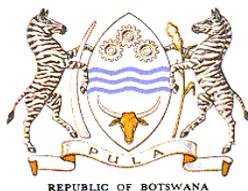


# **Guidelines on Bioavailability and Bioequivalence**

**First Edition**

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## 1 INTRODUCTION

NOTE: This guideline has been adapted from the SADC Guideline on Bioavailability and Bioequivalence.

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies should be submitted with each (except biological) application for the registration of a medicine.

To exert an optimal therapeutic action, an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect, the characteristics of the dosage form containing the API, should be well defined.

Comparison of the therapeutic performances of two pharmaceutical products containing the same API is a critical means of assessing the possibility of using either the innovator, or a multisource (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bioequivalence.

The objectives of this guideline are to:

- a) Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.
- b) Provide guidance on the design and conduct of studies and the evaluation of data.
- c) Provide guidance when *in vitro* instead of *in vivo* data may be used.
- d) Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products, where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

## 2 SCOPE

This guideline represents the current thinking on this subject. It does not create or confer any rights for or on any person and does not operate to bind the Drugs Regulatory Unit or the public.

The guideline addresses how to meet the BA and BE requirements as they apply to dosage forms intended for oral administration. It is also generally applicable to non-orally administered medicine products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal medicine products). It should be useful for applicants planning to conduct BA and BE studies during the investigational period for a new medicine application, BE studies intended for submission in multisource medicine applications, and BE studies conducted in the post-approval period for certain changes in both new medicine applications and multisource medicine applications.

### **3 DEFINITIONS**

#### **3.1 Active Pharmaceutical Ingredient (API )**

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

#### **3.2 Bioavailability**

Bioavailability refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the “absolute bioavailability” of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution vs. iv.), and the “relative bioavailability” as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

#### **3.3 Biobatch**

Biobatch refers to a batch used in a bioequivalence study.

#### **3.4 Bioequivalence**

Bioequivalence is defined as the absence of a significant difference in bioavailability between two pharmaceutically equivalent products or pharmaceutical alternatives under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

#### **3.5 Multisource (Generic) Pharmaceutical Product**

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent or bioequivalent.

#### **3.6 Pharmaceutical alternatives**

Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength.

#### **3.7 Pharmaceutical Dosage Form**

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution) suitable for administration to human and animal subjects.

#### **3.8 Comparable Dosage Form**

A comparable dosage forms refers to different formulations of the same product given by the same route (e.g capsules and tablets)

#### **3.9 Pharmaceutical Equivalence**

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to changes in dissolution and/or absorption.

### **3.10 Pharmaceutical Product**

Any preparation for human or veterinary use containing one or more APIs, with or without pharmaceutical excipients or additives, that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

### **3.11 Proportionally Similar Dosage Forms/Products**

Pharmaceutical products are considered proportionally similar in the following cases:

- When all APIs and inactive pharmaceutical ingredients (IPIs) are in exactly the same proportion between different strengths (e.g. a 100 mg strength tablet has all API and IPIs exactly half of a 200 mg strength tablet and twice that of a 50 mg strength tablet).
- When the active and inactive ingredients are not in exactly the same proportion but the ratios of IPIs to the total mass of the dosage form are within the limits defined by the Post-registration amendment guideline.
- When the pharmaceutical products contain high potency APIs and these products are of different strengths but are of similar mass.

The difference in API content between strengths may be compensated for by mass changes in one or more of the IPIs provided that the total mass of the pharmaceutical product remains within 10 % of the mass of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same IPIs should be used for all strengths, provided that the changes remain within the limits defined by the Post-registration amendment guideline.

### **3.12 Therapeutic Equivalence/Substitutable**

Two pharmaceutical products are therapeutically equivalent/substitutable if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Exceptions to the above definitions may be considered provided justification is submitted.

### **3.13 Biopharmaceutics Classification System (BCS)**

The BCS is a scientific framework for classifying medicinal substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of medicine absorption from immediate release (IR) solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, medicinal substances are classified as follows:

- Class 1: High solubility – High permeability
- Class 2: Low solubility – High permeability
- Class 3: High solubility – Low permeability
- Class 4: Low solubility – Low permeability

In addition, IR solid oral dosage forms are characterised as having rapid or slow dissolution.

### **3.14 Reference product**

A reference product is a pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product which is the market leader may be used as a reference product, provided

- a. It has been authorised for marketing and its efficacy, safety and quality has been established and documented.
- b. The DRU has approved the product to be used as a reference product prior to commencement of the study

## **4 DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS**

A bioequivalence study is basically a comparative bioavailability study designed to establish whether or not there is bioequivalence between test and reference products. In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

### **4.1 DESIGN**

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as parallel designs for very long half-life substances, could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required in which case the steady-state study design should be motivated.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of  $C_{max}$  and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80 % of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples above the LOQ during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80 % is recovered before 72 hours.

