RWANDA FDA
Rwanda Food and Drugs Authority

GUIDANCE ON APPLICATION FOR BIOPHARMACEUTICS CLASSIFICATION SYSTEM BASED BIOWAIVERS

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety and efficacy of human medicinal products in order to protect public health by increasing access and availability of essential medicines.

Considering the provisions of the technical Regulations N° CBD/TRG/010 Governing the registration of human medicinal products especially in its articles 6, 7, 8, 9, 12 and 32, and the Guidelines No DHT/GDL/001 on submission of documentation for registration of human medicinal products, the authority has to issue the *Guidance N° DAR/GDL/001G On Application for Biopharmaceutics Classification System Based Biowaivers*

Rwanda FDA adopted the Common Technical Document (CTD) Guidelines on Submission of Documentation for registration of human medicinal products. These guidelines have been developed to provide guidance to the applicants and the Authority in managing applications for registration of human medicinal products. These guidelines were developed in reference to the existing Ministry of Health (MOH) guidelines on submission of documentation for registration of Human Pharmaceutical Products which were domesticated based on Compendium of Medicines Evaluation and Registration for Medicines Regulation Harmonization in the East African Community, World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Registration of Medicines for Human Use (ICH) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

Dr. Charles KARANGWA
Ag. Director General

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

APIs	Active Pharmaceutical Ingredients
BCS	Biopharmaceutics Classification System
CoA	Certificate of Analysis
EMA	European Medical Association
f2	Similarity factor
ICH	International Conference on Harmonisation
LTR	Local Technical Representative
pKa	Dissociation constant
SD	Standard deviation
USFDA	United States Food and Drug Administration

DEFINITIONS

Absorption - the uptake of substance from a solution into or across tissues. As a time dependent process; absorption can include passive diffusion, facilitated passive diffusion (with a carrier molecule), and active transport. A Pharmaceutical Product is considered to be highly absorbed when the measured extent of absorption of the highest therapeutic dose is greater or equal to (≥) 85%. High absorption: ≥ 85% of the administered dose absorbed.

Active moiety (Active): is the term used for the therapeutically active entity in the final formulation of a medicine, irrespective of the form of the API. The active is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (and the active) is propranolol.

Active Pharmaceutical Ingredient (API): A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

Bioavailability: refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution *vs.* intravenous), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities in terms of peak (Cmax and Tmax) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects with respect to both efficacy and safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

Biopharmaceutics Classification System (BCS)-based biowaivers are meant to reduce the need for establishing *in vivo* bioequivalence in situations where *in vitro* data may be considered to provide a reasonable estimate of the relative *in vivo* performance of two products. The BCS is a scientific approach designed to predict pharmaceutical absorption based on the aqueous solubility and intestinal absorptive characteristics of the Pharmaceutical Product.

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

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. The selection of the comparator product is provided in the guidelines for selection of comparator product.

Critical dose pharmaceutical product - Pharmaceutical product where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse pharmaceutical reactions which may be persistent,

irreversible, slowly reversible, or life threatening, which could result in hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

Dose solubility volume (DSV) - the highest therapeutic dose [milligram (mg)] divided by the solubility of the substance [milligram/millilitre (mg/mL)] at a given pH and temperature. For example, if a Pharmaceutcial Product has a solubility of 31 mg/mL at pH 4.5 (37°C) and the highest dose is 500 mg, then DSV = 500 mg/31 mg/mL = 16 mL at pH 4.5 (37°C).

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

Generic Pharmaceutical Product is a pharmaceutically equivalent product that may or may not be therapeutically equivalent or bioequivalent. Generic pharmaceutical products that are therapeutically equivalent are interchangeable.

High solubility: A Pharmaceutical Product is classified as highly soluble if the highest therapeutic dose of the Pharmaceutical Product is completely soluble in 250 mL or less of solvent over the pH range of 1.2-6.8 at 37 ± 1°C, that is (i.e.), DSV ≤ 250 mL over the pH range.

Highest dose - highest approved therapeutic dose for the Pharmaceutical Product in Rwanda. If not currently approved in Rwanda, the highest proposed dose is applicable.

