Crossover Design on the Bioequivalence of Pharmaceuticals - A Case of Study

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Abstract. This study performs experimental design and analysis of variance in assessing the bioequivalence of two treatments, which involves evaluating the efficacy of different treatments administered to two distinct cohorts of patients: the control group and the test group. In order to compare the control group that received the reference medication, with the test/treatment group that received the investigational drug, a crossover experimental design was employed. The respective analysis of variance was conducted, taking into consideration both intra-subject and inter-subject variability in formulating the probabilistic model. This included specifying tests to detect carryover effects and period effects. The practical implementation of the proposed model involved validating the hypothesis, revealing that the carry-over effect was found to be not significant, when assessed at the usual levels of significance (1% and 5%). In terms of the treatments, it was concluded that there was statistical significance, leading to the assertion that the studied pharmaceuticals were not bioequivalent.

Keywords: experimental design · clinical trials · analysis of variance · bio-equivalence · computational methods

1 Introduction

Clinical trials play a crucial role in advancing medical knowledge and improving patient outcomes in a myriad of scenarios. For instance in [1], a randomized trial

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is performed so a decision-making for patients with acute myocardial infarction can be taken; in [2], the care management of insomnia occurring simultaneously with sleep apnea is studied; the authors of [3] compare the effectiveness of virtual reality game to clinic based therapy for chronic non-specific low back pain; in [4], it is described the allocation of patients to in headache clinical trials randomization and in [5] the meticulous designing protocols for cancer clinical trials is presented.

The publication in [6], offers various techniques for patient allocation in clinical trials, while the subsequent work in [7] by the same author provides a comprehensive overview on designing, analyzing, and interpreting such data in a straightforward manner, complete with historical context, present-day relevance, and future outlook. Similar works can be found in [8], where Bayesian adaptive biased-coin designs with Gaussian response are described for clinical trials. Also, the authors of [9] made some interesting considerations about randomization-based inference. The author of [10] made restricted randomization designs in headache clinical trials and the authors of [4] proposed the randomization, stratification, and treatment matching to allocation of patients.

Some recent works proposed to improve the efficiency of the clinical trials. In [11], the authors propose a new algorithm gaining efficiency in randomized controlled trials. The authors of [12] explore some recent innovations in clinical trials where a single therapeutic treatment is tested on several patient populations, each of which forms a basket, using Bayesian hierarchical models. A qualitative study is developed by the authors of [13], where some randomization methods in clinical trials are compared and evaluated. The authors of [14] explore statistical tools focused in clinical pharmacology under the theme of bioequivalent trials.

The current research places emphasis into the realm of bioequivalence trials, specifically focusing on the comparison of two treatments. The manuscript is divided into five sections, beginning with an introduction that sets the stage for the subsequent analysis. Section 2 provides a comprehensive overview of the bioequivalence of treatments, while Sect. 3 delves into the methodology employed in the study. Moving on to Sect. 4, various empirical issues are addressed, starting with fundamental statistical techniques, then progressing to the assessment of data normality and finally to the computation and interpretation of the ANOVA table results. Section 5 offers detailed discussions and final remarks on the findings of the study.

2 Preliminaries

The main objective of this research endeavor is to ascertain the efficacy of the prescribed treatment in patients and to examine and evaluate any pertinent clinical reactions. Specifically, the study in question centers on a comparative analysis between a control group and an experimental group receiving the treatment. Despite involving a limited number of individuals, it is hoped that the findings of this study case may offer valuable insights to guide therapeutic decisions for individuals experiencing similar medical conditions.

In detail, the aim is to evaluate the existence or not of bioequivalence between a pharmaceutical-treatment (T) and a reference-control pharmaceutical (R). To prove the existence of bio-equivalence between these two groups it is not necessary to conclude that one is better than the other, just that it is not worse. In a first phase, the bioavailability of people taking the drug is measured. This action consists of recording the concentration in some fluid over time, after taking the treatment (and reference respectively) and constructing for both the concentration versus time graph. This is followed by the calculation of the pharmacokinetic parameters of interest, such as maximum concentration area under the curve (AUC) or others.

