

Chapter 8. Bioavailability and Bioequivalence

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I. INTRODUCTORY REMARKS

Over the last 25 years, **Pharmacokinetics** has emerged as an integral part of drug development, especially when identifying a drug's biological properties. By pharmacokinetics, one means the application of kinetics to a Pharmakon, the Greek word used to specify drugs and poisons. The term thereby implies the time course and fate of drugs in the body. This general definition broadly embraces *absorption*, *distribution*, *metabolism* (biotransformation) and *excretion* (ADME). The linking of **Pharmacodynamics** (response) and pharmacokinetics offers a composite understanding both about how the drug affects the body and how the body affects the drug.

The most comprehensive insight about a drug's inherent pharmacokinetic properties is gained by studying an intravenous dose. This route of administration has the greatest quantitative potential, as it permits a mass balance approach to be applied to distribution, clearance and the body processes associated with excretion and metabolic elimination (e.g. renal, hepatic). The administration of a drug by other routes, notably oral, introduces an uncertainty that reflects the unknown fraction that is actually absorbed. Consequently, such doses alone cannot accurately identify the distribution and clearance processes.

The most important property of any non-intravenous dosage form, intended to treat a systemic condition, is the ability to deliver the active ingredient to the bloodstream in an amount sufficient to cause the desired response. This property of a dosage form has historically been identified as physiologic availability, biologic availability or *bioavailability*. Bioavailability captures two essential features, namely *how fast* the drug enters the systemic circulation (rate of absorption) and *how much* of the nominal strength enters the body (extent of absorption). Given that the therapeutic effect is a function of the drug concentration in a patient's blood, these two properties of non-intravenous dosage forms are, in principle, important in identifying the response to a drug dose. Onset of response is linked to the *rate* of drug absorption whereas the time-dependent extent of response is linked to the *extent* of drug absorption. While the bioavailability of each type of non-intravenous product (e.g. oral, inhalation, topical (e.g. patch), rectal, etc.) could be discussed, this chapter will of necessity focus only on orally administered products. They certainly represent the major pharmaceutical class in drug development and patient treatment.

Bioavailability following oral doses may vary because of either patient-related or dosage-form-related factors. Patient factors can include the nature and timing of meals, age, disease, genetic traits and gastrointestinal physiology. The dosage form factors include 1) the chemical form of the drug (e.g. salt vs. acid), 2) its physical properties (e.g. crystal structure, particle size), and 3) an array of formulation (e.g. non-active ingredients) and manufacturing (e.g. tablet hardness) variables.

Not surprisingly, bioavailability is of clinical, academic, and regulatory interest. The latter includes agencies that approve the sale of products in their nation(s), as well as reimbursement agencies. Applications from manufacturers seeking regulatory approval for a new drug (e.g. New Drug Application (NDA)) must furnish exhaustive information about a drug's pharmacokinetics. Typically, such evidence entails studies wherein the drug has been orally administered. While such trials may broadly be viewed as bioavailability studies, many are ostensibly designed to assess the drug's safety and efficacy via strategies of dose escalation and chronic administration. These studies will not be entertained in this chapter. The more pertinent interest in bioavailability relates to questions about absolute extent of absorption (absolute bioavailability), the importance of product formulation changes that are made during a new drug's development process, the comparability of different oral dosage forms (e.g. modified-release versus conventional products), and whether the products can be administered with meals. These facets will receive attention in this chapter.

Manufacturers seeking regulatory approval of competitive (generic) products (e.g. Abbreviated New Drug Application [ANDA]), must provide detailed bioavailability evidence showing head-to-head comparative

