National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

NAFDAC Guideline on Registration Requirements to Establish Interchangeability of Generic Pharmaceutical Products

1. INTRODUCTION

This guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the generic product without compromising the safety, quality and efficacy of the pharmaceutical product. This document is an adaptation of the WHO guidelines on registration requirements to establish interchangeability (Technical Report Series 1003, Annex 6)[1].

Generic 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 generic product is therapeutically equivalent and interchangeable with the comparator product.

This guidance is generally applicable to orally administered generic products as well as to certain non-orally administered pharmaceutical products (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products).

For other classes of product, including many biologicals and products manufacture by biotechnology, as well as non-biological complex products, the concept of interchangeability raises issues that are beyond the scope of this document.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification.

These guidelines should be interpreted and applied without prejudice to obligations incurred through the existing international Agreement on Trade-Related Aspects of Intellectual Property Rights[2] and the laws governing intellectual property rights in Nigeria [3,4].

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2. GLOSSARY

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

Bioavailability:

The rate and extent to which the API or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation.

Bioequivalence:

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bio-availabilities, in terms of rate (C_{max} and t_{max}) and extent of absorption (area under the curve [AUC]), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Biological pharmaceutical product:

Substances which cannot be fully characterized by physicochemical means alone and which therefore require the use of some form of bioassay.

Biopharmaceutics Classification System:

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying APIs based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the BCS takes into account the major factors that govern the rate and extent of API absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

Biowaiver:

The term biowaiver is applied to a regulatory pharmaceutical product approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

Comparator product:

The comparator product is a pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Dosage form:

The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

Equivalence requirements:

In vivo and/or in vitro testing requirements for approval of a generic pharmaceutical product for a marketing authorization.

Equivalence test:

A test that determines the equivalence between the generic product and the comparator product using in vivo and/or in vitro approaches.

Fixed-dose combination:

A combination of two or more APIs in a fixed ratio of doses. This term is used generically to mean a particular combination of APIs irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product (FPP).

Fixed-dose combination finished pharmaceutical product:

An FPP that contains two or more APIs.

Generic product:

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Generic pharmaceutical products that are therapeutically equivalent are interchangeable.

Innovator pharmaceutical product:

Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

Interchangeable pharmaceutical product:

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

In vitro equivalence dissolution test:

An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the generic product and the comparator product, typically in at least three media: pH 1.2, pH 4.5 and pH 6.8 buffer solutions.

In vitro quality control dissolution test:

A dissolution test procedure identified in the pharmacopoeia for routine QC of product batches, generally a one time-point dissolution test for immediate release products and a three or more time-points dissolution test for modified release products.

Multisource pharmaceutical products:

See Generic Products.

Non-biological:

Not involving or derived from biology or living organisms.

Pharmaceutical alternatives:

Products are pharmaceutical alternative(s) if they contain the same active pharmaceutical moiety or moieties but differ in dosage form (e.g. tablets versus capsules), strength, and/or chemical form (e.g. different salts or different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

Pharmaceutical equivalence:

Products are pharmaceutical equivalents if they contain the same molar amount of the same APIs in the same dosage form, if they meet comparable standards and if they are intended to be administered by the same route.

Quantitatively similar amounts (concentrations) of excipients:

The relative amount of excipient present in two solid oral FPPs is considered to be quantitatively similar if the differences in amount fall within the limits shown in the table below:

Excipient type	**Percentage difference (w/w) out of total product (core) weight**
Filler	5.0
Disintegrant	
Starch	3.0
Other	1.0

Binder	0.5
Lubricant	
Calcium or magnesium stearate	0.25
Other	1.0
Glidant	
Talc	1.0
Other	0.1

If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant) then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). The relative concentration of an excipient present in two aqueous solution FPPs is considered to be similar if the difference is ≤ 10%.