Knowing that the same individual must be subject to both the reference and to the treatment, the chosen design was a 2×2 crossover, given the importance of pairing. An even number of individuals were randomized into two groups. One of the groups received the reference pharmaceutical in the first period and, in the second period, the treatment. The second group received the treatment in the first period and the reference in the second period. The interval between the two periods of intake is supposed to be long enough to fade the effect of taking the first medication. This time interval is called washout (see Fig. 1) This type of design makes it possible to test whether there are reinforcement effects in the 2^{nd} period, whether the treatments are different or whether any tests should be carried out on individuals.

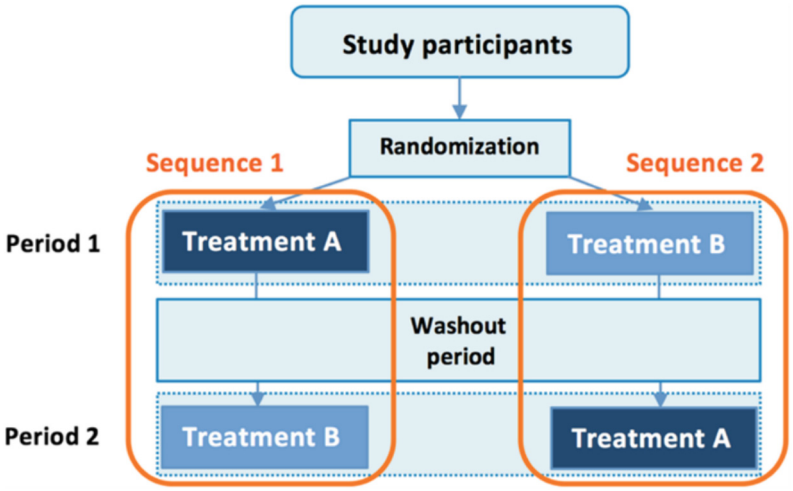


Fig. 1. Scheme of experimental design: 2×2 crossover. Source: [15].

To review some basic concepts of experimental design and analysis of variance [16–19] are recommended, among many others.

3 Theoretical Model

The statistical model used to determine bio-equivalence has as response variable Y_{ijk} a random variable (r.v.) whose observed value y_{ijk} corresponds to the i^{th} individual, in the k^{th} sequence of the j^{th} period, with $k = 1 \ldots p$, $i = 1 \ldots n_k$, and $j = 1, \ldots, p$. In general, data is given in tabular form (1).

$$\begin{array}{c|cccc} & \textit{Period } 1 & \textit{Period}2 & \cdots & \textit{Period } \mathrm{p} \\ \hline \textit{Sequence } 1 & y_{111} \ldots y_{n_1 11} & y_{121} \ldots y_{n_1 21} & \cdots & y_{1p1} \ldots y_{n_1 p1} \\ \textit{Sequence } 2 & y_{112} \ldots y_{122} & y_{221} \ldots y_{n_2 22} & \cdots & y_{1p2} \ldots y_{n_2 p2} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \textit{Sequence } \mathrm{g} & y_{11g} \ldots y_{n_g 1g} & y_{12g} \ldots y_{n_g 2g} & \cdots & y_{1pg} \ldots y_{n_g pg} \end{array} \tag{1}$$

The theoretical model is defined in Eq. (2).

$$Y_{ijk} = \mu + S_{ik} + P_j + F_{jk} + C_{jk} + \epsilon_{ijk}, \tag{2}$$

where

- μ is the global mean (or global effect);
- S_{ik} is the random effect of the $i-th$ individual at the $k-th$ sequence, $k = 1, \ldots, g,$ and $i = 1, \ldots, n_k$;
- P_j is the fixed effect of the $j-th$ period, $j = 1, \ldots, p$;
- F_{jk} is the fixed effect of the administered formulation at the $k-th$ sequence during the $j-th$ period (reference R or test T);
- C_{jk} is the carry-over first order fixed effect of the administered formulation at the $k-th$ sequence during the $j-1-th$ period;
- ϵ_{ijk} is the random error of Y_{ijk}.

