

INTERCHANGEABILITY OF MULTISOURCE PHARMACEUTICAL PRODUCT A REVIEW

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ABSTRACT

Multisource (generic) drug products may contain drug substances and drug products that meet compendial monograph standards of strength, quality, purity, and identity. Pharmaceutical equivalence per se does not ensure equivalent drug product performance as demonstrated by bioequivalence, nor does it ensure therapeutic equivalence. This Stimuli article examines pharmaceutical equivalence and suggests that multisource drug products that meet compendial monograph requirements may not be pharmaceutical equivalents and/or may not have the same drug product performance.

Key Words: Generic products, safety, bioequivalence & bioavailability.

INTRODUCTION

The guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products published by WHO¹ state that multisource products must satisfy the same standards of quality, safety and efficacy as those applicable to the corresponding innovator product. They recommend that quality attributes of a multisource product should be tested against the innovator product for which interchange is intended.

The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre- and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance.

Despite acceptance of the general objective, there is no agreement on the criteria for selecting a list of international comparator products, nor does a list of such products exist. The comparator product chosen is either the most widely used “leading” product on the market or the product that was first introduced in that market. For this reason, among others, significant differences may exist between the comparator products used in different countries.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the local authority. Regulatory authorities should

require the documentation of a multisource pharmaceutical product to meet the following:

- GMP;
- Quality control specifications; and
- Pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator’s (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of product, including – most evidently – parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of GMP and evidence of conformity with relevant Pharmacopoeial specifications. This guidance is generally applicable to orally administered multisource products, as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). For other classes of products, including many biologicals such as vaccines, animal sera and products derived from human blood and plasma, and products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are beyond the scope of this document, and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of *in vivo* bioequivalence studies include pharmacokinetic studies, Pharmacodynamic studies and comparative clinical trials. Direct practical demonstration of therapeutic equivalence in a clinical study usually requires large numbers of patients.

Such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons the science of bioequivalence testing has been developed over the last 40 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent/alternative and bioequivalent. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. In selected cases, *in vitro* comparison of dissolution profile of the multisource product with that of the comparator product, or dissolution studies, may be sufficient to provide indication of equivalence.

It should be noted that the concept of interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices like same molar amount of the same active pharmaceutical moiety(s) but in different dosage form (e.g., tablets vs capsules), and/or different chemical form (e.g. different salts or esters) may be acceptable provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights².

Pharmaceutically equivalent drug products are drug product that 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, and preservatives), expiration time, and, within certain limits, labeling.

Drug substances and drug products that solely meet the same compendial standard monograph standards should not be considered automatically as interchangeable products. The objective of this Stimuli article is to provide an understanding of interchangeability and substitutability of drug substances and drug products that meet compendial standards.

USP–NF would be an example denoting for ease of understanding compendial/ Pharmacopoeial methods or standard monograph.

LEGAL ASPECT

Multisource drug products that meet USP–NF monographs may not be pharmaceutical equivalents and/or may not have the same drug product performance. Designation of multisource drug products for interchangeability (substitution) generally is a matter of governmental (regulatory) approval. Regulatory approval for interchangeable multisource generic drug products is not identical in all countries. The US Food and Drug Administration (FDA) have very strict rules for the approval and marketing of generic drug products. These regulations must be considered during the development of both branded and generic drug products. Drug product performance also must be considered if any changes occur in the finished dosage form, including scale up, site changes, process changes, or other modifications that could have an effect on the drug product. Only multisource drug products that are pharmaceutical equivalents, bioequivalent, and therapeutic equivalents that have been approved by the appropriate regulatory agency (e.g., FDA), may be marketed as interchangeable. The WHO guideline should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights. The World Health Organization (WHO) states that “pharmaceutical equivalence does not necessarily imply bioequivalence and therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance”.³ However, amorphous and crystalline drug substances can be bioequivalent when manufactured in the same dosage form (e.g., oral tablet) if a manufacturer uses different excipients and manufacturing processes that produce bioequivalence *in vivo*.

DOCUMENTATION OF EQUIVALENCE FOR MARKETING AUTHORIZATION

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product in order to be considered interchangeable. Suitable test methods to assess equivalence are:

- (a) Comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that are reflective of the systemic exposure;

- (b) Comparative Pharmacodynamic studies in humans;
- (c) Comparative clinical trials; and
- (d) Comparative in vitro tests.