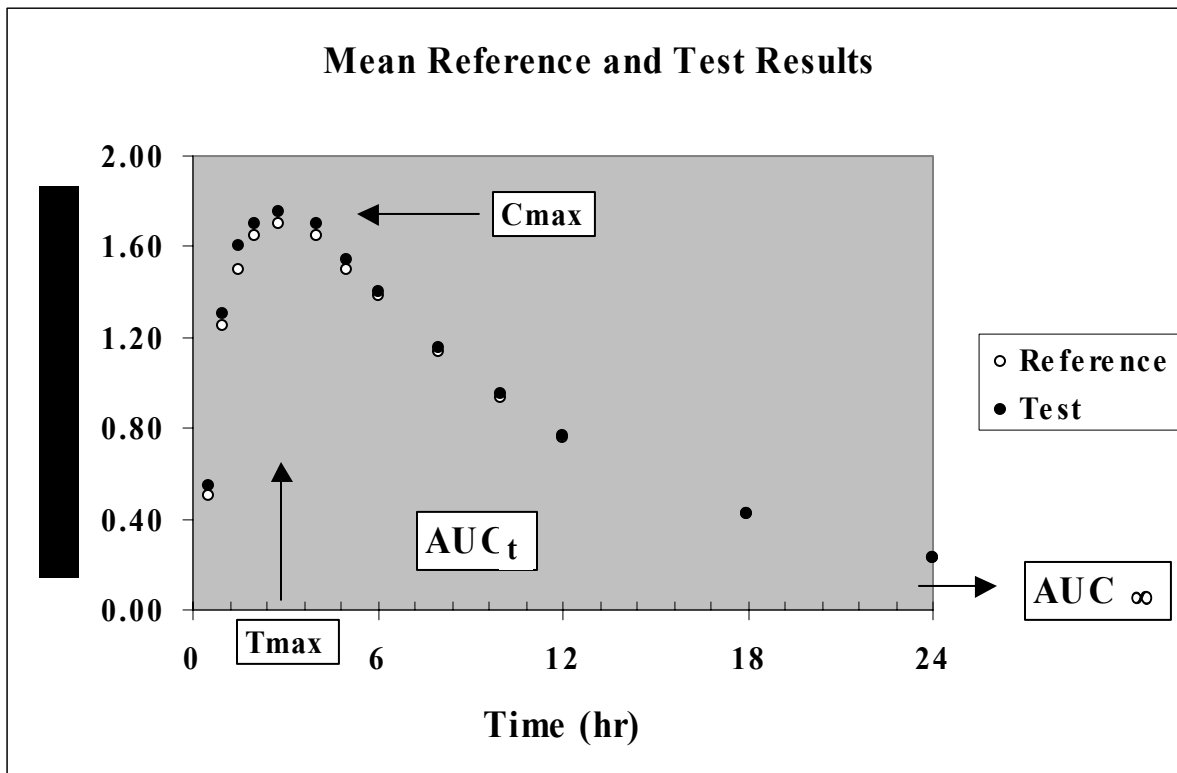


Figure 1: Illustration of the key metrics in a comparative bioavailability trial showing, for example, Test and Reference products. The maximum concentration (C_{max}) occurs at the T_{max} . The AUC_t is the total area under the concentration versus time profile to the last sampling time. The area to time infinity (AUC_{∞}) is the extrapolated area based on the AUC_t and the terminal constant (λ_z).

performance of their product against the innovator's product. Such trials are fundamentally designed to establish clinical equivalence particularly as it relates to interchangeability or substitutability. Such bioavailability information is particularly germane to this chapter.

II. COMPARATIVE BIOAVAILABILITY: A UNIVERSAL APPROACH

Most bioavailability studies, whether for a new or generic product, possess a common theme. A test is conducted to identify the quantitative nature of a specific product comparison. This comparison for a new drug may be, for example, to assess the performance of an oral formulation relative to that of an intravenous dose, or perhaps the performance of a modified-release formulation in comparison to a conventional capsule. For a generic product, it is typically a comparison of a competitive formulation with a reference product. Such commonality surrounding comparative bioavailability studies suggests a universal experimental approach.

All the studies to be described in this chapter basically attempt to establish a drug's concentration versus time profile following product administration in some form of comparative test. As shown in **Figure 1**, the two primary metrics for such concentration versus time profiles are the area under the curve (AUC) and the maximum observed concentration (C_{max}); the former customarily includes the AUC to the last

