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The minimum number of subjects 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 - 1,25 acceptable interval can be determined from Table 1 below (Reference 1).

Table 1 Sample sizes to attain a power of 70%, 80% and 90% in the case of the multiplicative model: $\alpha = 5\%$, $\theta_1=0.8$, $\theta_2=1.25$ and various CVs.

CV (%)	Power (%)	μ_T/μ_R							
		0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	70	10	6	4	4	4	4	6	16
7.5		16	6	6	4	6	6	10	34
10.0		28	10	6	6	6	8	16	58
12.5		42	14	8	8	8	12	24	90
15.0		60	18	10	10	10	16	32	128
17.5		80	22	12	12	12	20	44	172
20.0		102	30	16	14	16	26	56	224
22.5		128	36	20	16	20	30	70	282
25.0		158	44	24	20	22	38	84	344
27.5		190	52	28	24	26	44	102	414
30.0		224	60	32	28	32	52	120	490
5.0	80	12	6	4	4	4	6	8	22
7.5		22	8	6	6	6	8	12	44
10.0		36	12	8	6	8	10	20	76
12.5		54	16	10	8	10	14	30	118
15.0		78	22	12	10	12	20	42	168
17.5		104	30	16	14	16	26	56	226
20.0		134	38	20	16	18	32	72	294
22.5		168	46	24	20	24	40	90	368
25.0		206	56	28	24	28	48	110	452
27.5		248	68	34	28	34	58	132	544
30.0		292	80	40	32	38	68	156	642
5.0	90	14	6	4	4	4	6	8	28
7.5		28	10	6	6	6	8	16	60
10.0		48	14	8	8	8	14	26	104
12.5		74	22	12	10	12	18	40	162
15.0		106	30	16	12	16	26	58	232
17.5		142	40	20	16	20	34	76	312
20.0		186	50	26	20	24	44	100	406
22.5		232	64	32	24	30	54	124	510
25.0		284	78	38	28	36	66	152	626
27.5		342	92	44	34	44	78	182	752
30.0		404	108	52	40	52	92	214	888

Note: Less than 12 subjects should not be used even if the above table indicates that a power of 80% can be attained with less than 12 subjects.

To determine the number of subjects required, proceed as follows:

- Determine the CV% of the appropriate BA/BE parameter for the drug under investigation from published literature or an appropriate pilot study.
- Choose an appropriate mean test/ reference ratio that is envisaged for the BA/BE parameter (μ_T / μ_R). Ideally this value will be 1.00, however, in practice this is seldom the case so the choice of this ratio is at the discretion of the Sponsor/Applicant.

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- iii. Determine from the table the number of subjects required for the appropriate CV%, Power and μ_T/μ_R .

For example, if the drug under investigation has an AUC CV of 20% and if a μ_T/μ_R of 0.95 or 1.05 is selected, then a minimum of 20 and 18 subjects respectively will be required for a power of 80%.

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

Add-ons will be permitted but the number of subjects in the add-on should not exceed the initial number of subjects in the study, unless fully justified. The applicant must show that the data are homogeneous using appropriate statistical tests. The provision for add-ons must be made in the protocol *a priori*.

3.2.2 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:

- i. **Sex:** Subjects may be selected from either sex, however, the risk to women of childbearing potential should be considered on an individual basis.
- ii. **Age:** Between 18 and 55 years of age.
- iii. **Mass:** Have a body mass within the normal range according to accepted normal values for the Body Mass Index (BMI=weight in Kg divided by height in meters squared i.e. Kg /m²) or within 15% of ideal body mass e.g. Metropolitan Height and Weight Tables which can be found in the following reference: Statistical Bulletin (Metropolitan Life Foundation) Vol 64, No 1, Jan-Jun 1983, or any other such recognised reference.
- iv. **Informed Consent:** All subjects participating in the study must be capable of giving informed consent.
- v. **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.
- vi. **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 (less than 10 cigarettes per day) they should be identified as such and the possible influences of their inclusion on the study results should be discussed in the protocol.

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3.2.3 Inclusion of Patients

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

3.2.4 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 etc.) 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.

3.3 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.

- i. **Dosing:** The time of day for ingestion of doses should be specified.
- ii. **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).
- iii. **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.
- iv. **Concomitant Medication:** Subjects should not take other medicines during a suitable period before 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).
- v. **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.

