PHARMACY AND MEDICINES REGULATORY AUTHORITY

Quality Medicines for Malawi

Doc. No: PMRA-GD-REG-003-00
Effective Date: May 2023

GUIDANCE ON WAIVER OF IN VIVO BIOEQUIVALENCE REQUIREMENTS FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS.

TABLE OF CONTENTS

1- INTRODUCTION

These guidelines which is an annex on bioavailability/bioequivalence lays down the requirements for waiver of in vivo bioavailability/bioequivalence requirements for immediate release solid oral dosage forms. The guidance is based on the WHO Technical Report Series no 937, 2006; "Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms".

Any applicant who wishes to use the provision of this guidance should submit a completed PMRA Biowaiver Application Form as an electronic copy in Microsoft (MS) Word in CD format. The Application form can be downloaded from the PMRA website www.pmra.mw .

2- SCOPE

This document is intended to provide guidance on PMRA's biowaiver implementation. The requirements set in this guidance document are applicable to new applications for registration of a pharmaceutical product, amendment to a registered product and for re-instatement of a previously registered product. The list of APIs eligible and not eligible for a BCS-based biowaiver (based on the WHO Essential Medicines list for biowaivers) is in annex III to this document. It is therefore, 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

This guideline should be read in conjunction with WHO Guideline on Bioavailability/Bioequivalence and PMRA Guideline on submission of documentation for registration of multi-source (generic) finished pharmaceutical products (FPPs)

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 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.[1]

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

This guidance document is not applicable to locally acting medicines such as locally acting antacids and anti-helminthic medicines.

3- BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

Biopharmaceutics Classification system (BCS) is a scientific framework which divides APIs into four groups, according to their solubility and permeability properties.

Four classes have been established as follows:

a. Class I: high solubility –high permeability
b. Class II: low solubility –high permeability
c. Class III: high solubility –low permeability
d. Class IV: low solubility –low permeability

4- DEFINITIONS

High solubility: is when the highest oral dose or the highest dose / strength to be marketed dissolves completely in 250ml or less of aqueous media at 37 °C over a **pH range of 1.2–6.8**.

High permeability: A pharmaceutical product is considered highly permeable when 85% or more of the API is absorbed from the small intestine following oral administration.

[1]Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid dosage forms. (WHO Technical Report Series, No 937, 2006), Annex 8)

5- BIOWAIVER IS APPLICABLE TO THE FOLLOWING:

5.1 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.

5.2 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.

5.3 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.

5.4 Post approval changes: considered as major amendments in formulation, excipients and or manufacturing process. The changes are classified according to the potential impact on the formulation quality and performance.

6- CRITERIA FOR ACCEPTANCE OF BCS BASED BIOWAIVER FOR A PHARMACEUTICAL PRODUCT.

6.1 *rapidly dissolving* (release of > 85% of the labelled amount of drug in 30 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus at 37 °C and a volume of 900 ml (for a pharmaceutical product which contain a class I API);

6.2 contain a class II API that is a weak acid which has a dose: solubility ratio of 250ml or less at pH 6.8 provided that it dissolves rapidly (release of > 85% of the labelled amount of drug in 30 minutes) at pH 6.8 and similarly as determined by f_2 value or equivalent statistical evaluation to the comparator product in a standard media at pH 1.2, 4.5 and 6.8 at a rotational speed of 75rpm in the paddle apparatus or 100rpm in the basket apparatus at 37 °C and a volume of 900 ml;

6.3 class III API under application of more stringent dissolution criteria: *very rapidly dissolving* (release of > 85% of the labelled amount of drug in 15 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus

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

6.5 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

NB: Refer to appendix 1 for complete list of products eligible for biowaivers.

7. BIOWAIVERS BASED ON DOSE-PROPORTIONALITY OF FORMULATIONS

Approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

7.1. 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 flavours 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. The following are applicable conditions:

i. The amounts of different excipients or capsule contents are the same for the strengths considered and only the amount of the API has changed;

ii. 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.

c) The relative amount of an excipient presents in two solid oral FPPs falls within the limits shown in the below table.