Applicability of each of these four modalities is discussed in subsequent sections of this article. Detailed information is provided to conduct an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the most often used methods to document equivalence for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any above mentioned tests methods in the documentation of equivalence between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active pharmaceutical ingredient and the pharmaceutical product. Where an active pharmaceutical ingredient produces meaningful concentrations in an accessible biological fluid such as plasma, comparative pharmacokinetic studies can be performed. Where appropriate in vitro testing and BCS based biowaivers for immediate release pharmaceutical products can assure equivalence between the multisource product and the comparator product, in vitro studies may be sufficient. Where an active pharmaceutical ingredient does not produce measurable concentrations in an accessible biological fluid, comparative Pharmacodynamic studies are a further alternative to document equivalence. Comparative clinical trials may also be used to document equivalence. In certain cases when it is not possible to determine the pharmacokinetic profile or to find suitable Pharmacodynamic endpoints, comparative clinical trials can be considered appropriate.

WHEN EQUIVALENCE STUDIES ARE NOT NECESSARY

The following types of multisource pharmaceutical products are considered to be equivalent without the need for further documentation:

- (a) When the pharmaceutical product is to be administered as an aqueous intravenous solution containing the same active pharmaceutical ingredient in the same molar concentration as the comparator product. Bioequivalence testing is also not required when pharmaceutically equivalent products are to be administered by other parenteral routes (e.g. intramuscular, subcutaneous);
- (b) When pharmaceutically equivalent products are solutions for oral use (including syrups, elixirs, tinctures or other soluble forms but not suspensions), contain the active pharmaceutical ingredient in the same molar concentration as comparator product, and

contain essentially the same excipients in comparable concentrations;

- (c) When pharmaceutically equivalent products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;
- (d) When pharmaceutically equivalent products are gases;
- (e) When pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations;
- (f) When pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations;
- (g) When pharmaceutically equivalent products are aqueous solutions for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device, and contain the same active pharmaceutical ingredient(s) in the same concentration and essentially the same excipients in comparable concentrations.

WHEN IN VIVO EQUIVALENCE STUDIES ARE NECESSARY AND TYPES OF STUDIES REQUIRED

Except for the cases illustrated in section A where, recommends that documentation of equivalence with the comparator product be requested by registration authorities for a multisource pharmaceutical product.

In vivo studies

For certain medicines and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic bioequivalence study, a comparative Pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence⁴.

In vitro studies

For certain medicines and dosage forms, in vitro documentation of equivalence may be appropriate.

BIOEQUIVALENCE STUDIES IN HUMANS

General considerations

Provisions for studies in humans

Pharmacokinetic studies, Pharmacodynamic studies and clinical studies are all clinical trials and should be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the WHO Guidelines for

Good Clinical Practice (GCP) for Trials on Pharmaceutical Products⁵.

Justification of human bioequivalence studies

Most pharmacokinetic and Pharmacodynamic bioequivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject. It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks/benefits of a particular human study be thoroughly considered and that the chosen solutions be scientifically sound and ethically justified.

Selection of investigators

Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study.

Study protocol

The bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor.

Study design

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Pharmacokinetic bioequivalence studies on products designed to deliver the active pharmaceutical ingredient for systemic exposure serve two purposes: (i) they serve as surrogate for clinical proof of equivalence; and (ii) they provide an in vivo measure of pharmaceutical quality.

A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for pharmacokinetic bioequivalence studies.

Alternative study designs in patients

For active pharmaceutical ingredients design for product which are unsafe at high dose that are very potent or too toxic to administer in the usual dose to healthy volunteers it is recommended that the study be conducted at a lower strength.

Design considerations for drugs with long elimination half-lives

A single dose cross-over pharmacokinetic bioequivalence study of an oral product of a long elimination half-life drug can be conducted provided an adequate wash-out period is used. If the cross-over study is problematic, a pharmacokinetic bioequivalence study with a parallel design can be used.

Design considerations for multiple dose studies

In certain situations multiple dose studies may be considered appropriate. Multiple dose studies in patients are most useful in cases where the medicine is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses.

Design considerations for modified release products

Modified release products include extended release products and delayed release products. Bioavailability data must be obtained for all modified-release products. A single dose, non-replicate cross-over, fasting study comparing the highest strength of the multisource and the comparator product should be performed.