## 4.2 Number of Subjects

It is recommended that the number of subjects should be justified on the basis of providing at least 80 % power of meeting the acceptance criteria. The minimum number of subjects whose data is used for pharmacokinetic and statistical analysis should not be less than 12. If 12 subjects do not provide 80 % power, more subjects should be included.

A minimum of 20 subjects is required for modified release oral dosage forms.

The number of subjects required to provide an 80 % power of meeting and passing the acceptance criteria for the 0,8 to 1,25 acceptable interval, can be determined from Reference 1.

Alternatively, the sample size can be calculated using appropriate power equations, which should be presented in the protocol.

The provision for add-ons should be made in the protocol *a priori* clearly reflecting the maximum number of subjects to be included.

### 4.2.1 Selection of Subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers.

The inclusion/exclusion criteria should be clearly stated in the protocol.

In general, subjects should exhibit the following characteristics:

- a) **Sex:** Subjects may be selected from either sex. However, the risk to women of childbearing potential should be considered on an individual basis.
- b) **Age:** Subjects should be between 18 and 55 years of age.
- c) **Mass:** Subjects should have a body mass within the normal range according to accepted normal values for the Body Mass Index (BMI = mass in kg divided by height in meters squared, i.e. kg/m<sup>2</sup>), or within 15 % of the ideal body mass, or any other recognised reference.
- d) **Informed Consent:** All subjects participating in the study should be capable of giving informed consent.
- e) **Medical Screening:** Subjects should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile, special medical investigations may have to be carried out before, during and after the completion of the study.
- f) **Smoking/Drug and Alcohol Abuse:** Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included they should be identified as such and the possible influences of their inclusion on the study results should be discussed in the protocol.

### 4.2.2 Inclusion of Patients

If the API under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients instead, under suitable precautions and supervision. In this case the applicant should justify the use of patients instead of healthy volunteers.

### **4.2.3 Genetic Phenotyping**

Phenotyping and/or genotyping of subjects can be considered for exploratory bioavailability studies. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies) for safety or pharmacokinetic reasons.

If a drug is known to be subject to major genetic polymorphism, studies could be performed in cohorts of subjects of known phenotype or genotype for the polymorphism in question.

## **4.3 STANDARDISATION OF THE STUDY CONDITIONS**

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore, standardisation of the diet, fluid intake and exercise is recommended.

### **4.3.1 Dosing**

The time of day for ingestion of doses should be specified.

### **4.3.2 Fluid Intake at Dosing:**

As fluid intake may profoundly influence the gastric transit of orally administered dosage forms, the volume of fluid administered at the time of dosing should be constant (e.g. 200 ml).

### **4.3.3 Food and Fluid Intake:**

In fasted studies the period of fasting prior to dosing should be standardised and supervised. All meals and fluids taken after dosing should also be standardised in regard to composition and time of administration and in accordance with any specific requirements for each study.

### **4.3.4 Concomitant Medication:**

Subjects should not take other medicines for a suitable period prior to, and during, the study and should abstain from food and drinks which may interact with circulatory, gastrointestinal, liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices).

### **4.3.5 Posture and Physical Activity:**

As the bioavailability of an active moiety from a dosage form can be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

## **4.4 SAMPLE COLLECTION AND SAMPLING TIMES**

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma. However, in some cases, whole blood may be more appropriate for analysis.

### **4.4.1 When blood is collected:**

- a) The duration of blood sampling in a study should be sufficient to account for at least 80 % of the known AUC to infinity ( $AUC_{\infty}$ ). This period is approximately three terminal half-lives of the drug.

- b) For most drugs 12 to 18 samples including a pre-dose sample should be collected per subject per dose.
- c) Sample collection should be spaced such that the maximum concentration of drug in blood ( $C_{max}$ ) and the terminal elimination rate constant ( $K_{el}$ ) can be estimated.
- d) At least three to four samples above LOQ should be obtained during the terminal log-linear phase to estimate  $K_{el}$  by linear regression analysis.
- e) The actual clock time when samples are collected, as well as the elapsed time relative to drug administration, should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40 %) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

#### 4.4.2 When urine is collected:

- a) The volume of each sample should be measured immediately after collection and included in the report.
- b) Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life, so that the amount excreted to infinity ( $Ae_{\infty}$ ) can be estimated.
- c) Sufficient samples should be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose are usually appropriate.
- d) The actual clock time when samples are collected, as well as the elapsed time relative to drug administration, should be recorded.

