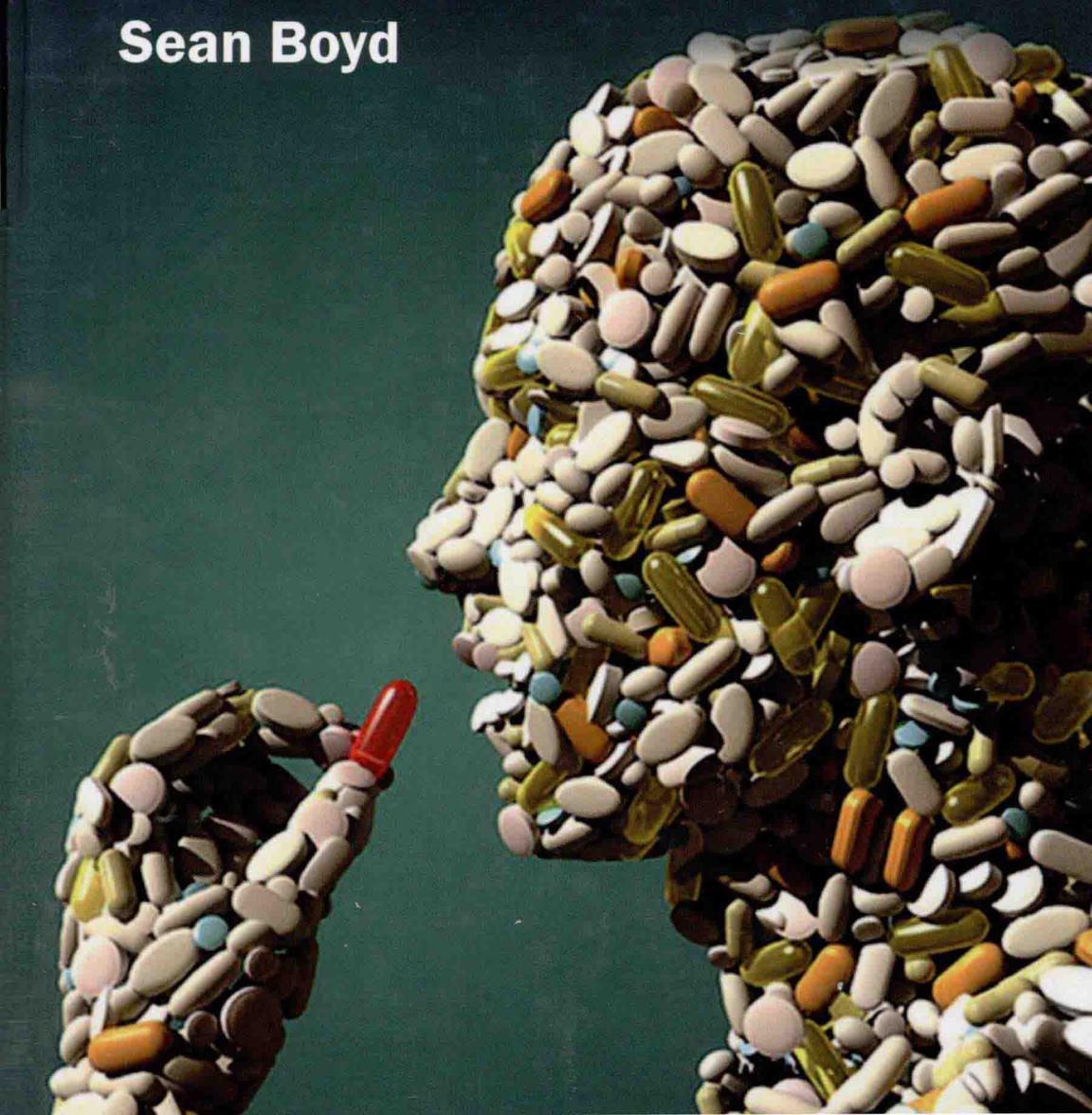
Pharmacokinetics

Advanced Principles and Applications

Sean Boyd



Pharmacokinetics: Advanced Principles and Applications

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Preface

Every book is a source of knowledge and this one is no exception. The idea that led to the conceptualization of this book was the fact that the world is advancing rapidly; which makes it crucial to document the progress in every field. I am aware that a lot of data is already available, yet, there is a lot more to learn. Hence, I accepted the responsibility of editing this book and contributing my knowledge to the community.

The advanced principles and applications of pharmacokinetics have been discussed in this book. It contains updated information and practical analyses regarding the study of drug pharmacokinetics in animals as well as humans. The aim of this book is to serve as a source of reference for scientists, researchers and clinicians and help them to logically develop their knowledge regarding this field from basics to advanced applications. The book consists of analyses of advanced theories which cover topics like bioequivalence studies, simulation theories on the basis of computers, pharmacogenomics in association with pharmacokinetics, drug interactions of herbal medicines and veterinary pharmacokinetics. It also covers practical aspects providing numerous examples of procedures and applications in advanced pharmacokinetics.