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

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

7.2. QUALIFICATION FOR BIOWAIVER BASED ON DOSE- PROPORTIONALITY OF FORMULATIONS

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

7.2.1 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;

7.2.2 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.

7.2.3 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.

7.3 As in the case of biowaivers 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.

8. IN VIVO BIOEQUIVALENCE REQUIRED FOR:

8.1 A product that contain excipients which could influence the absorption of the API;

8.2 A product that contain an API with a narrow therapeutic index;

8.3 A product designed to be absorbed from other sites e.g. from the oral cavity;

8.4 A product that is not listed on the Appendix I;

8.5 A fixed-dose combination product that contain an API where biowaiver is no applicable; and

8.6 Risk assessment: only if the risk of an incorrect biowaiver decision and an evaluation of the consequences (of an incorrect, biowaiver-based equivalence decision) in terms of public health and risks to individual patients are outweighed by the potential benefits accrued from the biowaiver approach may the biowaiver procedure be applied.

ANNEX I: BIOWAIVER APPLICATION FORM: BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

APPLICATION FOR BIOWAIVER – BIOPHARMACEUTICS CLASSIFICATION SYSTEM

(Pharmacy and Medicines Regulatory Authority Act [No. 9] of 2019 Part IV Section 62)

The Guidelines on application for grant of Biowaiver based on Biopharmaceutical Classification System to be consulted in completing this form.

This form is not to be used if a biowaiver is requested for additional strength(s) of a submitted product(s), in which case a separate "*Biowaiver Application Form: Additional Strengths,* should be used.

Administrative data

INN of active ingredient(s)
<< Please enter information here >>

Dosage form and strength
<< Please enter information here >>

Product MRA Reference number *(if product dossier has been accepted for PQTm assessment)*

<< Please enter information here >>

Name of applicant and official address
<< Please enter information here >>

Name of manufacturer of finished product and official address
<< Please enter information here >>

Name and address of the laboratory or Contract Research Organisation(s) where the BCS-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 attached documents is correct and true

Signed on behalf of

<company>

_____ (Date)

_____ (Name and title)

Justification for a Biopharmaceutics Classification System (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) as the 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 the drug 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 or reasons for non-linearity).
<< Please enter information here >>

1.4. Dosage form Please confirm that: • the dosage form is an immediate release product for systemic action • the posology is limited to oral administration • the administration without water is not included in the proposed posology
<< Please enter information here >>

1.0 COMMENTS FROM REVIEW OF SECTION 1 – PMRA *USE ONLY*

Solubility

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the WHO PQTm document *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.)

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 can be 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 indicate also location of 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 summarise 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 a solubility – pH profile

Theoretical pH	**Observed pH**	**Adjusted pH**	**Individual concentration at saturation (Cs) values**	**Cs (mean and CV(%))**	**Amount that can be 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		
Intermediate pHs	Experiment 1 Experiment 2	Experiment 1 Experiment 2	Experiment 1 Experiment 2 Experiment 3		

	Experiment 3	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		

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 >>

2.0 COMMENTS FROM REVIEW OF SECTION 2 – PMRA *USE ONLY*

Absorption / Permeability

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the WHO PQTm document *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.)

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 and negative control.
Please enclose a copy of the references.

<< Please enter information here >>

3.0 COMMENTS FROM REVIEW OF SECTION 3 – PMRA *USE ONLY*

Test product

4.1 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 quality part of the submission.
- 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 a capsule. 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 or tablets 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 study the 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 (%)**
Equivalence of the compositions or justified differences				

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.

<< Please enter information here >>

4.0 COMMENTS FROM REVIEW OF SECTION 4 – PMRA *USE ONLY*

Comparator product

5.1. Comparator product Please indicate location in the documentation of the following documents that should be enclosed: A copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate. A copy of the comparator product carton outer box. The name of the product, name and address of the manufacturer, 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 this biowaiver 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 source of this information.

