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Bioavailability Studies

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to define various terms relating to bioavailability studies
- be able to describe some of the past problems with bioavailability
- be able to describe a typical bioavailability study
- be able to evaluate data derived from a bioavailability study

The topic of this Chapter is studies which are carried out to evaluate different dosage forms. These studies called bioavailability or drug product evaluation studies might compare:-

i. two (or more) dosage forms made by two (or more) different manufacturers, e.g. innovator *versus* generic. These studies are called bioequivalence studies and they look at the similarity of F and ka values between the products studied.
ii. one type of dosage form with a 'standard' formulation, e.g. tablet *versus* intravenous or capsule *versus* solution. These are bioavailability studies designed to determine values of ka and F for the product under study. Changes in ka may be intentional (for slow release dosage forms). The F value may need to be determined.

Second brand or generic drug manufacturers are required to prove that their product is equivalent to previously marketed products which have demonstrated clinical efficacy. For most drugs, the second and subsequent manufacturer must show that their product is bioequivalent, i.e. same ka and F, as the product(s) on the market. During the development of new drugs and drug products, the original manufacturer will perform bioavailability studies on new products, comparing the product to be marketed with an intravenous dosage form, if possible.

References

- Albert, K.S. 1980 **Drug Absorption and Disposition: Statistical Considerations** Amer. Pharm. Assoc.
- Dittert, L.W. et al. 1972 **Guidelines for Biopharmaceutical Studies in Man** Amer. Pharm. Assoc.
- U.S. Food and Drug Administration (FDA)
  - FDA Enforcement Report Index
  - FDA Recalls and Safety Alerts
  - Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
    - Preface
    - Therapeutic Equivalence Evaluations Codes
- Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners from the Australian Department of Health and Ageing
  - Symbols page for the Schedule...note the equivalence symbol 'a'

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Definitions

Bioavailability [FDA CDER 2004] "This term means 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."

Pharmaceutical Equivalent [FDA CDER 2004] "Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (*e.g., chlordiazepoxide hydrochloride, 5mg capsules*). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling."

Pharmaceutical equivalents are the same drug entity, the same type of dosage form, the same dose and meet the same compendial requirements. For example Aspirin Tablets, U.S.P. of a particular strength. Although the U.S.P. monograph includes dissolution and chemical assay requirements there are no bioavailability requirements (at least in U.S.P. XX). Thus all Aspirin U.S.P. tablets of a particular dose would be pharmaceutical equivalents. Capsules of aspirin would not and neither would tablets of a different dose. Dosage forms containing different salt forms, esters or other chemical form are not pharmaceutical equivalents.

Pharmaceutical Alternatives [FDA CDER 2004] "Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (*e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules*). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient."

Pharmaceutical alternatives are drug prodcuts that can provide the same therapeutic moiety. Different dosage forms, doses and even salts can be pharmaceutical alternatives.

Therapeutic Equivalent [FDA CDER 2004] "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."

Thus, pharmaceutical equivalents that have been shown to be bioequivalent (and the same by other desterminations of clinical effect and safety profile) are therapeutic equivalents. Therapeutic equivalents would be expected to produce identical drug concentration time profiles and therapeutic response when administered under the same conditions. This is not the same as two pharmacologically similar (equivalent) compunds that may produce the same therapeutic response in some individuals ("*e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for the treatment of pain*").

Bioequivalent Drug Products [FDA CDER 2004] "This term describes pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(7)(B) of the Act describes one set of conditions under which a test and reference listed drug shall be considered bioequivalent:

```
the rate and extent of absorption of the test drug do not show
a significant difference  from the rate and extent of absorption
of the reference drug when administered at the same  molar
```

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dose of the therapeutic ingredient under similar experimental
conditions in either a  single dose or multiple doses; or