The following restrictions are considered:

$\sum_j P_j = 0$, $\sum_{j,k} F_{jk} = 0$, $\sum_{j,k} C_{jk} = 0$ and , $C_{0k} = 0$ conducting to

- $p-1$ effects P_j linearly independents;
- $(p-1)(g-1)$ effects F_{jk} linearly independents;
- $(p-1)(g-1)$ effects C_{jk} linearly independents.

The hypotheses inherent to the model (2) are:

- The S_{ik} are independent and Gaussian

$$S_{ik} \cap N(0, \sigma_s^2).$$

- The ϵ_{ijk} are independent and Gaussian

$$\epsilon_{ijk} \cap N(0, \sigma_e^2).$$

- The $\{S_{ik}\}$ and $\{\epsilon_{ijk}\}$ are mutually independent.

Table 1. Scheme of experimental design: 2×2 crossover, $n_k = n_1 = n_2$, $p = 2$, $g = 2$.

	Period I	*Period* II
Sequence 1 (RT)	$y_{111} \dots y_{n_1 11}$	$y_{121} \dots y_{n_1 21}$
Sequence 2 (TR)	$y_{112} \dots y_{122}$	$y_{221} \dots y_{n_2 22}$

We can conclude that Y_{ijk} are r.v. independents and Gaussian. Also, we need to evaluate the variability due the subjects, namely, to compute the proportion of total variability explained by the individuals.

The σ_s estimate is used to explain the variability inter-subject, the σ_e estimate is used to explain the variability intra-subject.

Considering the design *crossover* 2×2, $n_k = n_1 = n_2$, $p = 2$, $g = 2$ then the scheme of date presented in tabular form 1 is reduced to the form displayed in Table 1.

If we consider the administration of the drug test in the first period of the first sequence, we obtain the definition of the effect F_{jk} and the effect C_{jk} respectively given by Eqs. (3) and (4), noting that the effect carryover only occurs during the second period.

$$C_{jk} = \begin{cases} C_R, & if\ k = 1, j = 2 \\ C_T, & if\ k = 2, j = 2 \end{cases} \tag{3}$$

$$\begin{array}{lll} \textit{Sequence} & \textit{Period I} \& & \textit{Period II} \\ 1\ (RT) & \mu_{11} = \mu + P_1 + F_R \& & \mu_{21} = \mu + P_2 + F_T + C_R \\ 2\ (TR) & \mu_{12} = \mu + P_1 + F_T \& & \mu_{11} = \mu + P_2 + F_R + C_T \end{array} \tag{4}$$

and

$$\begin{cases} P_1 + P_2 = 0 \\ C_R + C_T = 0 \\ F_R + F_T = 0 \end{cases} \tag{5}$$

The fixed effect that occur in each period and in each sequence is given by the expected value for each individual μ_{jk} (4) imposing (5).

In a study of bioequivalence between pharmaceuticals, it is usual to consider the non existence of the carryover effect. This fact can be achieved with a long period of washout, allowing to eliminate the residuals of the drug administration. In this situation, the model is reduced to formula (6)

$$Y_{ijk} = \mu + S_{ik} + P_j + F_{jk} + \epsilon_{ijk}. \tag{6}$$

In the case of the model (2), the basic objectives are to test if $P_1 = P_2$, $C_R = C_T$, $T_R = T_T$ and the variability of the residuals σ_s.

4 Analysis of Variance

The comparison of the bio-availabilities of the two formulations can be made using variance analysis for crossover trials, with the model residuals being analyzed using either inter-subject variability or intra-subject variability. Then, define the following sums of squares with the usual interpretation. The total sum of squares (SST) with $N-1$ degree of freedom (d.f.) is given by formula (7).

$$SST = \sum_{k=1}^{2}\sum_{j=1}^{2}\sum_{i=1}^{n_k}\left(y_{ijk} - \overline{y}\right)^2, \tag{7}$$

with $N = 2(n_1 + n_2)$.