BIOAVAILABILITY/BIOEQUIVALENCE**3.4 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.

When blood is collected:

- i. The duration of blood sampling in a study should be sufficient to account for at least 80% of the known AUC to infinity (AUC_{∞}). This period is approximately three terminal half-lives of the drug.
- ii. For most drugs 12 to 18 samples including a pre-dose sample should be collected per subject per dose.
- iii. 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.
- iv. At least three to four samples should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.
- v. 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.

When urine is collected:

- i. The volume of each sample must be measured immediately after collection and included in the report.
- ii. 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_{∞}) can be estimated.
- iii. Sufficient samples must 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 are usually appropriate.

3.5 Characteristics to be Investigated**3.5.1 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.

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In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound.

- i. If the concentration of the active substance is too low to be accurately measured in the biological matrix.
- ii. If there is a major difficulty with the analytical method.
- iii. If the parent compound is unstable in the biological matrix.
- iv. If the half-life of the parent compound is too short thus giving rise to significant variability.

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

Sampling points should be chosen so that the plasma concentration *versus* time profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

- i. AUC_t , AUC_{∞} , C_{max} , t_{max} for plasma concentration *versus* time profiles.
- ii. AUC_{τ} , C_{max} , C_{min} , fluctuation (%PTF) and swing (%Swing) for studies conducted at steady state.
- iii. Any other justifiable characteristics (cf. Appendix I).
- iv. The method of estimating AUC-values should be specified.

3.5.2 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 must 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:

- i. Ae_t , Ae_{∞} as appropriate for urinary excretion studies.
- ii. Any other justifiable characteristics (cf. Appendix I).
- iii. The method of estimating AUC-values should be specified.

BIOAVAILABILITY/BIOEQUIVALENCE**3.5.3 Pharmacodynamic Studies**

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

- i. A dose response relationship should be demonstrated.
- ii. Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.
- iii. The complete effect curve should remain below the maximum physiological response.
- iv. All pharmacodynamic measurements/methods must be validated with respect to specificity, accuracy and reproducibility.

3.6 Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and 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 must be well characterised, 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. Validation should therefore address the following characteristics of the assay (Reference 2):

- i. Stability of stock solutions.
- ii. Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.
- iii. Specificity.
- iv. Accuracy.
- v. Precision.
- vi. Limits of detection and quantitation.
- vii. Response function.
- viii. Robustness and ruggedness.

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A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed.

Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation and all modifications should be reported and the scope of revalidation justified.

3.7 Reference Product

N.B. Products that are not registered in South Africa cannot be used as reference products in bioequivalence studies submitted in support of an application e.g. a product approved for marketing in another country(s) but not approved for marketing in South Africa cannot be used as a reference product.

3.7.1 Reference Products Registered and Marketed in South Africa

The reference product must be an innovator product registered with the Medicines Control Council (MCC) and must be procured in South Africa except that an "OLD MEDICINE" may be used as a reference product when no other such product has been registered and provided that it is available on the South African market. If more than one such product is available, then the product that is the market leader in South Africa should be used as the reference (e.g. IMS database).

3.7.2 Reference Products Registered but not Procured inside South Africa.

1. A foreign reference product can be used provided that the following evidence is submitted:
 - i. The reference product has an identical formulation (the same in all respects) as the innovator product marketed in South Africa.
 - ii. The reference product is manufactured by the same method as the innovator product marketed in South Africa.
 - iii. The reference product is manufactured at the same site as the innovator product marketed in South Africa.

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The intention of the above clause is to provide for the use of a reference product where that innovator product has been imported for use in South Africa.

2. As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in SA and must meet the f_2 requirements when tested in dissolution media of pH 1.2, 4.5 and 6.8, using an appropriate dissolution apparatus (see Guideline for Dissolution Testing).

The intention of the above clause is to make provision for dossiers submitted prior to the implementation of this guideline.