## 4.5 CHARACTERISTICS TO BE INVESTIGATED

### 4.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of, and the area under, the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Instances where this may be necessary are as follows:

- a) If the concentration of the API is too low to be accurately measured in the biological matrix.
- b) If there is a major difficulty with the analytical method.
- c) If the parent compound is unstable in the biological matrix.
- d) If the half-life of the parent compound is too short, thus, giving rise to significant variability.

Justification for not measuring the parent compound should be submitted by the applicant and bioequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen such that the plasma concentration *versus* time profiles can be defined adequately, thereby allowing accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

- a)  $AUC_t$ ,  $AUC_{\infty}$ ,  $C_{max}$ ,  $t_{max}$  for plasma concentration *versus* time profiles.
- b)  $AUC_{\infty}$ ,  $C_{max}$ ,  $C_{min}$ , fluctuation (% PTF) and swing (% Swing) for studies conducted at steady state.
- c) Any other justifiable characteristics
- d) The method of estimating AUC-values should be specified.

#### 4.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification should also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

- a)  $Ae_t$ ,  $Ae_{\infty}$  as appropriate for urinary excretion studies.
- b) Any other justifiable characteristics
- c) The method of estimating AUC-values should be specified.

#### 4.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, the applicant should submit justification for their use. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

- a) A dose-response relationship should be demonstrated.
- b) Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.
- c) The complete dose-effect curve should remain below the maximum physiological response.
- d) All pharmacodynamic measurements/methods should be validated with respect to specificity, accuracy and reproducibility.

#### 4.5.4 Chirality

Measurement of individual enantiomers in BE studies is recommended only when all of the following conditions are met, otherwise measurement of the racemate using an achiral assay is recommended.

- i) The enantiomers exhibit different pharmacodynamic and/or different pharmacokinetic characteristics;
- ii) Primary efficacy/safety activity is primarily due to the minor enantiomer;
- iii) Non-linear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the administration rate of the medicine) for at least one of the enantiomers.

## **4.6 BIO ANALYSIS**

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and current DRU Good Manufacturing Practices (cGMP).

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine, or any other suitable matrix, should be well characterised, and fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix (Refer to FDA Guideline on Validation of bioanalytical method).

## **4.7 STUDY PRODUCTS**

### **4.7.1 Reference and test Products**

Test products in an application for a generic product are normally compared with the comparable dosage form. The choice of reference product if not an innovator, should be justified by the applicant.

In the case of oral solid dosage forms for systemic action the test product should usually originate from a batch of at least one tenth (1/10) of the production scale unless otherwise justified.

### **4.7.2 Retention samples**

A sufficient number of retention samples of both test and reference products used in the bioequivalence study, should be kept for one year in excess of the accepted shelf-life, or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the DRU.

### **4.7.3 Sample handling**

A complete audit trail of procurement, storage, transport and use of both the test and reference products should be recorded.

## **4.8 DATA ANALYSIS**

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products, and to demonstrate that any clinically important difference is unlikely.

### **4.8.1 Statistical Analysis**

The statistical method for testing relative bioavailability (i.e. average bioequivalence) is based upon the 90 % confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g.  $AUC_t$ ,  $AUC_{\infty}$  and  $C_{max}$  should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for  $t_{\max}$  should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90 % confidence intervals, summary statistics such as geometric and arithmetic means, SD and % RSD, as well as ranges for pharmacokinetic parameters (minimum and maximum), should be provided.

#### 4.8.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges, should be stated beforehand in the protocol. Outlying data should be reported and appropriate explanation should be given.

#### 4.8.3 Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i) **AUC<sub>t</sub> - ratio**

The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods, e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs, has been described in the literature (References 2 and 3). Use of alternative methods should be stated *a priori* in the protocol and cannot be added retrospectively.

ii) **C<sub>max</sub> - ratio**

The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 80 – 125 %, calculated using log-transformed data.

In certain cases, e.g. in the case of highly variable API's, a wider interval or other appropriate measure may be acceptable, but should be stated *a priori* and justified in the protocol (See references 3 and 4).