After some calculations, we can find some decomposition's of interest. For example, if we add and subtract to each term of sum given by formula (7) the mean per individual $\overline{y}_{i.k}$

$$SST = \sum_{k=1}^{2}\sum_{j=1}^{2}\sum_{i=1}^{n_k}\left(y_{ijk} - \overline{y} + \overline{y}_{i.k} - \overline{y}_{i.k}\right)^2 \tag{8}$$

$$= \underbrace{\sum_{k=1}^{2}\sum_{j=1}^{2}\sum_{i=1}^{n_k}\left(y_{ijk} - \overline{y}_{i.k}\right)^2}_{\text{variability within the individuals}} \tag{9}$$

$$+ \underbrace{2\sum_{k=1}^{2}\sum_{i=1}^{n_k}\left(\overline{y}_{i.k} - \overline{y}\right)^2}_{\text{variability between the individuals relatively to global mean}}. \tag{10}$$

we get the equality given by formula (11) that provides a good way to analyse the individual variability.

$$SST = SS_{within} + SS_{between}. \tag{11}$$

Other decomposition's that evidence the other intended effects are those determined by the formulas (12) and (14).

$$SS_{between} = SS_{carry} + SS_{residual\ \ between}, \tag{12}$$

with

$$SS_{carry} = \frac{2n_1n_2}{n_1+n_2}\left[\left(\overline{y}_{.12} + \overline{y}_{.22}\right) - \left(\overline{y}_{.11} + \overline{y}_{.21}\right)\right]^2 \cap \chi^2_{[1]} \tag{13}$$

$$SS_{within} = SS_{pharmaceutical} + SS_{period} + SS_{residual\ \ within}, \tag{14}$$

with

$$SS_{pharmaceutical} = \frac{2n_1n_2}{n_1+n_2}\left[(\overline{y}_{.21}+\overline{y}_{.11})-(\overline{y}_{.22}+\overline{y}_{.12})\right]^2 \cap \chi^2_{[1]} \tag{15}$$

$$SS_{period} = \frac{2n_1n_2}{n_1+n_2}\left[(\overline{y}_{.21}+\overline{y}_{.11})-(\overline{y}_{.12}+\overline{y}_{.22})\right]^2 \cap \chi^2_{[1]} \tag{16}$$

The sum of the squares mean is defined as usual, the sum is divided by the number of degrees of freedom (df). All details are summarized in Table 2.

The last column of Table 2 concerns to the following significance tests:

- $$H_{0C} : C_T = C_R \text{ versus } H_{1C} : C_T \neq C_R.$$

  A rejection of H_{0C} means that there is no experimental evidence that the washout period is long enough. The process shall be ended. The following tests assume that there is no carryout effect.

- $$H_{0F} : F_T = F_R \text{ versus } H_{1F} : F_T \neq F_R.$$

  A rejection of H_{0F} means that there is experimental evidence that the pharmaceuticals have distinct effects, so there is no experimental evidence for bio-equivalence between them.

- $$H_{0\,s} : \sigma_s^2 = 0 \text{ versus } H_{1\,s} : \sigma_s^2 \neq 0.$$

  A rejection of H_{0s} means that there is experimental evidence that the individual effects are distinct effects, it means that the random factor S_{ik} is statistically significant.

- $$H_{0P} : P_1 = P_2 \text{ versus } H_{1P} : P_1 \neq P_2.$$

  A rejection of H_{0P} means that there is experimental evidence that the period has distinct effects.

Table 2. Anova Table.