3.7.3 Reference Products Registered in South Africa but not Marketed (Available) in South Africa

If a reference product is registered in SA but cannot be procured (i.e. is not available) in South Africa, then the reference product used can be obtained from outside South Africa provided that the product meets the following criteria:

- i. The reference product must be a conventional, immediate-release oral dosage form.
- ii. There is no documented evidence of bioavailability problems related to the active pharmaceutical ingredient(s) or the pharmaceutical product, or ingredients or products of similar chemical structure or formulations.
- iii. It must be documented that the pharmaceutical product is authorised for marketing by the health authority of a country with drug registration requirements acceptable to the MCC. In such instances the registration requirements of the country where the reference product was approved must be submitted.
- iv. It must be documented that the pharmaceutical product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same active pharmaceutical ingredient in the same dosage form in South Africa; or, that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity which currently markets the product in South Africa. The country of manufacture must be stated.
- v. Copies of the labelling for the reference as well as the innovator product marketed in South Africa, together with Certificates of Analysis for both products, analysed using the specifications for description, assay, content uniformity and dissolution proposed in the submission for the multi-source product, must be provided.

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- vi. The active pharmaceutical ingredient 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%)
 - an elimination half life of 24 hours or more
- vii. The active pharmaceutical ingredient must not be a pro-drug.
- viii. The dosage form:
- Contains a single API.
 - Contains the same quantity of medicinal ingredient as the innovator product registered in South Africa.
 - Is the same as the dosage form registered in South Africa with respect to colour, shape, size, weight, type of coating and other relevant attributes.

3.7.4 Reference Products for Combination Products

Combination products should in general, be assessed with respect to bioavailability and bioequivalence of individual active substances:

- i. Either individually (in the case of a new combinations), or
- ii. Using an existing combination as the reference.
- iii. In the former instance, immediate release oral dosage forms containing a single API can be used as the reference. These reference products may include "OLD MEDICINES".

Bioequivalence testing of such products will be permitted only for those products approved by the MCC.

BIOAVAILABILITY/BIOEQUIVALENCE**3.8 Study Products and Batch Size****3.8.1 Study Products**

The following information on test and reference products must be submitted:

- i. Assay of test and reference product.
- ii. Comparative dissolution profiles of the test and the reference product.
- iii. A CoA of the API used in the test product bio-batch as well as quality control data demonstrating compliance with the specifications.

In addition, the test and reference products must conform to the following:

- i. Test and the reference product should not differ by more than 5% in assay.
- ii. A sufficient number of retention samples of both test and reference products used in the bioequivalence study must be kept by the study sponsor 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 MCC.
- iii. A complete audit trail of procurement, storage, transport and other use of both the test and reference products must be recorded.

3.8.2 Batch Size

The bio-batch used in the bioequivalence study must satisfy the following requirements:

- i. The bio-batch must be a minimum of 100 000 units or at least 10% of the production batch which ever is greater.

If the bio-batch is less than 100 000 the applicant must motivate and justify the use of a smaller batch.

- ii. If the production batch is smaller than 100 000 units, a full production batch will be required.
- iii. A high level of assurance must be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale-up, this should be validated appropriately.

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3.9 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.

3.9.1 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) on the log-transformed scale, for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t , AUC_∞ , 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.

3.9.2 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.

3.9.2.1 Single-Dose Studies

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

i. AUC_t - ratio

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.

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 (Reference 2 and 3). Use of alternative methods *MUST* be stated *a priori* in the protocol and cannot be added retrospectively.

BIOAVAILABILITY/BIOEQUIVALENCE**ii. C_{\max} - ratio**

The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133% calculated using log transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125% will apply.

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

3.9.2.2 Steady-State Studies**i. Immediate Release Dosage Forms**

The acceptance criteria are the same as for single dose studies but using AUC_{τ} instead of AUC_t

ii. Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

▪ AUC_{τ} - ratio

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.

▪ $C_{\max (ss)}$ and $C_{\min (ss)}$

The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.75-1.33 (75 – 133%) 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.

3.10 Reporting of Results

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.

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3.10.1 Clinical Report

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

- i. A statement indicating the independence of the ethics committee.
- ii. Documented proof of ethical approval of the study.
- iii. A complete list of the members of the ethics committee, their qualifications and affiliations.
- iv. An independent monitor's report on the study.
- v. Names and affiliations of the all investigator(s), the site of the study and the period of its execution.
- vi. The names and batch numbers of the products being tested.
- vii. The manufacturing sites (address of the manufacturer of both the reference and the test product).
- viii. Expiry date of the reference product and the date of manufacture of the test product used in the study.
- ix. Assay and comparative dissolution profiles for test and reference products.
- x. CofA of the API used in the test product bio-batch.
- xi. A signed statement confirming that the test product used in the bio-study is the same as the one that is submitted for registration.
- xii. A summary of adverse events which must be accompanied by a discussion on the influence of these events on the outcome of the study.
- xiii. A summary of protocol deviations (sampling and non-sampling) which must be accompanied by a discussion on the influence of these adverse events on the outcome of the study.
- xiv. Subjects who drop out or are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.10.2 Analytical Report

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

- i. The full analytical validation report.
- ii. All individual subject concentration data.

