ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Evaluation and Marketing Authorization Lead Executive office

Guideline for Waiver of In vivo Bio equivalence study

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Document History

Version No.	Reason for Amendment	Effective Date
001	Newly developed document	01/06/2020
002	To make in line with the WHO-ML3 requirements	01/07/2021
003	The term 'well regulated market' was replaced by the 'reference authority' and the reference authority is defined and training was provided to the MA staff. The guideline are also amended with respect to the new nomenclature of the MA function	15/11/2023

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Table of content

ABBREVIATION

API:	Active Pharmaceutical Product
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BMR	Batch manufacturing Record
CoA	Certificate of Analysis
EFDA	Ethiopian Food and Drug Authority
EMA	European Medicine Agency
FDC	Fixed Dose Combinations
FPP	Finished Pharmaceutical Product
IR	Immediate Release
NMT	Not More Than
QC	Quality Control
U.S. FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
WHO	World Health Organization

1. INTRODUCTION

The term biowaiver is applied to a regulatory drug approval process where the efficacy and safety part of the dossier (application) is approved based on evidence of invitro equivalence other than through *in vivo* equivalence testing i.e. use of *in vitro* testing as a reliable surrogate for an *in vivo* BE study. A major advantage of the biowaiver procedure is the simplification of the product approval process and the reduction of the time required, thus reducing the cost of bringing new products to market.

This guidance lays down the requirements for waiver of in vivo bioavailability/bioequivalence requirements for immediate release solid oral dosage forms, dose-proportionality formulation and significant post approval changes.

Biowaiver can be applied only for products which meet requirements on pharmaceutical equivalent, as well as similarity in comparative dissolution tests.

For the APIs that have known evidence on BCS classes i.e for the API(s) in which the solubility data established in literatures, official recognize monographs, SmPC of innovator products, public assessment reports and guidelines such as ICH guidelines, WHO TRS documents and other reference authority guidelines), it may not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the drug substance solubility or permeability class. However, reference or a link to the information source should be provided.

There are different areas in which biowaiver is applicable for. These include:

1. **Formulation development for new drug product.** During development, formulation changes are inevitable resulting in differences between clinical batches used in Phase II (proof of principle), phase III (pivotal formulations) and ultimate commercial batches. Equivalence between initial batches (clinical) and commercial batches must be established.
2. **Line extensions:** These include new strengths, new dosage formulations for specific groups e.g. paediatric population. Applications for biowaivers of additional strengths of a submitted (test) product, based on proportionality of formulations and

comparative *in vitro* dissolution data, must include data on comparative dissolution between the different strengths of the test product and also against the respective strengths of the comparator product.

3. **Formulation development of a generic drug product**. A generic product must be comparable to the innovator product i.e. must be therapeutically equivalent and interchangeable. This means the generic product must be pharmaceutically equivalent and bioequivalent to meet therapeutic equivalence.
4. **Post approval changes**: considered as major variation in formulation, excipients and or manufacturing process. The changes are classified according to the potential impact on the formulation quality and performance.

2. DEFINITION

Biowaiver

The term biowaiver is applied to a regulatory drug approval process where the efficacy and safety information is considered for approval by use of in vitro testing as a reliable surrogate for an in vivo BE study

Comparator product

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice.

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.

Pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) 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 excipients and/or the manufacturing process and some other variables can lead to differences in product performance.

Reference authority

Is a national, regional or international body whose decision or public information are

considered by EFDA for its decision-making process with respect to the marketing authorization of medicinal products. WHO, WHO listed authorities and other national and regional bodies could be listed as reference authority as may be updated from time to time.

3. SCOPE

This document is intended to provide guidance on EFDA biowaiver implementation.The requirements set in this guidance document are applicable to new applications forregistration of a pharmaceutical product based on BCS classifications, dose proportionate formulation (usually for lower strengths) and variation to registered oral solid dosage form for systemic action products where the changes made have potential to affect the quality, safety and efficacy of the product. Multisource products whose bioavailability is self-evidence and do not require bioequivalence study not covered by this guidance document. Applicants are required to consult to the most current EFDA registration guideline for further reference when the in vivo bioequivalence is not necessary

Locally acting medicines such as locally acting antacids and anti-helminthic that do not require Bioequivalence study are not covered in this guidance document.