#### 4.8.4 Steady-State Studies

i) **Immediate Release Dosage Forms**

The acceptance criteria are the same as for single dose studies but using AUC<sub>∞</sub> instead of AUC<sub>t</sub>

ii) **Controlled/Modified Release Dosage Forms**

The acceptance criteria are as follows:

- **AUC<sub>∞</sub> - ratio**  
The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80 -1,25 (80 – 125 %).
- **C<sub>max (ss)</sub> and C<sub>min (ss)</sub>**  
The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,8 -1,25 (80 – 125 %), calculated using log-transformed data.
- **% Swing and % PTF**  
The 90 % confidence interval for the test/reference ratio should lie within

the acceptance interval of 0,80 -1,25 (80 – 125 %), calculated using log transformed data.

## **4.9 STUDY REPORT**

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation, complying with GCP, GLP and cGMP.

### **4.9.1 Clinical Report**

In addition to the protocol the clinical section of the bioequivalence study report should include the following:

- a) A statement indicating the independence of the ethics committee.
- b) Documented proof of ethical approval of the study.
- c) A complete list of the members of the ethics committee, their qualifications and affiliations.
- d) Names and affiliations of all investigator(s), the site of the study and the period of its execution.
- e) The names and batch numbers of the products being tested.
- f) The name and address of the manufacturer of both the reference and the test products.
- g) Expiry date of the reference product and the date of manufacture of the test product used in the study.
- h) Assay and dissolution profiles for test and reference products. Assay of the test product should be within 5% of the reference product.
- i) Certificate of analysis (CoA) of the API used in the test product bio-batch.
- j) A summary of adverse events which should be accompanied by a discussion on the influence of these events on the outcome of the study.
- k) A summary of protocol deviations (sampling and non-sampling) which should be accompanied by a discussion on the influence of these adverse events on the outcome of the study.
- l) Subjects who drop out or are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

### **4.9.2 Analytical Report**

The analytical section of the bioequivalence report should include the following clearly presented:

- a) The full analytical validation report.
- b) All individual subject concentration data.
- c) Calibration data, i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters, for the entire study.
- d) Quality control samples data for the entire study.
- e) Chromatograms from analytical runs for 20 % of all subjects or a minimum of 4 subjects, whichever is greater, including chromatograms for the associated standards and quality control samples.
- f) A summary of protocol deviations which should be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations should be justified.

### 4.9.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which should be clearly presented:

- a) All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

This data should be submitted in hard copy and also formatted on a CD in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns, which reflect the subject number, phase number, sequence, formulation, and sample concentration *versus* time data.

- b) The method(s) and programmes used to derive the pharmacokinetic parameters from the raw data.
- c) A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.
- d) Tabulated summaries of pharmacokinetic and statistical data.
- e) The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration *vs.* time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

### 4.9.4 Quality Assurance (QA)

- a) A signed QA statement, confirming release of the document should accompany the study report.
- b) A declaration should be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain its/their status of GCP and GLP and/or cGMP conditions. All audit certificates should clearly indicate the date of audit and the name(s), address (es) and qualifications of the auditor(s).
- c) The applicant should submit an independent monitor's certificate on the clinical portion of the study. This certificate should clearly indicate the date of monitoring and the name, address and qualifications of the monitor, and should be included in the study report.

## 5 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

### 5.1 ORALLY ADMINISTERED MEDICINAL PRODUCTS WITH SYSTEMIC ACTION

#### 5.1.1 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilised forms containing the same API(s) in the same concentration(s) as the reference product, and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

### **5.1.2 Suspensions**

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

### **5.1.3 Immediate Release Products – Tablets and Capsules**

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vitro* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms, based on comparative dissolution studies, may be acceptable (see 6 below and Dissolution guideline).

### **5.1.4 Modified Release Products**

Modified release products include delayed release products and extended (controlled) release products. In general, bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

### **5.1.5 Miscellaneous Oral Dosage Forms**

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because a patient, without proper chewing, might swallow them. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

### **5.1.6 Fixed Dose Combinations (FDC)**

Combination products should in general be assessed with respect to bioavailability and bioequivalence of individual active substances either separately (in the case of a new combination) or as an existing combination. The study in case of a new combination should be designed in such a way that the possibility of medicine-medicine interaction could be detected.

## **5.2 ORALLY ADMINISTERED DRUGS WITH LOCAL ACTION**

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required. Where these are not available justification should be provided.

## **5.3 PARENTERAL SOLUTIONS**

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same API in the same concentration as the currently approved product.

In the case of parenteral routes other than intravenous, e.g. intramuscular or subcutaneous - if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same API, and the same or comparable excipients as the reference, then bioequivalence testing is not required; provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For non-aqueous intramuscular dosage forms, monitoring is required until at least 80 % of the AUC<sub>∞</sub> has been covered.