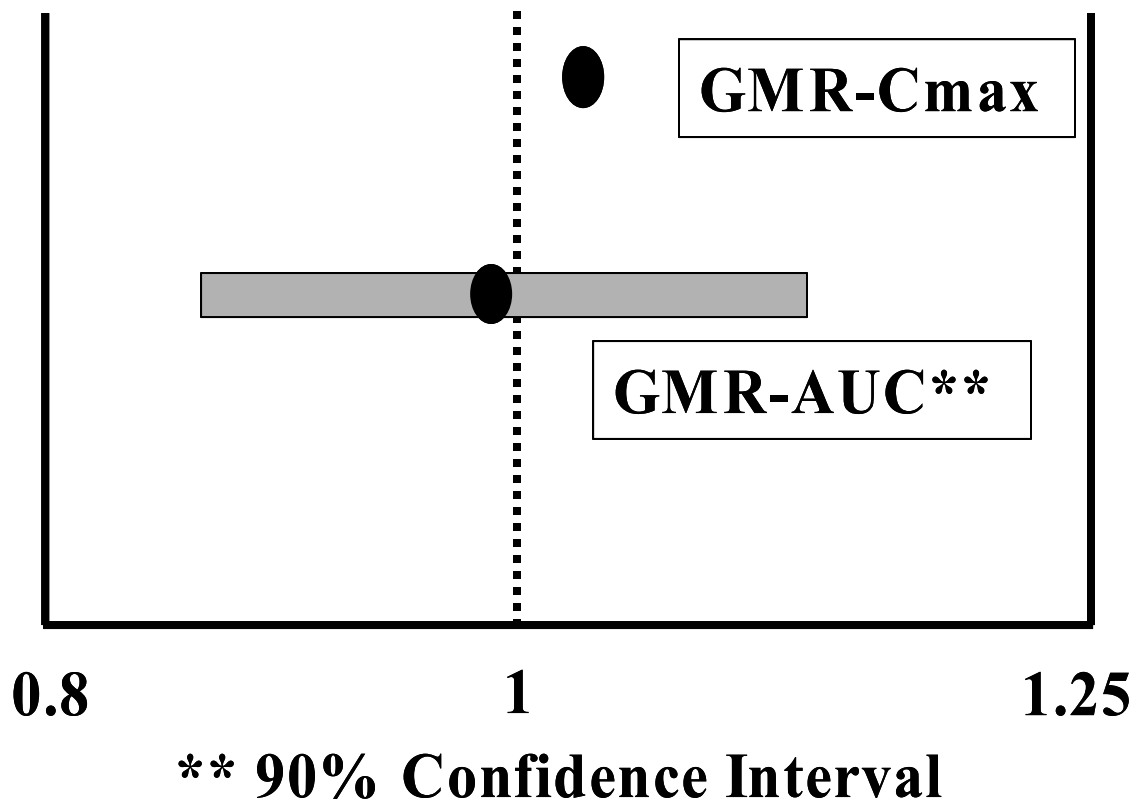


Figure 2: An illustration of the statistical criteria to be satisfied to gain equivalence status in a comparative bioavailability assessment. For example, in a bioequivalence trial, the geometric mean ratio for the test/reference Cmax (GMR Cmax) must be located between 0.8 and 1.25. The GMR AUC's (whether AUC_t or AUC_∞) and their computed 90% confidence intervals must reside completely within the 0.8 to 1.25

sampling time in a trial (AUC_t) and the extrapolated total AUC to time infinity (AUC_∞). The time at the maximum concentration (Tmax) is also of some minor interest.

After obtaining the profiles in a comparative trial, and computing the metrics, conclusions need to be reached regarding the comparison. Statistical methods are applied to test if the metrics are sufficiently similar to be considered equivalent. When the metrics are deemed equivalent, the drug concentration profiles are regarded as fundamentally the same. To achieve this equivalence, the study products' geometric mean ratios (eg. AUC test/AUC reference), as well as their projected 90% confidence intervals for the population mean ratio, must be located within an 80 to 125% window. For the maximum concentration (Cmax) some regulatory agencies consider it adequate if only the mean ratios are within the interval (See **Figure 2**).

The preceding universal approach will be recognized as a common thread in the trials to be identified in this chapter. The data requirements for such an approach fundamentally orchestrate the design of the studies, which will be seen to have a rather common or universal format.

III. COMPARATIVE BIOAVAILABILITY STUDIES FOR NEW DRUGS (NDA)

The initial oral formulation for a new drug is frequently used to conduct early human studies of safety and efficacy. Often, early oral bioavailability information about the drug (and this initial formulation) is

obtained by means of studies comparing it with an intravenous dose and/or a solution of the drug. Although such studies will not be described in this chapter, they employ the Universal Approach wherein the comparator is an intravenous dose or perhaps a solution of the drug.