4. BIOWAIVER BASED ON BIOPHARMACEUTICALCLASSIFICATION SYSTEM (BCS)

4.1.Biopharmaceutics classification system (BCS)

Biopharmaceutics Classification system (BCS) is a scientific framework for classifying APIs into four groups based on their aqueous solubility and intestinal permeability properties. According to the BCS, drug substances are classified as follows:

Class I: high solubility –high permeability

Class II: low solubility –high permeability

Class III: high solubility –low permeability

Class IV: low solubility –low permeability

When combined with the dissolution of the Finished Pharmaceutical Product, the BCS takes in to account three major factors that govern the rate and the extent drug absorption from

immediate Release (IR) solid oral dosage forms: in vitro dissolution, solubility and intestinal permeability.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo. However, when the in vivo dissolution of an IR solid oral dosage form is rapid or very rapid in relation to gastric emptying and the drug has high solubility, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal (GI) transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing class I and class III drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients.

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.

The recommended methods for determining solubility, permeability and in vitro dissolution are discussed below.

4.1.1. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is subject of a biowaiver request. A drug substance is considered **highly soluble,** when the highest oral dose or the highest single dose / strength to be marketed is soluble in 250 ml or less of aqueous media at 37±1°C, over a pH range of 1.2–6.8. A minimum of three replicate determinations of solubility at each pH condition is recommended.

4.1.2. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of

dose absorbed, not systemic BA) of a API in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capableof predicting the extent of drug absorption in humans can be used (e.g., in situ animal, invitro epithelial cell culture methods). 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.

4.1.3. Dissolution

In this guidance, a multisource product is considered to be

- **Rapidly dissolving** when no less than 85% of the labelled amount of the drug substance dissolves in 30 minutes 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 Simulated Gastric Fluid USP without enzymes; a pH 4.5 acetate buffer; and a pH 6.8 phosphate buffer or Simulated Intestinal Fluid USP without enzymes.
- **Very rapidly dissolving** when no less than 85% of the labeled amount of the drug substance dissolves in 15 minutes 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: a pH 1.2 HCl solution or Simulated Gastric Fluid USP without enzymes; a pH 4.5 acetate buffer; and a pH 6.8 phosphate buffer or Simulated Intestinal Fluid USP without enzymes.

4.2.Other parameters to be considered for BCS based biowaiver

4.2.1.Excipients used in the formulation

Excipients can sometimes influence motility and/or permeability in the gastrointestinal tract thereby affects the rate and extent of drug absorption. Therefore, the excipients used in the multisource product formulation should be scrutinized.

When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA

of the drug may be requested by the Authority. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic.

If the multisource product under consideration contains excipients that have been used beforein similar amounts in other formulations of the same API, it can be reasonably concluded that these excipients will have no unexpected consequences for the bioavailability of the product. If, however, the formulation contains different excipients, or amounts of the same excipients that are very different from usual, the Authority may choose to declare the biowaiver procedure inapplicable.

4.2.2.Risk Assessment

To minimize the risks of an incorrect biowaiver decision in terms of public health and risksto individual patients, the therapeutic indications of the API, known pharmacokinetic variations, food effects, etc. should be evaluated based on local clinical experience, taking into account the indications for which the API is prescribed in that country as well as specific pharmacokinetic population variations (for example CYP polymorphisms). Hence, as an addition to the excipients used in the formulation, the below conditions can serve as exclusion criteria from biowaiver.

- A product that contains an API with a narrow therapeutic index;
- A product designed to be absorbed from other sites e.g. from the oral cavity; and
- A fixed-dose combination product that contain an API where biowaiver is not applicable;

Only when there is an acceptable benefit–risk balance in terms of public health and risk to the individual patient should bioequivalence testing according to the guidance given in this section is permitted.

4.3.Selection of comparator (reference) product

Identification of comparator product is essential in the biowaiver application. The choice of

comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with its lot number and expiry date.

The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. However, the selected comparator must be a product approved by the reference authority. Applicant is advised to consult the most current EFDA guideline for the registration of medicines for the approach to be followed for the selection of the comparator product under the requirements for Bioequivalence study. Furthermore, applicant can follow guidance on selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic)products, annex 8, WHO TRS 992.