While editing this book, I had multiple visions for it. Then I finally narrowed down to make every chapter a sole standing text explaining a particular topic, so that they can be used independently. However, the umbrella subject sinews them into a common theme. This makes the book a unique platform of knowledge.

I would like to give the major credit of this book to the experts from every corner of the world, who took the time to share their expertise with us. Also, I owe the completion of this book to the never-ending support of my family, who supported me throughout the project.

Editor

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Section 1

Advanced Concepts

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Bioequivalence Studies

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1. Introduction

During last four decades there is an increased use of generic drug products in order to lower the healthcare cost. With increased availability and use of generic drug products, healthcare professionals are encountered with a large number of multisource products from which they have to select therapeutically equivalent products. Generic substitution is of concern not only for healthcare professionals but also for pharmaceutical industries, consumers and government officials. Many research papers have pointed out the concern regarding standards for approval of generic products which may not always ensure therapeutic equivalence (Boix-Montanes, 2011; Skelly, 2010; Tothfalusi et al., 2009; Midha et al., 2005; Chen & Lesko, 2001; Chen et al., 2000; Strom, 1987; Lamy, 1986). To alleviate this fear many guidelines/guidance and regulations covering the licensing of generic products have been introduced to ensure that the medicinal products reaching the market have well-established efficacy and safety profile (FDA, 1992, 1996, 2001a, 2001b, 2003, 2011; CDSCO, 2005; SFDA, 2005; Health Canada, 2004; CPMP, 2000; WHO, 1986).

Generally, demonstration of bioequivalence (BE) is the most appropriate method of ensuring therapeutic equivalence between two medicinal products. Bioequivalence studies should be conducted for comparison of medicinal products containing same active substance. Such studies need to be carefully designed to take into account biopharmaceutical, ethical, medical, pharmacokinetic, analytical and statistical considerations. The studies should be aimed to critically assess the possibility of alternate use of these products. In the 2003 United States Food and Drug Administration (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" (FDA, 2003).

Bioequivalence is actually the comparison of the bioavailability of two drug products. In the 2003 United States Food and Drug Administration (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 blood stream, 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" (FDA, 2003).

According to World Health Organization (WHO) guidelines, bioavailability is defined as:

"the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action" (WHO, 1986).

According to the United States Food and Drug Administration (FDA) "pharmaceutical equivalents" are drug products that contain identical active ingredients and are identical in strength or concentration, dosage form, and route of administration (FDA, 2011).

The CPMP (Committee for Proprietary Medicinal Products) guidance on bioavailability and bioequivalence confers the concept of therapeutic equivalence as:

"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"(CPMP, 2000).

In early 1960's extensive work in pharmacokinetics offered substantial evidence that composition and dosage form of a drug product can affect *in vivo* properties as well as therapeutic effects. These differences have been attributed to the effect of different drug excipients used, variations in manufacturing procedures and the properties of final dosage form on the rate and extent of the drug absorption from its site of administration. The importance of bioavailability came into lime-light after an incidence in Australia where a change in an inactive excipient of phenytoin formulation by the manufacturer resulted in low plasma levels of active drug leading to therapeutic failure and seizures in epileptic patients who were previously well-controlled with the same dose of same drug. Similarly in Europe marked variations in the plasma levels of digoxin were observed with different preparations of the drug resulting in either toxicity or therapeutic failure (Crawford et al., 2006; Welage et al., 2001; Soryal & Richens, 1992; Lindenbaum et al., 1971; Tyrer et al., 1970).

Bioequivalence and bioavailability studies are important during drug development of both new drug products and their generic equivalents. Provision of bioavailability and/or bioequivalence study data is an important element in support of Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and their supplements. The term generic drug product has been defined as "interchangeable multi-source pharmaceutical product". Generic products are the copies of brand-name drugs with same dosage form, strength, route of administration, intended use

