       |
|----------------|---------------------------------------|---|----|-----------------------------|---|----|--------------|---------------|---|-----------------------|
| Brands         | Sampling Time Post-Inoculation (Days) |   |    |                             |   |    | Product Code | Number Tested | Number Pyrogenic (%)<br>Response > 2.65 | Number Apyrogenic (%) |
|                | Fluid Thioglycolate Medium            |   |    | Soybean Casein Digest Broth |   |    |              |               |   |                       |
|                | 3                                     | 6 | 14 | 3                           | 6 | 14 |              |               |   |                       |
| M1             | -                                     | - | -  | -                           | - | -  | M1           | 10            | 0                                       | 10 (100%)             |
| M2             | -                                     | - | -  | -                           | - | -  | M2           | 10            | 0                                       | 10 (100%)             |
| M3             | +                                     | + | +  | -                           | - | -  | M4           | 10            | 0                                       | 10 (100%)             |
| M4             | -                                     | - | -  | -                           | - | -  | M5           | 10            | 0                                       | 10 (100%)             |
| M5             | -                                     | - | -  | -                           | - | -  | M7           | 10            | 4 (40%)                                 | 6 (60%)               |
| M6             | +                                     | + | +  | -                           | - | -  | C1           | 10            | 0                                       | 10 (100%)             |
| M7             | -                                     | - | -  | -                           | - | -  | C2           | 10            | 0                                       | 10 (100%)             |
| M8             | -                                     | - | -  | -                           | - | -  | C3           | 10            | 0                                       | 10 (100%)             |
| C1             | -                                     | - | -  | -                           | - | -  | C4           | 10            | 3 (30%)                                 | 7 (70%)               |
| C2             | -                                     | - | -  | -                           | - | -  | C5           | 10            | 3 (30%)                                 | 7 (70%)               |
| C3             | -                                     | - | -  | -                           | - | -  |              |               |   |                       |
| C4             | -                                     | - | -  | -                           | - | -  |              |               |   |                       |
| C5             | -                                     | - | -  | -                           | - | -  |              |               |   |                       |
| C6             | +                                     | + | +  | -                           | - | -  |              |               |   |                       |
| C7             | -                                     | - | -  | -                           | - | -  |              |               |   |                       |
| C8             | -                                     | - | -  | -                           | - | -  |              |               |   |                       |

**Notes:** M1 – M8 = brand codes for metronidazole samples for sterility test and C1 – C8 = brand codes for ciprofloxacin samples for sterility test. “+” = positive test, “-” = negative test. C1 – C5 are brand codes for ciprofloxacin samples used for pyrogen test while M1 – M5 are brand codes for metronidazole samples used for pyrogen test. (“M” stands for Metronidazole infusion; “1–8” means that 8 different brands (one from one company) were sampled and 1 vial containing 100 mL of each of these brands were tested. “C” stands for ciprofloxacin infusion; “1–8” means that 8 different brands (one from one company) were sampled and 1 vial containing 100 mL of each of these brands were tested.