the extent of absorption of the test drug does not show a significant
difference from  the extent of absorption of the reference drug
when administered at the same molar dose of  the therapeutic
ingredient under similar experimental conditions in either a
single dose  or multiple doses and the difference from the reference
drug in the rate of absorption of  the drug is intentional, is
reflected in its proposed labeling, is not essential to the
attainment of effective body drug concentrations on chronic use,
and is considered  medically insignificant for the drug.
```

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate."

Bioequivalence Requirement [Code of Federal Register 2003] means a requirement imposed by the Food and Drug Administration for the in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.

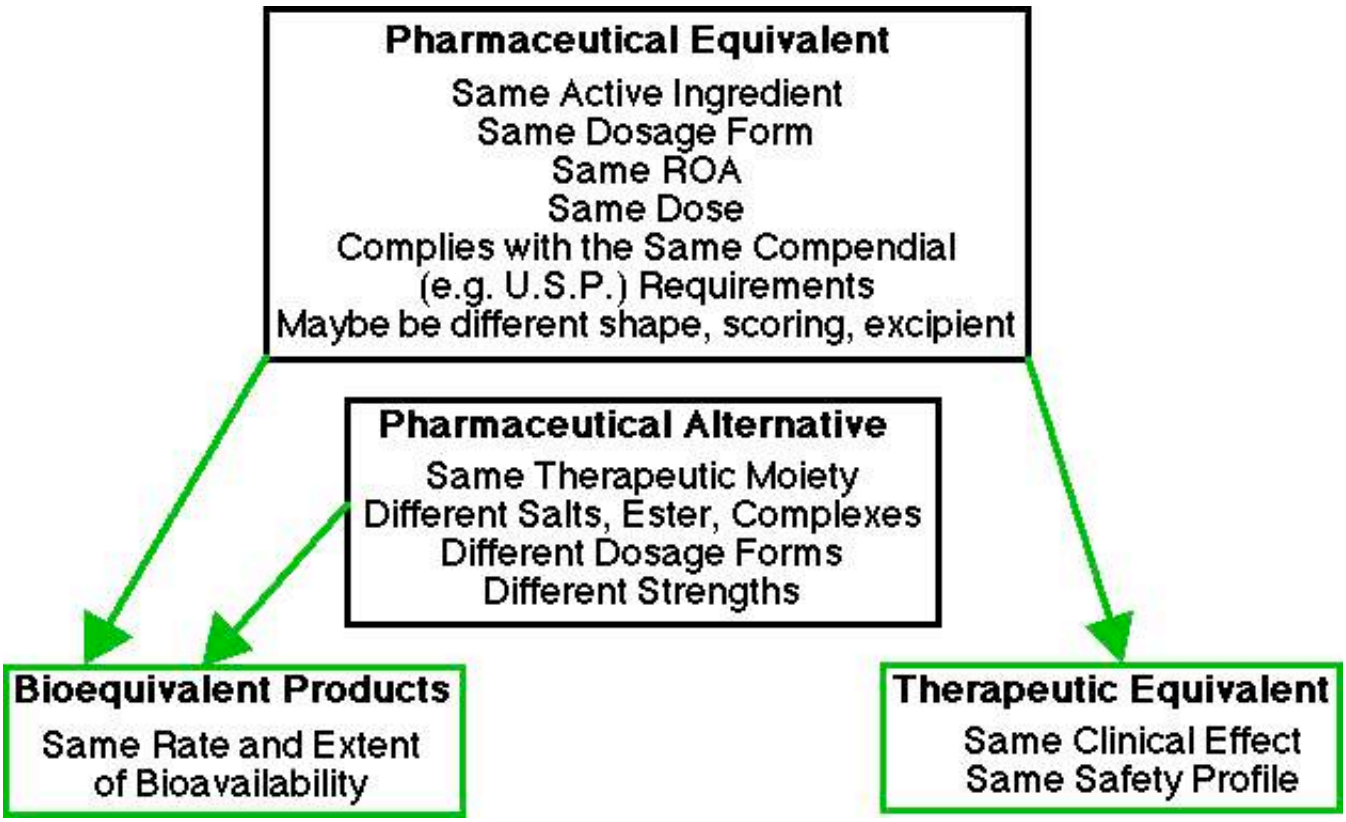


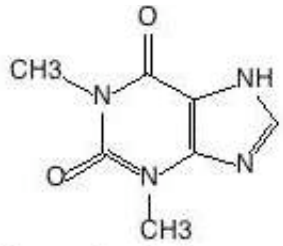
Figure 10.2.1 Summary of Bioavailability DEfinitions

Brand Name [Shargel and Yu, 1985] is the trade name of the drug.

Chemical Name [Shargel and Yu, 1985] is the name used by the organic chemist to indicate the chemical structure of the drug. The IUPAC Name.

Drug Product [Federal Register 1977] means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

Generic Name [Shargel and Yu, 1985] is the established, non proprietary or common name of the active drug in a drug product.



Chemical Structure

$C_7H_8N_4O_2$
Molecular Formula

180.17
Molecular Weight

3,7-dihydro-1,3-dimethyl-
1 H-purine-2,6-dione
Chemical Name

5967-84-0
CAS Number

Theophylline

Generic Name
US Approved Name

Brand Names

Tablet	Elixir	Capsule
Theo-Dur (Key)	Aerolate (Fleming)	Theospan (Laser)
Durapyl (McNeil)		Theobid (Glaxo)

Figure 10.2.2 A Collection of Names for the Same Drug
Brand names may be obsolete, taken from Billups, 1986

References

- Shargel, L and Yu, A.B.C. 1985 **Applied Biopharmaceutics and Pharmacokinetics**, 2nd ed., Appleton-Century-Crofts, Norwalk, CT, p129-131
- Billups, N.F. and Billups, S.M. 1986 **American Drug Index**, 30th ed., Lippincott, Philadelphia, PA
- Code of Federal Register
  - Title 21 Food and Drug
  - Part 320 Bioavailability and Bioequivalence Requirements
- Code of Federal Register, 2003, Title 21, Volume 5, Part 320 Bioavailability and Bioequivalence Requirements
- FDA, CDER Approved Drug Products with Therapeutic Equivalence Evaluations
- FDA, CDER Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (2002)
- Search for bioavailability in the PharmPK listserv archive

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Past Bioavailability Problems

There are a number of examples of drugs products which have exhibited bioavailability problems in the past. These examples are all pre-1976 and as mentioned in the text were included in the earlier edition of the book with no further examples reported [Gibaldi, 1984]. This is an indication that more attention is now being given to formulation development during drug development. More recent example may be found by searching the FDA Enforcement Pages.

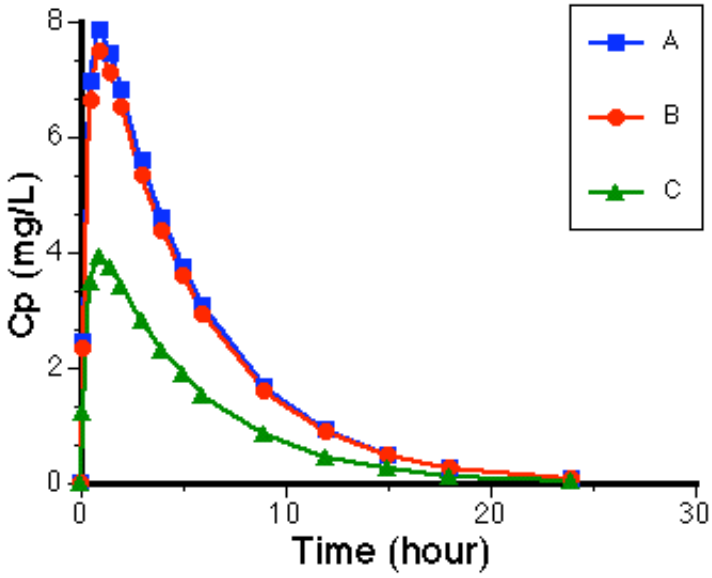

Figure 10.3.1 Plot of Cp *versus* Time

Chlorpropamide. With three products tested the peak plasma concentration after one brand was less than 1/2 the peak after the other two products (see Figure 10.3.1).