4.4.Criteria for acceptance of BCS based biowaiver for a pharmaceuticalproduct

a) **Dosage forms** of APIs which are highly soluble, highly permeable (BCS Class I) with acceptable excipient content and favorable risk-benefit analysis and which are rapidly dissolving are eligible for a biowaiver based on the BCS provided:

- The dosage form is *rapidly dissolving* (as defined in 4.1.3 of this guidance document) and the dissolution profile of the multisource product is similar to that of the comparator product in aqueous buffers at pH 1.2 or Simulated Gastric Fluid USP without enzymes, pH 4.5 and pH 6.8 or Simulated Intestinal Fluid USP without enzymes using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f2 \geq 50$ (or equivalent statistical criterion);
- If both the comparator and the multisource dosage forms are *very rapidly dissolving* (85% in 15 minutes) the two products are deemed equivalent and a profile comparison is not necessary.

b) Dosage form of APIs that are highly soluble and have low permeability (BCS ClassIII) are eligible for biowaiver provided that the following three conditions and the risk-benefit is additionally addressed in terms of extent, site and mechanism of absorption

- Both the comparator and the multisource dosage forms are very rapidly dissolving (release of > 85% of the labelled amount of drug in 15 minutes) in standard media at pH 1.2 or Simulated Gastric Fluid USP without enzymes, 4.5and 6.8 or Simulated Intestinal

Fluid USP without enzymes, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus.

- All the excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator product, as defined by WHO quality limits on allowable quantitative changes in excipients for a variations Annex I of this document.
- The risks of incorrect biowaiver decision in terms of the therapeutic index of and clinical indication for APIs is absent.

c) Fixed dose combination (FDC) product with class I and or III APIs meeting the dissolution criteria as specified above.

d) Evidence to show that the excipients included are the same (i.e. same ratios and amounts) as the comparator product or that the excipients used do not influence the absorption of the API

Note on Dissolution profile comparison: Approval of multisource formulations using comparative in vitro dissolution studies should be based on the generation of multimedia and multi point comparative dissolution profiles rather than a single-point dissolution test. For details refer to Annex IV of this guideline.

4.5.Regulatory applications of the BCS on post approval change

BCS-based biowaivers can be requested for significant changes such as change in composition, excipients and manufacturing process to a rapidly dissolving IR product containing highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the post-change product and both pre- and post-change products exhibit similar dissolution profiles. This approach is useful only when the drug products pre- and Post-change are pharmaceutical equivalent.

5. BIOWAIVERS 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.

5.1.Proportionally similar formulations

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

a) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has all the active and inactive ingredients exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength). For immediate release products, coating components, capsule shell, colour agents and flavors are not generally required to meet this requirement.
b) For a high potency API, where the amount of the API in the dosage form is relatively low(up to 10 mg per dosage unit or NMT 5% of the weight of the dosage form), the total weight of the dosage form remains similar for all strengths.

   For (b) a waiver is considered:

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

5.2.Qualification for biowaiver based on dose-proportionality of formulations

Dose-proportionality of formulations can be eligible for a biowaiver if

a) the multisource product at one strength (usually higher strength,) has been shown in in-vivo studies to be bioequivalent to the corresponding strength of the comparator product;
b) the other strengths of the multisource product are proportionally similar in formulation to that of the higher strength for which bioequivalence with the comparator has been confirmed as per section (a)
c) When both of these criteria (i.e. criteria under a & b above) are met and the dissolution profiles of the other strengths are shown to be similar to that of the higher strength, for which bioequivalence with the comparator has been confirmed, on a percentage released against time basis, the biowaiver procedure can be considered for the lower strengths.

Similar to the biowaiver based on the BCS, a biowaiver based on dose proportionality of formulations should be considered only when there is an acceptable benefit–risk balance in terms of public health and risk to the individual patient.

5.2.1. Immediate-release tablets

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

a) An in vivo equivalence study has been performed on at least one of the strengths of the formulation. As described in above, 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)
b) All strengths are proportionally similar in formulation to that of the strength studied (see section 5.1 above);
c) 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.

Similar to the biowaiver based on BCS, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three-dissolution media as recommended Annex IV of this guidance, the profile comparison with an f2 test is unnecessary.