## **5.4 TOPICAL PRODUCTS**

### **5.4.1 Local Action**

For topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test, refer to FDA Blanching Guidelines) is recommended to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

For topical formulations, other than simple solutions with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions, however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane diffusion will not be accepted as proof of efficacy, unless data are presented that show a correlation between release through a membrane and clinical efficacy.

Whenever systemic exposure resulting from locally applied/locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

### **5.4.2 Systemic Action**

For locally applied products with systemic action, e.g. transdermal products, a bioequivalence study is always required

## **5.5 PRODUCTS INTENDED FOR OTHER ROUTES OF ADMINISTRATION**

Products for local use (e.g. oral, nasal, inhalation, ocular, dermal, rectal, vaginal) intended to act without systemic absorption, the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

## **5.6 VARIATIONS OR POST-REGISTRATION AMENDMENTS**

For all post-registration changes that require proof of efficacy in accordance with the DRU Variation guideline, the requirements of this guideline will be applicable.

## **6 WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES**

Biowaivers will be considered under the circumstances detailed below.

## 6.1 IMMEDIATE RELEASE PRODUCTS

### 6.1.1 Biopharmaceutics Classification System (BCS) Class 1 Drug Substances

- a. When the drug product contains a Class 1 drug substance(s) (based on the BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients, a biowaiver may be acceptable.

The drug substances should be highly soluble, highly permeable and the dosage form rapidly dissolving (Appendix 1).

The API is uncomplicated, i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose-response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics, e.g.:
  - non linear pharmacokinetics,
  - variable or incomplete absorption,
  - an absorption window, i.e. site-specific absorption,
  - substantial first-pass metabolism (>40 %), or
  - an elimination half-life of 24 hours or more.
- There is no documented evidence of bioavailability problems related to the API(s) or the pharmaceutical product, or products of similar chemical structure or formulations.
- Is not a pro-drug.

In the case of multisource products, the reference product should be a conventional, immediate-release oral dosage form and the test and reference products should exhibit similar dissolution profiles.

Dosage forms should not be intended for absorption in the oral cavity, e.g. sublingual or buccal tablets.

BCS based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or similar pharmacokinetic studies.

- b. When the drug product contains a BCS Class 3 drug substance, if the multisource and comparator products
- (i) are very rapidly dissolving (no less than 85% in 15 minutes at pH 1.2, 4.5 and 6.8);
  - (ii) excipients are qualitatively the same and quantitatively very similar

A critical review of the risks of an inappropriate biowaiver decision (e.g. site – specific absorption, risk for transport protein interactions at the site, excipients composition and therapeutic risks) for products containing BCS class 3 should be submitted.

Relevant information to prove that the drug substance falls within the Class 1 or 3 classification (Reference 5) should be provided.

### 6.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (section 3.10 of this guideline) in its API and IPIs, a biowaiver may be acceptable.

Dissolution profiles are required for all strengths. The  $f_2$  similarity factor should be used to compare dissolution profiles from different strengths of a product. An  $f_2$  value  $\geq 50$  indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an  $f_2$  value  $< 50$ , it may be necessary to conduct an *in vivo* study. The difference factor,  $f_1$ , should also be submitted but will not be used as an acceptance criterion (Reference 6).

#### a) Lower strength dosage forms

The demonstration of bioequivalence *in vivo* of one or more of the lower strength(s) may be waived based on dissolution tests (Appendix 1) and an *in vivo* study on the highest strength.

#### b) Higher strength dosage forms

Conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength if an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

##### i) Multisource pharmaceutical products

- Linear elimination kinetics has been shown over the therapeutic dose range.
- The higher strength is proportionally similar to the lower strength.
- Comparative dissolution on the higher strength of the test and reference products is similar.

##### ii) New Chemical Entities

- Clinical safety and/or efficacy studies including dose desirability of the higher strength,
- linear elimination kinetics over the therapeutic dose range,
- the higher strength being proportionally similar to the lower strength, and
- the same dissolution procedures being used for both strengths and similar dissolution results obtained.

