ISSN: 0976-7126
Ucheokoro *et al.,* 17(2):6-11, 2026

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Bioequivalence Assessment of Five Brands of Antimalarial Drugs Marketed in Rivers State Using Statistical Tool

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Article info

Received: 03/12/2025

Revised: 28/01/2026

Accepted: 18/02/2026

www.ijplsjournal.com

Abstract

Malaria remains a major public health challenge in Sub-Saharan Africa, with artemether-lumefantrine (AL) as the first-line treatment for uncomplicated Plasmodium falciparum malaria. Ensuring bioequivalence among generic AL brands is crucial for therapeutic interchangeability and effective malaria control. This study evaluated the bioequivalence of four generic antimalarial brands (Drugs A, B, C, D) against a standard AL formulation using clinical recovery time as the primary endpoint in 80 malaria patients. An Indirect Assay Design (IAD) was employed, administering five antimalarial drug brands randomly to malaria patients. The primary outcome was time to clinical recovery (in hours) following completion of treatment. Bioequivalence was assessed using ANOVA and Logistic 4-parameter equivalence tests in JMP software version 17. Equivalence was declared when 90% confidence intervals for key parameters (growth rate, inflection point, lower/upper asymptotes) fell within predefined decision limits. Parameter estimates revealed Drug A was bioequivalent to Drug C shown in parameter estimate: -4.33; SE: 2.102; tRatio: -2.06; p=0.042). Equivalence testing confirmed Drugs A and C had comparable potency profiles: growth rate ratio (2.4:0.15), inflection point (1.3:0.65), lower asymptote (1.2:0.75), and upper asymptote (1.1:0.85). Drugs B and D failed equivalence criteria, indicating potential formulation differences affecting clinical efficacy. Drugs A demonstrated statistical bioequivalence to Drug C based on recovery time analysis, ANOVA and Logistic 4-parameter equivalence tests. These findings support their therapeutic interchangeability for uncomplicated malaria treatment. Drugs B and D require further quality assessment. This study validates the use of clinical recovery time as a practical bioequivalence endpoint in resource-limited settings where pharmacokinetic studies are challenging.

Keywords: Bioequivalence, Malaria treatment, Equivalence testing, Recovery time, Indirect Assay Design.

Introduction

Malaria is a global burden with high mortality reported in children in Sub Saharan Africa.[1-3]

In severe malaria, children can become anemic, have decreased levels of glucose, or cerebral malaria, just to mention a few. The World Health Organization (WHO) recommends the use of an artemisinin-based combination therapy (ACTs) for treatment of Plasmodium falciparum malaria. Artemether (AR) and lumefantrine (LF) combination product is one of the ACTs that has been approved for treating uncomplicated P. falciparum malaria.[4,5]

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Due to the development of drug-resistant malaria parasite, a combination product is the best way to fight such a risk. AR is derived from artemisinin and works by inhibiting synthesis of proteins in the parasites through production of free radicals.[6,7] AR has fast onset of action and a short half-life of about (2-3 hours).[6] It is available as an oral fixed dose combination with LF or as monotherapy dissolved in oil, that is given intramuscularly (IM). LF belongs to the class of antimalarials called arylamine alcohol. It kills parasites by destroying the hemoglobin in the parasites.[6,7] Absorption of LF is highly dependent on intake of a fatty meal and may have a lag time of up to 2 hours.[6,8] LF acts slowly, highest plasma concentration is obtained after 6-8 hours; and has a long elimination half-life of about 2-3 days in healthy human subjects and 4-6 days in P. falciparum infected patients.[9] Both AR and LF are highly protein bound i.e., 95.4 % and 99.7 % respectively.[9] Rectal administration of artemisinin derivatives has been reported to achieve acceptable therapeutic outcomes including in severe disease.[10]

A combination dosage form such as a rectal enema, containing both drugs, to be used as an emergency rescue treatment of children that have malaria was recently developed. When evaluating the bioavailability of a new formulation the reference product is an IV formulation. In certain situations, however, relative, or comparative bioavailability is used, such as when the drug is insoluble and cannot be administered as an IV. In such situations both the reference and test formulations are extravascular products. LF is such a drug as it is not available as an injectable formulation. Lumefantrine is highly dependent on food intake, probably due to the augmentation of the bile salt production, since it has been shown that the relative bioavailability is found to be increased by 16-fold when administered with a high fat diet.[8,11]