Variation Source	Sum of Squares	Degree of Freedom	Mean Sum of Squares	F
	SS	DF	MS	
Between				
Carry-over	SS_{carry}	1	SS_{carry}	$F_c = \frac{MS_{carry}}{MS_{res,btween}}$
Residuals	$SS_{res,between}$	$n_1 + n_2 - 2$	$\frac{SS_{res,between}}{n_1+n_2-2}$	$F_s = \frac{MS_{res,between}}{MS_{res,within}}$
Within				
pharmaceutical	$SS_{pharmaceutical}$	1	$SS_{pharmaceutical}$	$F_F = \frac{MS_{pharmaceutical}}{MS_{res,within}}$
Period	SS_{period}	1	SS_{period}	$F_F = \frac{MS_{period}}{MS_{res,within}}$
Residuals	$SS_{res,within}$	$n_1 + n_2 - 2$	$\frac{MS_{res,within}}{n_1+n_2-2}$	
Total	SST	$2(n_1 + n_2) - 1$	$\frac{SST}{2(n_1+n_2)-1}$	

The F statistic to each of the specified tests is displayed in the Table 2, and has a distribution F of Snedcor whose degrees of freedom are the degree of freedom of the numerator and denominator respectively.

The critical region, for a level of significance α is given by

$$\begin{aligned} F_{C|H_{0C}} &> F_{(1,n_1+n_2-2,1-\alpha)}, \\ F_{F|H_{0F}} &> F_{(1,n_1+n_2-2,1-\alpha)}, \\ F_{s|H_{0s}} &> F_{(n_1+n_2-2,n_1+n_2-2,1-\alpha)}, \\ F_{P|H_{0P}} &> F_{(1,n_1+n_2-2,1-\alpha)}, \end{aligned}$$

respectively.

5 Descriptive Data Analysis and Validation Tests

All data were classified and quantified using the software Matlab. The studied variable Y is the area under the concentration curve registered along the time (AUC). The data illustration is displayed in Table 3. For the case under study, $n_k = 6,\ p = 2$ and $g = 2$.

The reduced data display can be observed in a histogram (see Fig. 2) and in a qq-plot (see Fig. 3).

In both figures there is not a strong visual evidence of data with non Gaussian behavior. However some bias, with heavier tails can be observed on left. In a preliminary phase, it is useful to perform some normality tests.

In a standart normal distribution, the measures of asymmetry and Kurtosis are, respectively, 0 and 3. The third and fourth sampling moments of the observations, duly normalized, are given by formulas (17) and (18),

$$\sqrt{b_1} = \frac{\sum (y_{ijk\ norm})^3}{N}, \tag{17}$$

$$b_2 = \frac{\sum (y_{ijk\ norm})^4}{N}, \quad N = 2(n_1 + n_2). \tag{18}$$

If normality occurs, the estimators $\sqrt{B_1}$ and B_2 must be centered with mean 0 and 3 respectively and are assymptoticaly Gaussian (19) (20),

$$\sqrt{B_1} \dot{\sim} N(6, \frac{6}{N}) \tag{19}$$

$$B_2 \dot{\sim}\ N(3, \frac{24}{N}). \tag{20}$$

Table 3. Area under the concentration curve registered along the time (AUC).

Sequence	Individual	Period I	Period II
RT	1	6934.5	6458
RT	2	5330.5	3108.1
RT	5	5848.3	7079.4
RT	7	8405.2	6455.3
RT	8	7403.5	7125.7
RT	9	7409.4	8427.7
TR	3	7762.2	9034.2
TR	4	8137.3	8107.3
TR	6	4998.1	6455.3
TR	10	8763.9	10406
TR	11	8430.4	9239.6
TR	12	5053.4	5696.3

Also, the following results (21) (22) can be established:

$$\frac{\sqrt{B_1}}{6/N} \dot{\sim} \chi^2_{(1)} \tag{21}$$

$$\frac{(B_2-3)^2}{24/N} \dot{\sim} \chi^2_{(1)} \tag{22}$$

Moreover, the statistic defined by $B = \frac{N}{6}B_1 + \frac{N}{24}(B_2-3)^2$, proposed by Bera and Jarque, under the hypothesis of normality and for large samples, has an asymptotic chi-square distribution with 2 degree of freedom [20].