Digoxin. The text reports a number of bioavailability problems with digoxin. One example is particularly interesting. Doctors in Israel noticed 15 cases of digoxin toxicity between Oct/Dec 1975 with almost no reports for the same period the previous year. It was found that the local manufacturer had changed the formulation to improve dissolution without telling the physicians. Urinary data suggested a two-fold increase in availability of the new formulation.

Phenytoin. Again there are a number of examples in the text. One report described an incidence of phenytoin intoxication in Australia in 1968 and 1969. Apparently the tablet diluent was changed from calcium sulfate to lactose. Later studies showed that the bioavailability was higher from the dosage form containing lactose.

Other drugs with problems in the past include Acetazolamide, Aminosalicylate, Ampicillin, Aspirin, Ascorbic Acid, Chloramphenicol, Chlorothiazide, Diazepam, Furosemide, Iron, Levodopa + 10 (Gibaldi, 1984).

Bioavailability - Bioequivalence Studies

Bioavailability studies are designed to determine either an absolute bioavailability (relative to an IV formulation) or relative

bioavailability (with an alternate reference dosage form with good absorption characteristics). They can be used to compare different routes of administration, for example oral *versus* IV or IP *versus* IM.

Bioequivalence studies are designed to compare drug products. The objective is to determine if these products are bioequivalent. The dosage forms should be similar, especially the route of administration. For example, tablet *versus* tablet or maybe tablet *versus* capsule, given orally. These studies may be necessary before a generic product may be marketed. In general a relative bioavailability is determined which may be close to 100%.

Reasons for Bioequivalence Requirements

The FDA may decide to require bioavailability studies for a variety of reasons including:

- Results from clinical studies indicate that different drug products produce different therapeutics results.
- Results from bioavailability studies indicate that different products are not bioequivalent.
- Drug has a narrow therapeutic range.
- Low solubility and/or large dose.
- Absorption is considerably less than 100%

Some items to consider

Item 1. Sustained or extended release products such as topical patches can be very useful products. Ideally they can deliver a continuous amount of drug over an extended period of time. This psuedo zero order delivery can provide steady drug concentrations with few problems of peak and troughs values. Unfortunately if such a product fails delivery of the total dose over a much shorter time may results in toxic concentrations.

First try simulating a typical expected result for a multiple day patch using a dose of 5,400 μg (5.4 mg) over 72 hours with kel = 0.289 hr^{-1} and V = 87.5 L (1.25 L/kg). (Ritschel 1992). This simulation produces concentrations of approximately 2.5 μg/L (2.5 ng/ml). (rxlist 2004). A Class I recall (FDA 2004) reported "a potential seal breach" which could "result in an increased absorption of the" drug. Repeat the simulation with a duration of 12 or 24 hours to represent a more rapid drug release. Explore the problem as a Linear Plot - Java Applet

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References