**Table 2** Quantitation of Ciprofloxacin and Metronidazole Molecules in the Samples

| PRODUCT CODE | Absorbance Reading<br>( $\lambda= 278\text{nm}$ ) |       |       | Assay Calculation (E or C) |       |       |       |       | % Assay/% Label Claim | Inference |
|--------------|---|-------|-------|----------------------------|-------|-------|-------|-------|-----------------------|-----------|
|              | 1   | 2     | 3     | 1                          | 2     | 3     | Mean  | SD    |                       |           |
| C1           | 0.413   | 0.413 | 0.418 | 0.204                      | 0.204 | 0.206 | 0.205 | 0.001 | 102.50                | Pass      |
| C2           | 0.407   | 0.406 | 0.407 | 0.201                      | 0.201 | 0.201 | 0.201 | 0.000 | 100.50                | Pass      |
| C3           | 0.417   | 0.418 | 0.420 | 0.207                      | 0.207 | 0.208 | 0.207 | 0.000 | 103.50                | Pass      |
| C4           | 0.399   | 0.399 | 0.400 | 0.197                      | 0.197 | 0.197 | 0.197 | 0.000 | 98.50                 | Pass      |
| C5           | 0.407   | 0.408 | 0.406 | 0.201                      | 0.201 | 0.201 | 0.201 | 0.000 | 100.50                | Pass      |
| C6           | 0.399   | 0.399 | 0.398 | 0.197                      | 0.197 | 0.197 | 0.197 | 0.000 | 98.50                 | Pass      |
| C7           | 0.419   | 0.418 | 0.415 | 0.207                      | 0.206 | 0.205 | 0.206 | 0.001 | 103.00                | Pass      |
| C8           | 0.392   | 0.392 | 0.393 | 0.194                      | 0.194 | 0.194 | 0.194 | 0.000 | 97.00                 | Pass      |
| M1           | 0.380   | 0.380 | 0.381 | 0.520                      | 0.520 | 0.521 | 0.520 | 0.000 | 104.00                | Pass      |
| M2           | 0.375   | 0.373 | 0.372 | 0.514                      | 0.511 | 0.510 | 0.511 | 0.002 | 102.20                | Pass      |
| M3           | 0.380   | 0.380 | 0.379 | 0.520                      | 0.520 | 0.519 | 0.520 | 0.000 | 104.00                | Pass      |
| M4           | 0.379   | 0.380 | 0.382 | 0.519                      | 0.520 | 0.523 | 0.520 | 0.002 | 104.00                | Pass      |
| M5           | 0.340   | 0.338 | 0.340 | 0.465                      | 0.463 | 0.465 | 0.464 | 0.002 | 92.80                 | Fail      |
| M6           | 0.359   | 0.357 | 0.360 | 0.492                      | 0.489 | 0.493 | 0.492 | 0.002 | 98.40                 | Pass      |
| M7           | 0.365   | 0.366 | 0.365 | 0.500                      | 0.501 | 0.500 | 0.500 | 0.000 | 100.00                | Pass      |
| M8           | 0.366   | 0.367 | 0.367 | 0.501                      | 0.502 | 0.502 | 0.502 | 0.000 | 100.20                | Pass      |

**Notes:** C1 to C8 are product codes for the ciprofloxacin IV samples while M1 to M8 are product codes for the metronidazole IV samples.

**Table 3** pH Analysis for Ciprofloxacin IV and Metronidazole IV

| Ciprofloxacin IV |      |           | Metronidazole IV |      |           |
|------------------|------|-----------|------------------|------|-----------|
| Product Code     | pH   | Inference | Product Code     | pH   | Inference |
| C1               | 3.14 | Fail      | M1               | 4.58 | Fail      |
| C2               | 3.18 | Fail      | M2               | 4.29 | Fail      |
| C3               | 3.00 | Fail      | M3               | 4.34 | Fail      |
| C4               | 3.50 | Pass      | M4               | 4.54 | Fail      |
| C5               | 3.16 | Fail      | M5               | 4.74 | Fail      |
| C6               | 2.78 | Fail      | M6               | 4.35 | Fail      |
| C7               | 3.20 | Fail      | M7               | 5.12 | Pass      |
| C8               | 3.62 | Pass      | M8               | 4.90 | Pass      |

**Notes:** C1 to C8 = product codes for ciprofloxacin IV brands, M1 to M8 = product codes for metronidazole IV brands. The acceptable pH range [ciprofloxacin = 3.5–4.6 and metronidazole = 4.8–5.2].

### Sample Particulate Test Result

The eight brands of each drug/product were tested and all passed (Table 4) as the average cumulative particle size contaminants were well <10 µm. This means that all the brands were free of particulate contamination.

### Antibacterial Evaluation of the Samples

Susceptibility profiles of *S. typhi*, *P. aeruginosa* and *E. coli* against ciprofloxacin brands is indicated in Table 5. It was observed in the study that the IZDs of *S. typhi* were within the resistant and intermediate range.<sup>24</sup> *P. aeruginosa* and *E. coli* isolates were susceptible to all the ciprofloxacin

brands tested except 1 brand (C8). This brand showed no significant activity against any of the test organisms.

The lowest concentration of the metronidazole samples at which no growth of microorganism (*Peptostreptococcus* spp and *Lactobacillus* spp) was observed after incubation was considered at the MIC.<sup>25,26</sup> The result (Table 6) showed that each of the six brands had MIC of 100µg/mL against *Peptostreptococcus* spp while M5 gave MIC of 200µg/mL. M7 had no inhibition activities against *Peptostreptococcus* spp at all concentration. None of the brands gave activity against *Lactobacillus* spp at all concentration used (Table 6). This could be attributed to the concentrations used which might have been insufficient to inhibit the growth of the test microorganisms, at McFarland equivalent standard.

