DEVELOPING SOLID ORAL DOSAGE FORMS: PHARMACEUTICAL THEORY AND PRACTICE

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30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
32 Jamestown Road, London NW1 7BY, UK
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA
360 Park Avenue South, New York, NY 10010-1710, USA

First edition 2009

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-444-53242-8

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Typeset by Charon Tec Ltd., A Macmillan Company
www.macmillansolutions.com

Printed and bound in the United States of America

09 10 11 12 13 10 9 8 7 6 5 4 3 2 1

CHAPTER

15

Bioavailability and Bioequivalence

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15.1 GENERAL BACKGROUND

Substituting one oral dosage formulation for another has been a common practice for many years in the drug development industry, as well as in the clinic. During drug development, for example, industry scientists frequently evaluate different versions of investigational drug products or dosage formulations, and thereby often need to conduct bioequivalence studies. In turn, prescribing clinicians use the bioavailability and bioequivalence data provided on the product label to select an optimal treatment regimen for their patients. Consequently, the overall therapeutic success of any drug substitution in the clinic will ultimately depend on multiple factors. These factors include the pharmacokinetics of the comparator and reference drugs, as well as the appropriateness of the study design and statistical criteria that were used to initially demonstrate bioequivalence.

Bioequivalence has evolved as a specific regulatory requirement over the last 40 years. In the early 1960s, researchers noticed that the bioavailability of a therapeutic drug product could vary depending on its oral dosage formulation.[1] Almost 15 years later, in 1977, the US Food and Drug Administration (FDA) initially published their recommended procedures for sponsors to use in studies of bioequivalence.[1] Since then, the FDA has continued to refine and revise its guidance on bioequivalence, other international regulatory agencies have published their own guidelines, and pharmaceutical industry professionals worldwide have contributed their statistical expertise and scientific opinions. Nevertheless, several major controversies have yet to be resolved. Issues pertaining to the selection of the most appropriate statistical criteria to use to sufficiently demonstrate bioequivalence are still frequently debated. Other topics of discussion include a determination of exactly when (or under what specific circumstances) should formal tests of bioequivalence be required from a regulatory standpoint, and for which type or class of drug.

Under the Food, Drug and Cosmetic (FD&C) Act of 1938 and the 1962 Kefauver–Harris Amendment, sponsors were required to provide safety and efficacy data to support all claims for the active ingredients in a new drug product before it could be approved for sale. Scientific standards later set by the FDA, however, have since allowed sponsors to lawfully make appropriate drug substitutions without necessarily having to conduct additional time-consuming, and expensive, clinical safety and efficacy studies. That is, in the absence of additional clinical studies (and under specific circumstances), an appropriate set of biopharmaceutical, pharmacokinetic, and statistical evaluations may now be used to establish that a test drug formulation is bioequivalent (and thereby therapeutically interchangeable) with a reference drug formulation.

The information included in this chapter will provide the reader with an overview of the clinical, pharmacokinetic, and statistical issues associated with bioavailability and bioequivalence studies of oral dosage formulations. The current international regulatory perspectives will also be presented, along with a detailed comparison of the various criteria presently

being used in the pharmaceutical industry to demonstrate bioequivalence.

15.2 DEFINITIONS AND KEY CONCEPTS

Bioavailability essentially describes the overall rate and extent of drug absorption. Data from bioavailability studies are routinely used to identify a drug product's pharmacokinetics, optimize a therapeutic dose regimen, and support product labeling requirements. Bioequivalence, on the other hand, generally describes the extent to which the bioavailability of one particular drug product (i.e., the test product) compares with that of another known drug product (i.e., the reference product). Data from bioequivalence studies are often used to establish a link between different investigational drug formulations (e.g., an early phase 1 formulation versus a later phase 3 formulation). Bioequivalence studies may also be required during the post-approval period in certain situations, such as whenever a major change occurs in a manufacturing method for an approved drug product. Bioequivalence studies are also generally required to compare generic versions of a drug product with the corresponding reference-listed drug.

Regulatory requirements for bioavailability and bioequivalence data submitted with new drug applications (NDAs) and supplemental applications are specifically addressed in the US Code of Federal Regulations,[2] and a corresponding FDA guidance document has been published.[3] The following sections will provide an overview of the key concepts, and general underlying principles, of bioavailability and bioequivalence.

15.2.1 Bioavailability

When a drug is administered orally (or by any other extravascular route), a sufficient amount of the administered dose must be absorbed over a certain time period before the intended pharmacologic effect can manifest. Thus, the bioavailability of an orally administered drug clearly depends on a combination of factors, including the physiochemical characteristics of the drug formulation, and the physiological state of the gastrointestinal (GI) system.

Bioavailability of an oral dosage form is defined[3] 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."

From a pharmacokinetic perspective, two specific types of bioavailability can be considered: absolute bioavailability, and relative bioavailability. Absolute bioavailability is a special case in which the systemic exposure of an extravascular dosage form is determined relative to that of its intravenous (IV) dosage form. Relative bioavailability, in contrast, compares the rate and extent of absorption of one dosage formulation (e.g., oral solution) to another dosage formulation (e.g., oral capsule). Relative bioavailability can also sometimes compare the rate and extent of absorption for one drug product with two different administration routes (e.g., intramuscular and subcutaneous).