Bioequivalence (BE) testing aims to determine whether two drug products containing the same active ingredient are equivalent when administered in-vivo.[12,13] Specifically, it compares a test drug (T) to an innovator's formulation, known as the reference product (R). The core of BE assessment lies in comparing the pharmacokinetic properties of the two drug products. This involves a detailed statistical analysis, including calculating a 90% confidence interval (CI). BE is typically declared if this 90% CI falls within the established range of 80–125%.[12,13]

While this standard method, known as average BE, is widely accepted, it is not suitable for highly variable drugs or drug products. The expression "highly variable drugs" refers to those with a within-subject coefficient of variation of 30% or more, whether due to the drug substance or its formulation.[14] In BE studies, this variability refers to the residual variability that comes from the ANOVA analysis after excluding all other known factors. In the case of a 2 × 2 crossover design, residual variability is estimated after subtracting from the total data variability, the variability attributed to subjects, periods, sequences, and the administered pharmaceutical product.

Variability can arise from factors such as the drug characteristics or physiological conditions in patients. However, as within-subject variability increases, demonstrating BE becomes more challenging without increasing the sample size.[14] To address this issue, various methods have been proposed. This approach adjusts the BE limits based on the within-subject variability of the reference product.

It should be mentioned that sample size in BE testing is defined as the total number of patients or individuals that take part in the study.[14] Estimating the optimal number of participants is not always straightforward, considering that there are many different methods and formulas described in the literature and textbooks and in many cases a lot of inputs are required, like the expected effect size and the type I and II errors.[15-19] The advantages of an optimal sample size in studies are evident, such as an increase in statistical power, a reduction in bias, and an improvement in precision, accuracy, robustness, and the ability to conduct subgroup analyses.[20-25]

Methodology

The methodology framework of this study relies on the Indirect Assay Design (IAD). This technique is adopted because in the data, the doses of the standard and test preparations used as well as the "response" were observed for each dose produced. For each patient, the dose is fixed in

ISSN: 0976-7126
Ucheokoro *et al.*, 17(2):6-11, 2026

advance, the variable of interest is not the dose but the response it produces in each patient which in this study is the time it took the malaria patients to recover.

However, five (5) different antimalarial drugs, Drug A, Drug B, Drug C, and Drug D were administered to 80 adult malarial patients of both male and female gender and were compared among to determine their bioequivalence in order to ascertain the interchangeability of their use in curing uncomplicated malaria caused by Plasmodium falciparum. The antimalarial drugs were randomly administered to the patients and the time (in hours) it takes for each of the drugs to cure malaria on completion of the dosage was measured. Also, since the patients have different demographic characteristics, the time it takes for the drugs to cure malaria vary from one patient to another and from one treatment to the other.

Data Source

Secondary data were obtained from an Aligned national MDA programme datasets. Structurally harmonized datasets were used.

Methods of Data Analysis

The ANOVA test was used to check for equivalence in the different Anti-malarial drugs used for the study with the aid of the JMP software Version 17.

Specifically, BE trials were simulated under various conditions of within-subject variability, sample size, and differences between the test and standard drug products.[3]

Equivalence Test

In the Fit Curve platform, the Equivalence Test option gives an analysis for testing the equivalence of models across levels of the grouping variable. In the Bioassay data used for this study, five different drugs are compared and tested whether they are equivalent. A Logistic 4P showed a fit for four Parameters (Growth Rate, Inflection Point, Lower and Upper Asymptote).[26] If all the confidence intervals are inside the decision lines, then the two groups are practically equal. If a single interval falls outside the lines, then we cannot conclude that the groups are equal in terms of potency.

Ethical Considerations

The study used secondary, aggregated programme data with no personal identifiers. Ethical approval was not required as the analysis posed no risk to individuals and complied with accepted standards for public health programme evaluation. And for the purpose of confidentiality, the drug products brand names used for the study were represented with codes such as (Drug A, Drug B, Drug C, Drug D and Standard).

Statistical Software

All analyses were conducted using JMP and SPSS statistical software. Data management and visualization were performed within the same environment to ensure reproducibility.