It is important to remember that, in small samples, the measurements of asymmetry and Kurtosis can be significantly altered. The sample used in this work has 24 observations. Thus, there is the need of cautious with the results and their interpretation. Despite the sample bias being negative, the hypothesis that data are from a Gaussian population was not rejected. The values $\sqrt{b_1} = 0.3863$ and $b_2 = 2.8308$, led to test statistics values of, respectively,

$$\frac{\sqrt{b_1}}{6/N} = 0.5971,$$

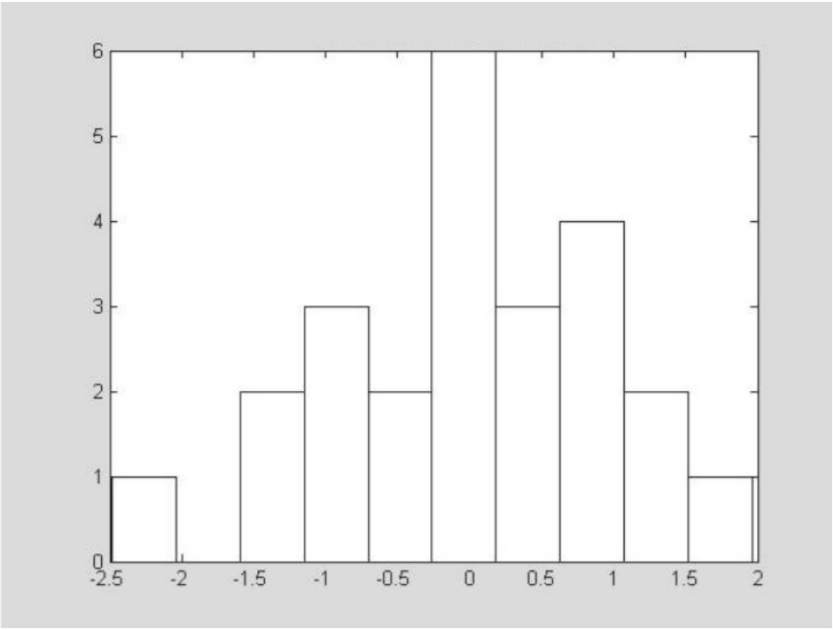


Fig. 2. Histogram of reduced AUC.

and

$$\frac{(b_2 - 3)^2}{24/N} = 0.0286.$$

Hence

$$b = 0.6257,$$

being clearly lower than the critical values obtained for a significance level of 5%, $\chi^2_{(0,95,1)} = 3.8415$, $\chi^2_{(0,95,1)} = 3.8415$, and $\chi^2_{(0,95,2)} = 5.9915$. The corresponding $p - values$ are 0.4397, 0.8656 and 0.7314, respectively, with evidence that the observations come from a normal population. Given the caution due to the small sample size, the results were confirmed by the non-parametric Kolmogorov Smnirnov test (KS), which compares the empirical distribution with the distribution of a reduced normal. The KS statistic conduced to $KS = 0.0880$. This value implies a $p - value = 0.9893$, so we do not have statistical evidence to reject the normality behavior hypothesis.

6 Empirical Application - Analysis of Variance

After some descriptive analysis and some validation tests, the computation to all values and complete the analysis of variance (ANOVA) table (see Table 4) were performed.

Table 4. ANOVA relatively to the area under the concentration curve registered along the time (AUC).

Variation Source	Sum of Squares	Degree of Freedom	Mean Sum of Squares	F	p-value
	SS	DF	MS		
Between	5.3031×10^7				
Carry-over	2.2937×10^7	1	2.2937×10^7	$F_c = 2.7593$	0.1277
Residuals	4.1563×10^7	10	4.1563×10^6	$F_s = 17.3563$	≈ 0
Within	8.8779×10^6				
Pharmaceutical	5.4721×10^6	1	5.4721×10^6	$F_F = 22.8511$	≈ 0
Period	1.0112×10^6	1	1.0112×10^6	$F_P = 4.2226$	0.0670
Residuals	2.3947×10^5	10	2.3947×10^4		
Total	6.1909×10^7	23			