- Gibaldi, M. 1984. **Biopharmaceutics and Clinical Pharmacokinetics**, 3rd ed., Lea & Febiger, page 143-152.
- U.S. Food and Drug Administration (FDA)
  - FDA Enforcement Report Index
  - FDA Recalls and Safety Alerts
  - Ritschel, W.A. 1992 Handbook of Basic Pharmacokinetics, 4th ed, Drug Intelligence Publications, Hamilton, IL, p 539
  - Fentanyl - Clinical pharmacology at www.rxlist.com
  - FDA report of a recall (Feb 2004) regarding a topical patch

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Bioavailability study characteristics

With recently introduced products properly conducted bioavailability studies will have been performed before the product is allowed to be marketed. However products which were approved some time ago may not have been tested as thoroughly. It is therefore helpful to be able to evaluate the testing which may have been undertaken. There are a number of situations where a pharmacist is required to evaluate bioavailability study testing. When selecting drug products for a prescription, product performance should be a most important criteria. Once it is established that two or more products are equivalent, then the choice of brand can be made on the basis of economic factors, cost etc.

The evaluation of a drug product bioavailability study involves the consideration of various factors.

Drug

The drug substance in each product must be the same. Bioavailability studies are conducted to compare two or more products containing the same chemical substance. We can't compare different chemical substances. The apparent volume of distribution and kel can be quite different for different drug substances, thus no interpretation of the results is possible. The first rule of bioavailability testing is that you compare the drug products with the same drug in each dosage from.

The only time that this rule is relaxed is in the case of pro-drug administration. A pro-drug is a compound which will form the drug of interest in the body. In this case it may be appropriate to compare the delivery of a dosage form containing the drug with another dosage form containing a pro-drug. This testing is generally conducted to evaluate the usefulness of the pro-drug, rather than a strict comparison of the drug products. Once the usefulness of the pro-drug is demonstrated comparisons between dosage forms all containing the pro-drug should be undertaken to evaluate the drug product performance.

Drug product

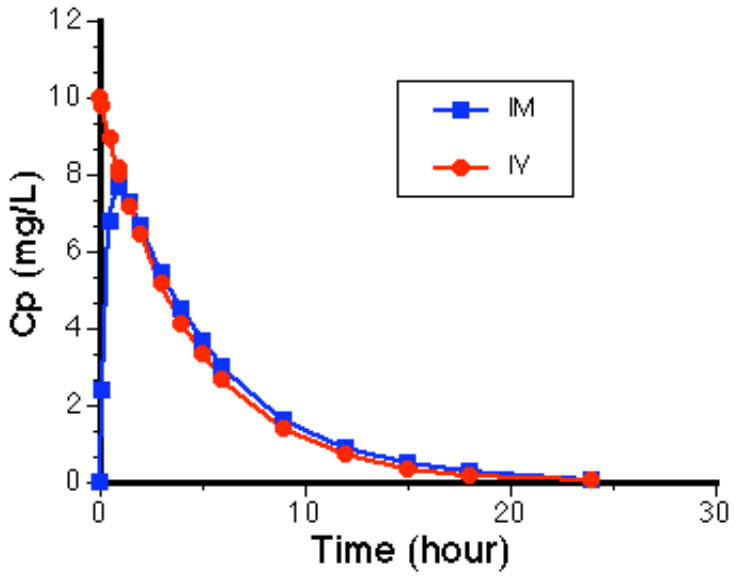

Figure 10.4.1 Plot of Cp *versus* Time after IV and IM Administration. NOTE: AUC are the same

Usually the comparison is made between two (or more) similar products, containing exactly the same chemical substance. However, different dosage forms can be compared (when they contain the same drug). For example we could compare an IM dosage form with an IV dosage form.

By calculating the AUC values we can determine the absolute bioavailability of the IM dosage form. In this case it appears to be close to 100%. The rate of absorption for the IM dose can be determined also, but of course no comparison is possible.

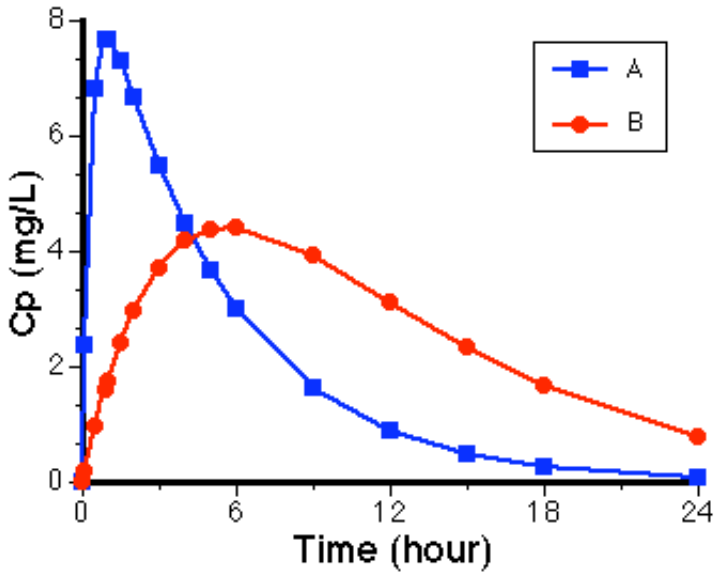

Figure 10.4.2 Plot of Cp *versus* Time for A and B with B having Slower Absorption

Alternately we could compare brand A tablet with brand B tablet or capsule.