When the oral dosage formulation undergoes changes during the drug development process, the deductive inference concept becomes a helpful tool. It circumvents the need to retest subjects or patients following each formulation change in order to reestablish product safety and efficacy. The fundamental tenet underpinning the logic is similar to that described later for generic product testing. First, it is assumed that the time-dependent drug concentrations in blood from an early formulation are intimately linked with the effects. Second, if a new formulation exhibits the same time-dependent drug concentrations (rate and extent of drug absorption), the new formulation is deemed "bioequivalent" and, by inference, has the same safety and efficacy.

To test reformulated dosage forms, the Universal Approach is employed. The fundamental nature of the study is similar to that described in detail within the "Bioequivalence" section of this chapter.

III.1. Outline of a typical product reformulation bioavailability study:

III.1.A. Objectives

To test the comparative bioavailability of a reformulated and original product and thereby to determine their equivalence.

III.1.B. Primary endpoints

Determine the time-dependent concentrations of the administered drug in the collected blood (or plasma/serum) of each subject following administration of the reformulated and original products.

III.1.C. Secondary endpoints

Determine the time-dependent concentrations of potentially important metabolites (active and contributing to the product's therapeutic response) in the collected blood (or plasma/serum) of each subject following administration of the reformulated and original products.

III.1.D. Exploratory endpoints

Determine the C_{max} , AUC_t , AUC_{∞} , T_{max} , λ_z and half-life of the primary (and secondary) endpoints following the reformulated and original products, for each subject.

III.1.E. Study design

The study shall be designed in such a way that the effects of formulation can be distinguished from other factors. When two formulations are compared, a randomized two-period, two-sequence crossover study is considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects.

All facets of the study are to be tightly controlled. Normally, subjects fast for 10 hours prior to product administration. A dose of the tested product is administered at the start of an experimental day with about 8 ounces (240 mL) of water. Further fluid will be withheld for about 2 hours; standardized meals are permitted beginning at four hours after drug administration. All subsequent meals will be carefully standardized at fixed intervals.

Sequential blood samples (about 12 to 18, including a pre-dose sample) shall be drawn at appropriate, specified, and carefully recorded times (to capture increasing and decreasing concentrations during the absorption, distribution and elimination phases). The collections are to continue for about three terminal drug half-lives in order to capture at least 80% of the total area. At least three to four samples need to be

obtained from the terminal log-linear phase to derive an acceptable estimate of the terminal constant (λ_z) from linear regression. For long half-life drugs, a truncated AUC (e.g. up to 72 hours) is generally considered adequate.

Blood samples or the harvested plasma/serum shall be analyzed for the administered drug or metabolites by means of a validated analytical method.

III.1.F. Planned sample

The appropriate subject number can be forecast, as described in the "Bioequivalence" section, via the ANOVA error variance associated with the specific metric (e.g. from an earlier study), the expected deviation of the reformulated products' metrics and the bioequivalence criterion (eg. 90% confidence that the estimated population mean ratio lies between 80 and 125%).

III.1.G. Study population

Healthy volunteers are normally selected, although for some drugs it may, of necessity, be best to conduct the trial in patients. See the "Bioequivalence" section.

III.1.H. Specific inclusion criteria

Healthy males or females will be included in the study population. Preferably, non-smokers will be employed.

III.1.I. Specific exclusion criteria

Women of childbearing potential are to be excluded if there is a potential risk. Other common exclusion criteria are identified in the "Bioequivalence" section.

III.1.J. Tools for assessing primary endpoints

A validated analytical method is needed for both the primary and secondary endpoints.

III.1.K. Specific criteria for early withdrawal and discontinuation

While the number and availability of subjects shall be sufficient to allow all periods of the study to be successfully completed without coercion, subjects shall retain the right to discontinue the trial. Discontinuation reasons may include adverse drug reactions or even personal preferences. All withdrawals must be reported.

III.1.L. Data analysis method:

Consult the Universal Approach (Figure 2) and the "Bioequivalence" section. In summary, ANOVA is to be used to identify the source contributions by factors including subjects, period, formulation and potential interactions. The geometric mean ratio together with the ANOVA residual mean error term are used to identify the statistical basis for the 90% confidence interval for the ratio of the population means (New Formulation/Original Formulation) of the identified metrics (e.g. AUC, Cmax).