Low absorption: less than (<) 85% of the administered dose absorbed.

Low solubility: A Pharmaceutical Product is classified as a low solubility compound if the highest therapeutic dose of the Pharmaceutical Product is not completely soluble in 250 mL of solvent at any pH within the pH range of 1.2-6.8 at 37 ± 1°C, i.e., DSV greater than (>) 250 mL at any pH within the range

Pharmaceutical alternatives: Pharmaceutical products are pharmaceutical alternatives if they contain the same active moiety but differ either in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength, administered by the same
route of administration but are otherwise not pharmaceutically equivalent. Pharmaceutical alternatives do not necessarily imply bioequivalence.

Pharmaceutical Dosage Form: A pharmaceutical dosage form is the form of the completed pharmaceutical product e.g. tablet, capsule, injection, elixir, suppository.

Pharmaceutical Equivalence: Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to changes in dissolution and/or absorption.

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

Proportionally Similar Dosage Forms/Products: Pharmaceutical products are considered proportionally similar in the following cases:

Rapidly dissolving product - a product in which not less than 85% of the labelled amount is released within 30 minutes or less during a product dissolution test under the conditions specified in these guidelines.

Solution - a homogenous mixture in a single phase with no precipitate.

Therapeutic Equivalence: Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent or are pharmaceutical alternatives and, after administration in the same

molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Very rapidly dissolving product - not less than 85% of the labelled amount is released within 15 minutes or less during a product dissolution test under the conditions specified in these guidelines.

I. INTRODUCTION

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e.*, it may represent a surrogate for *in vivo* bioequivalence. *In vivo*

bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble active pharmaceutical ingredients with known human absorption and considered not to have a narrow therapeutic index (see Section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

II. OBJECTIVES

To provide applicants of new pharmaceutical submissions with the information necessary to comply with respect to BCS-based biowaivers for comparative bioavailability studies to be used in support of the safety and efficacy of a pharmaceutical product.

When an application for a BCS-based biowaiver of comparative bioavailability studies versus a comparator product is submitted in support of the safety and efficacy of a pharmaceutical, the relevant Pharmaceutical Product and pharmaceutical product characteristics should meet the standards described in these guidelines in order to ensure compliance with the Regulations.

In vivo human data collected for the purpose of submission to Rwanda FDA should be collected in accordance with generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of subjects. They should be collected in compliance with the International Conference on Harmonisation (ICH) Guidelines (Topic E6) on Good Clinical Practice. The principles of Good Manufacturing Practice as indicated in Rwanda FDA GMP guidelines should be adhered to wherever applicable.

III. SCOPE

The data requirements and acceptance criteria outlined in these guidelines are intended to be applied to all applications for a BCS-based biowaiver of comparative bioavailability studies which provide pivotal evidence of the safety and efficacy of a product. These guidelines are designed to facilitate applicants seeking to waive bioequivalence studies, based on the BCS. Examples of cases where these guidelines apply are:

(a) Biowaivers for comparative bioavailability studies in support of the bioequivalence of subsequent-entry products;

(b) Biowaivers for bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials;

(c) Biowaivers for studies in support of significant post-approval changes and product line extensions; and

(d) Biowaivers for comparative bioavailability studies in support of Pharmaceutical Applications.

The scope of this document is limited to immediate-release and solid oral pharmaceutical pharmaceutical products that are intended to deliver medication to the systemic circulation.

Rwanda FDA has identified the Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS-based biowaiver application. Therefore, in some cases it is not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the Pharmaceutical Product solubility or permeability class.

IV. BCS CLASSIFICATION AND ELIGIBILITY OF A PHARMACEUTICAL PRODUCT

A biowaiver based on the BCS considers:

(a) the solubility and 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 (see below);

(c) the excipients used in the formulation (see below); and

(d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of, and clinical indications for, the API (for cases where an in vivo study would be required to demonstrate bioequivalence).