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- iii. 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).
- iv. Calibration data i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters for the entire study.
- v. Quality control samples for the entire study.
- vi. Chromatograms from analytical runs for 20% of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.
- vii. Analytical data from subjects who dropped out of the study due to an adverse drug event should also be presented.
- viii. A summary of protocol deviations which must be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations must be justified.

3.10.3 Pharmacokinetic and Statistical Report

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

- i. All drug concentration *versus* time data from the bio-study. This data must be submitted in hard copy and also formatted on a diskette 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 (Appendix 2).
- ii. The method(s) and programs used to derive the pharmacokinetic parameters from the raw data.
- iii. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.
- iv. Tabulated summaries of pharmacokinetic and statistical data.
- v. 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.
- vi. Drug concentration data of any subject withdrawn from the study due to an adverse drug event should also be submitted, but should not be included in the statistical analysis.

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- i. The study report should be accompanied by a signed QA statement confirming release of the document.
- ii. A declaration must 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 the status of GCP and GLP &/or cGMP conditions at the site(s). All audit certificates should clearly indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).
- iii. The applicant should submit an independent monitor's report on the clinical portion of the study. This report should clearly indicate the date of monitoring and the name, address and qualifications of the monitor and should be included in the study report.

3.11 Expiry Dates of Biostudies

The bioavailability/ bioequivalence study must have been completed not longer than three years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS**4.1 Orally Administered Drug Products Intended for Systemic Action****4.1.1 Solutions**

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

4.1.2 Suspensions

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

4.1.3 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* 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 Guideline for Dissolution Testing).

BIOAVAILABILITY/BIOEQUIVALENCE**4.1.4 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.

4.1.5 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 they might be swallowed by a patient without proper chewing. 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.

4.2 Orally Administered Drugs Intended for Local Action

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 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 active substance in the same concentration as the currently approved product.

In the case of other parenteral routes other than i/v., 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 active substance and the same or comparable excipients as the medicinal product currently approved, 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 intramuscular dosage forms monitoring is required until at least 80% of the AUC_{∞} has been covered.

4.4 Topically Administered Products**4.4.1 Locally Acting**

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended

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to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

Topical formulations, other than a simple solution, 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 there has been data to show the correlation between release through a membrane and clinical efficacy data.

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

4.4.2 Systemically Acting

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

4.5 Products Intended for Other Routes of Administration

Products for local use (oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration.) 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.

4.6 Variations or Post Registration Amendments

For all post registration changes that require proof of efficacy the requirements of this guideline will be applicable.

5. WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Bio-waivers will be considered under the circumstances detailed below.

5.1 Immediate Release Products

5.1.1 Class 1 Drug Substances

When the drug product contains a Class 1 drug substance(s) (based on the Biopharmaceutics Classification System, BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients

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a bio-waiver may be acceptable.

The drug substances must be highly soluble, highly permeable and the dosage form rapidly dissolving (see Guideline for Dissolution Testing).

The applicant must provide relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5).

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (See Section 2.9) in its active and inactive ingredients, a bio-waiver may be acceptable.

In such cases the demonstration of bioequivalence *in vivo* of one or more of the lower strength/s may be waived based on dissolution tests (see Guideline for Dissolution Testing) and an *in vivo* study on the highest strength.

1. **For Multi-source pharmaceutical products**, 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 when an *in vivo* BE study was performed on a lower strength of the same drug product provided that:
 - i. Linear elimination kinetics has been shown over the therapeutic dose range.
 - ii. The higher strength is proportionally similar to the lower strength.
2. **For New Chemical Entities** with questions on toxicity, bio-waivers for a higher strength will be determined to be appropriate based on:
 - i. Clinical safety and/or efficacy studies including dose desirability of the higher strength, and
 - ii. Linear elimination kinetics over the therapeutic dose range, and
 - iii. The higher strength being proportionally similar to the lower strength, and
 - iv. The same dissolution procedures being used for both strengths and similar dissolution results obtained.

