Medicines Control Authority of Zimbabwe

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.

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1. INTRODUCTION

This 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 MCAZ Biowaiver Application Form as an electronic copy in Microsoft (MS) Word in CD format and a hard copy. The Application form can be downloaded from the MCAZ website www.mcaz.co.zw .

2. SCOPE

This document is intended to provide guidance on MCAZ'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 Appendix I 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 MCAZ 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.

[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)

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

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.

4. BIOWAIVER IS APPLICABLE TO THE FOLLOWING[2]:

4.1. 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.

4.2. 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.

4.3. Formulation development of a generic drug product. A generic product must be comparable to the innovator product i.e. must be therapeutically equivalent and

[2] 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

interchangeable. This means the generic product must be pharmaceutically equivalent and bioequivalent to meet therapeutic equivalence.

4.4. 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.

5. CRITERIA FOR ACCEPTANCE OF BCS BASED BIOWAIVER FOR A PHARMACEUTICAL PRODUCT.

5.1. *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);

5.2. 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;

5.3. 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

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

5.5. 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.

6. IN VIVO BIOEQUIVALENCE REQUIRED FOR:

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

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

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

6.4. A product that is not listed on the Appendix I;

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

6.6. 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.