A pharmaceutical product is eligible for a BCS-based biowaiver providing:

- The Pharmaceutical Product(s) satisfy the criteria outlined in these guidelines;
- The pharmaceutical product is a conventional, immediate-release solid oral dosage form; and
- The pharmaceutical product is the same dosage form as the comparator product (e.g., a tablet versus a tablet).

Biowaivers based on BCS can be granted under the following conditions:

1. Dosage forms containing APIs which are highly soluble, and highly permeable (i.e. BCS classI), and are rapidly dissolving are eligible for a biowaiver based on the BCS provided:
    - the dosage form is *rapidly dissolving* (as defined in the Dissolution Guideline, i.e. no less than 85 % of the labelled amount of the API dissolves in 30 minutes) and
    - the dissolution profile of the multisource product is similar to that of the reference product at pH 1,2, pH 4,5 and pH 6,8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm (as described in the Dissolution Guideline) and meets the criteria of dissolution profile similarity,

    $f2 \geq 50$ (or equivalent statistical criterion). If both the comparator and the generic dosage forms are *very rapidly dissolving*, i.e. 85 % or more dissolution at 15 minutes or less in all 3 media under the above test conditions, the two products are deemed equivalent and a profile comparison is not necessary.

2. The appropriateness of the biowaiver is addressed, i.e. confirmation with supporting references, that no characteristic which requires an in vivo bioequivalence study is applicable.

Guidance on Application for Biopharmaceutics Classification System Based Bio waivers

In addressing the appropriateness of the BCS biowaiver the benefit-risk balance / ratio, clinical indications, food effect and any other relevant aspect should be included. Reference 12, WHO Technical Report Series 937 Annex 7 Section 9.2 and Annex 8 or the latest revision.

V. ADDITIONAL INFORMATION ON SEVERAL DOSAGE FORMS

Solutions: Pharmaceutically equivalent solutions for oral use (including syrups, elixirs, tinctures or other soluble forms but not suspensions), containing the active pharmaceutical ingredient in the same molar concentration as the comparator product, and containing only excipient(s) known to have no effect on gastrointestinal (GI) transit, GI permeability and hence absorption or stability of the active pharmaceutical ingredient in the GI tract are considered to be equivalent without the need for further documentation.

Pharmaceutically equivalent powders for reconstitution as solution, meeting the solution criteria above, are considered to be equivalent without the need for further documentation.

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

Fixed-dose combination products (including co-packaged products): Combination products should in general be assessed with respect to bioavailability and bioequivalence of APIs either separately (in the case of a new combination) or as an existing combination. The study in case of a new combination should be designed in such a way that the possibility of a pharmacokinetic and / or pharmacodynamic active-active interaction could be detected.

In general approval of FDC will be considered in accordance with the WHO Technical report series 929 "Guidelines for registration of fixed-dose combination pharmaceutical products 2005" or the latest revision and FDA "Guidance for Industry: Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV" October 2006 or the latest revision.

Medicines Intended For Local Action: Non-solution pharmaceutical products, which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc., application) and are intended to act without systemic absorption. In these cases, the bioequivalence is established through comparative clinical or pharmacodynamic, dermatopharmacokinetic studies and/or *in vitro* studies. In certain cases, active concentration measurement may still be required for safety reasons in order to assess unintended systemic absorption.

Parenteral Solutions: It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. In the event that this

information about the reference product cannot be provided by the applicant, it is incumbent upon the applicant to perform *in vivo* or *in vitro* studies to demonstrate that the differences in excipients do not affect product performance.

The influence of pH on precipitation should be clearly addressed and the absence of formation of sub-visible particulate matter over the physiological pH range be demonstrated.

Parenteral Aqueous solutions and Powders for reconstitution to be administered by parenteral routes (intravenous, intramuscular, subcutaneous) containing the same active pharmaceutical ingredient(s) in the same molar concentration and the same or similar excipients in comparable concentrations as the comparator product are considered to be equivalent without the need for further documentation.

Certain excipients (e.g. buffer, preservative, antioxidant) may be different provided the change in these excipients is not expected to affect the safety and/or efficacy of the medicine product.