In 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.

5.2.2. Delayed-release tablets and capsules

For delayed-release tablets, when the multisource product is in the same dosage form, but ina different strength and is proportionally similar in its active and inactive ingredients and hasthe same delayed-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profile, f2 > 50, in the recommended test condition for delayed- release product, i.e. dissolution test in acid medium (pH 1.2) for 2 hours followed bydissolution 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 tocore 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 lower strength to that of the approved strength (f2 > 50) under the test conditions recommended for delayed-release products (see above paragraph) is sufficient for a biowaiver.

5.2.3. Extended-release beaded capsules

For extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, dissolution profile comparison ($f2 \geq 50$) under one recommended test condition (normally the release condition) is sufficient for a biowaiver based on dose-proportionality of formulation.

5.2.4. Extended-release tablets

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, f2 ≥ 50, in three different pH buffers (between pH 1.2 and 7.5) and the QC media by the recommended test method.

For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison (f2 ≥ 50) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

5.3. Dissolution profile comparison for biowaivers based on dose-proportionality of formulations

As for biowaiver based on the BCS, a model independent mathematical approach (e.g. f-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 multisource and comparator product profiles should be the same:

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

— for 24 - hour extended-release products 1, 2, 4, 6, 8 and 16 hours.

Only one time-point should be considered after 85% dissolution from the comparator product. An f-value of 50 or greater (50–100) reflects equivalence (less than 10% difference) of the two curves, and thus equivalence of in vitro performance of the two products. To allow the use of the mean data, the coefficient of variation should not be more than 20% at the earliest time-point (e.g. 10 minutes in the case of the example given for immediate-release products), and should not be more than 10% at other time points.

6. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

- Filled application form as per the annexes i.e. Annex II for biowaver request based on BCS and Annex III for biowaver based on dose-proportionality formulation.
- For BCS based biowaver request, data supporting solubility and permeability of the

APIs should be reported and thereby, the BCS class of API should be specified based on the scientific data.

- For submission biowaiver request, data supporting dissolution attributes of the test and reference (comparator) products should be reported.
- Dissolution data obtained with 12 individual units of the test and reference (compactor) products using recommended test methods as outline in annex IV of this guidance. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percentage dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference (comparator) products in the three BCS media should also be included.
- Data supporting similarity in dissolution profiles between the test and reference (comparator) products in each of the three media, using the f2 matrics, where applicable.
- The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture. A list of excipients used with their amount and intended functions should be provided.

Annex I: Limits on the relative difference in the amount of excipientin two solid oral FPPs to be considered quantitatively similar in thatexcipient

Excipient type	Percentage difference (w/w) out of total product (core) weight
Filler	5.0
Disintegrant	
Starch	3.0
Other	1.0
Binder	0.5
Lubricant	
Calcium or magnesium stearate	0.25
Other	1.0
Glidant	
Talc	1.0
Other	0.1

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

Annex II: Bio waiver Application Form: Bio pharmaceuticalClassification System (BCS)

(Form-MEMA-005.001)

This application form is designed to facilitate information exchange between the Applicant and the EFDA on Medicines if the Applicant seeks to waive bioequivalence studies based onthe Biopharmaceutics Classification System (BCS).

For the APIs that have known evidence on BCS classes i.e for the API(s) in which the solubility data established in literatures, official recognize monographs, SmPC of innovator products, public assessment reports and guidelines such as ICH guidelines, WHO TRS documents and other reference authority guidelines), it may not necessary to provide data to support the BCS classification of the respective API(s) in theapplication i.e. data supporting the drug substance solubility or permeability class. However, reference or a link to the information source should be provided.4

Administrative data

1. Name of the product (brand and INN active ingredient(s))
<< *Please enter information here* >>
2. Dosage form and strength
<< *Please enter information here* >>
3. Name of applicant and official address
<< *Please enter information here* >>
4. Name of manufacturer of finished product and official address
<< *Please enter information here* >>
6. Name and address of the laboratory or Contract Research Organisation(s) where theBCS-based biowaiver solubility and dissolution studies were conducted
<< *Please enter information here* >>

I, the undersigned, certify, that the information provided in this application and the attacheddocuments is correct and true