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 ≥ 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 , must also be submitted but will not be used as an acceptance criterion (Reference 6).

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Note: Details on the performance of dissolution studies are described in the Guideline for Dissolution Testing and not in the BA-BE guideline.

5.2 Modified Release Products**5.2.1 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 bio-waiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a bio-waiver should be generated for each strength using the recommended dissolution test methods described in the Guideline for Dissolution Testing.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

- i. In the same dosage form but in a different strength, and
- ii. Is proportionally similar in its active and inactive ingredients, and
- iii. 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 Section 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed (see Guideline for Dissolution Testing).

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6 References

1. Sample size determination for bioequivalence assessment by means of confidence intervals. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, Vol. 29 No. 1 (1991) 1-8, E. Diletti, D. Hauschke and V.W. Steinijans.
2. Workshop Report: Shah, V.P. et al., *Pharmaceutical Research*: 2000; 17:1551-1557.
3. Evaluation of the Bioequivalence of Highly-Variable Drugs and Drug Products. *Pharm. Res.* 18:6 (2001) 728-733, L. Tothfalusi, L. Endrenyi, K.K. Midha, M. J. Rawson and J.W. Hubbard.
4. Limits for the Scaled Average Bioequivalence of Highly-Variable Drugs and Drug Products. *Pharm. Res.* 20:3 (2003) 382-389, L. Tothfalusi and L. Endrenyi.
5. Guidance for Industry. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.
6. Mathematical Comparison of Dissolution Profiles. *Pharm. Technol.* 20:6 (1996) 64-74, J.W. Moore and H.H. Flanner.

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APPENDIX 1 - Abbreviations and Symbols.

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_{∞}	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
AUC_{τ}	AUC during a dosage interval at steady state
MRT	mean residence time
Ae_t	cumulative urinary excretion from drug administration until time t
Ae_{∞}	Amount of unchanged drug excreted in the urine at infinite time (7-10 half lives).
$t_{1/2}$	elimination half-life
%PTF	$(C_{\max (ss)} - C_{\min (ss)}) / C_{av} \cdot 100$
%Swing	$(C_{\max (ss)} - C_{\min (ss)}) / C_{\min} \cdot 100$

MEDICINES CONTROL COUNCIL



DEPARTMENT OF HEALTH
Republic of South Africa



MEDICINES CONTROL COUNCIL

ADDENDUM 4

STABILITY STUDIES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

This guideline will come into effect from 1 October 2004.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES

MS M.P. MATSOSO

DATE: 29/4/2003

STABILITY

STABILITY STUDIES

The Tripartite guideline, which has been developed within the Expert Working Group (Quality) of the International Conference on Harmonization (ICH), provides a general indication on the requirements for stability testing. It primarily addresses the information required in applications for registration for new chemical entities and associated medicinal products. This guideline is adopted with only minor modifications. It contains aspects relating to testing conditions, numbers of batches to be tested and the requirements regarding follow-up stability data and applicants are advised to study this guideline carefully.

Applicants are reminded that the Tripartite guideline has now been included in the USP23 (<1196>) and latest updates appear on the ICH website.

Applicants are also referred to the following guidelines on the ICH website:

1. Stability Data Package for Registration in Climatic Zones III and IV (Q1F)
2. Photostability Testing (Q1B)

Appendices 1 and 2 attached to this guideline comprise -

APPENDIX 1 - GLOSSARY AND INFORMATION

APPENDIX 2 - APPROPRIATE TESTS

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APPENDIX 2

1 STABILITY TRIAL DESIGN

There shall be a written testing program designed to assess stability characteristics of dosage forms. The results of such stability testing shall be used in determining appropriate storage conditions and retest or expiry dates.

The design of the study should consider the methodology for determining the stability of the active substance and dosage forms. The following factors must be considered in designing a stability trial:

1.1 ACTIVE PHARMACEUTICAL INGREDIENT

1.1.1 New Chemical Entity

1.1.1.i General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

The actual studies to be carried out will depend on the nature of the active substance, but may include the effect of elevated temperatures or low temperatures, susceptibility to moisture, oxidation and the effect of light. The effect of pH and high oxygen atmosphere may be important for aqueous solutions or suspensions of the active substance.

1.1.1.ii Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

1.1.1.iii Formal Studies