### Discussion

Sterility testing determines whether or not the products have microbial contaminations and/or pyrogens. Intravenous infusions are expected to be sterile.<sup>20</sup> Membrane filtration method was used for concentration of contaminating organisms in the infusions. Presence of any living microorganisms in the product meant to be passed into the blood stream could result in nosocomial septicemia<sup>27,28</sup> and can consequently cause blood stream infections.<sup>29</sup> Contamination level as high as 18.75% in products that supposed to be sterile is alarming and calls for immediate caution and readdressing of the production system by the pharmaceutical companies concerned. Clinically

**Table 4** Test for Particulate Contamination, Ciprofloxacin IV and Metronidazole IV

| Brand Code | Cumulative Count (µm) 1 | Cumulative Count (µm) 2 | Cumulative Count (µm) 3 | Cumulative Counts (µm) Average | SD    | Particulate Limit (Size) | Inference |
|------------|-------------------------|-------------------------|-------------------------|--------------------------------|-------|--------------------------|-----------|
| M-1        | 0.10                    | 0.40                    | 0.15                    | 0.22                           | 0.161 | Not more than 10 µm      | Pass      |
| M-2        | 0.45                    | 0.35                    | 0.05                    | 0.28                           | 0.208 |                          | Pass      |
| M-3        | 1.80                    | 0.95                    | 0.05                    | 0.93                           | 0.875 |                          | Pass      |
| M-4        | 0.05                    | 0.00                    | 0.10                    | 0.05                           | 0.050 |                          | Pass      |
| M-5        | 0.15                    | 0.40                    | 0.15                    | 0.23                           | 0.144 |                          | Pass      |
| M-6        | 1.15                    | 0.20                    | 0.60                    | 0.65                           | 0.477 |                          | Pass      |
| M-7        | 0.15                    | 0.25                    | 0.35                    | 0.25                           | 0.100 |                          | Pass      |
| M-8        | 0.05                    | 0.00                    | 0.15                    | 0.07                           | 0.076 |                          | Pass      |
| C-1        | 1.05                    | 0.55                    | 0.15                    | 0.58                           | 0.451 | Pass                     |           |
| C-2        | 0.10                    | 0.30                    | 0.05                    | 0.15                           | 0.132 | Pass                     |           |
| C-3        | 0.00                    | 0.40                    | 0.20                    | 0.20                           | 0.200 | Pass                     |           |
| C-4        | 0.00                    | 0.55                    | 0.10                    | 0.22                           | 0.293 | Pass                     |           |
| C-5        | 0.10                    | 0.00                    | 0.45                    | 0.18                           | 0.236 | Pass                     |           |
| C-6        | 0.25                    | 0.45                    | 0.15                    | 0.28                           | 0.152 | Pass                     |           |
| C-7        | 0.00                    | 0.40                    | 0.65                    | 0.35                           | 0.328 | Pass                     |           |
| C-8        | 0.75                    | 0.30                    | 0.35                    | 0.47                           | 0.247 | Pass                     |           |

**Notes:** M-1 to M-8 = product codes for metronidazole IV brands, C-1 to C-8 = product codes for ciprofloxacin IV brands.



**Table 5** Antibacterial Activities of the Ciprofloxacin Brands

| Product Code (5µg) | Inhibition Zone Diameter (IZD) in mm |                               |                         |
|--------------------|--------------------------------------|-------------------------------|-------------------------|
|                    | <i>Salmonella typhi</i>              | <i>Pseudomonas aeruginosa</i> | <i>Escherichia coli</i> |
| C1                 | 17.0                                 | 35.0                          | 26.5                    |
| C2                 | 16.0                                 | 35.0                          | 25.0                    |
| C3                 | 18.5                                 | 32.0                          | 25.0                    |
| C4                 | 17.0                                 | 35.0                          | 28.0                    |
| C5                 | 14.5                                 | 35.5                          | 25.5                    |
| C6                 | 17.0                                 | 35.0                          | 25.5                    |
| C7                 | 16.0                                 | 35.0                          | 26.0                    |
| C8                 | 4.5                                  | 0.0                           | 0.0                     |