Signed on behalf of<company> _____Date)_____

(Name and title)_____

1. Justification for a BCS Biowaiver
1.1. Active Pharmaceutical Ingredient (API) Please confirm that the proposed product contains the same active substance (e.g. salt, ester, ether, isomer) asthe comparator.
<< *Please enter information here* >>
1.2. Therapeutic Index of the API Please enclose a copy of the comparator product labelling and literature references employed to support that thedrug does not exhibit a narrow therapeutic index for all authorised indications
<< *Please enter information here* >>
1.3. Pharmacokinetic properties of the API Please enclose a copy of the literature references employed to document the PK properties (PK linearity orreasons for non-linearity).
<< *Please enter information here* >>
1.4. Dosage form Please confirm that: the dosage form is an immediate release product for systemic actionthe posology is limited to oral administration, the administration without water is not included in the proposed posology
<< *Please enter information here* >>
COMMENTS FROM REVIEW OF SECTION 1 – EFDA o*fficial use only*
2. Solubility Completion of this section is not necessary for the API(s) *in which the solubility data established in literatures, official recognize monographs, SmPC of innovator products, public assessment reports and guidelines such as ICH guidelines, WHO TRS documents and other reference authority guidelines).*
2.1. Maximum therapeutic dose of the API Please enclose a copy of the labelling of the comparator product to document the maximum single dose that canbe administered in a single administration (e.g. two tablets together).
<< *Please enter information here* >>

2.2. Stability of the drug in the physiological pH range Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract. Please discuss the ability of the analytical method to distinguish the API from its degradation products.
<< *Please enter information here* >>
2.3. Method of solubility determination Please describe method and conditions (e.g. shake flask method at 37±1ºC)Please also describe the solubility study protocol.
<< *Please enter information here* >>
2.4. Solubility study dates Please indicate dates of study protocol, study conductance and study report
<< *Please enter information here* >>
2.5. Analytical method validation Please summaries the results and indicate location in the documentation.
<< *Please enter information here* >>
2.6. Results Please indicate location of the solubility study report. Please fill in the following table for the necessary pH values. Add as many rows as necessary to create asolubility – pH profile
<< *Please enter information here* >>
2.7. Plot the Solubility – pH profile Please attach the plot of the pH-solubility profile based on the above data
<< *Please enter information here* >>
COMMENTS FROM REVIEW OF SECTION 2 – EFDA official *USE ONLY*

Theoretical pH	Observed pH	Adjusted pH	Individual concentrationat	Cs (mean and	Amount that can be

			saturation (Cs) values	CV(%))	dissolved in 250 mL
pH 1.2	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermdiate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 4.5	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 6.8	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Other intermediate pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		

3. Absorption / Permeability

Completion of this section is not necessary for the API(s) *in which the bioavailability (BA) and permeability data established in literatures, official recognize monographs, SmPC of innovator products, public assessment reports and guidelines such as ICH guidelines, WHO TRS documents and other reference authorities guidance documents.*

3.1. Human mass balance studies

Summarise results of all studies found in the literature.

Please enclose a copy of the references describing human mass balance studies of the API.

<< *Please enter information here* >>
3.2. Human absolute bioavailability studies Summarise results of all studies found in the literature. Please enclose a copy of the references describing human absolute bioavailability of the API.
<< *Please enter information here* >>
3.3. Supportive studies Summarise results of all studies found in the literature regarding in vivo or in situ intestinal perfusion animal models or in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) with a positive andnegative control. Please enclose a copy of the references.
<< *Please enter information here* >>
COMMENTS FROM REVIEW OF SECTION 3 – EFDA official use only
4. Test product
4.1 Tabulation of the composition of the formulation(s) proposed for marketing andthose used for comparative dissolution studies • Tabulate the composition of each product strength using the table below. • For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of acapsule. A copy of the table should be filled in for the film coating/hard capsule, if any. • Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules ortablets whichever is greater) and manufacturing method should be the same as for production scale. **Please note:** 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 studythe respective formulation was used

Composition of the batches used for comparative dissolution studies	
Batch number	
Batch size (number of unit doses)	

Date of manufacture				
Comments, if any				
Comparison of unit dose compositions and of clinical FPP batches(duplicate this table for each strength, if compositions are different)				
Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)

4.2 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

Equivalence of the compositions orjustified differences	

COMMENTS FROM REVIEW OF SECTION 4 – EFDA official use only

5. Comparator product

5.1. Comparator product

A copy of product labelling (summary of product characteristics), as authorized in country of purchase, andtranslation into English, if appropriate.