Results and Discussion

Table 1: Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	37.998457	1.050771	36.16	<.0001*
Preparation [Drug A]	-4.333771	2.101543	-2.06	0.0427*
Preparation [Drug B]	-2.365533	2.101543	-1.13	0.2639
Preparation [Drug C]	-4.334051	2.101543	-2.06	0.0426*
Preparation [Drug D]	15.450929	2.101543	7.35	<.0001*

Source: *JMP software output*

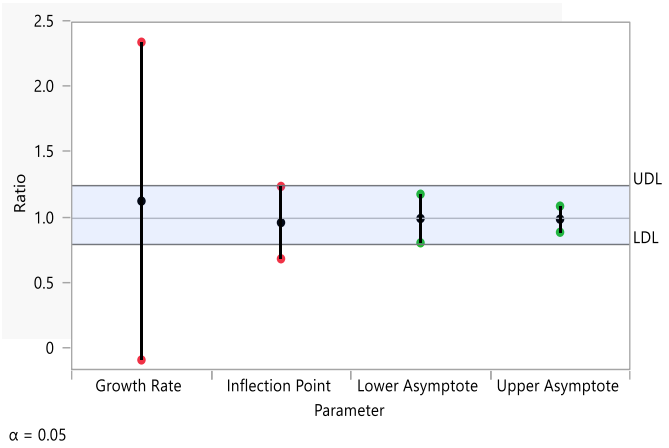

Figure 1: Equivalence test for Drug A

ISSN: 0976-7126
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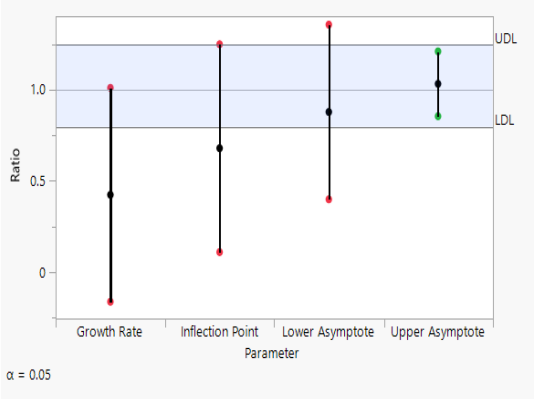

Figure 2: Equivalence test for Drug B

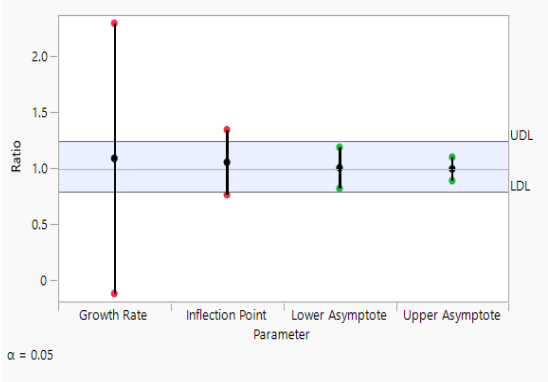

Figure 3: Equivalence test for Drug C

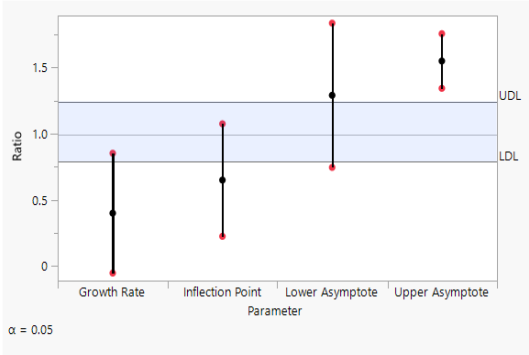

Figure 4: Equivalence test for Drug D

Table 1 showed the parameter estimates of each drug. Drug A and Drug C were shown to be equivalent with a parameter estimate of -4.33 respectively and standard error, tRatio and probability to be 2.102, -2.06 and 0.042 respectively for drugs A and C.

In figures 1 and 3, equivalence test was seen to have drug A and Drug C equivalent with each other with the evidence in their closely related ratios and respective upper and lower detective limit for the following parameters as growth rate 2.4:0.15, inflation point 1.3:0.65, lower asymptote 1.2:0.75 and upper asymptote 1.1:0.85. Drugs B and D failed equivalence criteria, indicating potential formulation differences affecting clinical efficacy.

Conclusion

Drugs A demonstrated statistical bioequivalence to Drug C based on recovery time analysis, ANOVA and Logistic 4-parameter equivalence tests. These findings support their therapeutic interchangeability for uncomplicated malaria treatment. This is wholly applied in the pharmaceutical drug delivery system. Drugs B and D require further quality assessment. This study validates the use of clinical recovery time and some pharmaceutically valid parameters as a practical bioequivalence endpoint in resource-limited settings where pharmacokinetic studies are challenging.

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Cite this article as:
Ucheokoro A.S., Ogoke U.P. and Abali S. O. (2026). Bioequivalence Assessment of Five Brands of Antimalarial Drugs Marketed in Rivers State Using Statistical Tool. *Int. J. of Pharm. & Life Sci.,* 17(2):6-11.

Source of Support: Nil
Conflict of Interest: Not declared
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