Composition of the comparator product used in dissolution studies		
Batch number		
Expiry date		
Comments, if any		
Ingredients	**Unit dose (mg)**	**Unit dose (%)**

5.4. Identify the source of the comparator product (where it was purchased), the method of shipment, and storage conditions of the comparator product from the time of purchase until completion of the comparative dissolution studies.

Please attach relevant copies of the following documents proving the stated conditions:

A copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.

Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
<< Please enter information here >>

5.5. 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.
<< Please enter information here >>

5.0 COMMENTS FROM REVIEW OF SECTION 5 – PMRA *USE ONLY*

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 included and 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 comparator product 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 in vivo absorption
<< Please enter information here >>

6.0 COMMENTS FROM REVIEW OF SECTION 6 – PMRA *USE ONLY*

Comparative in vitro dissolution

7.1. Comparative in vitro dissolution Information regarding the comparative dissolution studies should be included below to provide adequate evidence 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 • 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 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, filtration and storage. Deviations from the sampling protocol should also be reported.

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 and storage

<< 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 any calculations 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 the BCS biowaiver.
<< Please enter information here >>

7.0 COMMENTS FROM REVIEW OF SECTION 7 – PMRA *USE ONLY*

Quality assurance

8.1. Internal quality assurance methods Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.
<< Please enter information here >>

8.2. Auditing and inspections Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.
<< Please enter information here >>

8.0 COMMENTS FROM REVIEW OF SECTION 8 – PMRA *USE ONLY*

CONCLUSIONS AND RECOMMENDATIONS – PMRA *USE ONLY*

ANNEX II: BIOWAIVER APPLICATION FORM: ADDITIONAL STRENGTH

APPLICATION FOR BIOWAIVER - ADDITIONAL STRENGTH

(Pharmacy and Medicines Regulatory Authority Act [No. 9] of 2019 Part IV Section 62)

The Guidelines on application for grant of Biowaiver on Additional Strength to be consulted in completing this form.

This form is not to be used, if the Applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS), in which situation a separate "*Biowaiver Application Form - Biopharmaceutics Classification System, "* should be used.

Administrative data

1.0 Particulars of the Product

Name of the Medicine
< Please enter information here >
INN of active ingredient(s)
< Please enter information here >
Dosage form and strengths
< Please enter information here >

Name of applicant and official address
< Please enter information here >

Name of manufacturer of finished product and official address
< Please enter information here >

2.0 Particulars of the Applicant

Name of applicant and official address
< Please enter information here >

3.0 Manufacturer(s)

Name of manufacturer of finished product and official address
< Please enter information here >

4.0 Research facility(ies)

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 attached documents 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

- Please state the location of the master formulae in the quality part of the submission.
- 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.
- 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.

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)	**Unit dose (mg)**	**Unit dose (%)**	**Biowaiver batch (kg)**	**Biowaiver batch (%)**

1.2 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.

<< 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 and state the location of these references in the dossier.
- State concentrations at which non-linearity occurs and any known explanations. Particular attention should be paid to absorption and first-pass metabolism

<< Please enter information here >>

1.4 COMMENTS FROM REVIEW OF SECTION 1.1 - 1.3 – PMRA *USE ONLY*

2. Reference strength

2.1. Reference strength

In this context, the reference strength is the strength of the FPP that was compared to the MRA Comparator product in an *in vivo* bioequivalence study.

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 employed in 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)	**Unit dose (mg)**	**Unit dose (%)**	**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 >>

2.5 COMMENTS FROM REVIEW OF SECTION 2.1 – 2.4 – PMRA *USE ONLY*

3. Comparison of Test and Reference strengths

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	Function	Strength (label claim)

and Quality Standard		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. Any deviations from direct proportionality should be identified and justified in detail.

<< Please enter information here >>

3.3 COMMENTS FROM REVIEW OF SECTION 3.1 – 3.2 – PMRA *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 the Quality guideline (*Guideline on Submission of Documentation for a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part*, Appendix 1), comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution 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 to provide 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.