A copy of the comparator product carton outer box. The name of the product, name and address of themanufacturer, batch number, and expiry date should be clearly visible on the labelling.

This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in thisbiowaiver submission.

<< Please enter information here >>

5.2. Name and manufacturer of the comparator product and official address

<< *Please enter information here* >>		
5.3. Qualitative (and quantitative, if available) information on the composition of the comparator product Please tabulate the composition of the comparator product based on available information and state the sourceof this information.		
Composition of the comparator product used in dissolution studies		
Batch number		
Expiry date		
Comments, if any		
Ingredients	Unitdose(mg)	Unit dose (%)
5.4. Potency (measured content) of the comparator product as a percentage of labelclaim, 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 thisbiowaiver submission.		
COMMENTS FROM REVIEW OF SECTION 5 – EFDA official use only		
6. Comparison of test and comparator formulations		
6.1. Identify any excipients present in either product that are known to impact *in vivo* absorption processes A literature-based summary of the mechanism by which these effects are known to occur should be includedand relevant full discussion enclosed, if applicable.		
<< *Please enter information here* >>		
6.2. 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 comparatorproduct as required by the guidance documents should be summarized here for assessment.		

<< *Please enter information here* >>
6.3. 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 invivo absorption
<< *Please enter information here* >>
COMMENTS FROM REVIEW OF SECTION 6 – EFDA official use only

7. Comparative in vitro dissolution
7.1. Comparative in vitro dissolution Information regarding the comparative dissolution studies should be included below to provide adequateevidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier. **Please state the location of:** the dissolution study protocol(s) in this biowaiver application; the dissolution study report(s) in this biowaiver application and the analytical method validation report in this biowaiver application
<< *Please enter information here* >>
7.2. Dissolution study dates Please indicate dates of study protocol, study conductance and study report
<< *Please enter information here* >>
7.3. Summary of the dissolution conditions and method described in thestudy report(s) Summary provided below should include the composition, temperature, volume, and method of de-aeration ofthe 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, filtration and storage. Deviations from the sampling protocol should also be reported.
<< *Please enter information here* >>
7.3.1. Dissolution media: Composition, temperature, volume, and method of de-aeration
<< *Please enter information here* >>
7.3.2. Type of apparatus and agitation speed(s) employed
<< *Please enter information here* >>

7.3.3. Number of units employed
<< *Please enter information here* >>
7.3.4. Sample collection: method of collection, sampling times, sample handling, filtration andstorage
<< *Please enter information here* >>
7.3.5. Deviations from sampling protocol
<< *Please enter information here* >>
7.4. Summarize the results of the dissolution study(s) Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and anycalculations used to determine the similarity of profiles **for each set of experimental conditions**.
<< *Please enter information here* >>
7.5. Summarize conclusions taken from dissolution study(s) Please provide a summary statement of the studies performed.
<< *Please enter information here* >>
7.6. Dissolution specifications Please provide proposed dissolution specifications and discuss them in relation to the results obtained in theBCS biowaiver.
COMMENTS FROM REVIEW OF SECTION 7 – EFDA official use only

Annex III: Biowaiver Application Form: Dose-proportionalityformulations (Form-MEMA-006.001)

This application form is designed to facilitate information exchange between the Applicant and the EFDA if a biowaiver is requested for additional strength(s) of the submitted product(s).

A request for a waiver from the requirement for conducting bioequivalence studies on additional strengths of the product submitted for assessment to the EFDA can be made based on the proportionality of the formulations of the series of strengths. If additional strengths are proposed and a biowaiver for these strengths is sought, the following information should be provided

Final assessment of the proportionality of the proposed formulations and the acceptability of the comparative dissolution data will be made during the evaluation of Quality part of the dossier.