Therapeutic equivalence: Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and, after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

3. WHEN EQUIVALENCE STUDIES ARE NOT NECESSARY

In the following circumstances, generic pharmaceutical products are considered to be equivalent without the need for further documentation:

(a) when the pharmaceutical product is to be administered parenterally as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product;

(b) when pharmaceutically equivalent products are solutions for oral use (e.g. syrups, elixirs and tinctures), optic or ophthalmic products contain the API in the same molar concentration as the comparator product, contain the same functional excipients in similar concentrations (if the API is BCS Class I) and the same excipients in similar concentrations (for APIs from other BCS classes);

(c) when pharmaceutically equivalent products are in the form of powders for reconstitution as an aqueous solution and the resultant solution meets either criterion (a) or criterion (b) above;

(d) when pharmaceutically equivalent products are gases;

(e) when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations;

(f) when pharmaceutically equivalent products are aqueous solutions for nebulization or nasal drops, intended to be administered with essentially the same device, contain the same API(s) in the same concentration and contain the same excipients in similar concentrations.

4. WHEN EQUIVALENCE STUDIES ARE NECESSARY

Except for the cases discussed in section 3, these guidelines recommend that documentation of equivalence with the comparator product be required by registration authorities for a generic pharmaceutical product [5]. Studies must be carried out using the product intended for marketing.

5. IN VIVO EQUIVALENCE STUDIES IN HUMANS

5.1 General Consideration

5.1.1 Provisions for studies in humans

Pharmacokinetic trials are clinical studies and should therefore be carried out in accordance with the provision and prerequisites for a clinical study, as outlined in the NAFDAC Guidelines for good clinical practice for trials on pharmaceutical products[6] and with NAFDAC good laboratory practices[7]. Additional guidance for organisations performing in vivo equivalence studies is available from WHO [8].

5.1.2 Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent.

The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed on and signed by the investigator and sponsor and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol, attachments and appendices should be scientifically and ethically appraised by an appropriately constituted ethics committee.

For studies to be conducted in Nigeria, the signed and dated study protocol should be approved by NAFDAC before commencing the study.

The study report should be submitted using the **NAFDAC BTIF format** which can be gotten from NAFDAC website.

6. PHARMACOKINETIC COMPARATIVE BIOAVAILABILITY (BIOEQUIVA LENCE) STUDIES IN HUMANS

6.1 Design of pharmacokinetic studies

In general, for a bioequivalence study involving a generic product and a comparator product, a randomized, two-period, two-sequence, single-dose, cross-over study conducted with healthy volunteers is the preferred study design.

In this design each subject is given the generic product and the comparator product in randomized order. An adequate wash-out period should follow the administration of each product.

It should be noted, however, that under certain circumstances an alternative, well-established and statistically appropriate study design may be more suitable.

6.1.1 Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers, it is recommended that the study be conducted using the API at a lower strength in healthy volunteers.

For APIs that show unacceptable pharmacological effects in healthy volunteers, even at lower strengths, a study conducted in patients may be required.

6.1.2 Considerations for active pharmaceutical ingredients with long elimination half-lives

Ideally the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured.

If the cross-over study is problematic owing to a very long elimination half-life, a bioequivalence study with a parallel design may be more appropriate. A parallel design may also be necessary when comparing some depot formulations.

For both cross-over and parallel design studies of oral products, sample collection time should be adequate to ensure completion of gastrointestinal (GI) transit of the pharmaceutical product and absorption of the API.

Blood sampling should be conducted for up to 72 hours following administration. Sampling beyond this time is not generally necessary for immediate-release products.

6.1.3 Considerations for multiple-dose studies

Multiple dose studies in patients are most useful in cases where the API being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses. In this case, the study is performed without interrupting therapy even for a cross-over study.

The dosage regimen used in multiple dose studies should follow the usual dosage recommendations.

Other situations in which multiple dose studies may be appropriate are as follows:

- cases where the analytical sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
- for extended-release dosage forms with a tendency to accumulate (in addition to single-dose studies).
- In steady-state studies, the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least five times the terminal half- life).
- Appropriate dosage administration and sampling should be carried out to document the attainment of a steady state.

6.2 Subjects

6.2.1 Number of subjects

The number of subjects required for a 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;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval around the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

The number of subjects recruited should always be justified by the sample size calculation provided in the study protocol.

A minimum of 12 subjects is required.