For the most part, absolute bioavailability is generally determined by comparing the extent of drug absorption after an extravascular versus an intravenous (e.g., infusion or bolus) administration. Thus, valid extravascular and IV data are both typically required for the calculation of absolute bioavailability. In operational terms, this means two series of pharmacokinetic samples must be collected—one extravascular series, and one IV series—using a suitable biological matrix (e.g., blood, plasma or serum), and appropriate sampling schedules. In addition, drug concentrations from each series must be analyzed using a validated drug assay.

Measured concentration data from each series are then plotted, and the area under the drug concentration–time curves (AUC) estimated (e.g., by applying a numerical integration formula such as the trapezoidal rule). Assuming clearance remains constant AUC is directly proportional to the amount of drug absorbed. Thus absolute oral bioavailability (F) can be calculated:

$$F = \frac{D_{iv}}{D_{po}} \cdot \frac{AUC_{po}}{AUC_{iv}}$$

where:

D_{iv} and D_{po} are the intravenous and oral doses administered, respectively

AUC_{iv} and AUC_{po} are the AUC estimates for the intravenous and oral routes, respectively.

In contrast to absolute bioavailability, relative bioavailability essentially compares the rate and extent of absorption of one dosage formulation (e.g., oral solution) to that of another (e.g., oral capsule). Over the course of a typical drug development cycle, several relative bioavailability studies could potentially be required (e.g., to compare the *in vivo* performance of an earlier stage formulation versus the later stage formulation). Depending on the overall pace of drug development, new dosage formulations are often still being prepared while a new molecular entity progresses from the nonclinical stage into the early clinical stage. In cases where the final product is intended as a solid

oral dosage form, for example, oral solutions or suspensions might be the only formulations ready for use. Solid prototype formulations, such as capsules, might also be ready for use in early phase 1; however these prototypes are often far from the final marketable form. Under these types of circumstances, therefore, an estimate of the drug's relative bioavailability is needed.

Relative bioavailability (F_{rel}) can be calculated:

$$F_{rel} = \frac{D_A}{D_B} \cdot \frac{AUC_B}{AUC_A}$$

where:

D_A and D_B are the doses administered for drug formulation A and B, respectively

AUC_A and AUC_B are the AUC estimates for the A and B formulations, respectively.

15.2.2 Bioequivalence

Bioequivalence is defined[3] 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."

From a regulatory perspective, and for various strategic reasons, bioequivalence studies may need to be conducted before a product is approved for use in the clinic or during the post-approval period. Depending on the particular research objective, for example, a pre-approval bioequivalence study might be required in an NDA submission to demonstrate the therapeutic link between the early phase dosage formulation and the to-be-marketed formulation. Bioequivalence studies are also typically required in abbreviated NDAs for generic versions of brand name drugs.

Two oral drug products can generally be considered to be bioequivalent if their respective concentration–time profiles are so similar that it would be unlikely that they would produce clinically significant differences in the pharmacological response. In other words, bioequivalent drug products with essentially the same systemic bioavailability should thus be able to produce similar, and predictable, therapeutic effects. Pharmacokinetic assessments in bioequivalence studies of solid oral drug products, therefore, typically include statistical comparisons of AUC and maximum concentration (C_{max}). Different measures are sometimes needed to describe drug exposure. For example, partial AUC truncated to the median T_{max} of the reference product can be used to describe early drug exposure. C_{max} is used to describe peak exposure. For a single dose study, both $AUC_{0-\tau}$ and $AUC_{0-\infty}$ are used to measure the total exposure. If a multiple dose study is appropriate, the $AUC_{0-\tau}$ at steady state (where τ is the dosing interval) is used to describe total exposure.

Pharmacodynamic assessments may also sometimes be performed. For instance, if the systemic exposure of the drug is too low to be reliably detected or if an appropriate bioanalytical methodology cannot be developed to support a pharmacokinetic assessment, an appropriate pharmacodynamic assessment (i.e., a reliable and predictable surrogate marker) may suffice. Pharmacodynamic measurements are usually not recommended if pharmacokinetic measurements are available.

Pharmacokinetic bioequivalence methods can be quite challenging for drugs with minimal systemic bioavailability. Drug classes that typically show minimal systemic bioavailability are ophthalmic, dermal, intranasal, and inhalation drugs. Nevertheless, pharmacodynamic assessments are not routinely used to show bioequivalence, for several reasons. First, very few validated, predictable surrogate biomarkers are available that are also considered acceptable surrogates by the regulatory authorities. Secondly, pharmacodynamic studies generally require prohibitively large sample sizes since intra- and inter-subject variability levels tend to be relatively high. Some examples of biological markers that have been successfully used for bioequivalence testing are skin blanching[4] with corticosteroids, and stomach acid neutralization with antacids.[5]

15.2.3 Pharmaceutical Equivalence and Therapeutic Equivalence

Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredient, in the same amount, with identical dosage forms, and identical routes of administration. Furthermore, drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents (as described above) that are expected to produce the same clinical effects, and have similar safety profiles when they are administered to patients under the same conditions as specified in the product labeling information.

Therapeutic equivalence is thus an ultimate measure of the interchangeability of two distinct drug products or formulations. Therapeutic equivalence may be reasonably inferred from results of appropriately designed *in vivo* pharmacokinetic bioequivalence studies.

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