Co-administration of food with oral pharmaceutical products may influence drug bioavailability and in certain cases also pharmacokinetic bioequivalence. In addition to physiological changes in the gastro-intestinal tract, food can affect the release of the active pharmaceutical ingredient from the formulation. A concern with modified release products is the possibility that food may trigger a sudden and abrupt release of the active pharmaceutical ingredient leading to "dose dumping". This would most likely be manifested as a spike in plasma concentration time profile. Therefore, a pharmacokinetic bioequivalence study under fed conditions is generally required for orally administered modified release pharmaceutical products.

Subjects

Number of subjects

The number of subjects required for a sound pharmacokinetic bioequivalence study is determined by:

- The error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- By the significance level desired (5%);
- By the power level desired;
- By the expected mean deviation from the reference product compatible with bioequivalence and with safety and efficacy;
- With 90% Confidence Interval around the geometric mean ratio to be within 80%-125% bioequivalence limits for log transformed data.

The number of subjects to be used in the study should be estimated by considering the standards that must be passed. It should be calculated by appropriate methods (see statistical analysis and acceptance criteria below). The number of recruited subjects should always be justified with the sample size calculation provided in the study protocol. A minimum of 12 subjects is required.

Drop-outs and withdrawals

Sponsors should enter a sufficient number of subjects in the study to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse drug reaction, personal reasons) must be reported.

Selection of subjects

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion/exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both genders, the sponsor may wish to include both, males and females in the study.

Monitoring the health of subjects during the study

During the study the health of volunteers should be monitored so that onset of side effects, toxicity, or any intercurrent disease may be recorded and appropriate measures taken.

Considerations for genetic phenotyping

Phenotyping for metabolizing activity can be of importance for studies with high clearance drugs that are metabolized by enzymes that are subject to genetic polymorphism, e.g. Propranolol.

Study standardization

Standardization of study conditions is important to minimize the magnitude of variability other than in the pharmaceutical products. Standardization should concern exercise, diet, fluid intake, posture, restriction of the intake of alcohol, caffeine, certain fruit juices, and concomitant medicines in the time period before and during the study.

Fed studies are also required in bioequivalence studies of modified release formulations. The objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. Drugs should be administered according to the dosing regimen, within 30 min. after the meal has been completed.

Investigational product

An investigational product is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. Test products must be manufactured under GMP regulations.

It is recommended that potency and in vitro dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to performance of an equivalence study. Content of the active pharmaceutical ingredient(s) of the comparator

product should be close to the label claim, and the difference between two products should preferably not be more than +/-5%.

Choice of comparator product

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in premarketing studies and post-marketing monitoring schemes. A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and to a lack of interchangeability with the innovator.

The selection of the comparator product is usually made at the national level by the drug regulatory authority. A national drug regulatory authority has in principle options which are listed in order of preference:

- To choose the innovator product, if this product has been granted a national marketing authorization, for which quality, safety and efficacy has been established ("national innovator"); or - to choose the WHO comparator product, all of which have been granted marketing authorization, for which quality, safety and efficacy have been established, and which have reference to a manufacturing site and which is to be purchased in that country as cited in the list; or

- To choose the innovator product, i.e. a product for which a marketing authorization has been granted in a well regulated (ICH or associated country) and which is to be purchased from that market or

- In the case an innovator product cannot be identified – or is no longer available - and no appropriate product is mentioned in the above referred WHO list, the choice of the comparator must be made carefully and must be justified comprehensively by the applicant. The most important selection criteria in order of preference are: - approval in ICH- and associated countries, - "pre-qualified" by WHO, - extensive documented use in clinical trials reported in peer-reviewed scientific journals, and - long and unproblematic post-market surveillance.

A product approved based on comparison with a non domestic comparator product may not be interchangeable with currently marketed domestic products.

In the context of regional harmonization efforts, there may be advantages to choose a list regional comparator products for which quality, safety and efficacy has been established, in order to increase access to medicines WHO has initiated a list of comparator products ("WHO comparator product") for equivalence assessment of

interchangeable multisource products which provides recommendations for choosing comparator product in cases where the innovator product is not available⁶.

Study conduct

Selection of dose

In bioequivalence studies the molar equivalent dose of multisource and comparator product should be used. Generally the marketed strength with the greatest sensitivity to bioequivalence assessment should be administered as a single unit.

In certain cases a study performed with a lower strength can be considered acceptable if a lower strength is chosen for reasons of safety. Alternatively the application of AUC truncated to 3 x median t_{max} of the comparator formulation would avoid problems of lack of assay sensitivity in many cases.

Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max} , AUC and other parameters. Sampling points should include a pre-dose sample, at least 1-2 points before C_{max} , 2 points around C_{max} and 3-4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. An alternative approach is to use the truncated AUC approach, which curtails the numbers of samples required to define the elimination phase and allows more samples to be devoted to the elucidation of C_{max} . The exact timing for sample collection depends on the nature of the active pharmaceutical ingredient and the input function from the administered dosage form.

Sample collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the active pharmaceutical ingredient. In most cases the API or metabolites are measured in serum or plasma. If the active pharmaceutical ingredient is excreted predominantly unchanged in the urine, urine can be sampled. When urine is collected at the study centre the volume of each sample must be measured immediately after collection and included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters.

However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the t_{max} and the maximum concentration. Blood samples should be processed and stored under conditions that have shown not to cause degradation of the analytes.

Parameters to be assessed

In bioavailability studies the shape of and the area under the plasma concentration versus time curves are mostly

used to assess extent (AUC) and rate (C_{max} , t_{max}) of absorption. Sampling points or periods should be chosen such that the concentration versus time profile is adequately defined to allow calculation of relevant parameters. For single dose studies the following parameters should be measured or calculated:

- Area under the plasma/serum/blood concentration-time curve from time zero to time t (AUC0-t), where t is the last time point with measurable concentration for individual formulation. The method of calculating AUC-values should be specified. In general AUC should be calculated using the linear/log trapezoidal integration method. The exclusive use of compartmental based parameters is not recommended.
- C_{max} is the maximum or peak concentration observed representing peak exposure of active pharmaceutical ingredient (or metabolite) in plasma, serum or whole blood. AUC0-t and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence.

When urine samples are used cumulative urinary recovery (A_e) and maximum urinary excretion rate are employed instead of AUC and C_{max} .

Studies of metabolites

General recommendations

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite.

Inactive pro-drugs

Also for inactive prodrug, demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured. However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound. In the context of this guideline, a parent compound can be considered to be an inactive pro-drug if it has no or very low contribution to clinical efficacy.

Use of metabolite data as surrogate for active parent compound

The use of a metabolite as a surrogate for an active parent compound is not encouraged. This can only be considered if the applicant can adequately justify that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also

the option of using a higher single dose in the bioequivalence study. Due to recent developments in bioanalytical methodology it is unusual that parent drug cannot be measured accurately and precisely. Hence, the use of a metabolite as a surrogate for active parent compound is expected to be accepted only in exceptional cases. When using metabolite data as a substitute for active parent drug concentrations, the applicant should present any available data supporting the view that the metabolite exposure will reflect parent drug and that the metabolite formation is not saturated at therapeutic doses⁷.

Measurement of individual enantiomers

A non-stereoselective assay is currently acceptable for most pharmacokinetic bioequivalence studies. When the enantiomers have very different pharmacological or metabolic profiles, assays that distinguish between the enantiomers of a chiral active pharmaceutical ingredient may be appropriate.

Use of fed state studies in bioequivalence determination

Immediate release formulations

Fasted state studies are generally preferred. When the product is known to cause gastrointestinal disturbances if given in the fasted state, or if labeling restricts to administration to the fed state only, then the fed state pharmacokinetic bioequivalence study becomes the preferred method. The details of the meal may depend on local diet and customs.

Modified release formulations

Food effect studies are necessary for all multisource modified release formulations to ensure the absence of "dose dumping". The latter signals a formulation failure such that the dose is released all at once rather than over an extended period of time. This results in a "spike" in plasma concentrations time profile. A high fat meal is recommended to provide maximum perturbation to challenge the robustness of release from the formulation with respect to prandial state.

Active pharmaceutical ingredients quantification

All analytical test methods used to determine the active compound and/or its biotransformation product in the biological fluid must be well-characterized, fully validated and documented. The objective of the validation is to demonstrate that a particular method used for quantitative measurement of analytes in a given biological matrix, such as blood, plasma, serum or urine, is reliable and reproducible for the intended use. Applicable principles of GLP should be followed in the conduct of chemical analysis⁸.