In some situations, reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed as an alternative to conducting a pilot study.

In order to use a two-stage design, adjustments must be made to protect the overall Type 1 error rate and maintain it at 5%.

The proposed statistical plan must be clearly defined in the study protocol, including the adjusted significance level that is to be employed during each analysis.

6.2.2 Drop-outs and withdrawals

Sponsors should select a sufficient number of study subjects 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 reaction or personal reasons) must be reported.

If a subject is withdrawn due to an adverse event after receiving at least one dose of the study medication the subject's plasma/serum concentration data should be provided.

The concentration–time profiles of subjects who exhibit pre-dose concentrations higher than 5% of the corresponding C_{max} should be excluded from the statistical analysis.

The concentration–time profiles of subjects who exhibit pre-dose concentrations equal to or less than 5% of the corresponding C_{max} should be included in the statistical analysis without correction.

6.2.3 Exclusion of subject data

Potential reasons for excluding subject data and the procedure to be followed should be included in the study protocol.

Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable. Retesting of subjects is not recommended

6.2.4 Selection of subjects

Clear criteria for inclusion and exclusion should be stated in the study protocol.

The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study.

Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study.

Generally subjects should be between the ages of 18 and 55 years and their weight should be within the normal range with a body mass index between 18 and 30 kg/m2.

The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history and a physical examination. If necessary, special medical investigations may be carried out before and during studies, depending on the pharmacology of the individual API being investigated.

The ability of the volunteers to understand and comply with the study protocol has to be assessed.

Subjects who are being or have previously been treated for any GI problems or convulsive, depressive or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If a parallel design study is planned, standardization of the two groups of subjects is important in order to minimize variation not attributable to the investigational products. Special considerations for genetic phenotyping should be done for products with phenotype-linked metabolism.

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

6.2.5 Monitoring the health of subjects during the study

In keeping with GCP [6] the health of volunteers should be monitored during the study so that the onset of side-effects, toxicity or any intercurrent disease may be recorded and appropriate measures taken.

The incidence, severity, seriousness and duration of any adverse event observed during the study must be reported.

The probability that an adverse event is due to the FPP should be judged by the investigator.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

6.3 Investigational product

6.3.1 Generic pharmaceutical product

The generic pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product.

Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs.

Test products must be manufactured under GMP regulations.

Batch control results, lot number, manufacturing date and, if possible, expiry date for the generic product should be stated.

Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and

are produced with the same formulation and similar equipment and process to that planned for commercial production batches.

A bio batch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding that future scale-up for production batches will not be accepted unless supported by in vitro and/or in vivo data as applicable.

6.3.2 Choice of comparator product

The innovator pharmaceutical product sourced from an SRA region is the choice comparator product for a generic pharmaceutical product. Innovator product may also be sourced from a secured supply chain within the country (preferably the product should be sourced directly from the Marketing Authorisation Holder within the country). In the case that no innovator product can be identified, you may wish to refer to the WHO guidance for the selection of comparator pharmaceutical products for equivalence assessment of interchangeable generic products [9] for further guide on the alternative comparator product to use. NAFDAC will make final determination of the suitability of comparator product. It is advised that the Agency be consulted for the choice of comparator for yet to be conducted bioequivalence study.

It is recommended that potency and in vitro dissolution characteristics of the generic and the comparator pharmaceutical products be ascertained prior to the performance of an equivalence study.

Content of the API(s) of the comparator product should be close to the label claim and the difference between two products being compared should not be more than ± 5%.

If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within ± 5%, potency correction may be required on the statistical results from the bioequivalence study.

6.4 Study Conduct

6.4.1 Selection of strength

In bioequivalence studies the molar equivalent dose of generic and comparator product must be used.

For a series of strengths that can be considered proportionally formulated (see section 7.3) the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength.

A higher dose, i.e. more than one dosage unit, may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximal daily dose of the dosage regimen.

In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety or if the API is highly soluble and its pharmacokinetics are linear over the therapeutic range.

6.4.1.1 Non-linear pharmacokinetics

When the API in a series of strengths, which are considered proportionally formulated, exhibits non-linear pharmacokinetics over the range of strengths, special consideration is necessary when selecting the strength for study.

