# GUIDELINE ON REGISTRATION REQUIREMENTS TO ESTABLISH THE INTERCHANGEABILITY OF PHARMACEUTICAL DRUG PRODUCTS

**Document Number:** PE&R/GL/IP/009
**Document History:** 1st Edition
**Effective Date:** 01-Nov-2024

**Drug Regulatory Authority of Pakistan**
**Islamabad-Pakistan**

# 1. HISTORY

This is the first edition of these guidelines.

# 2. APPLICATION

This document applies to pharmaceutical drug products for human use only.

# 3. SCOPE

This guideline is intended to provide recommendations on conducting bioequivalence (BE) studies during both the development and post-approval phases.

Deviations from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided.

# Table of Contents

# 4. INTRODUCTION

BE for drug products with systemic action is largely established via clinical pharmacokinetic (PK) BE studies or comparative in vitro dissolution studies. This document provides guidance to the industry, when defining requirements for approval of pharmaceutical drug products. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of a drug product without compromising the safety, quality and efficacy.

The Drug Regulatory Authority of Pakistan (DRAP) ensures that all pharmaceutical products conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end user.

This guidance is generally applicable to **orally administered drug products** as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g., transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Some information applicable to locally acting products is also provided in this document. Pharmaceutical drug products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the generic drugproduct is therapeutically equivalent and interchangeable with the comparator product. It should be noted that interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use.

# 5. LEGAL FRAMEWORK

Drug Regulatory Authority of Pakistan Act 2012 was promulgated in November 2012 to provide for effective coordination and enforcement of The Drugs Act 1976 (XXXI of 1976) and to bring harmony in inter-provincial trade and commerce of therapeutic good. The section 7(a)(ix) provides implementation of internationally recognized standards including bioequivalence studies in order to determine the quality, safety and efficacy of drug products approved for grant of market authorization. The Bio-Study Rules 2017, notified under SRO 697 (I)/ 2018shall be applied on all BE Studies conducted on human subjects.

# 6. DOCUMENTATION OF EQUIVALENCE FOR MARKETING AUTHORIZATION

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

- comparative pharmacokinetic studies in humans, in which the API and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and $C_{max}$ that reflect the systemic exposure.
- comparative pharmacodynamics studies in humans.
- comparative clinical trials.
- comparative in vitro tests.

Currently, the method which have been used most often to document equivalence for most orally administered pharmaceutical products for systemic exposure are conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods. Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products depends on many factors, including the characteristics of the API and the pharmaceutical product.

Where an API produces measurable concentrations in an accessible biological fluid, such as plasma, comparative pharmacokinetic studies can be performed. This type of study is considered gold standard in equivalence testing; however, where appropriate, in vitro testing, e.g., BCS based biowaivers for immediate release pharmaceutical products, can also assure equivalence between the multisource product and the comparator product. Where an API does not produce measurable concentrations in an accessible biological fluid and a BCS based biowaiver is not an option, comparative pharmacodynamics studies may be an alternative method for documenting equivalence.

### 6.1 When equivalence studies are not necessary

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

a. when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients (e.g.,

buffer, preservative and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product. The same principles are applicable for parenteral oily solutions but, in this case, the use of the same oily vehicle is essential. Similarly, for micellar solutions, solutions containing complexing agents or solutions containing co solvents of the same qualitative and quantitative composition of the functional excipients are necessary in order to waive equivalence studies and the change of other excipients should be critically reviewed.

