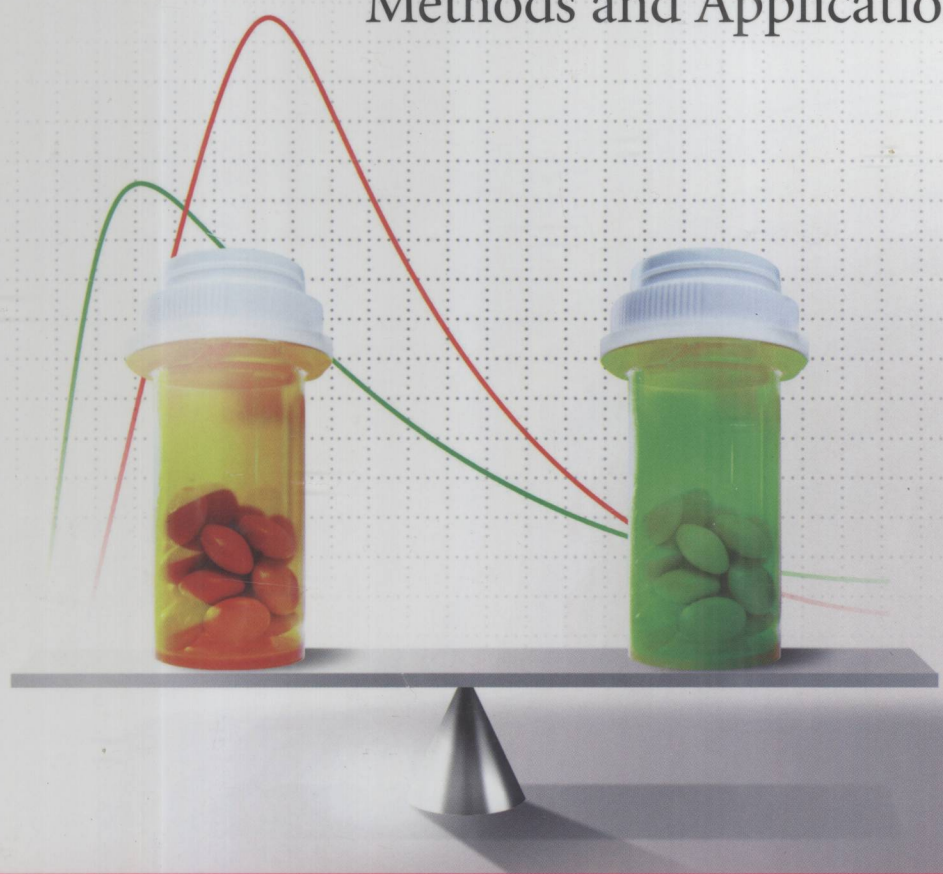
DIETER HAUSCHKE, VOLKER STEINIJANS
and IRIS PIGEOT

Bioequivalence Studies in Drug Development

Methods and Applications



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STATISTICS IN PRACTICE

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Methods and Applications

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Bioequivalence Studies in Drug Development

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The book is for

- *my family, for their encouragement: Carmen, Simon, Andreas, Eva and Andi (Dieter Hauschke)*
- *Helga, Eva and Uwe (Volker Steinijans)*
- *my husband Jürgen and the BIPS, for their neverending patience (Iris Pigeot)*

Preface

The design, performance, and evaluation of bioavailability and bioequivalence studies have received major attention from academia, the pharmaceutical industry and health authorities over the last couple of decades. Hence, the focus of the book is to provide an up-to-date overview of available methods, adopting a practical approach via numerous examples using real data. We also include recent methodology, most notably on the concepts of population and individual bioequivalence.

This book is a useful reference for clinical pharmacologists, biopharmaceutical scientists, reviewers from regulatory affairs, and biometricians working in the pharmaceutical industry. In addition, the presented material provides a springboard for all scientists from academia who are conducting research in this area of biopharmaceutics and clinical pharmacokinetics.

The book consists of 10 chapters, which cover planning, conduct, analysis, and reporting of bioequivalence studies according to current regulatory requirements. The methods are illustrated by a large number of real datasets. Moreover, the corresponding SAS® code is provided to assist the reader in implementing the analysis.