Notes: IZD ≤ 15 = Resistant; 16–20 = Intermediate and ≥ 21 = Susceptible.<sup>24</sup>

important, microbiological contamination is most dangerous for patients when it affects parenteral therapy.<sup>30</sup> In this case, pathogens can directly reach the systemic circulation and cause catheter-related blood stream infection (CR-BSI)<sup>31</sup> or travel to various organs and induce organ failure.<sup>32</sup> Nosocomial infections would be widespread and would be important contributors to morbidity and mortality. This has public health implications causing increasing economic and human health impact. Increasing number of people exposed to contaminated products, increased frequent impaired immunity (due to age, illness and treatments failures), and introduction of new microorganisms can potentially lead to increased bacterial resistance to antibiotics. A pyrogen level of 10% in

intravenous fluids is high and poses a serious cause of concern. Obviously, infusion of pyrogenic product into already debilitated patients could only worsen the patients' condition and decrease their chances of survival. Pyrogens of microbial origin are metabolic products of microorganisms. The most potent pyrogens are the endotoxins produced from the cell walls of the Gram-negative bacteria (lipopolysaccharide).<sup>33</sup> Endotoxin is heat stable, potent Toll-like receptor 4 (TLR4) agonist that triggers the inflammatory cascade in a dose-dependent manner.<sup>3,34</sup> Consequently, that can lead to serious fever, chills, sepsis and irreversible shock. Low active pharmaceutical ingredient (API) observed in few of the samples is equivalent to low dosage of the drug. This could lead to ineffective treatment of patient when administered.<sup>35</sup> It can also easily lead to organisms developing resistance to the drugs. The acidic pH of some of the products could upset the metabolic processes in the body if they are infused. Acidic pH of the blood stream leads to metabolic acidosis and oxidative stress all of which have negative impact to health.

Intravenous fluids are expected to be free from particulate contaminations.<sup>20</sup> Generally, particulate contamination of parenteral fluids or solutions refers to the presence of unwanted, mobile and/or undissolved particles in the solution. These particles can find their way into the IV fluid during mixing (of pharmaceutical or nutritional ingredients) and/or product filling and capping (packaging). The particulate contaminants can be detectable particles that are visible

**Table 6** MIC of the Metronidazole Samples Against *Peptostreptococcus* and *Lactobacillus* spp

| Organism                      | Brand Codes | Concentration (µg/mL) |     |    |    |      |     |     |     |
|-------------------------------|-------------|-----------------------|-----|----|----|------|-----|-----|-----|
|                               |             | 200                   | 100 | 50 | 25 | 12.5 | 6.3 | 3.1 | 1.6 |
| <i>Peptostreptococcus</i> spp | M1          | –                     | –   | +  | +  | +    | +   | +   | +   |
|                               | M2          | –                     | –   | +  | +  | +    | +   | +   | +   |
|                               | M3          | –                     | –   | +  | +  | +    | +   | +   | +   |
|                               | M4          | –                     | –   | +  | +  | +    | +   | +   | +   |
|                               | M5          | –                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M6          | –                     | –   | +  | +  | +    | +   | +   | +   |
|                               | M7          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M8          | –                     | –   | +  | +  | +    | +   | +   | +   |
| <i>Lactobacillus</i> spp      | M1          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M2          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M3          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M4          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M5          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M6          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M7          | +                     | +   | +  | +  | +    | +   | +   | +   |
|                               | M8          | +                     | +   | +  | +  | +    | +   | +   | +   |

Notes: (–) no growth/inhibition; (+) growth/no inhibition.

on visual inspection with sizes  $\geq 50 \mu\text{m}$  or sub-visible particles that are not detectable on visual inspection with sizes varying between 2 and  $50 \mu\text{m}^{36}$ . Both visible and sub-visible particulate contaminations in parenteral fluids or solutions are dangerous<sup>36-40</sup> as these fluids are meant to pass through the blood vessels. The present study showed that the drug products are free from both visible and sub-visible particulate contaminations and their use cannot lead to the deleterious effects of particulate contamination.

The findings from this research have reaffirmed the need to constantly keep-up with the quality profiles of these pharmaceutical products, especially the intravenous infusions, while maintaining sterility, efficacy, exact required active ingredients, and other physicochemical parameters. This is important, as irreversible grievous consequences can result from these inefficiencies.