b. when pharmaceutically equivalent products are solutions for oral use (e.g. syrups, elixirs and tinctures), contain the API in the same molar concentration as the comparator product, contain the same functional excipients in similar concentrations (if the API is BCS Class I) and the same excipients in similar concentrations (for APIs from other BCS classes);
c. when pharmaceutically equivalent products are in the form of powders for reconstitution as an aqueous solution and the resultant solution meets either criterion (a) or criterion (b) above.
d. when pharmaceutically equivalent products are gases.
e. when pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations. Certain excipients (e.g., preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided their use is not expected to affect bioavailability, safety and/or efficacy of the product.
f. when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations (note that a waiver would not apply to other topical dosage forms like gels, emulsions or suspensions, but might be applicable to oily solutions if the vehicle composition is sufficiently similar.
g. when pharmaceutically equivalent products are aqueous solutions for nebulization or nasal drops, intended to be administered with essentially the same device, contain the same API(s) in the same concentration and contain the same excipients in similar concentrations (note that this waiver does not apply to other dosage forms like suspensions for nebulization, nasal drops where the API is in suspension, nasal sprays in solution or suspension, dry powder inhalers or pressurized metered dose inhalers in solution or suspensions). The pharmaceutical product may include different excipients provided their use is not expected to affect bioavailability, safety and/or efficacy of the product.

For situations (b), (c), (e), (f) and (g) above it is responsibility of the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are the same and that they are in concentrations similar to those in the comparator product or, where applicable (i.e. (a), (e) and

(g)), that their use is not expected to affect the bioavailability, safety and/or efficacy of the product.

### 6.2 When equivalence studies are necessary and types of studies required

Except for the cases discussed in section 3, this document recommends that documentation of equivalence with the comparator product be required for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing.

# 7. TYPE OF STUDIES

### 7.1. In Vivo Studies

All Studies including comparative pharmacokinetic studies & comparative clinical trials or any other studies involving human subjects shall only be conducted after approval from the Clinical Studies Committee (CSC) as per the Bio-Study Rules, 2017.

For certain APIs and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic comparative bioavailability (bioequivalence) study, a comparative pharmacodynamic study or a comparative clinical trial is conducted. In vivo documentation of equivalence is necessary when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence. Examples include:

a. oral, immediate-release pharmaceutical products with systemic action, except for the conditions outlined in section 8.
b. non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin inserted contraceptives.
c. modified-release pharmaceutical products designed to act systemically, except for the conditions outlined in section 8
d. fixed-dose combination (FDC) products with systemic action, where at least one of the APIs requires an in vivo study.
e. non-solution pharmaceutical products, which are for non- systemic use (e.g., for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption.

In the case of non-solution pharmaceutical products for non-systemic use, the equivalence is established through, e.g., comparative clinical or pharmacodynamic studies, local availability studies and/or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e., to assess unintended systemic absorption.

### 7.2. In Vitro Studies

For certain APIs and dosage forms, in vitro documentation of equivalence may be appropriate. In vitro approaches for systemically acting oral products are discussed in relevant section .

# 8. INVESTIGATIONAL PRODUCT

### 8.1 Multisource Pharmaceutical Product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch control results, lot number, manufacturing date and, if possible, expiry date for the multisource product should be stated. Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and are produced with the same formulation and similar equipment and process to that planned for commercial production batches.

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

### 8.2 Choice of comparator product

. The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance. However, these products may not always be easy to obtain or may no longer be available on the market.
Following options for selection of a comparator product may be exercised in order of preference:

i. Nationally authorized innovator drug product
ii. An innovator product approved by a stringent regulatory authority, i.e. a country associated to The International Conference on Harmonisation of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH) but do not have national registration.

iii. A product having approval in an ICH-associated country;
iv. WHO-recommended comparator product included in the international list of comparator products
v. A product approved in reference regulatory authorities as approved by Registration Board
vi. In case that no innovator or comparator product can be identified according to the above, the choice of the comparator should be made carefully and should be comprehensively justified by the applicant. In this case, the most important selection criteria in order of preference are:

a. Extensive documented use in clinical trials reported in peer reviewed scientific journals,
b. A long and unproblematic period of post-market surveillance

Additionally, these comparators should conform to all appropriate compendial quality standards. It is recommended that potency and in vitro dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to the performance of an equivalence study. Content of the API(s) of the comparator product should be close to the label claim and the difference between two products being compared should not be more than ± 5%. If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within ± 5%, potency correction may be required on the statistical results from the bioequivalence study.

### 8.3 Selection of strength

In bioequivalence studies the molar equivalent dose of multisource and comparator product must be used. For a series of strengths that can be considered proportionally formulated the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose, i.e., more than one dosage unit, may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximal daily dose of the dosage regimen.