and toxicity profile as the original innovator drug. Concern about lowering healthcare costs has resulted in an increase in the use of cheaper generic drug products instead of branded products. The innovator drugs are protected from copying by patents that last for 20 years from the first filing of the new chemical entity. Many people are concerned why generic drugs are often cheaper than the brand-name versions. It is because all the development work and clinical trials on new chemical entity are carried out by innovator to get initial drug approval which is later on reflected in its high price whereas the generic manufacturers only need to submit the bioequivalence data of the generic product to get a product license. The new products need to undergo bioequivalence testing before they are marketed. The difference may exist in absorption reflected in differing bioavailability profile of various brands, production batches or dosage forms of a drug. This can lead to either over- or under-medication if one entity is substituted for the other. The under-medication can lead to therapeutic failure and on the other hand over-medication can lead to toxicity. To avoid such risk it is best to study the bioavailability of all products but practically it is not possible. So each drug and any change in formulation must be considered individually while keeping in mind the real medical need for such studies in order to ensure efficacy and safety of these drugs. Many clinicians while switching or interchanging the different products are concerned with the safety and effectiveness of the new product. This concern is because of the fact that small changes in bioavailability can lead to significant changes in the efficacy or safety of the drug. Bioequivalence studies are designed with this concern in mind and to devise the strategies that minimize the risk to the patient. So when the generic product is pharmaceutically equivalent as well as bioequivalent to the innovator drug, then it is expected to be therapeutically equivalent (Kowalski et al., 2006; Crawford et al., 2006; FDA, 2003; Welage et al., 2001; Vasquez & Min, 1999; Banahan & Kolassa, 1997; Benet & Goyan, 1995; Marzo and Balant, 1995; WHO, 1986).

2. Design and conduct of bioequivalence studies

The basis of a bioequivalence study is the comparison of the drug product to be tested with an appropriate reference product (branded innovator drug). In bioequivalence studies an applicant compares the systemic exposure profile of a test drug to that of a reference drug product. Bioequivalence of two products can be assessed using *in vitro* standards, pharmacokinetic profile, clinical or pharmacodynamic end points. Different approaches for determination of bioequivalence of a drug product are:

- An *in vivo* test in humans in which the concentration of the active ingredient and when appropriate, its active metabolites, in blood, plasma, serum or other suitable biological fluid is measured as a function of time.
- An *in vivo* test in humans in which the urinary excretion of the active ingredient and when appropriate, its active metabolites are measured as a function of time.
- An *in vitro* test that has been correlated with and is predictive of human bioavailability profile or the one acceptable to FDA (e.g. dissolution rate test) that ensures human *in vivo* bioavailability.
- An *in vivo* test in humans in which an appropriate pharmacological effect of the active ingredient and when appropriate, its active metabolites are measured as a function of time if this effect can be measured with adequate accuracy, sensitivity and reproducibility.

- Well-controlled clinical trials that establish the efficacy and safety of the drug product, for purpose of determining bioavailability, or comparative clinical trials, for purpose of demonstrating bioequivalence.
- Any other approach considered adequate by the FDA to measure bioavailability or ascertain bioequivalence.

Bioequivalence for most of oral tablets or capsules is demonstrated *in vivo* by comparing the rate and extent of absorption that is bioavailability of the generic product with that of the innovator product. This is done by measuring the active ingredient concentration in blood, plasma, serum or other biological fluids over a certain period of time for both the generic and innovator products, also called test and reference drugs respectively. By doing so the bioequivalence studies frequently rely on pharmacokinetic measures such as area under the concentration-time curve (AUC) and peak drug concentration (Cmax) (Niazi, 2007; FDA, 2001a, 2003; Pidgen, 1996; Nation & Sanson, 1994).

2.1 Study design

Many authors have debated whether multi-dose or single-dose studies should be used to assess bioequivalence. Generally single-dose pharmacokinetic studies are recommended for both immediate- and modified-release drug products as they are more sensitive in assessing the active ingredient released from drug into circulation. For assessing bioequivalence of two formulations of a drug, two-sequence, two-period, crossover study is conducted after administration of single dose under fasted conditions. In crossover design the subjects serve as their own controls and they crossover from one treatment to the other. A large variability in drug clearance often exists among the individuals. However the intrasubject variation is usually smaller relative to inter-subjects variability. Parallel studies are appropriate if the drug has extremely long half life, repeated pharmacokinetic profile is difficult to obtain, or residual pharmacodynamic effects are relevant. Furthermore, if carry over effects from one treatment period to another are of concern or if intrasubject variability is high, then replicated design is used. Nonreplicate study designs are usually recommended for bioequivalence studies of most of the orally administered, modified-release and immediate-release dosage forms. Replicate study designs are often recommended for bioequivalence studies of highly variable drug products (intra-subject coefficient of variation $\geq 30\%$), including those that are modified-release, immediate release, and other orally administered drug products. Replicate study designs have several scientific advantages compared to nonreplicate designs. (SFDA, 2005; FDA, 2001a, 2003; Welage et al., 2001; Nation & Sanson, 1994; Steinijans et al., 1992; Metzler, 1989).

2.2 Study subjects

The subjects should be selected with the objective of minimizing variability and permitting detection of difference between the drug products. Therefore, the study is normally carried out with healthy subjects. The study is performed in accordance with the Declaration of Helsinki for biomedical research involving human subjects (WMA Declaration of Helsinki, 2008) and the Guideline for Good Clinical Practice (FDA, 1996). The subjects recruited for bioequivalence studies should be 18 years of age or older and