For APIs exhibiting non-linear pharmacokinetics within the range of strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest marketed strength.

For APIs with non-linear pharmacokinetics within the range of strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the bioequivalence study should be conducted on at least the lowest strength (or a strength in the linear range).

For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength.

6.4.2 Study standardization

Standardization should cover exercise, diet, fluid intake and posture, as well as the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified period before and during the study.

6.4.3 Co-administration of food and fluid with the dose

FPPs are usually given after an overnight fast of at least 10 hours and participants are allowed free access to water.

On the morning of the study no water is allowed during the hour prior to FPP administration. The dose should be taken with a standard volume of water (usually 150 – 250mL).

Two hours after FPP administration, water is again permitted as often as desired.

A standard meal is usually provided four hours after FPP administration. All meals should be standardized and the composition stated in the study protocol and report.

There are situations when the investigational products should be administered following consumption of a meal (under fed conditions). These situations are described below.

6.4.3.1 Immediate-release formulations

Fasted state studies are generally preferred. However, when the product is known to cause GI disturbances if given to subjects in the fasted state, or if the labelling of the comparator product restricts administration to subjects in the fed state, then a fed-state study becomes the preferred approach.

For products with specific formulation characteristics (e.g. micro emulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required, unless the product is only taken in a fasted or fed state.

Typically a meal meeting the composition recommendations identified in section 6.4.3.2 should be employed in fed state studies. The exact composition of the meal may depend on local diet and customs in the region where study is being conducted.

The test meal should be consumed beginning 30 minutes prior to administration of the FPP.

6.4.3.2 Modified-release formulations

In addition to a study conducted under fasted conditions, food effect studies are necessary for all generic, modified-release formulations to ensure that the interaction between the varying conditions in the GI tract and the product formulations does not differentially impact the performance of the generic and comparator products.

The subject should start eating the meal 30 minutes before the FPP is administered and complete eating the meal prior to FPP administration.

6.4.4 Wash-out interval

The wash-out period should be the same for all subjects and should normally be more than five times the median terminal half-life of the API.

Consideration should be given to extending this period in some situations, e.g. if active metabolites with longer half-lives are produced or if the elimination rate of the API has high variability between subjects.

Just prior to administration of the treatment during the second study period, blood samples should be collected and assayed to determine the concentration of the API or metabolites.

The minimum wash-out period should be at least seven days unless a shorter period is justified by a short half-life.

The adequacy of the wash-out period can be estimated from the pre- dose concentrations of the API in the second study period and should be less than 5% of the observed C_{max}.

6.4.5 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.

For most APIs the number of samples necessary will be higher to compensate for between- subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the $AUC_{0-\infty}$ can be accrued but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.

6.4.6 Sample fluids and their collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the API.

In most cases the API or its metabolites are measured in serum or plasma.

If it is not possible to measure the API in blood, plasma or serum, the API is excreted unchanged in the urine and there is a proportional relationship between plasma and urine concentrations; urine can be sampled for the purpose of estimating exposure.

Blood, plasma, serum and urine samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes.

Details of these conditions should be included in the analytical validation report (see section 7.5).

The sample collection methodology must be specified in the study protocol.

6.4.7 Parameters to be assessed

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate (C_{max}, t_{max}) and extent (AUC) of exposure.

For single-dose studies, the following parameters should be measured or calculated:

- area under the plasma, serum or blood concentration–time curve from time zero to time t (AUC_{0-t}), where t is the last sampling time- point with a measurable concentration of the API in the individual formulation tested. The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies;
- C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

AUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition it is recommended that the following parameters be estimated:

- area under the plasma, serum or blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last}/K_e$; C_{last} is the last measurable analyte concentration and Ke is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the FPP at which C_{max} is observed

For additional information the elimination parameters can be calculated:

- $t_{1/2}$ is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUC_T is AUC over one dosing interval (τ) at steady state;
- C_{max} ;
- C_{min} (C_{tau}) is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage difference between C_{max} and C_{min}

As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and a modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

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

6.4.8 Studies of metabolites

Generally evaluation of bioequivalence will be based on the measured concentrations of the API released from the dosage form rather than the metabolite.