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

### 8.4 Non-linear pharmacokinetics

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

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

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

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

# 9. QUANTIFICATION OF API

For the measurement of concentrations of the active compound and/or metabolites in biological matrices, such as serum, plasma, blood and urine, the applied bioanalytical method should be well characterized, fully validated and documented to a satisfactory standard in order to yield reliable results.
The validation of bioanalytical methods and the analysis of subject samples for clinical trials in humans should be performed following the principles of good clinical practice (GCP), good laboratory practice (GLP) and the most up-to-date guidelines from DRAP & other Reference Regulatory Authorities (RRAs).
State-of-the-art principles and procedures for bioanalytical method validation and analysis of study samples should be employed. The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are:

- selectivity;
- lower limit of quantification;
- the response function and calibration range (calibration curve performance);
- accuracy;
- precision;
- matrix effects;

- stability of the analyte(s) in the biological matrix;
- stability of the analyte(s) and of the internal standard in the stock and workingsolutions, and in extracts throughout the entire period of storage and processing conditions.

In general:

- the analytical method should be able to differentiate the analyte(s) of interest and, if employed, the internal standard from endogenous components in the matrix or other components in the sample;
- the lower limit of quantification (LLOQ), being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision;
- the response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and 6–8 non-zero samples covering the expected range;
- within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte, the QC samples, at a minimum of three different concentrations;
- matrix effects should be investigated when using mass spectrometric methods;
- stability of the analyte in the stock solution and in the matrix should be proven covering every step taken during sample preparation and sample analysis, as well as the storage conditions used;
- when more than one analyte is present in subject samples, it is recommended to demonstrate the stability of the analytes in the matrix in the presence of the other analytes under standard conditions such as freeze–thaw testing, short-term room temperature storage and long-term freezer storage.
- where changes are made to an analytical method that has already been validated, a full validation may not be necessary depending on the nature of the changes implemented. A partial validation may be acceptable;
- a cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method;
- analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified;

- calibration and QC standards should be processed in an identical manner and at the same time as the subjects' samples from the same run;
- reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or SOP. Reinjection of a full analytical run or of individual calibration standard samples or QC samples, simply because the calibration or QCs failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable as this may affect and bias the outcome of such a study;
- when analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis (ISR)). ISR should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used;
- the samples from one subject (all periods) should be analysed in the same analytical run if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).
The results of subject sample determination should be given in the analytical report together with calibration and QC sample results, repeat analyses, reinjections and reintegrations (if any) and a representative number of sample chromatograms.

# 10. STATISTICAL ANALYSIS

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval around the ratio of the log- transformed population means (multisource/comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance. To establish bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the formulations being compared (i.e. leading to the same decision whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and $C_{max}$) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of either common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Normally the ANOVA model should include formulation, period, sequence and subject factors. Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance. The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products. The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery if required.

For $t_{max}$ descriptive statistics should be given. Where $t_{max}$ is considered clinically relevant, median and range of tmax should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary. Generally, the sample size is not calculated to have enough statistical power for $t_{max}$. However, if $t_{max}$ is to be subjected to a statistical analysis, this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the $t_{max}$ estimate. For parameters describing the elimination phase ($t_{1/2}$) only descriptive statistics should be given. Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable.

## 10.1 Acceptance Ranges

***$AUC_{0-t}$ - ratio***

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80.00–125.00%. If the API is determined to possess a narrow therapeutic index (NTI) the bioequivalence acceptance range should be restricted 90.00–111.11%. The same criterion applies to the parameter AUCτ in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

***$C_{max}$ - ratio***

For maximal concentration data, the acceptance limit of 80.00–125.00% should be applied to the 90% confidence interval for the mean $C_{max}$ ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC ratio, and in certain cases this variability can make proving bioequivalence challenging. If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate. The same criterion applies to the parameters $C_{max}$ and $C_{tau}$ in multiple-dose studies.

***$t_{max}$ - difference***

Statistical evaluation of tmax makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. In such a case, comparison of the median and range data for each product should be undertaken. For other pharmacokinetic parameters the same considerations as outlined above apply.