Administrative data
1. Name of the product (Brand name & INN of active ingredient(s))
< *Please enter information here* >
2. Dosage form and strengths
< *Please enter information here* >
3. Product WHO Reference numbers *(if available for any strengths of the product line, including the reference strength)*
< *Please enter information here* >
4. Name of applicant and official address
< *Please enter information here* >
5. Name of manufacturer of finished product and official address
< *Please enter information here* >
6. Name and address of the laboratory or Contract Research Organisation(s) where the biowaiver dissolution studies were conducted *(if applicable)*

< *Please enter information here* >

I, the undersigned, certify, that the information provided in this application and the attacheddocuments is correct and true

Signed on behalf of<company>__(Date)

(Name and title)

1. Test product

1.1 Tabulation of the composition of formulation proposed for marketing

- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of acapsule. A copy of the table should be filled in for the film coating or hard capsule, if any.
- Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules ortablets whichever is greater) and manufacturing method should be the same as for production scale.

Composition of the batch used for comparative dissolution studies

Batch number for biowaiver batch	
Batch size (number of unit doses)	
Date of manufacture	
Expiry date	
Comments, if any	

Unit dose compositions and FPP batch composition

Ingredients (Quality standard)	Unitdose(mg)	Unitdose(%)	Biowaiverbatch (kg)	Biowaiverbatch (%)

1.2 Potency (measured content) of test product as a percentage of label claim as pervalidated assay method

This information should be cross-referenced to the location of the Certificate of Analysis (CoA)

in thisbiowaiver submission.
<< *Please enter information here* >>
1.3 Pharmacokinetics State whether the drug displays linear or non-linear pharmacokinetics • Provide literature-based support for your response and append all references cited in the response andstate the location of these references in the dossier. • State concentrations at which non-linearity occurs and any known explanations. Particular attentionshould be paid to absorption and first-pass metabolism
<< *Please enter information here* >>
Comments from review of Section 1.1 - 1.3 – EFDA OFFICIAL USE ONLY

2. Reference

2.1. Reference strength In this context, the reference strength is the strength of the FPP that was compared to the Comparator product inan *in vivo* bioequivalence study.
<< *Please enter information here* >>
2.2. Tabulation of batch information for the reference strength The biobatch of the reference strength (batch employed in the *in vivo* bioequivalence study) should be employedin the comparative dissolution studies.

Batch information for batch used for comparative dissolution studies	
Batch number	
Batch size (number of unit doses)	
Date of manufacture	
Expiry date	
Comments, if any	

Unit dose compositions and FPP batch composition

Ingredients (Quality standard)	Unitdose(mg)	Unitdose(%)	Batch(kg)	Batch(%)

2.3. Batch confirmation

If the batch of reference strength employed in the comparative dissolution studies was not the biobatch of the reference strength (batch employed in the *in vivo* bioequivalence study), the following information should be provided:

- Batch number of biobatch
- Justification for use of a batch other than the biobatch
- Comparative dissolution data for batch employed vs. (historical data for) biobatch
- As an Appendix, executed batch manufacturing records (BMR) for batch employed in dissolution studies

<< *Please enter information here* >>

2.4 Potency (measured content) of reference 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.

<< *Please enter information here* >>

Comments from review of Section 2.1 – 2.4 – EFDA official *use only*

3. Comparison of Test and Reference

3.1. Tabulation of batch information for the test and reference strengths

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 or hard capsule, if any.

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*

TOTAL					

**each ingredient expressed as a percentage of the total core*

3.2. Confirmation of Proportionality

Applicant should confirm that the test and reference strength formulations are directly proportional. Anydeviations from direct proportionality should be identified and justified in detail.

<< *Please enter information here* >>

Comments from review of Section 3.1 – 3.2 – EFDA official *use only*

4. Comparative *in vitro* dissolution:

Studies comparing different strengths of the test product

- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- As per Annex IV- Recommendation for conducting and assessing a dissolution profile of this guidancedocument, comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposeddissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.
- Summary information regarding the comparative dissolution studies should be included below toprovide a complete summary of the data supporting the biowaiver request.