III.2. Development of a new formulation (e.g. modified release product)

Delayed-release products typically release the active ingredient at a time later than immediately after administration, thereby sometimes exhibiting an absorption lag time. The first modified-release product requires an NDA. The purpose of the required studies is to determine if the following conditions are met:

- a. The drug product meets the controlled release claims made for it;
- b. The bioavailability profile rules out the occurrence of what is called "dose dumping", which is the premature release of the drug from the dosage form;
- c. The formulation provides consistent performance between individual dosage units;

- d. The steady state performance, in comparison to an available conventional product, is equivalent. If, based on accumulated evidence between circulating concentrations of the drug and response, the modified-release product is different, clinical studies will be needed to show the impact of such differences.

The study requirements for modified-release products permit some flexibility, but shall include the following:

- a. A single dose crossover comparison of a conventional, immediate release, product and the modified release product (ideally, the study would also include a solution or suspension of the same drug in the same strength);
- b. A single dose food-effect study;
- c. A steady-state study.

For the first two study requirements above, the Universal Approach is again needed. While summary information about the food effect study is presented here, further details of a food effect study are presented in the "Bioequivalence" section. The steady-state study requirements will not be presented in this chapter because they do not have a similar "comparative" character. The primary requirements for the two comparative studies are:

III.3. Objective A

To test the comparative bioavailability of a modified-release and immediate-release product and thereby to determine their equivalence.

III.3.A. Primary endpoints

Determine the time-dependent concentrations of the administered drug in the collected blood (or plasma/serum) of each subject following administration of the modified-release and immediate-release products.

III.3.B. Exploratory endpoints

Determine the C_{max} , AUC_i , AUC_{∞} , T_{max} , λ_z and half-life of the primary (and secondary) endpoints following the modified-release and immediate-release products, for each subject. Some agencies will also require the area over the usual dosing interval for the modified-release product.

III.3.C. Study elements

The fasting study shall be designed in such a way that the effects of the formulation can be distinguished from other factors. When two formulations are compared, a randomized two-period, two-sequence crossover study is considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects.

Doses are given to subjects following an overnight fast. All remaining aspects are to be controlled as outlined in the "Bioequivalence" section. Data analysis is also conducted as described in that section. However, it should be recognized that differences in C_{max} can be anticipated because the fundamental drug release properties for the modified-release and immediate-release products are different. The potential impact of such differences needs to be weighed in the light of concentration versus response evidence.

III.4 Objective B

To test the effect of food upon the bioavailability of a modified-release product.

III.4.A. Primary endpoints

Determine the time-dependent concentrations of the administered drug in the collected blood (or plasma/serum) of each subject following administration of the product under fasting and fed conditions.

III.4.B. Exploratory endpoints

Determine the C_{max} , AUC_t , AUC_{∞} , T_{max} , λ_z and half-life of the primary (and secondary) endpoints following administration of the modified-release product in each period, for each subject.

III.4.C. Study elements

This fasting/fed study shall be designed in such a way that the potential effects of the meal upon the formulation can be distinguished from other factors. When the formulation is tested as required, a randomized two-period, two-sequence, crossover study is considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects.

Doses are given to subjects following an overnight fast. In one period, the fast is continued, whereas in the other period a meal is given before dose administration. For meal administration, please refer to the food-effect study described in the "Bioequivalence" section. Typically, both fasting and fed periods become common four hours after dose administration when normal food ingestion cycles are permitted.

All study aspects are controlled as outlined in the "Bioequivalence" section. Data analysis is also conducted as described in that section and under "Universal Approach".

IV. COMPARATIVE BIOAVAILABILITY FOR GENERIC DRUG PRODUCTS (ANDA): BIOEQUIVALENCE STUDIES

The deductive inference concept is also central to bioequivalence testing. The foundation is set, first, through evidence that a specified, approved, reference drug product (e.g. tablet from the innovative manufacturer) has shown acceptable safety and efficacy through an array of clinical trials. Second, a widely held view is embraced that the time-dependent drug concentrations in blood from such a reference product are intimately linked with the therapeutic effects. Third, a principle is adopted, namely that chemically equivalent (same amount of the same active ingredient) and pharmaceutically equivalent products (same dosage form; e.g. conventional tablet), that exhibit the same rate and extent of drug absorption, are bioequivalent. Fourth, bioequivalent products by inference are considered therapeutically equivalent.