## 10.2 Reporting of Results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with GCP and GLP rules. The relevant ICH guideline can be used in the preparation of the study report. The responsible investigator(s) should sign the respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. Results of in vitro dissolution tests conducted in media with pHs of 1.2, 4.5 and 6.8 and the QC media, if different, should be provided. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

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

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, together with all calibration standards and QC samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between FPP administration and blood sampling, in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any deletion of data should be

documented and justified.

Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for. All adverse events that occurred during the study should be reported together with the study physician's classification of the events. Further, any treatments given to address adverse events should be reported.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the study protocol the reasons for the deviations should be stated.

# 11. SPECIAL CONSIDERATIONS

### 11.1.Fixed dose combinations (FDCs)

If the bioequivalence of FDC products is assessed by in vivo studies, the study design should follow the same general principles as described in previous sections. The multisource FDC product should be compared with the pharmaceutically equivalent comparator FDC product. In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator. Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes. Statistical analyses should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

### 11.2. Highly variable active pharmaceutical ingredients

A "highly variable API" has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA CV. Proving the bioequivalence of pharmaceutical drug products containing highly variable APIs can be problematic because the higher the ANOVA CV, the wider the 90% confidence interval. Thus, large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.

Although there is variability in how regulatory authorities deal with the issue of highly variable APIs, the most rigorous of the current approaches involve the scaling of bioequivalence

acceptance criteria based on the intrasubject standard deviation observed in the relevant parameters for the comparator product. Of the two most common assessment parameters $C_{max}$ is subject to the highest variability and hence is the parameter for which a modified approach is most needed.

For highly variable pharmaceutical drug products it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated cross-over bioequivalence study be conducted and reference- scaled average bioequivalence be employed to widen the acceptance interval for the Cmax parameter, if the intrasubject variability for $C_{max}$ following replicate administrations of the comparator product is > 30%. If this is the case the acceptance criteria for $C_{max}$ can be widened to a maximum of 69.84–143.19%. The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for $C_{max}$ is defined based upon the intrasubject variability seen in the bioequivalence study using scaled average bioequivalence according to [U, L] = exp [± k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the intrasubject standard deviation of the log-transformed values of $C_{max}$ of the reference product. Table A6.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

**Acceptance Level of different levels of variability**

| Intrasubject CV (%) | Lower limit | Upper Limit |
|---|---|---|
| 30 | 80.00 | 125.00 |
| 35 | 77.23 | 129.48 |
| 40 | 74.62 | 134.02 |
| 45 | 72.15 | 138.59 |
| ≥50 | 69.84 | 143.19 |

$$CV\ (\%) = \sqrt{(e\ \hat{}\ (S\_WR\ \hat{}2) - 1)}$$

The Geometric Man Ration (GMR) for $C_{max}$ should lie within the conventional acceptance range of 80.00–125.00%.

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

For multiple-dose studies, a similar approach can be applied to the following parameters if the intrasubject variability for the parameter is found to be > 30%: $C_{max}$, $C_{tau}$ and partial AUCs if required. The standard bioequivalence acceptance criterion will apply to AUCτ without scaling. The approach to be employed should be clearly defined prospectively in the study protocol. The regulatory authority of the country to which the study data will be submitted should be consulted before commencing the study to confirm that the proposed approach is acceptable for that jurisdiction

# 12. IN VITRO EQUIVALENCE TESTING

Over the past three decades, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a Quality Control test, is now emerging as a surrogate equivalence test for certain categories of orally administered, pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) similarity in *in vitro* dissolution profiles, in addition to excipient comparisons and a risk–benefit analysis, can be used to document equivalence of a multisource product with a comparator product.

## 12.1 In Vitro Equivalence Testing In Context Of The Biopharmaceutics Classification System

### 12.1.1 Biopharmaceutics Classification System

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

Combining the dissolution results and a critical examination of the excipients of the pharmaceutical product with these two properties of the API takes the four major factors that govern the rate and extent of API absorption from immediate release, solid dosage forms into account. On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having “very rapid”, “rapid”, or “not rapid” dissolution characteristics.