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, sample handling 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 any calculations 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 >>

4.5. COMMENTS FROM REVIEW OF SECTION 4.1 – 4.4 – PMRA *USE ONLY*

5. Comparative *in vitro* dissolution:

Studies comparing each strength of the test product to equivalent strength 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

- 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 MRA comparator product as identified on the registration guideline should be employed.
- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the Quality guideline (*Guideline on Submission of Documentation for a Generic Finished Pharmaceutical Product (FPP): Quality Part*, Appendix 1), comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution 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 to provide a complete summary of the data supporting the biowaiver request.

5.1. Purchase, shipment and storage of the comparator product
As per the documentation requirements for comparator products, please attach relevant copies of documents (e.g. receipts) proving the stated conditions.

<< Please enter information here >>

5.2. 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.

<< Please enter information here >>

5.3. 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 >>

5.4. 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.

5.4.1. Dissolution media: Composition, temperature, volume, and method of de-aeration

<< Please enter information here >>

5.4.2. Type of apparatus and agitation speed(s) employed

<< Please enter information here >>

5.4.3. Number of units employed

<< Please enter information here >>

5.4.4. Sample collection: method of collection, sampling times, method of filtration, sample handling and storage

<< Please enter information here >>

5.4.5. Deviations from sampling protocol

<< Please enter information here >>

5.5. Summarize the results of the dissolution study(s)

Please 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**.

<< Please enter information here >>

5.6. Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

<< Please enter information here >>

5.7. COMMENTS FROM REVIEW OF SECTION 5.1 – 5.6 – PMRA *USE ONLY*

CONCLUSIONS AND RECOMMENDATIONS – PMRA *USE ONLY*

ANNEX III: LIST OF SUBSTANCES FOR BCS BASED BIOWAIVER

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
abacavir	200mg	high	low	3	5.3		antiretroviral	
acetazolamide	250 mg	low	Low (?)	4/2	Not eligible for biowaiver		Anti-glaucoma medicine	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
acetylsalicylic acid	500 mg	high	high	1	5.1		NSAID, antimigraine medicine	
acetylsalicylic acid	100 mg	high	high	1	5.1		antithrombotic medicine	
acyclovir	200 mg	high	low	3	5.3		Anti-herpes medicines	
albendazole	400 mg	low	low (?)	4/2	Not eligible for biowaiver		Ant-helminthic	Chewable tablet; unknown whether poor BA is due to poor solubility or poor solubility and poor permeability

allopurinol	100 mg	high	high	1	5.1		gout	
aluminium hydroxide	500 mg			NR	NA		antacid	Use for local effect
amiloride hydrochloride	5 mg	high	high	1	5.1		diuretic	
amitriptyline hydrochloride	25 mg (*1*)	high	high	1	5.1		Psychotherapeutic medicine	
amlodipine	5 mg	high	high	1	5.1		Anti-hypertensive medicine	
amodiaquine	200 mg	high	Borderline BA	3/1	5.3	CYP2C8	antimalarial	Extent of first pass

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
(base)			> 75%			polymorphism, increased risk for agranulocytosis and liver toxicity		metabolism uncertain

amoxicillin (a) + clavulanic acid (c)	(a) 500 mg + (c) 125 mg	(a) high + (c) high	(a) high + (c) borderline absorption >73% (radioac-tive excretion)	(a) 1 + (c) 3/1	5.3		antibacterial	combination should be tested according to clavulanic acid requirements
amoxicillin anhydrous	500 mg	high	high	1	5.1		antibacterial	
artemether (a) + lumefantrine (l)	(a) 20 mg + (l) 120 mg	(a and l) unknown	low (a and l)	(a) 4/3 + (l) 4/3	Not eligible for biowaiver		antimalarial	
ascorbic acid	50 mg	high	high	1	5.1		vitamin	
atenolol	100 mg	high	low	3	5.3		Anti-angina, antihypertensive, antiarrhythmic and used in heart failure	
azithromycin	500 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	Unknown whether poor BA is due to poor solubility or