When a manufacturer thereby wishes to gain therapeutic equivalence by introducing a competitive generic product into the marketplace, it is not necessary to conduct the full array of trials needed for the first (innovative) product. If equivalence has been demonstrated, according to prescribed study requirements, appropriately determined metrics (Figure 1), and statistical criteria (Figure 2), the generic product by inference is regarded as therapeutically equivalent to the innovative drug product.

The design of and requirements in, bioequivalence studies are fundamentally satisfied through single dose administrations, although there is a lingering interest in multiple dose testing. The focus is on the rate and extent of absorption of the active ingredient, although some jurisdictions (e.g. FDA) continue to show an interest in the primary active metabolite(s). In some cases, notably drugs that exhibit non-linear pharmacokinetics, the dose strength to be tested may be dictated by whether the drug's non-linearity is attributable to the absorption or elimination phase (Health Canada). As a general principle, the studies are designed to test inherent product absorption properties. Thereby, the trials generally specify healthy normal controls that exhibit circumscribed demographics.

Comparative evidence may require not only studies in a fasting condition, but following a specified meal. The latter permit drug formulations to be evaluated under "stressed conditions". If it is shown that competitive products are bioequivalent under both fasting and fed conditions, there is greater confidence that they are therapeutically equivalent when used in patients.

IV.1 Testing competitive (generic) products under fasting conditions

The following describes the requirements for most orally administered products, including tablets, capsules and modified-release dosage forms. Nevertheless, it is best to check with each regulatory agency regarding current or special drug- or product-specific requirements

The bioequivalence study conclusions are commonly extended to all strengths of the products provided the active and inactive ingredients conform to regulatory requirements of proportionality. When these requirements are violated, representative strengths of each formulation type shall be tested.

IV.1.A. Objectives

To test the comparative bioavailability of a test and reference product and thereby to determine their equivalence.

IV.1.B. Primary endpoints

Determine the time-dependent concentrations of the administered drug in the collected blood (or plasma/serum) of each subject following administration of the test and reference products.

IV.1.C. Secondary endpoints

Determine the time-dependent concentrations of potential important metabolites (active and contributing to the product's therapeutic response) in the collected blood (or plasma/serum) of each subject following administration of the test and reference products.

IV.1.D. Exploratory endpoints:

Determine the C_{max} , AUC_t , AUC_{∞} , T_{max} , λ_z and half-life of the primary (and secondary) endpoints following each of the test and reference products, for each subject.

IV.1.E. Study design

The study shall be designed in such a way that the effects of formulation can be distinguished from other factors. If two formulations are compared, a randomized two-period, two-sequence crossover study is considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects. Replicate studies, although not mandated, offer the advantage of providing a comparison of intra-subject variances for the test and reference products.

All facets of the study are to be tightly controlled. The full characteristics, including lot numbers and expiry dates of the test and reference products, shall be known. Normally, subjects fast for 10 hours prior to product administration. Normally, the highest safe strength/dose of the test or reference product will be administered at the start of an experimental day with about 8 ounces (240 mL) of water. Further fluid will be withheld for about 2 hours; standardized meals are to be permitted beginning at four hours after drug administration. All subsequent meals will be carefully standardized according to a fixed schedule.

For most drugs, subjects shall not be permitted to recline until at least two hours after product ingestion. Physical activity and posture is to be standardized to limit variable effects on gastrointestinal blood flow and motility. Blood samples (about 12 to 18, including a pre-dose sample) shall be drawn at appropriate, specified, and carefully recorded times (to capture increasing and decreasing concentrations during the absorption, distribution and elimination phases). The collections are to continue for about three terminal

drug half-lives in order to capture at least 80% of the total area. At least three to four samples need to be obtained from the terminal log-linear phase to derive an acceptable estimate of the terminal constant (λ_z) from linear regression. For long half-life drugs, a truncated AUC (e.g. up to 72 hours) is generally considered adequate.

Blood samples or the harvested plasma/serum shall be analyzed for the administered drug or metabolites by means of a validated analytical method.

IV.1.F. Planned sample

While most jurisdictions support a minimum of 12 subjects in a bioequivalence trial, the likelihood of a successful outcome is improved with an increase in the subject number. The appropriate subject number can be forecast via the ANOVA error variance associated with the specific metric (e.g. from published data or a pilot study), the expected deviation of the test product's metric from that of the reference product (e.g. 0.05) and the bioequivalence criterion (e.g. 90% confidence that the estimated population mean ratio lies between 80 and 125%).