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

*“Oral FPPs containing an API possessing a narrow therapeutic index are not eligible for a so-*

*called biowaiver based on the BCS approach".*

### 12.1.2 High Solubility

An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended.

### 12.1.3 High Permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. Ideally the mass balance study or comparison with an intravenous comparator dose would be conducted at the same dose as that used for the solubility classification. If this is not possible, dose linearity of pharmacokinetics should be used to justify the use of other doses.

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

In vivo intestinal perfusion in humans is an acceptable alternative test method. When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

Supportive data can be provided by the following additional test methods:

i. in vivo or in situ intestinal perfusion using animal models;
ii. in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco 2) using a method validated using APIs with known permeabilities, although data from neither method (i) nor (ii) would be considered acceptable on a stand-alone basis.

In these experiments, high permeability is assessed with respect to the high permeability of a series of reference compounds with documented permeabilities and values of the absorbed fraction, including some for which fraction of dose absorbed is at least 85%

## 12.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the Biopharmaceutics Classification System

For exemption from an in vivo bioequivalence study, an immediate release, multisource product should exhibit "very rapid" or "rapid" in vitro dissolution characteristics depending on the BCS properties of the API. In vitro data should also demonstrate the similarity of dissolution profiles between the multisource and comparator products

### 12.2.1 Very rapidly dissolving

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

- pH 1.2 HCl solution or buffer;
- a pH 4.5 acetate buffer;
- a pH 6.8 phosphate buffer.

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

### 12.2.2 Rapidly dissolving

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

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

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

# 13. QUALIFICATION FOR A BIOWAIVER BASED ON BIOPHARMACEUTICS CLASSIFICATION SYSTEM

A biowaiver based on the BCS considers:

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

Only when there is an acceptable risk–benefit balance in terms of public health and risk to the individual patient, bioequivalence testing should be waived and the in vitro methods described in this section applied as a test of product equivalence.

## 13.1 Risk reduction and assessment of excipients

The risk of reaching an incorrect decision that the multisource product is equivalent to the comparator product can be reduced by correct classification of the API and by following the recommendations for dissolution testing and comparison of the dissolution profiles. In all cases it should be further demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g. by effects on GI motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

In all cases, well established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API, **e.g. mannitol, sorbitol or surfactants**, should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

For biowaivers for products containing **Class 1** APIs there is some flexibility in the excipients employed, with the exception of critical excipients as discussed above. It is recommended that the excipients employed be present in the comparator product or be present in other products which contain the same API as the multisource product and which have marketing authorizations in ICH associated countries.

For biowaivers for products containing **Class 3** APIs all excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator

product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation.

As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS.

## 13.2 Sub- and supra-bioavailable products

A further consideration is the potential risk to public health and to the individual patient, should an inappropriate decision with respect to bioequivalence be reached. Essentially there are two possible negative outcomes. The first arises when the multisource product is sub bioavailable. In this case substitution of the comparator with the multisource product could lead to reduced therapeutic efficacy. APIs which must reach a certain concentration to be effective (e.g. antibiotics) are most susceptible to problems of sub bioavailability. The second negative outcome arises when the multisource product is supra bioavailable. In this case substitution of the comparator with the multisource product could lead to toxicity. APIs which exhibit toxic effects at concentrations close to the therapeutic range are most susceptible to problems of supra bioavailability. For these reasons therapeutic index is an important consideration in determining whether the biowaiver based on BCS can be applied or not.

## 13.3 Dissolution profile comparison

Approval of multisource formulations using comparative in vitro dissolution studies should be based on the generation of comparative dissolution profiles rather than a single point dissolution test.

# 14. DISSOLUTION CRITERIA FOR BIOWAIVERS BIOPHARMACEUTICS CLASSIFICATION SYSTEM ACCORDING TO THE PROPERTIES OF ACTIVE PHARMACEUTICAL INGREDIENT.