In rare cases it may be necessary to measure concentrations of a primary active metabolite rather than those of the API if concentrations of the API are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to decide beforehand and state in the study protocol, which chemical entities (API or metabolite) will be analysed in the samples and to identify the analyte whose data will be used to assess bioequivalence.

When measuring active metabolites, wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

6.4.9 Measurement of individual enantiomers

A non-stereoselective assay is acceptable for most bioequivalence studies. A stereospecific assay measuring the individual enantiomers should be employed when the enantiomers exhibit different pharmacokinetic properties, different pharmacodynamic properties and the exposure of the enantiomers, as estimated by their AUC ratio or C_{max} ratio, changes when there is a change in the rate of absorption.

6.5 Quantification of active pharmaceutical ingredient

For the measurement of concentrations of the active compound and/or metabolites in biological matrices, such as serum, plasma, blood and urine, the applied bioanalytical method should be well characterized, fully validated and documented to a satisfactory standard in order to yield reliable results.

The validation of bioanalytical methods and the analysis of subject samples for clinical trials in humans should be performed following the principles of good clinical practice (GCP), good laboratory practice (GLP) and the most up-to-date guidelines from stringent regulatory authorities (SRAs) on the topic of bioanalytical method validation (e.g. EMA Guideline on bioanalytical method validation).

State-of-the-art principles and procedures for bioanalytical method validation and analysis of study samples should be employed. The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are:

- Selectivity
- lower limit of quantification;
- the response function and calibration range (calibration curve performance);
- accuracy;
- precision;
- matrix effects;
- stability of the analyte(s) in the biological matrix;
- stability of the analyte(s) and of the internal standard in the stock and working solutions, and in extracts throughout the entire period of storage and processing conditions.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).

The results of subject sample determination should be given in the analytical report together with calibration and QC sample results, repeat analyses, reinjections and reintegrations (if any) and a representative number of sample chromatograms.

6.6 Statistical analysis

Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the generic product and the comparator product is unlikely.

The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval around the ratio of the log- transformed population means (generic/comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance[10].

To establish bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit.

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 either 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 analysis of variance (ANOVA).

Normally the ANOVA model should include formulation, period, sequence and subject factors.

Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery if required.

For t_{max} descriptive statistics should be given.

Where t_{max} is considered clinically relevant, median and range of tmax should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary.

However, 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.

6.7 Acceptance ranges

AUC_{0-t} – ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80.00–125.00%. If the API is determined to possess a narrow therapeutic index (NTI) the bioequivalence acceptance range should be restricted to 90.00–111.11%.

The same criterion applies to the parameter AUC_T in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

C_{max} - ratio

For maximal concentration data, the acceptance limit of 80.00–125.00% should be applied to the 90% confidence interval for the mean C_{max} ratio.

If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate.

The same criterion applies to the parameters C_{max} and C_{tau} in multiple-dose studies.

t_{max} - difference

Statistical evaluation of tmax makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects.

In such a case, comparison of the median and range data for each product should be undertaken.

6.8 . Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with GCP and GLP rules.

Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given.

Results of in vitro dissolution tests conducted in media with pHs of 1.2, 4.5 and 6.8 and the QC media, if different, should be provided.

In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

The bioanalytical validation report should be attached. This report should include the information recommended in the SRA guidance chosen as a guide for the bioanalytical portion of a study (see section 6.5).

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

The report should be done using the **NAFDAC BTIF template**.

6.9 Special considerations

6.9.1 Fixed-dose combination products

If the bioequivalence of FDC products is assessed by in vivo studies, the study design should follow the same general principles as described in previous sections.

The generic FDC product should be compared with the pharmaceutically equivalent comparator FDC product.

In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator [11].

The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes.

6.9.2 Clinically important variations in bioavailability

A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition.

6.9.3 "Highly variable active pharmaceutical ingredients"

A "highly variable API" has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA CV [12 – 15].

Large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.