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								poor solubility and poor permeability
benznidazole	100 mg	high	low	3	5.3		American trypanosomiasis	
biperiden hydrochloride	2 mg	high	Insufficient literature	3/1	5.3		Anti-parkinson medicine	
carbamazepine	200 mg	Low (neutral)	high	2	Not eligible for biowaiver		Antiepileptic, psychotherapeutic medicine	scored tablet
cefixime	400 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability

chloramphenicol	250 mg	high	low	3	5.3	Narrow therapeutic index	antibacterial	
chloroquine phosphate or sulfate	150 mg	high	high	1	5.1		DMARD, antimalarial	
chlorpheniramine hydrogen maleate	4 mg	high	BA 25-59%, first pass	3/1	5.3	CYP2D6 polymorphism	antiallergic	Extent of first pass metabolism uncertain
chlorpromazine hydrochloride	100 mg	high	low	3	5.3		psychotherapeutictic medicine	
ciprofloxacin hydrochloride	250 mg	high	BA 70–82%, possible first pass, high in Caco-2 cells	3/1	5.3		antibacterial	Extent of first pass metabolism uncertain

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
clofazimine	100 mg	Insufficient	low	4/3	Not eligible for		Antileprosy medicine	

		literature			biowaiver at present			
clomifene citrate	50 mg	high	Insufficient literature	3/1	5.3		ovulation inducer	
clomipramine hydrochloride	25 mg	high	66% excreted in the urine, the remainder being eliminated in the faeces	3/1	5.3		Psychotherapeutic medicine	Lack of absolute bioavailability data
cloxacillin (as sodium salt)	1000 mg	high	low	3	5.3		antibacterial	
codeine phosphate	30 mg	high	low	3	5.3	risk of abuse	Opiod analgesic, diarrhoea in adults	
dapsone	100 mg	Low (weak base)	high	2	Not eligible for biowaiver	G6PD deficiency	Antileprosy medicine	
diazepam	5 mg	high	high	1	5.1		psychotherapeutic medicine	scored tablet
didanosine	200 mg	high	low	3	5.3		antiretroviral	Buffered chewable dispersible tablet

didanosine	400 mg	high	low	3	see comment		antiretroviral	Unbuffered enteric coated capsule →not eligible for biowaiver in this dosage form
digoxin	250 µg	high	high	1	5.1		Antiarrhythmic and used in heart failure	

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
diloxanide furoate	500 mg	low (*2*)	low (?)	4/2	Not eligible for biowaiver		antiprotozoal	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
doxycline hydrochloride	100 mg	high	high	1	5.1		antibacterial	
efavirenz	200 mg	low (*1*)	low (?)	4/2	Not eligible for biowaiver		antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability

enalapril	2.5 mg	high	low	3	5.3		Antihypertensive medicine	
ergocalciferol	1.25mg (50 000 IU)	high	low	3	5.3		vitamin	
erythromycin stearate + ethylsuccinate	250 mg	low	low	4	Not eligible for biowaiver		antibacterial	
ethambutol hydrochloride	400 mg	high	low	3	5.3	Risk of dose related ototoxicity	Antituberculosis medicine	
ethinylestradiol	50 µg	high	Borderline, BA 40-50%, first pass	3/1	5.3		estrogen	Extent of first-pass metabolism uncertain
ethinylestradiol (e) + levonorgestrel (l)	30 µg + 150 µg	high	(e) borderline, BA 40–50%, first pass + (l) high	3/1 + 1	5.3		Hormonal contraceptive	Extent of first-pass metabolism uncertain; combination should be tested according to