Other parenterals bioequivalence studies are required. For intramuscular dosage forms, monitoring is required until at least 80 % of the AUC∞ has been covered.

Topical Products: Pharmaceutically equivalent topical products prepared as aqueous solutions containing the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. In the event that this information about the reference product cannot be provided by the applicant, it is incumbent upon the applicant to perform *in vivo* or *in vitro* studies to demonstrate that the differences in excipients do not affect product performance.

Topical Products for Local Action: The human vasoconstrictor test (blanching test) is recommended to prove bioequivalence of other topical preparations containing corticosteroids intended for application to the skin and scalp. Validated visual and/or chromometer data will be necessary.

Simple topical solutions with bacteriostatic, bactericidal, antiseptic and/or antifungal claims may qualify for a waiver based on appropriate validated *in vitro* test methods, e.g. microbial growth inhibition zones.

For other topical formulations clinical data (comparative clinical efficacy) will be required.

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

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

Topical Products for Systemic Action: For other locally applied products with systemic action, e.g. transdermal products, a bioequivalence study is always required.

Otic and ophthalmic products: Pharmaceutically equivalent otic or ophthalmic products prepared as aqueous solutions and containing the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided use of these excipients is not expected to effect safety and/or efficacy of the product.

Aerosols, nebulisers, nasal sprays: Pharmaceutically equivalent solutions for aerosol or nebuliser inhalation or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, containing the same active pharmaceutical ingredient(s) in the same concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

The pharmaceutical product may include different excipients provided their use is not expected to affect safety and/or efficacy of the product.

Particle size distribution may be used in support of proof of efficacy for inhalations. The Anderson sampler or equivalent apparatus should be used. In addition appropriate information should be submitted to provide evidence of clinical safety and efficacy.

Gases: Pharmaceutically equivalent gases are considered to be equivalent without the need for further documentation.

Miscellaneous Oral Dosage Forms

Pharmaceutical products subject to buccal or sublingual absorption are not eligible for a biowaiver application. Rapidly dissolving pharmaceutical products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because a patient, without proper chewing, might swallow them. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same API/moiety.

Modified Release Products

Modified Release Products include delayed release products and extended (controlled) release products (as defined in the P&A guideline). In general, bioequivalence studies are required.

- **Beaded Capsules - Lower Strength:** For extended release beaded capsules where the strength differs only in the number of beads containing the API, a single-dose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested. Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods and media described in the Dissolution guideline.

- **Extended release tablets – Lower strength:** For extended release tablets when the pharmaceutical product is:
    a. in the same dosage form but in a different strength, and
    b. is proportionally similar in its APIs and IPIs, and
    c. has the same drug/API 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.

When the highest strength (generally, as usually the highest strength is used unless a lower strength is chosen for reasons of safety) of the multisource product is bioequivalent to the highest

strength or dosel of the reference product, and other strengths are proportionally similar in formulations and the dissolution profiles are similar between the dosage strengths, biowaiver can be considered to lower / other strengths.

- **Products Intended for Other Routes of Administration**

It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. In the event that this information about the comparator product cannot be provided by the applicant, it is incumbent upon the applicant to perform *in vivo* or *in vitro* studies to demonstrate that the differences in excipients do not affect product performance.

BIOWAIVER REQUIREMENTS

In order for a pharmaceutical product to qualify for a biowaiver, criteria with respect to the composition and *in vitro* dissolution performance of the pharmaceutical product should be satisfied. The pharmaceutical product acceptance requirements are described below.

The pharmaceutical products are classified in BCS on the basis of following parameters:

- Solubility
- Permeability
- Dissolution

Class Boundaries

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labelled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Solubility Determination

pH-solubility profile of test drug in aqueous media with a pH range of 1 to 7.5.

Shake-flask or titration method.

Analysis by a validated stability-indicating assay.

Permeability Determination

1. Extent of absorption in humans:
    - Mass-balance pharmacokinetic studies.
    - Absolute bioavailability studies.
    - Intestinal permeability methods:
2. In vivo intestinal perfusions studies in humans.
    - In vivo or in situ intestinal perfusion studies in animals.
    - In vitro permeation experiments with excised human or animal intestinal tissue.
    - In vitro permeation experiments across epithelial cell monolayers.