For highly variable FPPs it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated cross-over bioequivalence study be conducted and reference-scaled average bioequivalence be employed to widen the acceptance interval for the Cmax parameter, if the intrasubject variability for C_{max} following replicate administrations of the comparator product is > 30%.

If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84–143.19%.

The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for C_{max} is defined based upon the intrasubject variability seen in the bioequivalence study using scaled average bioequivalence according to $[U, L] = \exp[\pm k \cdot sWR]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and

sWR is the intrasubject standard deviation of the log-transformed values of C_{max} of the reference product.

The geometric mean ratio (GMR) for C_{max} should lie within the conventional acceptance range of 80.00–125.00%.

The standard bioequivalence acceptance criterion for AUC should be maintained without scaling.

If the intrasubject variability for C_{max}, following replicate administration of the comparator, is found to be < 30%, standard bioequivalence acceptance criteria should be applied to both AUC and C_{max} without scaling.

For multiple-dose studies, a similar approach can be applied to the following parameters if the intrasubject variability for the parameter is found to be > 30%: C_{max}, C_{tau} and partial AUCs if required.

The standard bioequivalence acceptance criterion will apply to AUC_T without scaling.

The approach to be employed should be clearly defined prospectively in the study protocol.

7. IN VITRO EQUIVALENCE TESTING

7.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System

7.1.1 Biopharmaceutics Classification System

The BCS is based on aqueous solubility and intestinal permeability of the API. It classifies the API into one of four classes [16]:

- Class 1: high solubility, high permeability;
- Class 2: low solubility, high permeability;
- Class 3: high solubility, low permeability;
- Class 4: low solubility, low permeability.

On the basis of solubility and permeability of the API, excipient nature, excipient content and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive in vivo bioequivalence testing for certain categories of immediate release FPPs.

Oral FPPs containing an API possessing a narrow therapeutic index are not eligible for a so-called biowaiver based on the BCS approach.

7.1.1.1 High solubility

An API is considered highly soluble when the highest single therapeutic dose as defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8.

The pH solubility profile of the API should be determined at 37 ± 1 °C in aqueous media.

A minimum of three replicate determinations of solubility at each pH condition is recommended.

7.1.1.2 High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose [17].

Absolute bioavailability or mass balance study data obtained from published literature may be accepted as evidence if it can be clearly established that the data were derived from appropriately designed studies.

7.1.2 Determination of dissolution characteristics of generic products in consideration of a biowaiver based on the Biopharmaceutics Classification System

For exemption from an in vivo bioequivalence study, an immediate release, generic product should exhibit very rapid or rapid in vitro dissolution characteristics (BCS Class I and III), depending on the BCS properties of the API.

In vitro data should also demonstrate the similarity of dissolution profiles between the generic and comparator products.

Dissolution data obtained from published literature may be accepted as evidence if it can be clearly established that the data were derived from appropriately designed studies.

7.1.2.1 Very rapidly dissolving

A generic product is considered to be very rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 15 minutes at 37 ± 1 °C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Pharmacopoeia buffers (e.g. Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatine (e.g. capsules or caplets) due to the possibility of cross-linking.

7.1.2.2 Rapidly dissolving

A generic product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 30 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer

- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatine (e.g. capsules or caplets) due to the possibility of cross-linking.

7.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

A biowaiver based on BCS considers:

(a) the solubility and intestinal permeability of the API
(b) the similarity of the dissolution profiles of the generic and comparator products in pH 1.2, 4.5 and 6.8 media
(c) the excipients used in the formulation
(d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of and clinical indications for the API

Assessment of excipients

In all cases, well established excipients in usual amounts should be used in generic products.

Excipients that might affect the bioavailability of the API, e.g. mannitol, sorbitol or surfactants, should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

For bio waivers for products containing Class 1 APIs there is some flexibility in the excipients employed, with the exception of critical excipients as discussed above.

For bio waivers for products containing Class 3 APIs all excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator product [18].

7.3 In vitro equivalence testing based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a generic product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

7.3.1 Proportional formulations

For the purpose of this guidance proportional formulations can be defined in two ways, based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths. For immediate release products, coating components, capsule shell, colour agents and flavours are not generally required to meet this requirement.