Medicine	**Highest oral strength[i]**	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)[ii]**	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**

								ethinylestradiol requirements
ethinylestradiol (e) + norethisterone (n)	35 µg + 1 mg	high	(e) borderline, BA 40–50%, first pass + (n) high	3/1 + 1	5.3		hormonal contraceptive	extent of first-pass metabolism un-certain; combination should be tested according to ethinylestradiol requirements
ferrous salt	equivalent to 60 mg iron	high (see footnote)	low	3	5.3		antianaemia medicine	commonly used salts: see footnote
ferrous salt (fs) + folic acid (fa)	equivalent to 60 mg iron + 400 µg folic acid	(fs) high + (fa) high	(fs) low + (fa) low (urinary recovery 28.5%) (*2*)	3 + 3/1	5.3		antianaemia medicine (during pregnancy)	lack of absolute bioavailability data; commonly used salts: see footnote; combination should be tested according to ferrous salt requirements
fluconazole	50 mg	high	high	1	5.1		antifungal	
folic acid	5 mg	high	low (?)	3/1	5.3		antianaemia medicine	lack of absolute bioavailability data

furosemide	40 mg	low	low (?)	4/2	Not eligible for biowaiver	highly variable BA	medicine used in heart failure, diuretic	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
glibenclamide	5 mg	low	low (?)	4/2	Not eligible for biowaiver		antidiabetic agent	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
glyceryl trinitrate	500 µg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA	local absorption	antianginal medicine	sublingual application
griseofulvin	250 mg	Low (neutral)	high	2	Not eligible for biowaiver		antifungal	

haloperidol	2 mg	Borderline <0.01 mg/ml2	low	4/3	Not eligible for biowaiver		Psychothepeutic medicine	
hydralazine hydrochloride	50 mg	high	low	3	5.3		Antihypertensive medicine	
hydrochlorothiazide	25 mg	high	low	3	5.3		Antihypertensive medicine, diuretic and used in heart failure	scored tablet
ibuprofen	400 mg	Low, weak acid (p*K* a4.4, 5.2)	high	2	5.2		NSAID, antimigraine medicine	
indinavir sulfate	400 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (–)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
iopanoic acid	500 mg	low, weak acid (p*K* a4.8) (*2*)	high	2	Not eligible for biowaiver		radiocontrast media	Insufficiently soluble in water (15 µg/ml) to be eligible for biowaiver

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
isoniazid	300 mg	high	borderline	3/1	5.3		Antitubercolusis medicine	
isoniazid (i) + ethambutol (e)	(i) 150 mg + (e) 400 mg	(i) high + (e) high	(i) borderline + (e) low	(i) 3/1 + (e) 3	See footnoteg	ocular toxicity	antituberculosis medicine	
isosorbide dinitrate	5 mg	high	Sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA		Antianginal medicine	sublingual
ivermectin	6 mg	Practically insoluble in water D:S > 6000 ml	low (?)	4/2	Not eligible for biowaiver		antifilarial	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
lamivudine	150 mg	high	high	1	5.1		antiretroviral	
levamisole hydrochloride	150 mg	high	borderline	3/1	5.3		anthelminthic	

levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(l) high + (c) high	(l) high + (c) insufficient data (BAhumans58%, BAdogs88%)	(l) 1 + (c) 3/1	5.3	narrow therapeutic index	antiparkinson medicine	extent of human first-pass metabolism; metabolism uncertain ; combination should be tested according to carbidopa requirements

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
levonorgestrel	30 µg	high	high	1	5.1		Hormonal contraceptive	
levonorgestrel	750 µg × 2 (pack of two)	high	high	1	5.1		Hormonal contraceptive	
levothyroxine sodium salt	100 µg	high	low	3	5.3	Narrow therapeutic index	thyroid hormone	
lithium carbonate	300 mg	high	high	1	5.1	Narrow therapeutic index	psychotherapeutic medicine	

lopinavir (l) + ritonavir (r)	(l) 133.3 mg + (r) 33.3 mg	(l) low + (r) low	(l) low (insufficient data) (?) + (r) low (?)	(l) 4/2 + (r) 4/2	Not eligible for biowaiver		antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
mebendazole	500 mg	low	low (?)	4/2	NA		anthelminthic	Chewable tablet, antihelminthics usually applied orally for local action in GI tract, solubility more important than permeability, but unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
mefloquine hydrochloride	250 mg	low2	low (?)	4/2	Not eligible for biowaiver		antimalarial	unknown whether poor BA is due to poor solubility or poor solubility and poor permeability