By comparing the AUC values and ka values we can make comparisons concerning both the extent and rate of absorption. In this case A appears to be faster than B but the extent of absorption doesn't appear to be all that different.

Subjects

A number of factors of concern include health, age, weight, enzyme status, number. Studies with humans must be carefully evaluated and approved by an Institutional Review Board (IRB). There must be an optimal risk/benefit ratio and given that in most bioavailability studies (with healthy volunteers) there is little direct benefit to the individual any risks should be minimal. All subjects must give informed consent that includes a requirement that they be provided with clear descriptions of their risks and benefit to participation.

Health

Usually a study is designed so that each subject takes each product in turn. Thus the effect of the individual subject can be eliminated or reduced. Such a study design is called a cross-over design. Even though each subject will act as their own control it is usually best to have subjects of similar kinetic characteristic so that major variations are not introduced. Thus healthy volunteers are often preferred by drug product evaluation studies. Informed consent should be obtained from each volunteer and some biochemical and medical examination will be used to confirm their medical state. For some drugs there may be special disease states which may cause the exclusion of some volunteers. For example, in one study we looked at propranolol products, and otherwise healthy volunteers with a past history of asthma were excluded from this study.

Age

As you will see later, age can have a significant effect on drug pharmacokinetics. Elderly patients and young children can have quite different kinetics compared with young adults. In the interest of a better matched group, subjects between the ages of 18 to 35 years

are preferred. Kinetic changes usually aren't important until age greater than 60.

Weight

The apparent volume of distribution is usually proportional to weight in subjects of normal weight for height. However, in overweight (or underweight) subjects the V in L/kg maybe somewhat different. Again to better match the subjects, normal weights are preferred. Insurance weight tables may be useful.

Enzyme status

Smokers or subjects taking certain other drugs may have altered kinetics for the drug of interest. This can be caused by alteration of enzyme activity or by drug-drug interactions. These effects add complications to a study and an attempt is usually made to minimize these factors.

Number

The number of subjects included in the study should be sufficient to see any real (maybe 20% variation) differences in bioavailability. Usually 10 - 20 subjects are used in these studies. In clinical studies where the end-point is some clinical response, much larger numbers are required because of the greater variability in clinical response.

Assay

The same assay method should be used for all phases of the study. It is not much use using one assay for product A samples and another assay for product B samples. This wouldn't be done in a single study, however, if you were trying to compare the results from one study with those from another, different assay methods may have been used. For example products A and B may have been compared with one assya method. In another study products B and C may have been compared with a second assay method. Comparison of products A and C may not be valid. One assay method may pick up an interference which is not indicative of the drug concentration or the bioavailability. The assay method should be sensitive and specific.