The Bioanalytical Method Validation Conference held in Arlington University at Texas USA in January 2000

made several recommendations for the conduct of analysis of biological samples in a pharmacokinetic study⁹. Some important recommendations are:

- Validation comprises before-study and within-study phases. During the pre-study phase stability of the stock solution and spiked samples in the biological matrix, specificity, sensitivity, accuracy, precision and reproducibility should be provided.
- Validation must cover the intended use of the assay.
- The calibration range must be appropriate to the study samples. A calibration curve should be prepared in the same biological matrix as the samples in the intended study by spiking the matrix with known concentrations of the analyte
- If an assay is to be used at different sites, it must be validated at each site, and cross-site comparability established.
- An assay which is not in regular use requires sufficient revalidation to show that its performance is according to the original validated test procedures. The revalidation study must be documented, usually as an appendix to the study report.
- Within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged.
- If different studies are to be compared and the samples from the different studies have been assayed by different methods, and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.
- Spiked quality control samples at a minimum of three different concentrations in duplicate should be used for accepting or rejecting the analytical run.
- All the samples for one subject (all periods) should be analysed in the same analytical run, if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol, and/or SOP. Any modification of the method during the analysis of study samples will require adequate revalidation. Results of study sample determination should be reported in the analytical report together with calibration and QC sample results, repeat analyses (if any), and a representative number of sample chromatograms.

Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence.

The statistical method for testing pharmacokinetic bioequivalence is based upon the determination of the 90% confidence interval around the ratio of the log transformed population means (multisource/ comparator) for the pharmacokinetic parameters under consideration

and by carrying out two one sided tests at the 5% level of significance¹⁰.

All concentration-dependent pharmacokinetic parameters (e.g. AUC and C_{max}) should be log transformed using either common logarithms to the base 10 or natural logarithms. The choice of common or natural logs should be consistent and should be stated in the study report. Logarithmically transformed concentration-dependent pharmacokinetic parameters should be analysed using ANOVA. Usually the ANOVA model includes the formulation, period, sequence or carry-over and subject factors.

Parametric (normal-theory) methods are recommended for the analysis of log-transformed bioequivalence measures. The general approach is to construct a 90% confidence interval for the quantity $\mu_T - \mu_R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is contained in the stated limits. Due to the nature of normal-theory confidence intervals this is equivalent to carrying out two one-sided tests of hypothesis at the 5% level of significance¹⁰⁻¹¹. The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products. The same procedure should be used for analyzing parameters from steady-state trials or cumulative urinary recovery, if required. Usually for t_{max} descriptive statistics should be given. If t_{max} is to be subjected to a statistical analysis this should be based on non-parametric methods and should be applied to untransformed data.

Methods for identifying and handling of possible outlier data should be specified in the protocol. As outliers may be indicative of product failure, post hoc deletion of outlier values is generally discouraged. An approach of dealing with data containing outliers is to apply distribution-free (nonparametric), statistical methods¹².

Acceptance ranges

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80-1.25. If the therapeutic range is particularly narrow the acceptance range may need to be reduced based on clinical justification.

C_{max} -ratio

In general acceptance limit 0.80-1.25 should be applied to the C_{max} -ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and in certain cases a wider acceptance range (e.g. 0.75-1.33) may be acceptable. In exceptional cases, a simple requirement for the point estimate to fall within a bioequivalence limit of 0.80-

1.25 may be acceptable with appropriate justification in terms of safety and efficacy.

t_{max} -difference

Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with Good Clinical Practice rules⁶. The respective ICH guideline¹³ can be used in the preparation of the study report.

All measured concentrations for each subject and the sampling time should be tabulated for each formulation. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Deletion of data should be justified.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject-formulation combination together with descriptive statistics.

Special considerations

Fixed combination products

If the pharmacokinetic bioequivalence of combination products is assessed by in vivo studies the study design should follow the same general principles as described in previous sections. In this study the multisource combination product should be compared with the pharmaceutically equivalent comparator combination product. In certain cases (e.g. when no comparator combination product is available on the market) separate products administered in free combination can be used as a comparator¹⁴.

Clinically important variations in bioavailability

Innovators should make all efforts to provide formulations with good bioavailability characteristics. A "high variable" pharmaceutical product is one in which the active pharmaceutical ingredient itself is not highly variable, but the formulation is one of poor pharmaceutical quality. If a better formulation is being developed over time by the innovator this should then serve as the comparator product.