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
DL-methionine	250 mg	high	high	1	5.1		antidote	
metformin hydrochloride	500 mg	high	low	3	5.3		Antidiabetic agent	
methyldopa	250 mg	high	low	3	5.3		Antihypertensive medicine	
metoclopramide hydrochloride	10 mg	high	low	3	5.3		antiemetic	
metronidazole	500 mg	high	high	1	5.1		Abtiprotozoal antibacterial	
morphine sulfate	10 mg	high	insufficient data (BA ~ 30% but extensive first pass)	3/1	5.3	risk of abuse	Opiod analgesic	extent of first pass metabolism uncertain
nelfinavir mesilate	250 mg	low	low (?)	4	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor

								permeability
neostigmine bromide	15 mg	high	low	3	5.3		muscle relaxant	
nevirapine	200 mg	Low (weak base)	high	2	Not eligible for biowaiver		antiretroviral	
niclosamide	500 mg	low	low (?)	4/2	NA		anthelminthic	Chewable tablet, antihelminthics usually applied orally for local action in GI tract, solubility

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								more important than permeability,
nicotinamide	50 mg	high	high	1	5.1		vitamin	
nifedipine	10 mg	Low, weak acid, solubility at pH 7 0.0056 mg/ml2	high	2	Not eligible for biowaiver		antioxytocic	
nifurtimox	250 mg	high	low	3	5.3		American trypanosomiasis	
nitrofurantoin	100 mg	low, weak acid, solubility at pH 7.0 0.374 mg/ml (p*K* a7.2 (25 °C)) (*2*)	high	2	Not eligible for biowaiver		antibacterial	Not soluble enough at pH 6.8 to be eligible for biowaiver
norethisterone	5 mg	high	high	1	5.1		progestogen	

nystatin	500 000 IU	–	–	NR	NA		antifungal	local effect
paracetamol	500 mg	high	high	1	5.1		NSAID, antimigraine medicine	
penicillamine	250 mg	high	low	3	5.3		antidote	
phenobarbital	100 mg	high	high	1	5.1	Narrow therapeutic	antiepileptic	

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
						index		
phenoxymethyl penicillin (as potassium salt)	250 mg	high	high	1	5.1		antibacterial	

phenytoin sodium salt	100 mg	low, weak acid, sol. at pH 6.8 1.7 mg/ml (*4*) p*K* a 8.3 (25 °C)) (*2*)	high	2	5.2	narrow therapeutic index, non-linear pharmaco-kinetics	antiepileptic	
potassium iodide	60 mg	high	high	1	5.1		thyroid hormones and antithyroid medicines	
praziquantel	600 mg	low (neutral)	high	2	Not eligible for biowaiver		anthelminthic, antischistosomal, antitrematode	
prednisolone	25 mg	high	high	1	5.1		antiallergic	
primaquine diphosphate	15 mg	high	high	1	5.1		antimalarial	
proguanil hydrochloride	100 mg	high	high	1	5.1		antimalarial	
promethazine hydrochloride	25 mg	high	high	1	5.1	CYP2D6 polymorph ism	antiemetic	

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
propranolol hydrochloride	40 mg	high	high	1	5.1		antimigraine medicine	
propylthiouracil	50 mg	high	high	1	5.1		antithyroid medicine	
pyrantel embonate	250 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
pyrazinamide	400 mg	high	borderline	3/1	5.3	Liver toxicity	antituberculosis medicine	
pyridoxine hydrochloride	25 mg	high	high	1	5.1		vitamin	
pyrimethamine	25 mg	borderline; < 0.1 mg/ml3	low	4/3	Not eligible for biowaiver		antipneumocystosis and antitoxoplasmosis medicine	

quinine bisulfate or sulfate	300 mg	high	high	1	5.1		antimalarial	
ranitidine hydrochloride	150 mg	high	low	3	5.3		Antiulcer medicine	
retinol palmitate	110 mg (200 000 IU)	low (*3*)	low (?)	4/2	Not eligible for biowaiver		vitamin	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
riboflavin	5 mg	high	high	1	5.1		vitamin	