The BCS categorizes Pharmaceutical Products into one of four BCS classes based on these characteristics. For the purposes of these guidelines, Pharmaceutical Products are classified as follows:

Class I: high solubility, high absorption

Class II: low solubility, high absorption

Class III: high solubility, low absorption

Class IV: low solubility, low absorption

BCS-based biowaiver applications will only be considered for immediate-release solid oral dosage forms containing eligible Pharmaceutical Products if the required data, as described in these guidelines, ensures the similarity between the proposed pharmaceutical product and the appropriate comparator product.

If a BCS-based biowaiver is granted and the product subsequently fails a bioequivalence test, this must be reported immediately with an assessment of the failure.

BCS Class 1 Pharmaceutical Products

Although the assessment of the potential impact of excipients on absorption would be simplified if the excipients employed in the proposed product are qualitatively the same and quantitatively similar to those in the comparator product, some differences in formulation are permitted except in excipients affecting bioavailability as discussed above. When there are differences in excipients between the test and comparator product, a justification should provide information on attempts and challenges encountered with the use of qualitatively and quantitatively similar excipients.

BCS Class III Pharmaceutical Products

Excipients in the proposed product formulation should be qualitatively the same and quantitatively very similar to that of the comparator product as per the proportionality policy.

Batch requirements

The batches of pharmaceutical product used for all biowaiver testing should, at a minimum, conform to the requirements for the 'biobatch' employed in *in vivo* comparative bioavailability trials designed to demonstrate the bioequivalence of a pharmaceutical product to a comparator product. Pilot scale batches must be at least 100,000 units or 1/10 the size of commercial scale, whichever is greater.

The measured Pharmaceutical Product content of the batches employed must meet requirements with respect to label claim, and the content should be within 5% of the measured content of the comparator product batch(es) used in comparative testing.

For higher risk pharmaceutical products meeting either of the following conditions, biowaiver testing should be conducted with at least one batch of production (commercial) scale:

1. The product is a low dose form, when the tablet/capsule strength is 5 mg or lower and/or the Pharmaceutical Product forms 2% weight per weight (w/w) or less of the total mass of the tablet/capsule content; or

2. When the chosen manufacturing process is prone to variability and/or scale-up difficulties (e.g., direct compression process for manufacturing a low dose product); complex (e.g., use of coating technology to add the Pharmaceutical Product to inert granules, lyophilisation, microencapsulation); and/or uses new technologies (e.g., nanotechnology).

VI. ADMINISTRATIVE BIOWAIVER REQUIREMENTS

Trade name of the test product:

Trade/Proprietary name means the (trade or brand) name which is unique to a particular pharmaceutical product and by which it is generally identified (and by which it is registered in the country of manufacture).

INN of active ingredient(s):

Approved / INN / generic name in relation to a pharmaceutical product means the internationally recognised non-proprietary name of such a drug or such other name as the PPB may determine.

Dosage form and strength

Dosage form of the product shall mean the form in which the pharmaceutical product is presented, e.g. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation (e.g. vial, ampoule, dental cartridge, etc), and the type of content (eg. powder for reconstitution, solution, suspension, oily solution, etc.) shall also be stated.

Strength of a pharmaceutical product shall be given per unit dosage form or per specified quantity:

e.g. mg per tablet, mg per capsule, mg/mL, mg per 5mL spoonful, mg per G, etc.

Name of applicant and official address

The application for the registration of a drug shall be made only by:

- the License/patent holder

- the manufacturer
- an authorised Local Technical Representative (LTR) of the manufacturer or License/patent holder

The name, physical address, telephone number, fax number, and e-mail address of the applicant shall be provided.

Name of manufacturer of finished product

Provide the name of manufacturer of finished product and full physical address of the manufacturing site. The name, physical address, telephone number, fax number, and e-mail address of the manufacturer shall be provided. Where different activities of manufacture of a given product are carried out at different manufacturing sites, the above particulars shall be provided for each site and the activity carried out at the particular site shall be stated as shown in the table below.