IV.1.G. Study population

To minimize variability and focus on the comparison of the two formulations, healthy volunteers are to be selected, although for some drugs it may, of necessity, be best to conduct the trial in patients. Subjects will ordinarily be between 18 and 55 years of age and within the accepted normal range for Body Mass Index. Clinical laboratory tests, notably to assess cardiac, renal and hepatic function, are to be normal based on subject screening. Furthermore, subjects will have undergone an extensive review of medical history and received a comprehensive medical examination.

IV.1.H. Specific inclusion criteria

Healthy males or females will be included in the study population. Preferably, non-smokers will be employed.

IV.1.I. Specific exclusion criteria

Women of childbearing potential are to be excluded if there is a potential risk. Subjects shall not have a history of alcohol or drug abuse. Subjects shall not be receiving drugs for any medical condition. There is to be no known allergy to the administered drug or formulation. As a rule, alcoholic beverages and over-the-counter drugs shall be avoided during the days immediately preceding a trial and for an appropriate interval during the active sample collection period of the trial.

IV.1.J. Tools for assessing primary endpoints

A validated analytical method is needed for both the primary and secondary endpoints.

IV.1.K. Specific criteria for early withdrawal and discontinuation

While the number and availability of subjects shall be sufficient to allow all periods of the study to be successfully completed without coercion, subjects shall retain the right to discontinue the trial. Discontinuation reasons may include adverse drug reactions or even personal preferences. All withdrawals must be reported.

IV.1.L. Data analysis method

All study information, including exploratory endpoints shall be presented for each subject following the test and reference products. ANOVA is to be used to identify the source contributions by factors including subjects, period, formulation and potential interactions. The geometric mean ratio together with the ANOVA residual mean error term are used to identify the statistical basis for the 90% confidence interval for the ratio of the population means (Test/Reference) of the identified metrics (e.g. AUC, C_{max}).

Health Canada's Part A Guide (See "Suggested Readings") provides an amplified section illustrating the calculations.

IV.2. Testing competitive (generic) products under fed conditions

Food-effect studies are recommended particularly for modified-release dosage forms and, in some jurisdictions, for an array of conventional solid oral products.

Commonly, aside from the incorporation of a meal, the same testing methods are to be used as described above for the fasting condition. Therefore, only the study design is presented below.

IV.2.A. Study design

The fed study is to be designed in such a way that the effects of formulation can be distinguished from other factors. If two formulations are being compared, a randomized two-period, two-sequence crossover study is commonly considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects. Replicate studies, although not mandated, offer the advantage of providing a comparison of intra-subject variances for the test and reference products.

All facets of the study are to be tightly controlled. The full characteristics, including lot numbers and expiry dates, of the test and reference products shall be known. Normally, subjects fast for 10 hours prior to ingesting a standardized meal. The meal is to provide the greatest changes from the gastrointestinal physiology of a fasting state. A meal with high-fat and high-calorie content is recommended (e.g. 150, 250 and 500-600 calories from protein, carbohydrate, and fat, respectively). The meal shall be ingested over a period of 30 minutes or less. The product dose shall be ingested 30 minutes after start of the meal.

Generally, the highest safe strength/dose of the test or reference product will be administered with about 8 ounces (240 mL) of water. Further fluid shall be withheld for about 2 hours; standardized meals will be permitted beginning at four hours after drug administration. All subsequent meals will be carefully standardized.

For most drugs, subjects shall not be allowed to recline until at least two hours after product ingestion. Physical activity and posture shall be standardized to limit effects on gastrointestinal blood flow and motility. Blood samples (about 12 to 18, including a pre-dose sample) are to be drawn at appropriate, specified, and carefully recorded times (to capture increasing and decreasing concentrations during the absorption, distribution and elimination phases). The collections shall continue for about three terminal drug half-lives in order to capture at least 80% of the total area. At least three to four samples shall be obtained from the terminal log-linear phase to derive an acceptable estimate of the terminal constant (λ_z) from linear regression. For long half-life drugs, a truncated AUC (e.g. up to 72 hours) is generally considered adequate.

Blood samples or the harvested plasma/serum are to be analyzed for the administered drug or metabolites by means of a validated analytical method.

V. REPRESENTATIVE WELL DESIGNED TRIALS

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VI. SUGGESTED READINGS

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