## Conclusion

About eighty-one percent (81.25%) of the infusions have acceptable good microbiological quality. However, the 18.75% that failed the tests is a concern knowing that these are lifesaving products. Generally, the findings of this study suggest improvement and stringencies in the regulations of infusion pharmaceutical products in circulation in the region and in Nigeria generally. This study has shown that there are still some sub-standard metronidazole and ciprofloxacin infusions in circulation in South-east of Nigeria. These infusions commonly used in the health-care facilities for various interventions could actually lead to nosocomial infections because of poor microbiological quality.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Bah-Traore N. Quality assurance and safety issue of pharmaceutical products marketed in developing countries. Dissertation. Mathematisch Naturwissenschaftlichen Fakultät, Rheinische Friedrich-Wilhelms-Universität Bonn vorgelegt von. 2012. <https://d-nb.info/1044082860/34>.
- Atata R, Ibrahim Y, Akanbi A, Abdul I, Sani A, Ahmed R. Microbiological quality of some brands of intravenous fluids produced in Nigeria, College of Health Sciences, University of Ilorin, Nigeria. *Afr J Biotechnol*. 2007;6(19):2197–2200. doi:10.5897/AJB2006.000-5439
- Waite C, Waite P, Pirmohamed M. Intravenous therapy. *Postgrad Med J*. 2004;80:1–6. doi:10.1136/pgmj.2003.010421
- National Clinical Guideline Centre (UK). Intravenous Fluid Therapy: intravenous Fluid Therapy in Adults in Hospital [Internet]. (NICE Clinical Guidelines, No. 174.) 5, Principles and protocols for intravenous fluid therapy. London: Royal College of Physicians (UK); Dec. 2013. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK333103/>. Accessed 26 December 2019.
- Beecham GB, Tackling G. *Peripheral Line Placement*. StatPearls, ed. Treasure Island (FL): StatPearls Publishing; 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539795/>. Accessed 26 December 2019.
- Revelas A. Healthcare-associated infections: a public health problem. *Niger Med J*. 2012;53(2):59–64. doi:10.4103/0300-1652.103543
- Paut O, Rémond C, Lagier P, Fortier G, Camboulives J. Severe hyponatremic encephalopathy after pediatric surgery: report of seven cases and recommendations for management and prevention. *Ann Fr Anesth Reanim* 2000;19:467–473
- Omoifo CE, Edomwonyi NP, Idogun SE. Incidence of hyponatraemia following the use of three different intravenous fluids in paediatric surgery. *Afr J Paediatr Surg*. 2018;15:69–72. doi:10.4103/ajps. AJP5\_40\_16
- CDC. Epidemiologic notes and reports nosocomial bacteremia's associated with Intravenous Fluids therapy-USA. *MMWR*. 1997;46(51):1227.
- Armour A. Dilutional hyponatraemia: a cause of massive fatal intraoperative cerebral oedema in a child undergoing renal transplantation. *J Clin Pathol*. 1997;50:444–446. doi:10.1136/jcp.50.5.444
- Arieff AI, Ayus CJ, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *Br Med J*. 1992;304:1218–1222. doi:10.1136/bmj.304.6836.1218
- Garuba HA, Kohler JC, Huisman AM. Transparency in Nigeria's public pharmaceutical sector: perceptions from policy makers. *Global Health*. 2009;5:14–22. doi:10.1186/1744-8603-5-14
- Raufu A. Nigeria leads fight against 'killer' counterfeit drugs. *Bull World Health Organ*. 2006;84:690–694.
- Akunyili D. The fight against counterfeit drugs in Nigeria. In: Kotalik J, Rodriguez D, editors. *Global Corruption Report*. London, UK: Pluto Press; 2006:96–100.
- The British Pharmacopoeia (BP). The department of health Published by the British pharmacopoeia commission, London, III, 2017.
- Mwambete KD, Justin-Temu M, Fazleabbas FS. Microbiological assessment of commercially available quinine syrup and water for injections in Dar Es Salaam, Tanzania. *Trop J Pharm Res*. 2009;8(5):441–447. doi:10.4314/tjpr.v8i5.48088
- National Research Council (US). *Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals*. 8th ed. Washington (DC): National Academies Press (US); 2011. <https://www.ncbi.nlm.nih.gov/books/NBK54050/doi:10.17226/12910>.
- Veterinary Surgeon Act Cap V3 LFN 2004, Federal Republic of Nigeria. The Care and Use of Animals for Scientific Purposes. 2014.
- Animal Diseases (Control) Act. Cap A17 LFN, 2004, Federal Republic of Nigeria The Care and Use of Animals for Scientific Purposes. 2004.
- The International Pharmacopoeia. *Parenteral Preparations*. 9th ed. 2016; 1–4.
- The United States Pharmacopoeial Convention. U. S. Pharmacopoeia-National Formulary: USP monographs: ciprofloxacin and metronidazole infusions, 2017.
- Waltrich KK, Hoscheid J, Prochnau IS. Antimicrobial activity of crude extracts and fractions of Vernonia polyanthes Less (assa-peixe) flowers. *Revista Brasileira De Plantas Medicinai*. 2015;17(4 Suppl.2):909–914. doi:10.1590/1983-084X/14\_110
- Okore V. *A Standard Laboratory Technique in Pharmaceutics and Pharmaceutical Microbiology*. 2nd ed. Nigeria: Naphtali prints; 2004:6–24.
- CLSI. CLSI supplements M100. 27th ed. In: *Performance Standards for Antimicrobial Susceptibility Testing*. Wayne, PA: Clinical and Laboratory Standards Institute; 2017; 1-15.
- Okoye EL, Uba BO, Uhobo PC, Oli AN, Ikegbonam MN, Evaluation of the antibacterial activity of methanol and chloroform extracts of *Alchornea cordifolia* Leaves. *J Sci Res Rep*. 2014;3(1):255–262. doi:10.9734/JSRR/2014/4328