The major application of BCS is to provide criteria for biowaiver of multisource products. It is recommended that products containing the following BCS classes of APIs be eligible for a biowaiver:

- BCS Class 1 APIs, if the multisource and comparator product are *very rapidly dissolving or similarly rapidly dissolving*;
- BCS Class 3 APIs, if the multisource and comparator product are *very rapidly dissolving*.

1. Dosage forms of APIs that are highly soluble, highly permeable (BCS Class 1) with acceptable excipient content and favourable risk–benefit analysis and which are rapidly dissolving, are eligible for a biowaiver based on the BCS provided:

   i. the dosage form is **rapidly dissolving** and the dissolution profile of the multisource product is similar to that of the comparator product in aqueous buffers at pH 1.2, pH 4.5 and pH 6.8 using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);

   ii. if both the comparator and the multisource dosage forms are **very rapidly dissolving** the two products are deemed equivalent and a profile comparison is not necessary.

Dosage forms of APIs that are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers provided all the criteria (a–d) as provided in 8.2. and the risk–benefit is additionally addressed in terms of extent, site and mechanism of absorption.

In general, the risks of reaching an inappropriate biowaiver decision need to be more critically evaluated when the extent of absorption is lower (especially if absolute bioavailability < 50%); therefore, it is essential that the excipients in the proposed product formulation be scrutinized carefully. In order to minimize the risk of an inappropriate decision, excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator.

If it is deemed that the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS when both the comparator and the multisource dosage forms are very rapidly dissolving (85% dissolution in 15 minutes as mentioned above).

### 14.1 In Vitro equivalence based on dose proportionality of formulations

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

### 14.2 Proportional formulations

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

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has exactly half of all the active and inactive ingredients contained in a tablet of 100 mg strength and twice what would be contained in a tablet of 25 mg strength). For immediate release products, coating components, capsule shell, color agents and flavors are not generally required to meet this requirement.

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

For (ii) a waiver is considered:

- if the amounts of the different excipients or capsule contents are the same for the strengths concerned and only the amount of the API has changed;
- if the amount of filler is changed to account for the change in amount of API: the amounts of other core excipients or capsule content should be the same for the strengths concerned.

### 14.3 Qualification of biowaivers based on dose proportionality of formulations

#### 14.3.1 <u>Immediate release tablets:</u>

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

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

ii. all strengths are proportionally similar in formulation to that of the strength studied;

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

As for the BCS based biowaiver, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in section 9.2, the profile comparison with an $f_2$ test is unnecessary.
In the case where an immediate release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.
If approval of one strength of a product is based on a BCS based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS based biowaivers as opposed to a biowaiver based on dose-proportionality.

### 14.3.2 Delayed release tablets and capsules

For delayed release tablets, for a series of strengths of a multisource product where the strengths are proportionally similar in formulation to that of the strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the recommended test condition for delayed release product, e.g. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro resistant coating with respect to the surface area (not to core weight) to have the same gastro resistance (mg/cm2).

For delayed release capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$) under the test conditions recommended for delayed release products (see above) is sufficient for a biowaiver.

### 14.3.3 Extended release tablets and capsules

i. For extended-release tablets, when there is a series of strengths of a multisource product that are proportionally similar in their active and inactive ingredients and have the same API release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if

they exhibit similar dissolution profiles to the highest strength, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the QC media by the recommended test method.

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

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

### 14.4 Dissolution profile comparison for biowaivers based on dose proportionality of formulations

As for biowaivers based on the BCS, a model-independent mathematical approach (e.g. $f_2$ test) can be used for comparing the dissolution profiles of two products. The dissolution profile of the two products (reference strength and additional strength) should be measured under the same test conditions. The dissolution sampling times for both reference strength and additional strength profiles should be the same. For example:

- for immediate release products 5, 10, 15, 20, 30, 45 and 60 minutes;
- for 12-hour extended-release products 1, 2, 4, 6, 8 and 12 hours;
- for 24-hour extended-release products 1, 2, 4, 6, 8, 16 and 24 hours.
-