(ii) For an FPP, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit or not more than 5% of the weight of the dosage form), the total weight of the dosage form remains similar and the amounts of different excipients are the same for all strengths.

7.3.2 Qualification for bio waivers based on dose-proportionality of formulations

7.3.2.1 Immediate-release tablets

A biowaiver based on dose proportionality of formulations for a series of strengths of a generic product, when the pharmaceutical products are manufactured with the same manufacturing process, may be granted when:

(i) an in vivo equivalence study has been performed on at least one of the strengths of the formulation. The strength studied will usually be the highest strength, unless a lower strength is chosen for reasons of safety or the API is highly soluble and displays linear pharmacokinetics)

(ii) all strengths are proportionally similar in formulation to that of the strength studied

(iii) the dissolution profiles for the different strengths are similar at pH 1.2, 4.5, 6.8 and for the QC media, unless justified by the absence of sink conditions. If the different strengths of the test product do not show similar dissolution profiles owing to the absence of sink conditions in any of the above media, this should be substantiated by showing similar dissolution profiles when testing the same dose per vessel (e.g. two tablets of 5 mg versus one tablet of 10 mg) or by showing the same behaviour in the comparator product.

If both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in section 7.2, the profile comparison with an f_2 test is unnecessary.

In the case where an immediate release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.

If approval of one strength of a product is based on a BCS based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS based bio waivers as opposed to a biowaiver based on dose-proportionality.

7.3.2.2 Delayed-release tablets and capsules

For delayed release tablets, for a series of strengths of a generic product where the strengths are proportionally similar in formulation to that of the strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the recommended test condition for delayed release product, e.g. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro resistant coating with respect to the surface area (not to core weight) to have the same gastro resistance (mg/cm^2).

7.3.2.3 Extended-release tablets and capsules

(a) For extended-release tablets, when there is a series of strengths of a generic product that are proportionally similar in their active and inactive ingredients and have the same API release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if they exhibit similar dissolution profiles to the highest strength, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the QC media by the recommended test method.

(b) For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

(c) For extended-release, beaded capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, a dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

7.4 Reporting of biowaiver request

There is a separate reporting format for biowaiver request. For Biopharmaceutics Classification System (BCS) based biowaiver request, use the **Biowaiver Application Form: BCS**. For Additional Strength based biowaiver request, use the **Biowaiver Application Form: Additional Strength**.

Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two finished pharmaceutical product (FPPs) (e.g. test and comparator or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, and 15, 20, 30, 45 and 60 minutes for an immediate-release dosage form). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs the time-points should be set to cover the entire duration of expected release, e.g. in addition to earlier time points: samples at 1, 2, 3, 5 and 8 hours should be collected for a 12-hour release and additional test intervals would be necessary for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. Ph. Int. buffers are recommended; other pharmacopoeia buffers with the same pH and buffer capacity are also acceptable. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes the profiles are considered similar (no calculations required). Otherwise:

- similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2)

$$f_2 = 50 \log \left\{ \left[1 + {}^1/_n \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

  where Rt and Tt are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point.

  An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar;
- a maximum of one time point should be considered after 85% dissolution of the reference (comparator) product has been reached;
- in the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for determination of each profile.
- mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data the percentage coefficient of variation at time-points up to 10 minutes should be not more than 20% and at other time-points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;

- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 2

Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the biopharmaceutics classification system

Introduction

The BCS was proposed in 1995 by Amidon et al. [16]. It is a scientific framework that divides active pharmaceutical ingredients (APIs) into four groups according to their solubility and permeability. The recommended method for determination of the solubility is described below. Please refer to the Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability for further explanation of BCS classification and qualification of multisource products for a biowaiver based on the BCS [19].

This text was drafted based on the Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms [20], the Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability [19] and the Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system [21].

Recommendations for conducting experiments for assessing solubility of APIs

Prior to the experiment, a solubility study protocol should be prepared describing the equipment and procedures in detail. The protocol should include, for example, methods of sample preparation, experimental conditions such as temperature, method and rate of agitation, method of solid/solution separation of the API, and method of sample analysis. The source and purity of the API to be used in the study should also be recorded in the protocol, as well as the methods that will be used to characterize the material.