We are grateful to our colleagues Anton Drollmann, Christian Gartner, Kai Grosch, Dietrich Knoerzer, Olaf Michel, Rüdiger Nave, and Stephen Senn for comments on individual chapters, Martin Burke, Edgar Diletti, and Marc Suling for contributing SAS® code and generating the figures. We are also grateful for editorial help to Regine Albrecht, Elena Gamp, Beate Riedlinger, Rita Sauter, and Birgit Schroeder. At Wiley & Sons, we thank Wendy Hunter for providing continuous support during the production process.

Finally, we take responsibility for any errors in the book. Comments are most welcome for the preparation of further editions.

Dieter Hauschke
Volker Steinijans
Iris Pigeot

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Introduction

Comparison of therapeutic performance of two medicinal products containing the same active substance is critical for assessing the possibility of supplanting an innovator with any essentially similar medicinal product. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products. Assuming that, in the same subject, similar plasma concentration-time courses will result in similar concentrations at the site of action and thus in similar effects, pharmacokinetic data instead of therapeutic results may be used to demonstrate bioequivalence as an established surrogate marker for therapeutic equivalence.

The design, performance and evaluation of bioequivalence studies have received major attention from academia, the pharmaceutical industry and health authorities over the last couple of decades. Since 2003 there has been international consensus and current regulatory guidelines (Committee for Proprietary Medicinal Products (CPMP), 2001; Food and Drug Administration (FDA), 2003) require the demonstration of average bioequivalence between a test and a reference formulation, which means equivalence with regard to the population means.

The purpose of this chapter is to provide some essential features of bioequivalence trials. In particular we shall

- give the underlying definitions;
- explain when bioequivalence studies are performed;
- refer to the design and conduct of these studies.

1.1 Definitions

Although the beginning of the search for bioequivalence standards dates back to the early 1970s, there is no International Conference on Harmonization (ICH) Guidance on

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bioavailability and bioequivalence. Thus, the definitions given in the following primarily reflect the current guidelines of the US Food and Drug Administration and the European Committee for Proprietary Medicinal Products (FDA, 2003; CPMP, 2001). However, in order to illustrate how these concepts developed, other definitions are also cited.

1.1.1 Bioavailability

In the 2003 FDA guidance,

> 'Bioavailability is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.'

This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action. Such processes may also be influenced by drug properties such as permeability and the influences of presystemic enzymes and/or active transporters (e.g., p-glycoprotein).

To avoid an inconsistent use of the term 'absorption', Chiou (2001) suggested that absorption be defined as movement of drug across the outer mucosal membranes of the GI tract, while bioavailability be defined as availability of drug to the general circulation or site of pharmacological actions.

1.1.2 Bioequivalence

One of the operationally most feasible definitions of bioequivalence was given at the BIO-International '94 Conference in Munich (Skelly, 1995),

> 'Two pharmaceutical products are considered to be equivalent when their concentration vs. time profiles, from the same molar dose, are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects.'

It is this definition that comes closest to the operational procedure of comparing concentration-time profiles, or suitable metrics characterizing such profiles, in order to assess bioequivalence.

However, this practical definition was not adopted in the 2001 CPMP guidance on bioavailability and bioequivalence, which hardly changed its previous 1991 definition (CPMP, 2001),

> 'Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same.'

The definition of pharmaceutical equivalents and alternatives is given as,

> 'Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet

> the same or comparable standards. They are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety, or in the dosage form or strength. It is well known that pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.'

Although the 2001 CPMP definition of bioequivalence addresses both similar efficacy, and similar safety, it should be noted that it is virtually impossible to conclude similar safety on the basis of a bioequivalence study with its limited number of subjects and limited exposure time. The conjecture appears to be that similarity of the concentration-time profiles, in particular similarity of the maximum concentrations, may serve as a surrogate marker for the similarity of the adverse event profiles to be anticipated.

In the 2003 FDA guidance,

> 'Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.'

The FDA definition explicitly mentions rate and extent of drug availability as the two primary characteristics of the concentration-time profile. It is this concept of similarity in rate and extent of drug absorption which continues to define the bioequivalence metrics for rate and extent, and thereby the basis of the bioequivalence assessment.