#### 14.4.1 <u>In vitro equivalence testing for non-oral dosage forms</u>

In the case of intravenous micellar solutions with the same qualitative and quantitative composition of the surfactant, but significant changes to other excipients, an in vitro comparison might avoid the need for in vivo studies if a similar micellar system and API release from the micelle after dilution of the FPP or API administration into the blood system is ensured.
Locally applied, locally acting products in the form of aqueous suspensions containing the same API(s) in the same molar concentration and essentially the same excipients in comparable concentrations might be waived from the demonstration of equivalence by means of local availability, pharmacodynamic or clinical studies if in vitro characterization is able to ensure a similar crystallographic structure and particle size distribution as well as any other in vitro test specific for each dosage form, e.g. dissolution. The methodological details for the techniques mentioned below are not covered in these guidelines. Additional information regarding these techniques should be sought from guidelines produced by SRAs or from state-of-the-art literature.

(a) Suspensions for nebulization with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if

the particles in the suspensions are shown to have the same crystallographic structure and particle size distribution as those from the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution. In addition, the nebulized droplets should exhibit a similar aerodynamic particle size distribution to that of the comparator product.

(b) Suspensions for nebulization with different qualitative and quantitative composition might be granted a waiver if, in addition to the requirements defined above under (a), the difference in excipient composition does not alter the nebulizer efficiency (e.g. by the presence or absence of a different surfactant or preservative) and the aerodynamic particle size distribution (e.g. altering product hygroscopicity by the presence of a different amount of salt as isotonic agent). To this end the appropriate state-of-the-art in vitro test should be conducted to ensure product equivalence. Any difference in excipients should be critically reviewed because certain excipients that are considered irrelevant in other dosage forms (e.g. preservative, substance to adjust tonicity or thickening agent) may affect safety and/or efficacy of the product.

(c) Nasal drops where the API is in suspension with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution to that of the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(d) Nasal drops where the API is in suspension, with qualitative or quantitative differences in excipient composition with respect to the comparator product, might be waived from in vivo studies if, in addition to the requirements defined above under (c), the difference in excipient composition does not affect efficacy and safety (e.g. a different preservative may affect the safety profile due to greater irritation of the nasal passages and a different viscosity or thixotropy may affect the residence time in the site of action). Therefore, any difference in excipients should be critically reviewed.

(e) Nasal sprays in solution with the same qualitative and quantitative composition in excipients can be granted waivers based on a battery of in vitro tests as defined by SRAs (*18*, *25*).

(f) Nasal sprays in solution with qualitative and quantitative differences in the excipient composition might be waived if, in addition to showing similarity in the battery of in vitro tests referenced under (e), differences in excipients are critically reviewed as described above under (d).

(g) Nasal sprays in suspension with the same qualitative and quantitative composition in excipients might be waived if, in addition to the battery of in vitro tests referenced

above under (e), the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(h) Nasal sprays in suspension with qualitative and quantitative differences in excipient composition might be waived if, in addition to the battery of in vitro tests referenced above under (e) and (g), differences in excipients are critically reviewed as described above under (d).

(i) In the case of pressurized metered dose inhalers in solution or suspension, in vivo studies might be waived if similarity is shown in a battery of in vitro tests as described in specific guidelines produced by SRAs. A waiver of in vivo studies for a dry powder inhaler (DPI) is not considered feasible unless the device for the DPI is identical to the comparator.

(j) For pharmaceutically equivalent topical gel products, equivalence can be demonstrated by means of in vitro membrane diffusion studies when the products contain essentially the same excipients in comparable concentrations and the API(s) in the product are in solution (*27*).

(k) Otic and ophthalmic suspensions with the same qualitative and quantitative composition in excipients might be granted a
waiver if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test,
e.g. dissolution.

(l) Products acting locally in the GI tract containing highly soluble APIs (as defined by the BCS) in immediate release dosage forms might be waived from in vivo equivalence studies based on the same dissolution requirements as are applied for the BCS-based biowaiver.

### 14.4.2 In vitro equivalence testing for scale up and post approval changes

Although these guidelines refer primarily to registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following permissible changes to formulation or manufacturing after FPP approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics. More information on when dissolution testing may be used to support product variations is provided in WHO guidance on variations in pharmaceutical products.