Characterization of the solid API should be completed prior to the investigation. The depth of the characterization will depend on the existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is needed. In some cases, it may be necessary to characterize the solid starting material as well as the solid residue remaining after equilibrium has been reached and sampling has been completed. For a discussion of the factors that should be considered when planning the solid-state characterization studies, see Avdeef et al. [22].

Solubility experiments should preferably be carried out with the shake flask method, which is used to determine equilibrium solubility, although other methods are possible if justified. A discussion of the factors that should be considered when designing the study can be found in Avdeef et al. [22]. The conditions employed should be fully described in the study protocol.

The pH-solubility profile of the API should be determined over the pH range of 1.2–6.8 at 37 ± 1 °C. Measurements should be made in triplicate under at least three pH conditions, pH 1.2, 4.5 and 6.8, as

well as at the pH of any known solubility minima in aqueous media within that pH range. Pharmacopoeia buffer solutions are recommended for use in solubility experiments (see, e.g. chapter 5.5 Dissolution test for solid oral dosage forms in The International Pharmacopoeia [23]). Factors such as common ion effects and ionic strength should be considered when selecting buffers for the study. The pH should be verified after addition of the API and at the end of the experiment with a calibrated pH meter. Samples should be taken at several time-points to ensure that the equilibrium solubility has been reached. Strong agitation followed by a period of sedimentation is suggested, to achieve solubility equilibrium.

A description of the method(s) of solid/solution separation employed, including details such as filter type and pore size or centrifugation speed, should be provided in the study protocol. Sedimentation, centrifugation and filtration are the standard methods of separation. The factors described by Avdeef et al. [22] should be considered when selecting the most appropriate approach for the API under study.

A validated, stability-indicating analytical method should be employed for determination of the solubility of APIs, e.g. high-performance liquid chromatographic analysis (see chapter 1.14.4 High-performance liquid chromatography in The International Pharmacopoeia [23]) or an alternative, validated stability-indicating assay.

A study report should be created after the experiment detailing the actual experimental conditions, results (raw data plus mean values with standard deviations), and any observations, for example, the degradation of an API as a result of pH or buffer composition. The section describing the experimental conditions should include initial and equilibrium pH of solutions and de facto buffer concentrations. If applicable, filter adsorption studies should be documented. Any deviations from the protocol should be noted and justified.

The dose/solubility ratio is calculated as follows: highest single therapeutic dose (mg) divided by solubility (mg/mL). An API is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8, i.e. the dose/solubility ratio is ≤ 250[19].

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Abbreviation

Ae:	Cumulative urinary recovery
ANOVA:	Analysis of variance
API:	Active Pharmaceutical Ingredient
AUC:	Area under the Curve
BCS:	Biopharmaceutics Classification System
BTIF:	Bioequivalence Trial Information Form
C_{last}:	last quantifiable concentration
C_{max}:	maximum concentration
C_{tau}:	last quantifiable concentration at steady state
CV:	Coefficient of Variation
EMA:	European Medicines Agency
FDA:	United States Food and Drug Administration
FDC:	Fixed Dose Combination
FPP:	Finished Pharmaceutical Product
GCP:	Good Clinical Practice
GI:	gastrointestinal
GLP:	Good Laboratory Practice
GMP:	Good Manufacturing Practice
GMR:	Geometric Mean Ratio
Ke:	elimination rate constant
NAFDAC:	National Agency for Food and Drug Administration and Control
NTI:	Narrow Therapeutic Index
QC:	Quality Control
SOP:	Standard Operating Procedure
SRA:	Stringent Regulatory Authority
sWR:	within-subject standard deviation of reference product
Tmax:	Time at maximum concentration
WHO:	World Health Organisation

Templates

1. Bioequivalence Trial Information form (BTIF)
2. Biowaiver Application Form (BAF)
   a. NAFDAC BCS Biowaiver Template
   b. NAFDAC Additional Strength Biowaiver Template.