26. Jayshree D, Dhruva J. Antidermatophytic Activity of some medicinal plants, phytochemical analysis and isolation of active fractions from *Piper longum*. *J Pure Appl Microbio*. 2013;7(4):3207–3312.
27. Oli AN, Okoli KC, Ujam NT, Adje DU, Ezeobi I. Health professionals' knowledge about relative prevalence of hospital-acquired infections in Delta State of Nigeria. *Pan Afr Med J*. 2016;20:24 (20):148. doi:10.11604/pamj.2016.24.148.9270
28. Macias AE, Huertas M, de Leon SP, et al. Contamination of intravenous fluids: a continuing cause of hospital bacteremia. *Am J Infect Contr*. 2010;38(3):217–221. doi:10.1016/j.ajic.2009.08.015
29. Ejiofor OS, Ajunwa OM, Ezeudu CE, et al. The bacteriology and its virulence factors in neonatal infections: threats to child survival strategies. *J Pathog*. 2018;2018:4801247. doi:10.1155/2018/4801247
30. Larmené-Beld KHM, Frijlink HW, Taxis K. A systematic review and meta-analysis of microbial contamination of parenteral medication prepared in a clinical versus pharmacy environment. *Euro J Clin Pharmacol*. 2019;75:2. doi:10.1007/s00228-019-02631-2
31. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci*. 2014;4 (2):162–167. doi:10.4103/2229-5151.134184
32. Minasyan H. Sepsis: mechanisms of bacterial injury to the patient. *Scand J Trauma Resusc Emerg Med*. 2019;27(1):19. doi:10.1186/s13049-019-0596-4
33. Sandle T Assessing non-endotoxin microbial pyrogens in relation in pharmaceutical processing. Peer Reviewed: Pharmaceutical Processing. 2015.
34. Fullerton JN, Segre E, De Maeyer RPH, Maini AAN, Gilroy DW. Intravenous endotoxin challenge in healthy humans: an experimental platform to investigate and modulate systemic inflammation. *J Visualiz Exp*. 2016;111:53913. doi:10.3791/53913
35. Oli AN, Itumo CJ, Okam PC, et al. Carbapenem-resistant enterobacteriaceae posing a dilemma in effective healthcare delivery. *Antibiotics (Basel)*. 2019;8:4. doi:10.3390/antibiotics8040156
36. Lehr HA, Brunner J, Rangoonwala R, Kirkpatrick CJ. Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle. *Am J Respir Crit Care Med*. 2002;165(4):514-520. doi:10.1164/ajrccm.165.4.2108033
37. Benlabed M, Martin Mena A, Gaudy R, et al. Analysis of particulate exposure during continuous drug infusion in critically ill adult patients: a preliminary proof-of-concept in vitro study. *Intensive Care Med Exp*. 2018;6(1):38. doi:10.1186/s40635-018-0205-2
38. Contaldo C, Meier C, Elsherbiny A, et al. Human recombinant erythropoietin protects the striated muscle microcirculation of the dorsal skinfold from postischemic injury in mice. *Am J Physiol Heart Circ Physiol*. 2007;293(1):H274–83. doi:10.1152/ajpheart.01031.2006
39. Perez M, Décaudin B, Abou Chahla W, et al. Effectiveness of in-line filters to completely remove particulate contamination during a pediatric multidrug infusion protocol. *Sci Rep*. 2018;8(1):7714. doi:10.1038/s41598-018-25602-6
40. Leopoldino RW, Costa HT, Costa TX, Martins RR, Oliveira AG. Potential drug incompatibilities in the neonatal intensive care unit: a network analysis approach. *BMC Pharmacol Toxicol*. 2018;19 (1):83. doi:10.1186/s40360-018-0265-7

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