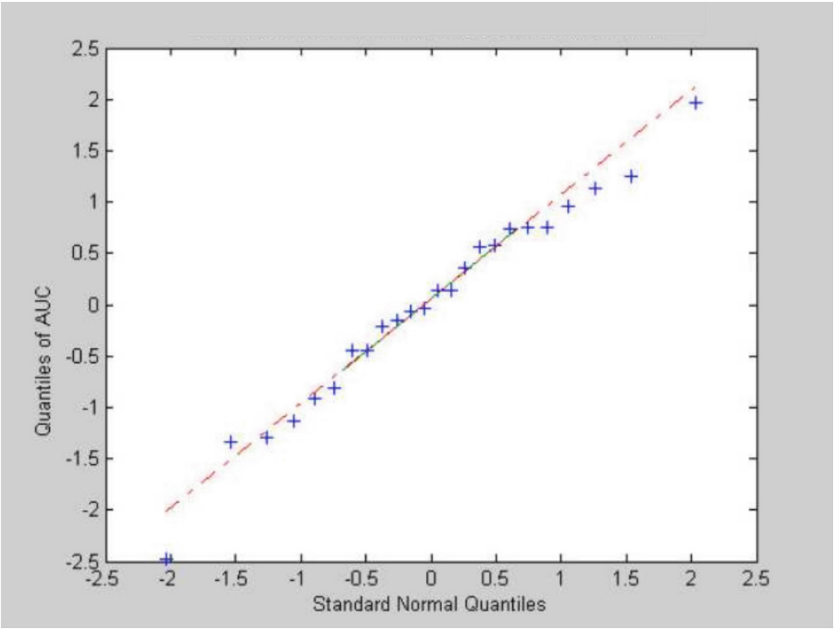


Fig. 3. Qq-plot of reduced AUC.

According to the $p - values$ displayed in last column (on right) of Table 4 the conclusion is that, relatively to each of the identified tests there are distinct decisions.

- For the test concerning the wash-out period,

$$H_{0C} : C_T = C_R \text{ versus } H_{1C} : C_T \neq C_R,$$

it was obtained $p - value = 0.1277$. There is not statistical evidence to reject H_{0C} for the usual values of the level of significance. This means that there is statistical evidence that the washout period is long enough. There is statistical evidence for usual levels of significance that there is no carry-out effect. The process shall continue.

- On what concerns the effects of the reference and the treatment,

$$H_{0F} : F_T = F_R \text{ versus } H_{1F} : F_T \neq F_R,$$

it was obtained $p - value \approx 0$. The rejection of H_{0F} for any value of significance level means that there is experimental evidence that both have distinct effects, so there is no experimental evidence for bio-equivalence between them.

- Relatively to the effects of the individuals,

$$H_{0\,s} : \sigma_s^2 = 0 \text{ versus } H_{1\,s} : \sigma_s^2 \neq 0,$$

it was obtained $p - value \approx 0$. A rejection of H_{0s} for any value of significance level means that there is an experimental evidence that the individual effects are distinct, implying that the random factor S_{ik} is statistically significant.
- The effects of the period are evaluated by the hypothesis

$$H_{0P} : P_1 = P_2 \text{ versus } H_{1P} : P_1 \neq P_2.$$

The $p - value = 0.0670$, thus, considering the significance level of 5% there is no statistical evidence to reject the null hypothesis. However, for the level of significance $6.7010\% < \alpha < 10\%$ there exists experimental evidence to reject H_{0P}, meaning that there exists experimental evidence that the period has distinct effects. In that case the authors recommend [21] for details on optimal crossover designs as well as [22] to perform a 2×2 crossover design.

7 Final Remarks

The main objective of the present manuscript was to identify if the treatment (test pharmaceutical) and the reference (reference pharmaceutical) were bioequivalent. To find a conclusion about it was necessary to verify some assumptions, such as the normality of the observed variable Y. It was verified that existed statistical evidence that data came from a Gaussian population. Also, there was not statistical evidence of the carryout effect existence, i.e., the washout period is long enough. The period effect was significant only for values of significance above 6.7010%. This fact validates the continuation of the execution of the remaining tests, concluding that there is no bioequivalence of the studied pharmaceuticals.

In future work, we intend to update the data base, in order get more data, and to explore it following a distinct battery of tests proposed on the book by the author in [7].

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