# 15. GLOSSARY

**Definitions:**

Some important terms used in this guidance document are defined below. They may have different meanings in other contexts.

**Bioavailability**

The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. Reliable measurements of active pharmaceutical ingredient (API) concentrations at the site(s) of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can therefore be defined as the rate and extent to which the API or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations it is generally accepted that in the same subject an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the site(s) of action.

**Bioequivalence**

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

**Biological pharmaceutical product.**

A biological pharmaceutical product is a synonym for biological product or biological (as described in the reports of the Expert Committee on Biological Standardization in the World Health Organization (WHO) Technical Report Series). The definition of a pharmaceutical substance used in treatment, prevention or diagnosis as a "biological" has been variously based on criteria related to its source, its amenability to characterization by physicochemical means alone, the requirement for biological assays or arbitrary systems of classification applied by regulatory authorities. For the purposes of WHO, including the current document, the list of substances considered to be biologicals is derived from their earlier definition as "substances which cannot be fully characterized by physicochemical means alone and which therefore require the use of some form of bioassay". However, developments in the utility and applicability of physicochemical analytical methods, improved control of biological and biotechnology based production methods and an increased applicability of chemical synthesis to larger molecules, have made it effectively impossible to base a definition of a biological on any single criterion related to methods of analysis, source or method of production. Nevertheless many biologicals are produced using in vitro culture systems.

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

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

**Comparator product**

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 992, Annex 8 (2015)) should be used to identify a suitable alternative comparator product.

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

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

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

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

**Fixed-dose combination finished pharmaceutical product**

An FPP that contains two or more APIs.

**Generic product**

See multisource pharmaceutical products.

**Innovator pharmaceutical product**

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

**Interchangeable pharmaceutical product**

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

**In vitro equivalence dissolution test**

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

**In vitro quality control dissolution test**

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

**Multisource pharmaceutical products**

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

**Non-biological**

Not involving or derived from biology or living organisms.

**Pharmaceutical alternatives**

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

**Pharmaceutical equivalence**

Products are pharmaceutical equivalents if they contain the same molar amount of the same APIs in the same dosage form, if they meet comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the API solid-state properties, the excipients and/or the manufacturing process and other variables can lead to differences in product performance.

**Therapeutic equivalence.**

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

**Acronyms:**

| | |
|---|---|
| **API** | Active Pharmaceutical Ingredient |
| **AUC** | Area Under Curve |
| **BCS** | Biopharmaceutics Classification System |
| **BE** | Bioequivalence |
| **CSC** | Clinical Studies Committee |
| **DPI** | Dry Powder Inhaler |
| **DRAP** | Drug Regulatory Authority of Pakistan |
| **FPPs** | Finished Pharmaceutical Product |
| **GCP** | Good Clinical Practices |
| **GI** | Gastrointestinal |
| **GLP** | Good laboratory Practices |
| **GMP** | Good Manufacturing Practices |
| **ICH** | International Conference on Harmonization |
| **PK** | Pharmacokinetics |
| **PMDA** | Pharmaceuticals and Medical Devices Agency of Japan |
| **RRA** | Reference Regulatory Authority |
| **SRAs** | Stringent Regulatory Authorities |
| **WHO** | World Health Organization |

# 16. REFERENCES

1. The DRAP Act, 2012.
2. The Drugs Act, 1976.
3. The Drug (Licensing, Registering, & Advertising) Rules 1976.
4. The Bio-study Rules, 2017 notified vide SRO S.R.O. 697 (I)/2018 dated 05th June 2018.
5. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability WHO Technical Report Series, No. 1003, Annex 6.
6. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (2015) WHO Technical Report Series, No. 992, Annex 8.
7. ICH harmonised guideline on Bioequivalence for Immediate Release Solid Oral Dosage Forms (M13A).
8. ICH harmonised guideline on Biopharmaceutics Classification System-Based Biowaivers (M9).
9. ICH harmonised guideline on Guideline for Good Clinical Practice (E6).

**DRUG REGULATORY AUTHORITY OF PAKISTAN**
Prime Minister National Health Complex, Park Road,
Islamabad, Pakistan
**www.dra.gov.pk**