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
rifampicin	300 mg	low (am-amphiphilic) (p*K* 1.7, 7.9) (*1*)	high	2	Not eligible for biowaiver		antileprosy and antituberculosis medicine	
rifampicin (r) + isoniazid (i)	(r) 300 mg + (i) 150	(r) low + (i) high	(r) high + (i) borderline	(r) 2 + (i) 3/1	Not eligible for biowaiver		antituberculosis medicine	

	mg							
rifampicin (r) + isoniazid (i) + pyrazinamide (p)	(r) 150 mg+ (i) 150 mg+ (p) 500 mg	(r) low + (i) high + (p) high	(r) high + (i) borderline + (p) borderline	(r) 2 + (i) 3/1 + (p) 3/1	Not eligible for biowaiver		antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p) + ethambutol- (e)	(r) 150 mg+ (i) 75 mg + (p) 400 mg (e) 275 mg	(r) low + (i) high + (p) high + (e) high	(r) high + (i) borderline + (p) border- line + (e) low	(r) 2 + (i) 3/1 + (p) 3/1 + (e) 3	Not eligible for biowaiver		antituberculosis medicine	
ritonavir	100 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
salbutamol	4 mg	high	high	1	5.1		Antiasthmatic and	

sulfate							COPD	
saquinavir	200 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor

Medicine	**Highest oral strength**[i]	**Solubility**	**Permeability**	**BCS class**	**Dissolution test (for biowaiver)**[ii]	**Potential risks**	**Indication(s) according to WHO EML**	**Comments and special dosage form indications**
								permeability
senna	7.5mg (sennoside)	–	–	NR	NA		laxative	local effect
spironolactone	25 mg	borderline	low	4/3	Not eligible for biowaiver		diuretic	
stavudine	40 mg	high	high	1	5.1		antiretroviral	

sulfamethoxazole (s) + trimethoprim (t)	400 mg + 80 mg	(s) low (amphiphil) + (t) low (weak base)	(s) high + (t) high	(s) 2 + (t) 2	Not eligible for biowaiver	G6PD deficiency	antibacterial	
sulfasalazi ne	500 mg	low	low	4	NR		Gastrointestinal , anti-inflammatory medicine	Used for local action in the gastrointestinal tract
thiamine hydrochlori de	50 mg	high	low	3	5.3		vitamin	
triclabenda zole	250 mg	insufficien t literature	low	4/3	Not eligible for biowaiver		Antischistosomal antitrematode	
trimethopri m	200 mg	Low (weak base)	high	2	Not eligible for biowaiver		antibacterial	
valproic acid sodium salt	500 mg	high	high	1	see comment		antiepileptic, psychotherapeutic-tic medicine	enteric-coated tablet not eligible for biowaiver in this dosage form

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
verapamil hydrochloride	80 mg	low (weak base)	high	2	Not eligible for biowaiver		Antianginal and antiarrhythmic medicine	
warfarin sodium salt	5 mg	high (soluble in less than 1 of water) (*1*)	high	1	5.1	narrow therapeutic index	medicines affecting coagulation	
zidovudine	300 mg	high	high	1	5.1		antiretroviral	
zinc sulfate	10mg (per unit dosage form)	high	low	3	5.3		Diarrhoea in children	

Biowaivers not applicable or relevant, locally acting, no significant systemic absorption, absorption from the oral cavity or dosage form not designed for immediate release.

i The highest dose strength is based on the highest oral strength according to the WHO Essential medicines List
ii The dissolution testing procedure depends on the BCS classification of the API, based on solubility and permeability. The testing procedures are as defined in section 5 of the **Annex To Guideline On Submission Of Documentation For**

Registration Of A Multi-Source (Generic) Finished Pharmaceutical Products (Fpps): *Guideline On Waiver Of In Vivo Bioequivalence Requirements For Immediate-Release Solid Oral Dosage Forms Rev 0_2008.*