Name of the Manufacturer	Full Physical address of the Manufacturing Site	Activity at the site

A copy of a valid manufacturing License shall be provided for each site. Only products entirely manufactured at sites that meet PPB's requirements for current Good Manufacturing Practice shall be eligible for registration.

Name of the Laboratory or Contract Research Organisation(s)

Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted.

VII. TEST PRODUCT

There should be a tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

- Please state the location of the master formulae in the specific part of the dossier) of the submission.
- Tabulate the composition of each product strength using the table 2.1.1

- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating/hard gelatine capsule, if any.

- Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used. Provide a comparison of unit dose compositions (if compositions are different) equivalence of the compositions or justified differences

Potency (measured content) of test product as a percentage of label claim as per validated assay method. This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.

Well-established excipients in usual amounts should be employed in the proposed pharmaceutical product. A description of the function and a justification for the relative amount of each excipient is required. Excipients that might affect the bioavailability of the Pharmaceutical Product e.g., mannitol, sorbitol, or surfactants, should be identified and their impact discussed. These critical excipients should not differ qualitatively or quantitatively between the test product and comparator product.

VIII. COMPARATOR PRODUCT

Comparator product: Enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

Provide the name and manufacturer of the comparator product including full physical address of the manufacturing site)

Provide the qualitative (and quantitative, if available) information on the composition of the comparator product

Tabulate the composition of the comparator product based on available information and state the source of this information.

Provide relevant copies of documents (e.g. receipts) proving the purchase, shipment and storage of the comparator product

Provide the potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product. This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.

IX. COMPARISON OF TEST AND COMPARATOR PRODUCTS

1. Formulation

1.1. Impact of excipients

Identify any excipients present in either product that are known to impact on *in vivo* absorption processes. Provide a literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

1.2. Comparative qualitative and quantitative differences between the compositions of the test and comparator products

Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products. The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

1.3 Impact of the differences between the compositions of the test and comparator products

Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption

X. IN VITRO DISSOLUTION

The applicant shall provide complete information on the critical quality attributes of the Pharmaceutical Product and finished product for both the test and comparator product including, but not limited to: polymorphic form; enantiomeric purity; partition coefficient; acid, base, amphoteric or neutral nature; dissociation constant (pKa); and any information on bioavailability or bioequivalence problems with the substance or pharmaceutical product, including literature surveys

and applicant derived studies. All study protocols including standards, quality assurance and testing methods must be appropriately detailed and validated according to current regulatory guidelines's and policies.

Information regarding the comparative dissolution studies should be included to provide adequate evidence supporting the biowaiver request. State the location of:

- the dissolution study protocol(s) in this biowaiver application
- the dissolution study report(s) in this biowaiver application
- the analytical method validation report in this biowaiver application

1. Test Conditions

The following conditions should be employed in the comparative dissolution studies to characterise the dissolution profile of the product. A profile of the solubility of the Pharmaceutical Product should be developed for the physiological pH range of 1.2 - 6.8 employing the following conditions:

- Amount: One unit of the strength for which a biowaiver is requested with the highest dose of the Pharmaceutical Product being used.
- **Methodology: Basket apparatus (USP I), paddle apparatus (USP II) or similar method with justification**
- **Agitation:** Paddle apparatus at 50 revolutions per minute (rpm) or basket apparatus at 100 rpm
- Dissolution media: Provide the composition, temperature, volume, and method of de-aeration. At a minimum, Aqueous buffers solutions of pH 1.0 - 1.2, 4.5, 6.8, and at the pKa of the Pharmaceutical Product (if within pH range of 1.2-6.8). The pH for each test solution should be confirmed before and after the addition of the Pharmaceutical Product in order to ensure pH stability of the buffered medium.
- **Volume of media: ≤ 900 mL**
- Sample collection system: Provide Sample collection system: method of collection, sampling times, sample handling and storage. At a minimum the following sampling times points 10, 15, 20 and 30 minutes.