It is interesting to note that there were various attempts to move away from this initial concept of rate and extent of drug absorption, particularly as some of the traditional rate characteristics such as C_{max} were identified as rather indirect, and frequently poor, measures of the true absorption rate. Steinijans *et al.* (1995a, 1996) proposed that bioequivalence assessment should focus on shape analysis of the concentration-time curves rather than on absorption rates. Chen *et al.* (2001) presented the concept of early, peak and total exposure, which at that time was under examination by the FDA. However, none of these alternative concepts were directly reflected in the corresponding guidelines.

1.1.3 Therapeutic equivalence

The 2001 CPMP guidance on bioavailability and bioequivalence also addresses the concept of therapeutic equivalence,

> 'A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally

recognized as not having an influence on safety and efficacy and comply with labeling requirements with respect to excipients. However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant will probably be necessary.'

1.2 When are bioequivalence studies performed

1.2.1 Applications for products containing new active substances

During the development of a new active substance (new chemical entity) intended for systemic action, bioequivalence studies are necessary as bridging studies between (i) pivotal and early clinical trial formulations; (ii) pivotal clinical trial formulations, especially those used in the dose finding studies, and the to-be-marketed medicinal product.

1.2.2 Applications for products containing approved active substances

In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence. The CPMP guidance (2001) devotes an entire section to the necessity of bioequivalence studies for various dosage forms, taking into consideration the concepts underlying the Biopharmaceutics Classification System (Amidon *et al.*, 1995), i.e., high solubility, high permeability for the active substance, and high dissolution rate for the medicinal product. This section also addresses special topics such as

- Exemptions from bioequivalence studies in the case of oral immediate release forms (*in vitro* dissolution data as part of a bioequivalence waiver).
- Post approval changes.
- Dose proportionality of immediate release oral dosage forms (bioequivalence assessment for only one dose strength).
- Suprabioavailability (which necessitates reformulation to a lower dosage strength, otherwise the suprabioavailable product may be considered as new medicinal product, the efficacy and safety of which have to be supported by clinical studies).

1.2.3 Applications for modified release forms essentially similar to a marketed modified release form

The requirements for modified release forms are stated in the CPMP Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (1999), which differentiates between prolonged, delayed and transdermal release forms.

Prolonged release formulations can be assessed as bioequivalent on the basis of single-dose and multiple-dose studies, which are designed to demonstrate that

- The test formulation exhibits the claimed prolonged release characteristics of the reference.
- The active drug substance is not released unexpectedly from the test formulation (dose dumping).
- Performance of the test and reference formulation is equivalent after single dose and at steady state.
- The effect of food on the *in vivo* performance is comparable for both formulations when a single-dose study is conducted comparing equal doses of the test formulation with those of the reference formulation administered immediately after a predefined high fat meal. This study should be conducted with the same strength(s) as those of the pivotal bioequivalence studies.

In the case of prolonged release single unit formulations with multiple strengths, a single-dose study under fasting conditions is required for each strength. Studies at steady state may be conducted with the highest strength only, if certain criteria for extrapolating bioequivalence studies (linear pharmacokinetics, same qualitative composition, etc.) are fulfilled. For multiple unit formulations of a medicinal product showing linear pharmacokinetics with multiple strengths, a single-dose study under fasting conditions on the highest strength is sufficient, provided that the compositions of the lower strengths are proportional to that of the highest strength, the formulations contain identical beads or pellets, and the dissolution profiles are acceptable.

For delayed release formulations, postprandial bioequivalence studies are necessary as food can influence the absorption of an active substance administered in an enteric-coated formulation.

The bioequivalence of a transdermal drug delivery system (TDDS) in comparison to the innovator's product should usually be assessed after single dose as well as after multiple dose administration. When marketing authorization of multiple strengths is required, the bioequivalence study can be performed with the highest dosage strength provided that exact proportionality in the formulation is given, i.e., the composition is the same, and the strength is proportional to the effective surface area of the patch, and that there is an acceptable *in vitro* release test (CPMP, 1999).

1.3 Design and conduct of bioequivalence studies

1.3.1 Crossover design and alternatives

A bioequivalence study should be designed in such a way that the formulation effect can be distinguished from other effects. In the standard situation of comparing a test formulation (T) with a reference formulation (R), the two-period, two-sequence crossover design is the RT/TR design. Subjects are randomly allocated to two treatment sequences; in sequence 1, subjects receive the reference formulation and test formulation in periods