Note: Details on conducting dissolution studies are described in Appendix 1

## 6.2 MODIFIED RELEASE PRODUCTS

### 6.2.1 Beaded Capsules – Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods described in Appendix 1.

### 6.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

- a) in the same dosage form but in a different strength, and

- b) is proportionally similar in its active and inactive ingredients, and
  - c) has the same drug release mechanism,
- an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For sections 6.2.1 and 6.2.2 above, the  $f_2$  factor should be used to compare profiles from the different strengths of the product. An  $f_2$  value of  $\geq 50$  can be used to confirm that further *in vivo* studies are not needed (Appendix 1). The difference factor,  $f_1$ , should also be submitted but will not be used as an acceptance criterion (Reference 6)

### **6.3 IN VITRO DISSOLUTION**

Dissolution studies are necessary and consequently required. *In vitro* dissolution testing forms part of the assessment of a bioequivalence waiver request based on criteria derived from the concepts underlying the BCS

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## 8 ABBREVIATIONS

$C_{\max}$	maximum plasma concentration
$C_{\min}$	minimum plasma concentration
$C_{\max (ss)}$	maximum plasma concentration at steady-state
$C_{\min (ss)}$	minimum plasma concentration at steady-state
$C_{av}$	average plasma concentration
$t_{\max}$	time to $C_{\max}$
$AUC_t$	area under the plasma/serum/blood concentration-time curve from time zero to time t where t is the last time point with measurable concentration.
$AUC_{\infty}$	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
$AUC_{\tau}$	AUC during a dosage interval at steady state
MRT	mean residence time
$Ae_{\infty}$	amount excreted at infinity
$Ae_t$	amount excreted at time t
Kel	elimination rate constant
BA/BE	Bioavailability/Bioequivalence
GLP	Good Laboratory Practices
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
BCS	Biopharmaceutics Classification System
ANOVA	Analysis of variance
FDC	Fixed Dose Combinations
LOQ	Limit of quantification
SD/RSD	Standard deviation
QA	Quality Assurance
BMI	Body Mass Index
API	Active Pharmaceutical Ingredient
EP	European Pharmacopoeia
USP	United States Pharmacopoeia
BP	British Pharmacopoeia
IVIVC	<i>In vitro in vivo</i> correlation
MRA	Medicines Regulatory Authority
SOP	Standard Operating Procedure

## 9 APPENDIX 1

### DISSOLUTION GUIDELINE

#### 1 INTRODUCTION

This guideline describes the setting of dissolution specifications as a quality control requirement and also describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing.

Although intrinsic dissolution of the active pharmaceutical ingredient (API) is an important consideration when formulating solid oral dosage forms, the dissolution behaviour of solid oral dosage forms provides important information to ensure drug product quality. Hence, dissolution testing has been established as an extremely valuable tool to monitor batch-to-batch consistency. The primary utility of a dissolution test is, therefore, to establish dissolution specifications for relevant drug products for the purposes of quality assurance.

Dissolution testing can also be useful in providing information on drug product quality following certain post-approval changes made to the product, such as changes in formulation, manufacturing process, site of manufacture and the scale-up of the manufacturing process.

In addition, where solid oral dosage forms have been proportionally formulated in different strengths, and the drug follows linear kinetics, dissolution data can be used in support of a biowaiver for lower strengths of such dosage forms, provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

Drug absorption from oral dosage forms depends on adequate release of the active pharmaceutical ingredient (API) from the product. Physico-chemical factors, such as dissolution or solubility of the drug under physiologic conditions, and its permeability through the membranes of the gastrointestinal tract, play pivotal roles in this respect. Due to the critical nature of these factors, dissolution of a drug product *in vitro* can, in certain instances, be relevant to anticipate the *in vivo* characteristics/results.

In summary, dissolution testing can serve several purposes:

- a) Quality assurance
  - To get information on the test batches used in BA/BE studies and pivotal clinical studies to support specifications for quality control
  - To be used as a tool in quality to demonstrate consistency in manufacture
  - To get information on the reference product used in BA/BE studies and pivotal clinical studies
  -
- b) Bioequivalence surrogate inference
  - To demonstrate similarity between reference products from different countries
  - To demonstrate similarities between different formulations of an active substance and the reference medicinal product
  - To collect information on batch to batch consistency of the products to be used as basis for the selection of appropriate batches for the *in vivo* study

## 2 SETTING DISSOLUTION SPECIFICATIONS

- a) For new drug products, dissolution specifications should be based on data obtained from acceptable clinical, pivotal bioavailability and/or bioequivalence batches.
- b) In the case of multisource pharmaceutical products, the dissolution specifications are generally the same as the reference product.

These specifications should be confirmed by comparison of the dissolution performance of the multisource pharmaceutical product and reference product from an acceptable bioequivalence study.

If the dissolution performance of the multisource pharmaceutical product is substantially different from that of the reference product and the *in vivo* data remain acceptable, a different dissolution specification for the multisource pharmaceutical product may be set.

- c) A single point specification for immediate release dosage forms and a multipoint specification for modified release dosage forms are generally applicable for quality control, batch release and stability testing purposes.