- Temperature of media: 37 ± 1°C
- Replicates: Not less than 12 units per batch at each pH medium tested

1.1. Additional information

Dissolution tests should be conducted using fully validated dissolution methods and analytical techniques. Care should be taken to ensure the pH of the medium is maintained throughout each

trial. To prevent continued dissolution, collected samples should be filtered immediately. Additional testing may be required under the pH conditions within the range of 1.0 - 6.8 at which the Pharmaceutical Product displays minimum solubility.

Simulated gastric fluid without enzymes may be employed in lieu of the pH 1.2 buffer [or 0.1 N hydrochloride (HCl)] medium, and in the same fashion, simulated intestinal fluid without enzymes may be employed in lieu of the pH 6.8 buffer medium. Surfactants should not be employed in dissolution testing for a BCS-based biowaiver. The use of enzymes may be justified when gelatin capsules or tablets with a gelatin coating are being compared.

At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data, the percent coefficient of variation at the earlier point should be not more than 20% and at other time points should be not more than 10%. Because f2 values are sensitive to the number of dissolution time points, only one measurement should be included after 85% dissolution of the product. Compilation of historical data is not acceptable.

1.2. Proportionally similar formulations

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the generic product at one strength has been shown to be bioequivalent to the corresponding strength of the reference product.

- the further strengths of the generic product are proportionally similar in formulation to that of the studied strength.
- When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to the one of the studied strength on a percentage released vs. time basis, the biowaiver procedure can be considered for the further strengths.

When the pharmaceutical product is the same dosage form but of a different strength and is proportionally similar in its API, a biowaiver may be acceptable.

2. Summary of the results

Provide a summary of the dissolution conditions and method described in the study report(s). The summary provided should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

Comparative *in vitro* dissolution tests should be conducted using a minimum of two batches of each of the proposed product and comparator product. For biowaiver purposes the dissolution profiles, in three media of the test and the comparator product should be tested for similarity.

Provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles for each set of experimental conditions.

Discussions and conclusions

Provide discussions and conclusions taken from dissolution study(s) in form of a summary statement of the studies performed.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics. The tabular presentation should include standard deviation (SD) and coefficient of variation.

The report should include an identification of all excipients, and qualitative and quantitative differences between the test and comparator products with comments on how these excipients or differences may impact dissolution and *in vivo* absorption.

A full description of the analytical methods employed, including validation, should be provided.
A detailed description of all test methods and solutions, including test and reference batch information [unit dose (mg and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] examined is required. The dissolution report should also include information on the dissolution conditions such as apparatus, de-aeration, filtration process during sampling, volume, etc.

The f2 similarity factor should be used to compare dissolution profiles from different products and/or strengths of a product. An f2 value ³50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f2 value < 50, it may be necessary to conduct an *in vivo* study. However, when both test and reference products dissolve 85% or more of the label amount of the API in ≤15 minutes similarity is accepted without the need to calculate f2 values.

If an application is submitted to Rwanda FDA subsequent to that of either the European Medical Association (EMA) or United States FDA, the reporting format can be identical to that of those agencies; however, the information provided must be consistent with the requirements of these guidelines.

3.1. *Acceptance criteria*

BCS Class I Pharmaceutical Products: The test product and comparator product should display either very rapid or similarly rapid *in vitro* dissolution characteristics (> 85% dissolved in ≤ 30 minutes) under the defined conditions in order to be eligible for a biowaiver. The similarity of dissolution profiles are demonstrated when the f2 value is ≥ 50. Profile comparison (f2 testing) is not necessary for very rapidly dissolving products (> 85% dissolved in ≤ 15 minutes). BCS Class III Pharmaceutical Products: The test product and comparator product should display very rapid *in vitro* dissolution (> 85% dissolved in ≤ 15 minutes) characteristics under the defined conditions in order to be eligible for a biowaiver.

3.2. *Additional Strengths of a Pharmaceutical Product*

When equivalence to a comparator product for one strength in a series of strengths is established on the basis of a BCS-based biowaiver, a waiver from the requirement for conducting studies with other strengths cannot then be granted based on the proportionality principles as described in Rwanda FDA' requirements on Bioequivalence. Other strengths in the product line must conform to the requirements for a BCS-based biowaiver in comparison to the pharmaceutically equivalent comparator product of the same strength.