Highly variable drugs

A "highly variable drug" has been defined as active pharmaceutical ingredient with a within-subject variability of $\geq 30\%$ in terms of the ANOVA-CV¹⁵. Moreover "highly variable drugs" are generally safe drugs with shallow dose-response curves. Proving the bioequivalence of drug products containing "highly

variable drugs" is problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. The following approaches to this problem are currently being applied in different drug regulatory jurisdictions:

(i) Some regulatory authority permit the use of broadened bioequivalence limits provided there is adequate justification¹⁶, for example, the regulatory agency could broaden the bioequivalence limits from 0.8-1.25 to 0.75-1.33 taking into consideration the therapeutic category of the drug;

(ii) Some regulatory authorities permit the use of scaling to broaden the bioequivalence limits. In a two-period design, the limits are scaled to the residual standard deviation, or in a replicate design, to the within-subject standard deviation of the comparator formulation¹⁷⁻¹⁹;

(iii) Some regulatory authority allow the following acceptance criteria: "Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic AUC and C_{max} between test and reference products is within the acceptable range of $\log(0.8) - \log(1.25)$ "²⁰;

(iv) Some do not allow for any adjustments²¹.

Application of truncated AUC in bioequivalence determination

In bioavailability studies it is generally recommended that plasma concentrations should be followed for at least three half-lives post-dose. Potent drugs found in plasma at low concentrations usually require sophisticated and expensive equipment to be able to measure the active pharmaceutical ingredient in the terminal portions of the plasma concentration versus time curve. On the other hand the disposition phase does not illustrate formulation differences between the multisource product and comparator product in bioequivalence decision-making process^{22 & 23}.

The evidence suggests that for immediate release formulations it is unnecessary to take blood samples beyond 4 times t_{max} ²⁴. There are two important advantages to the use of truncated areas: (i) more blood samples can be clustered around t_{max} to give greater precision in the estimation of both t_{max} and C_{max} ; and (ii) the lack of need for high assay sensitivity in order to define the disposition phase. The applicability of the truncated AUC approach merits particular consideration in the following cases: (i) where low concentrations occur in the terminal portion of the plasma concentration versus time curve, which may not be quantifiable by means of an adequately validated, sensitive analytical method; and (ii) for products of active pharmaceutical ingredients with long half-lives.

CONCLUSION

The interchangeability of multisource generic drug products is a major concern for physicians, pharmacists, and others, who prescribe, dispense, purchase, or pay /reimburse for drugs. Because the formulation and method of manufacture of the drug product can affect its bioavailability and stability, the multisource generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the reference listed drug. Pharmaceutical equivalence of drug substances and drug products is determined by the relevant regulatory agencies who review the manufacturer's submission that contains experimental evidence that the drug substances meet quality standards and perform similarly as measured by bioequivalence or other tests.

DISCLAIMER

The authors do not claim anything; the purpose of this review article solely educational. The requirements mentioned in the article are general requirements and should not be considered as guidelines. Referring and abiding to WHO, USFDA or respective country guidelines for submission of product registration is highly recommended.

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Decision-tree for use in identifying a comparator pharmaceutical product

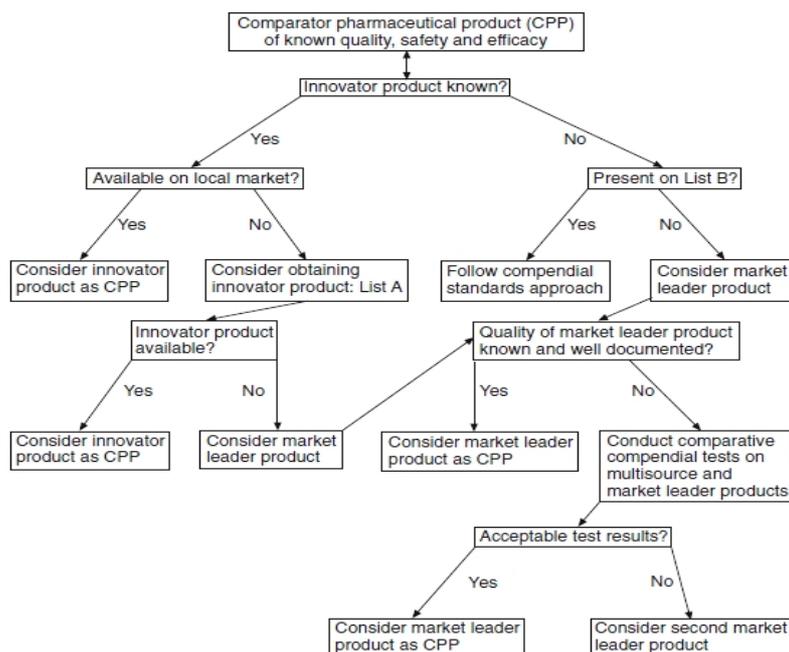


Figure: - 1 Decision tree for use in identifying a comparator product
Decision-tree for use in identifying a Comparator Pharmaceutical Product (CPP)