Once dissolution specifications are set, the drug product should comply with those specifications throughout its shelf-life.

Testing should continue through the three stages of testing unless the product conforms at stage 1 or 2.

Setting dissolution specifications for multisource pharmaceutical products may be classified in three categories as described below.

### 2.1 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST AVAILABLE

In this instance the quality control dissolution test should be the test described in the BP, USP or EP. Use of any other pharmacopoeia should be justified to the DRU.

It is recommended that a dissolution profile be generated by taking samples at 15-minute intervals, or less, using the specified pharmacopoeial method for test and reference products (12 units each).

Additional dissolution data may also be required when scientifically justified, e.g. when the pharmacopoeia does not specify a dissolution test for all API's in a combination product.

If appropriate the pharmacopoeial specification may be adopted.

### 2.2 PHARMACOPOEIAL PRODUCT DISSOLUTION TEST NOT AVAILABLE

Comparative dissolution testing, using test and reference products under a variety of test conditions, is recommended.

The test conditions may include different dissolution media (pH 1.2 to 6.8), addition of surfactant, or use of an official basket or paddle apparatus with varying agitation.

In all cases, profiles should be generated as previously recommended.

The medium which exhibits optimum discrimination should be selected.

The dissolution specifications should be set based on available bioequivalence and other data. In addition, the method used should be justified and validated.

### 2.3 SPECIAL CASES

For poorly water soluble drug products (e.g. glyburide), dissolution testing at more than one time point, and preferably a dissolution profile, is recommended for quality control purposes. Alternatively, the use of the USP apparatus 4 (Flow-Through Method) should be considered for the development of dissolution specifications for such products.

If a monograph for a multipoint product is not included in the BP, USP, Eur Ph the monographs for the individual components should be used to set the dissolution requirements for each.

## 3 IN VITRO DISSOLUTION TESTING IN SUPPORT OF A BIOWAIVER (Bioequivalence Surrogate Inference)

### 3.1 IMMEDIATE RELEASE DRUG PRODUCTS WITH CLASS 1 API'S

In the Biopharmaceutics Classification System (BCS) an API is classified as having high or low solubility and high or low permeability.

- a) An API is considered to be *highly soluble* when the highest dose strength is soluble in  $\leq 250$  ml of aqueous buffer over the pH range of 1,0 to 7,5.

An API is considered to be *highly permeable* when:

- i) the extent of absorption in humans is determined to be greater than 90 % of an administered dose in the absence of documented instability in the gastrointestinal tract, or
- ii) high permeability has been determined experimentally (Reference 5) and reported in the literature.

According to the BCS, a Class 1 API is both *highly soluble* and *highly permeable*.

An immediate release (IR) dosage form can be classified as either rapidly or slowly dissolving. It is considered *rapidly dissolving* when not less than 85 % of the label amount of the API dissolves within 30 minutes, using USP Apparatus 1 at 100 rpm (or Apparatus 2 at 50 rpm) in a volume of 900 ml, or less, in each of the following three media:

- acidic media such as 0,1N HCl (pH 1.2)
- pH 4,5 buffer
- pH 6,8 buffer

When an immediate release drug product is *rapidly dissolving* and contains a Class 1 API, a biowaiver for the multisource product may be granted on the basis of acceptable dissolution data.

### 3.2 PROPORTIONALLY SIMILAR DOSAGE FORMS

When a biowaiver is requested for lower strengths of drug products which are proportionally formulated, the following dissolution testing is required:

- a) Dissolution of test and reference products should be conducted in each of the following three media:
- acidic media such as 0,1 N HCl
  - pH 4,5 buffer
  - pH 6,8 buffer

- b) Dissolution profiles of test and reference products should be compared, as described below, for each of the three media.  
Similarity in dissolution profiles should be assessed using  $f_1$  and  $f_2$ , but only  $f_2$  data will be used as the acceptance criterion.  
An  $f_2$  value  $\geq 50$  indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.
- c) When both the test and reference products dissolve to the extent of 85 % or more of the label amount in  $\leq 15$  minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.
- d) Dissolution data in support of biowaivers for higher strength, proportionally similar, dosage forms will not normally be considered. However, if a successful biostudy was carried out on a lower strength for reasons of safety, dissolution testing on higher strengths will be considered.

### 3.3 FOREIGN REFERENCE PRODUCTS

Bioequivalence studies submitted where a foreign reference product has been used, will require demonstration of similarity between the foreign product and the innovator/reference product marketed in Botswana.