Design

Usually a complete cross-over design is used. With this design each subject receives all products with a wash-out period between each dose administration.

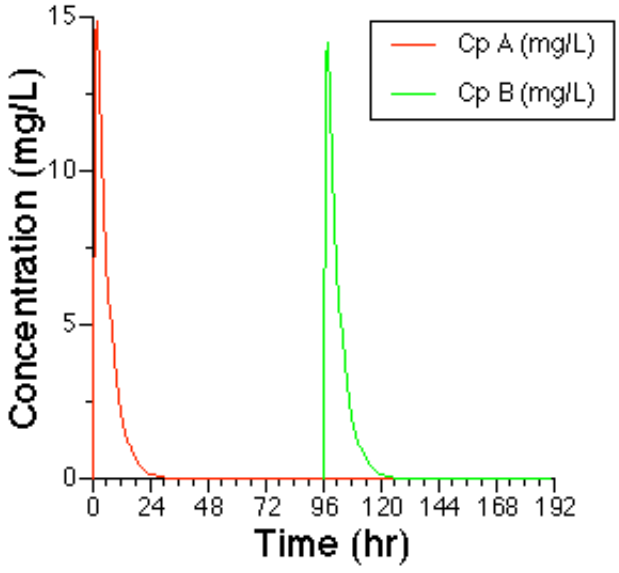

Figure 10.4.3 Figure Showing Concentrations After Two Separate Drug Administrations

Table 10.4.1 Two Product Example

	Week 1	Week 2	
Group 1	A	B	
Group 2	B	A	for two products

Table 10.4.2 Three Product Example

	Week 1	Week 2	Week 3	
Group 1	A	B	C	
Group 2	B	C	A	
Group 3	C	A	B	
Group 4	A	C	B	
Group 5	C	B	A	
Group 6	B	A	C	for three products

When more than 3 or 4 products are involved it has been suggested that a different design is used whereby each subject will get maybe 3 or 4 products of a possible 8 to 12. This type of design, possibly an incomplete block design, usually requires more subjects to get the same information, but it does mean that each subject is not required to take as many doses. It is harder to recruit subjects for longer studies.

Data analysis

Statistics

The rate of absorption can be characterized by the ka value and also the time of peak concentration. The extent of drug absorption is characterized by the F value or the peak concentration or total AUC values. Any differences in the average values of these parameters can then be analyzed statistically to determine the significance of the differences. The 5 % confidence levels is usually used as the criteria of acceptance. The analysis of variance is a technique for separating the effect of product, subject, and sequence. The significance of each of these factors can be tested.

Table 10.4.3 Analysis of Variance Table for Three-Way Cross-Over Study

Source of Variation	d.f.	SS	MS	F	Significance Level
Total	35	44.6	-	-	-
Subject	11	28.3	2.58	10.1	$p < 0.001$
Week	2	0.14	0.068	0.27	n.s.
Treatment	2	11.0	5.55	21.8	$P < 0.001$
Residual	20	5.09	0.255	-	-

In this example two effects are significant. There appears to be a significant effect due to treatment and subject. This would indicate that the subjects are significantly different from each other and that the treatments are significantly different in terms of the parameter measured. It is quite common that Cp or AUC values are significantly different for different subjects, because of their different weights or size. The different treatments would appear to be bio-inequivalent.

By these studies the relative bioavailability of two or more products can be determined. Hopefully with proper testing we can ensure that drug products labeled to contain equivalent chemical amounts will be bioequivalent as well.

Generate typical data from a simulated bioavailability study and analyse the data using an Analysis of Variance (ANOVA).

SAS file

```
DATA BIOAV;
INPUT FORM GROUP SUBJ AUC;
CARDS;

...data here...

PROC MEANS;
PROC ANOVA;
  CLASSES FORM GROUP SUBJ;
  MODEL AUC = FORM GROUP SUBJ;
  MEANS FORM GROUP SUBJ /DUNCAN;
```

References

- FDA Guidance Statistical Approaches to Establishing Bioequivalence

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