4.1. Please state the location of:

- the dissolution study protocol(s) in the dossier the dissolution study report(s) in the dossier
- the analytical method validation report in the dossier

<< *Please enter information here* >>

4.2. Summary of the dissolution conditions and method described in the study report(s)

Summary provided below 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.
<< *Please enter information here* >>
4.2.1. Dissolution media: Composition, temperature, volume, and method of de-aeration
<< *Please enter information here* >>
4.2.2. Type of apparatus and agitation speed(s) employed
<< *Please enter information here* >>
4.2.3. Number of units employed
<< *Please enter information here* >>
4.2.4. Sample collection: method of collection, sampling times, method of filtration, samplehandling and storage
<< *Please enter information here* >>
4.2.5. Deviations from sampling protocol
<< *Please enter information here* >>
4.3. Summarize the results of the dissolution study(s) Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and anycalculations used to determine the similarity of profiles **for each set of experimental conditions**.
<< *Please enter information here* >>
4.4. Summarize conclusions taken from dissolution study(s) Please provide a summary statement of the studies performed.
<< *Please enter information here* >>
Comments from review of Section 4.1 – 4.4 – EFDA official *use only*
5. Comparative in vitro dissolution: Comparing each strength of the test product to equivalentstrength of comparator product; only to be submitted in case in vitro dissolution data between different strengths of Test product(see Section 4) are not similar studies

- This section is applicable in cases where, due to low solubility of the API, similar comparative dissolution between differing strengths is difficult to achieve. The WHO comparator product as identified onthe programme's website should be employed.
- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- Annex IV- Recommendation for conducting and assessing a dissolution profile of this guidance, comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolutionmedium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.
- Summary information regarding the comparative dissolution studies should be included below toprovide a complete summary of the data supporting the biowaiver request

5.1. 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 thisbiowaiver submission.

<< *Please enter information here* >>

5.2. Please state the location of:

- the dissolution study protocol(s) in the dossier
- the dissolution study report(s) in the dossier
- the analytical method validation report in the dossier

<< *Please enter information here* >>

5.3. Summary of the dissolution conditions and method described in the study report(s)

Summary provided below 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.

<< *Please enter information here* >>

5.3.1. Dissolution media: Composition, temperature, volume, and method of de-aeration
<< *Please enter information here* >>
5.3.2. Type of apparatus and agitation speed(s) employed
<< *Please enter information here* >>
5.3.3. Number of units employed
<< *Please enter information here* >>
5.3.4. Sample collection: method of collection, sampling times, method of filtration, samplehandling and storage
<< *Please enter information here* >>
5.3.5. Deviations from sampling protocol
<< *Please enter information here* >>
5.4. Summarize the results of the dissolution study(s) Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and anycalculations used to determine the similarity of profiles **for each set of experimental conditions**.
<< *Please enter information here* >>
5.5. Summarize conclusions taken from dissolution study(s) Please provide a summary statement of the studies performed.
<< *Please enter information here* >>
CONCLUSIONS AND RECOMMENDATIONS – EFDA official *use only*

Annex IV: Recommendations for conducting and assessingcomparative dissolution profiles

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

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

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

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

$$f_2 = 50 \text{ LOG } \{[1+1/n \, \Sigma^{n}t=1 \, (Rt - Tt)^{2}]^{-0.5} \times 100\}$$

  Where Rt and Tt are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar;

- a maximum of one time-point should be considered after 85% dissolution of the

reference (comparator) product has been reached;

- in the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2 . To use mean data the percentage coefficient of variation at time-points up to 10 minutes should be not more than 20% and at other time-points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- Surfactants should be avoided in comparative dissolution testing.

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

REFERENCE

1. WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth report.*Geneva, World Health Organization, 2020, Annex 12(WHO Technical Report Series, No.1025)
2. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, Guidance for Industry U.S. FDA, December 2017
3. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization, 2015, Annex 7(WHO Technical Report Series, No. 992)
4. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization, 2015, Annex 8(WHO Technical Report Series, No. 992)
5. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006, Annex 7(WHO Technical Report Series, No. 937)
6. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006, Annex 8 (WHO Technical Report Series, No. 937)

7. Waiver of In Vivo Bioavalability and Bioequivalence studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, Guidance for Industry. Center for Drug Evaluation and Research (CDER), August 2000. Food and Drug Administration, U.S. Department of Health and Human Services.
8. E. Gupta, D.M Barends, E. Yamashita, K.A. Lenzt, A.M. Harmsze, V.P. Shah, R.A. Lipper. (2006) Review of global regulations concerning biowaivers for immediate release solid oral dosage forms. European Journal of Pharmaceutical Sciences