- a) Dissolution of test and reference products should be conducted in each of the following three media:
- acidic media such as 0,1 N HCl (pH 1.2)
  - pH 4,5 buffer
  - pH 6,8 buffer
- b) Dissolution profiles of test and reference products should be compared as described in section 4 of this appendix for each of the three media.  
Similarity in dissolution profiles should be assessed using the difference factor ( $f_1$ ) and the similarity factor ( $f_2$ ) but only  $f_2$  data will be used as the acceptance criterion.  
An  $f_2$  value  $\geq 50$  indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.
- c) When both the test and reference products dissolve to the extent of 85 % or more of the label amount in  $\leq 15$  minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

### 3.4 POST-REGISTRATION / APPROVAL AMENDMENTS

When amendments are made to pharmaceutical products, manufacturing procedures, and other associated processes including change of site, their impact on quality should be demonstrated. The following describes the use of dissolution testing as an indicator of quality which may be applicable as described below.

The following dissolution tests are recommended:

#### 3.4.1 Types of dissolution testing

- a) **Case A**

Dissolution testing should be conducted as a release test according to the original submission, or in accordance with compendial requirements, for that product.

**b) Case B**

Dissolution testing should be conducted as a multipoint test in the application/compendial medium at intervals such as 15, 30, 45, 60 and 120 minutes, or until an asymptote is reached for the proposed and currently registered formulation.

**c) Case C**

Dissolution testing should be conducted as a multipoint test in distilled water, 0,1 N HCl (pH 1.2) and buffer at pH 4,5 and 6,8 for the proposed, and currently registered formulations, at intervals such as 15, 30, 45, 60 and 120 minutes, or until either 90 % of drug from the drug product is dissolved, or an asymptote is reached.

In the case of poorly soluble drugs, comparisons may be made using alternative compendial methods and media that have been appropriately justified.

### **3.4.2 Types of amendments**

**a) Minor variation**

(i) In the event that the Minor variation change made is such that there is unlikely to be an effect on the quality and performance of a dosage form, Case A dissolution testing is appropriate.

(ii) In the event that the changes, which were made, have a significant impact on the quality and performance of a dosage form, Case B dissolution testing is appropriate. However, if the change is made to a product containing a BCS class 1 compound 85 % should be dissolved in 15 minutes in the media used in (accordance with) the application or compendial requirements.

For low permeability, high solubility drugs, dissolution profiles should be generated in the application/compendial medium as previously described for Case B dissolution testing. For high permeability, low solubility compounds, multipoint dissolution profiles should be carried out according to Case C dissolution testing.

Profiles of the currently used product and the proposed product, should be proven to be similar, according to the  $f_2$  requirements as describe in this Guideline.

**c) Major variation**

In the case of changes that are likely to have a significant impact on formulation quality and performance, *in vivo* bioequivalence testing should be conducted unless otherwise justified. Case B or Case C dissolution testing may also be required. Biowavers may also be considered if a proven *in vitro/in vivo* correlation (IVIVC) has been established.

## **4 COMPARISON OF DISSOLUTION PROFILES**

A dissolution profile comparison may be carried out using a simple model-independent approach to assess overall profile similarity as well as similarity or differences at each dissolution sample time point.

This approach uses a difference factor ( $f_1$ ) and a similarity factor ( $f_2$ ) to compare dissolution profiles (Reference 6). The difference factor ( $f_1$ ) calculates the percentage

(%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t]\} \cdot 100$$

Where  $n$  is the number of time points,  $R_t$  is the dissolution value of the reference batch at time  $t$ , and  $T_t$  is the dissolution value of the test batch at time  $t$ .

The similarity factor ( $f_2$ ) is a logarithmic reciprocal square root transformation of the sum of squared errors, and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

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

A specific procedure to determine difference and similarity factor is as follows:

- a) Determine the dissolution profile of two products, i.e. of the test and reference products (using 12 units each).
- b) Using the mean dissolution values from both curves at each time interval, calculate the difference factor ( $f_1$ ) and similarity factor ( $f_2$ ) using the above equations.
- c) For curves to be considered similar,  $f_1$  values should be close to 0, and  $f_2$  values should be close to 100. Generally, the  $f_1$  values up to 15 (0 to 15) and  $f_2$  values greater than 50 (50 to 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model-independent method is most suitable for dissolution profile comparisons when three to four or more dissolution time points are available. The following recommendations should also be considered:

- i) The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both profiles should be the same (e.g. 15, 30, 45, 60 minutes, etc.).
- ii) Only one measurement should be considered after 85 % dissolution of both products have occurred.
- iii) To allow use of mean data, the percent coefficient of variation (CV) at the earlier time points (e.g. 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.