XI. QUALITY ASSURANCE

Provide the internal quality assurance methods stating the location in the biowaiver application where internal quality assurance methods and results are described for each of the study sites.

1. Internal quality assurance methods

Provide the internal quality assurance methods and results are described for each of the study sites.

2. Monitoring, Auditing and Inspections

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. Provide the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.

XII. DECLARATION

The declaration must be signed, dated and authenticated by an Official stamp. No Applications will be evaluated without authenticated declaration.

XIII. SUMMARY REQUIREMENTS

BCS-based biowaiver are applicable for an immediate release finished pharmaceutical product if:

i. the active pharmaceutical ingredient has been proven to exhibit high solubility and complete absorption (BCS class I; for details see Section III) and;
ii. either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and;
iii. excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see Section IV.2).

BCS-based biowaiver are also applicable for an immediate release finished pharmaceutical product if:

i. the active pharmaceutical ingredient has been proven to exhibit high solubility and limited absorption (BCS class III; for details see Section III) and
ii. very rapid (> 85 % within 15 min) in vitro dissolution of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and
iii. excipients that might affect bioavailability are qualitatively and quantitatively the same and
iv. other excipients are qualitatively the same and quantitatively very similar (see Section IV.2).

Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing BCS class III than for BCS class I active pharmaceutical ingredient.

XIV. ACTIVE PHARMACEUTICAL INGREDIENT

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the active pharmaceutical ingredient characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical.

Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see Sections *III.1* and *III.2*). Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The active pharmaceutical ingredient should not belong to the group of 'narrow therapeutic index' drugs (see Section 4.1.9 on narrow therapeutic index drugs).

XIV.1 Solubility

The pH-solubility profile of the active pharmaceutical ingredient should be determined and discussed. The active pharmaceutical ingredient is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active pharmaceutical ingredient to a buffer.

XIV.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose, complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from either:

i. absolute bioavailability or
ii. mass-balance studies could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption. Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged active pharmaceutical ingredient in the gastric or intestinal fluid. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

In addition, highly soluble active pharmaceutical ingredients with incomplete absorption, i.e. BCS-class III compounds, could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and *in vitro* dissolution (see also Section *IV.2* Excipients). The more restrictive requirements will also apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed *in vitro* permeability investigations including reference standards may also be considered supportive to *in vivo* data.

XV. FINISHED PHARMACEUTICAL PRODUCT

In vitro Dissolution

General Aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro/in vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at Ph values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in Section 3.1.2 of the main guideline text. In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.

Comparative *in vitro* dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation. Usual experimental conditions are e.g.:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation:
  i. paddle apparatus - usually 50 rpm
  ii. basket apparatus - usually 100 rpm

- Sampling schedule: e.g. 10, 15, 20, 30 and 45 min

i. Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended)
ii. Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.

Complete documentation of *in vitro* dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

Evaluation of in vitro dissolution results

Finished pharmaceutical products are considered 'very rapidly' dissolving when more than 85 % of the labelled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labelled amount) dissolution. *f2*-testing **(see Appendix 1)** or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in terms of

their clinical/therapeutical relevance is considered inappropriate since the investigations do not reflect any *in vitro/in vivo* correlation.

Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable active pharmaceutical ingredients (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

If a biowaiver is applied for a BCS-class III active pharmaceutical ingredient excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters.

As a general rule, for both BCS-class I and III active pharmaceutical ingredients well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range. Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on:

- gastrointestinal motility
- susceptibility of interactions with the active pharmaceutical ingredient (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product.

XVI. FIXED COMBINATIONS (FCS)

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I or III and the excipients fulfil the requirements outlined in Section XV.2. Otherwise *in vivo* bioequivalence testing is required.

DOCUMENT REVISION HISTORY

Date of Revision	Revision Number	Document Number	Change Made
01/06/2021	Rev_0	DAR/GDL/001G	First Issue

End of document