بسم الله الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

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An Optimal Solution to Bioequivalence Problem

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A Thesis submitted to the Department of Statistics, Faculty of Economics and Political Science, Cairo University in partial fulfillment of the requirements for the Ph. D. in Statistics.

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To my helpful parents.

To my supportive husband.

To my lovely kids.

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An Optimal Solution to Bioequivalence Problem

Abstract

In recent years, many generic drug products become available in the drug market, but do these generic products have the same quality, safety, and efficacy as their brand-name products?! bioequivalence testing could provide an answer to the former question. The proposed dissertation presents three different approaches for the assessment of bioequivalence between the generic and the brand-name drug products. The first is a test for bioequivalence using coefficient of variation. The second is a statistical algorithmic approach for bioequivalence assessment. And the third is a mathematical programming approach for average bioequivalence testing. Neither of them relies on any impractical assumption, and all of them give essential information about the analyzed data. Furthermore, the required computations for any of them are simple. However, the use of the first approach is recommended when the Inverse Gaussian distribution could be assumed to be the probability distribution of the data under consideration. And in the case of having a too small sample size " 4 or 5 " , when it is costly or risky to conduct the experiment, the use of the third approach is recommended. Otherwise, it is better to use the second approach.

Keywords

- Bioequivalence problem.
- Bioavailability.
- Crossover design.
- Inverse Gaussian distribution
- Mathematical programming approach.
- Nonparametric tests.

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Title of thesis: An Optimal Solution to Bioequivalence Problem

Summary of the thesis: In recent years, many generic drug products become available in the drug market, but are these generic products have the same quality, safety, and efficacy as their brand- name products?! Bioequivalence testing could provide an answer to the former question. The problem of exhibiting the equivalence of two formulations has been examined using several approaches during the last decade. Different designs, criteria, models, and testing have been used. The proposed dissertation presents three different approaches for the assessment of bioequivalence between the generic and the brand-name drug products. The first is a test for bioequivalence using coefficient of variation. The second is a statistical algorithmic approach for bioequivalence assessment. And the third is a mathematical programming approach for average bioequivalence testing. Neither of them relies on any impractical assumption, and all of them give essential information about the analyzed data. Furthermore, the required computations for any of them are simple. However, the use of the first approach is recommended when the Inverse Gaussian distribution could be assumed to be the probability distribution of the data under consideration. And in the case of having a too

small sample size " 4 or 5 " , when it is costly or risky to conduct the experiment, the use of the third approach is recommended. Otherwise, it is better to use the second approach.

This dissertation consists of five chapters organized as follows:

Chapter 1 is an introductory chapter which reviews the basic concepts of bioequivalence problem and other related fields. It presents the importance of bioequivalence studies, the concepts of bioequivalence, bioavailability, and the most commonly used experimental designs in bioequivalence studies. It contains a literature review for the almost available statistical work in bioequivalence Problem.

Chapter 2 presents the use of coefficient of variation test as a tool, in the case of having Inverse Gaussian parmacokinetic responses, to test whether the test formulation is bioequivalent to the reference formulation or not. It presents the coefficient of variation definition and its importance together with the reasons for assuming the Inverse Gaussian distributions as probability distributions for the observations under study. It also presents the Kolmogorov-Smirnov test and test the equality of two Inverse Gaussian's coefficients of variation. It contains the suggested algorithm and the goodness of fit test. Finally, it presents some illustrative numerical examples.

Chapter 3 presents a statistical algorithmic approach for solving the bioequivalence problem. In the first part of the algorithm, some informal diagnostic processes are presented to facilitate the comparison between the test and reference formulations. In the second part, an intersection- union test based on disaggregate nonparametric criteria is presented for the assessment of bioequivalence between the two formulations of interest. The algorithmic approach is constructed under a two important practical bioequivalence designs. These designs are the parallel and the 2×2 standard crossover designs. This chapter discusses the advantages of using an aggregate criterion and presents the importance of the nonparametric methods in the statistical inference. It proposes the statistical algorithmic approach and finally, it contains two illustrative examples using real data sets.

Chapter 4 presents the problem of average bioequivalence from the mathematical programming point of view. A mathematical model is to be formulated to present the

bioequivalence testing problem. The assessment of the average bioequivalence between the test and reference formulations is accomplished by solving the suggested mathematical program under the parallel and the standard 2×2 crossover designs. This chapter presents mathematical programming concepts, the theory of testing statistical hypotheses, and the mathematical programming representation for testing statistical hypotheses. It presents the proposed mathematical model and illustrates it by two illustrative examples. Also, it contains testing the Binomial parameter in the developed statistic used in the proposed model to enable us to compare the assessment of average bioequivalence using the mathematical programming model and the nonparametric tests.

Chapter 5 contains conclusions and points for further research.

Appendices (A) and (B) contain the Quick basic (version 4.0) and the GAMS (version 20.0) computer commands used in chapters 2 an 4 respectively. These computer commands are found in the contained CD.

Contents

Glossary of Notation

Notation	Definition	Page Number
BE	Bioequivalence	1
PK	pharmacokinetic	1
T formulation	test formulation	2
R formulation	reference formulation	2
FDA	food and drug administration	2
NDA	new drug application	2
ANDA	abbreviated new drug application	2
BA	Bioavailability	3
AUC	area under the blood or plasma concentration time curve	3
Cmax	peak drug concentration	4
Tmax	time to peak drug concentration	4
ABE	average bioequivalence	4
PBE	population bioequivalence	5
IBE	individual bioequivalence	5
CDER	center for drug evaluation and research	6
IG	Inverse Gaussian	14
pdf	probability density function	14
KS	Kolmogorov-Smirnov	17
cdf	commulative distribution function	17
CV	coefficients of variation	18
iid	identically independent random variables	19