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GUIDANCE ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF A MULTI-SOURCE (GENERIC) FINISHED PHARMACEUTICAL PRODUCTS (FPPS)

GUIDANCE ON SUBMISSION OF DOCUMENTATION FOR INTERCHANGEABILITY

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1- INTRODUCTION

This guiding document is annex to the "Pharmacy and Medicines Regulatory Authority (PMRA) Guidelines on Submission of Documentation for Registration of a Multi-Source (Generic) Finished Pharmaceutical Products (FPPs)" lays down the requirements for submission of documentation for interchangeability for applications for registration of finished pharmaceutical products (FPPs). The guidance is based on the WHO Technical Report Series no 992, 2015, Annex 7; "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability".

Guidance documents are meant to assist the industry on how to comply with regulatory requirements for registration of multisource (generic) pharmaceutical products. Guidance documents are administrative instruments to ensure fairness, consistence and effectiveness in implementing statutory requirements and do not have force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that PMRA reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy or quality of a pharmaceutical product.

This document is intended to provide guidance on the format of the bioequivalence submission as part of the application for registration. Bioequivalence data should be presented according to the format of this guide. Applicants should submit a completed Bioequivalence Trial Information Form (BTIF) as an electronic copy in **Microsoft (MS) Word** in CD. Bioequivalence Trial Information Form (BTIF) can be downloaded from the Authorities website www.pmra.mw . This application form is designed to facilitate information exchange between the Applicant and the PMRA and to facilitate the review process of the applications for registration.

2- SCOPE

This document is intended to provide guidance on the drug submissions which rely on comparative bioavailability studies to establish safety and efficacy. Frequently, the safety and efficacy of a given drug product is established on the basis of a "pivotal" comparative bioavailability (bioequivalence) study or studies. The requirements set in this guidance document are applicable to but are not limited to:

1. the introduction of a new subsequent-entry drug product or multi-source (generic) preparations on the basis of "equivalency" with a marketed reference product.
2. the introduction of new dosage forms (e.g., tablet to capsule) or new strengths of a product;
3. changing the formulation or manufacturing procedures for a product; and
4. "bridging" between the to-be-marketed formulation and the formulation(s) used in clinical trials.

Bio-equivalence data is required from all oral preparations except aqueous solutions at the time of administration. Orally or parenterally administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only. Also, bio-equivalence study is required from preparations indicated for serious conditions requiring assured therapeutic response. Instead of bio-equivalence trial, comparative clinical trial using clinical or pharmacodynamic endpoints can be presented. These endpoints should be justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted.

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). Applicants should consult other applicable guidelines such as International Conference for Harmonization (ICH), other WHO guidelines relating to safety, efficacy and quality of FPPs where applicable.

3- WAIVER REQUESTS

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product. For requests for waiver of in vivo comparative bioavailability studies based on the Biopharmaceutics Classification System (BCS), applicant should refer to the "PMRA Guideline on Waiver of in Vivo Bioequivalence Requirements for Immediate-Release Solid Oral Dosage Forms" and applicable WHO guideline documents.

For products where several strengths are to be submitted for the same product, justification supporting a waiver of the requirement for in vivo studies should be provided for each strength. Applicants should use the appropriate application form (PMRA Biowaiver for Additional Strengths Application Form) of a waiver of in vivo bioequivalence requirement for additional strengths. The justification for a waiver may address issues such as the nature of the kinetics of the drug (e.g., linear versus non-linear), and the proportionality of the strengths for which a waiver is sought to the strength on which a comparative bioavailability study was conducted. The statement of justification for waiver should include supporting data (e.g., comparative dissolution data).

4- DOCUMENTATION TO BE SUBMITTED

In addition to the completion and submission of the Bioequivalence Trial Information Form (BTIF), the following information should be submitted:

4.1 Comparative BA and Bioequivalence (BE) Study Reports

Clinical study reports are to be structured in accordance with ICH E3: *Structure and Content of Clinical Study Reports*. This section of the submission should include a detailed description of each study performed to establish the relative bioavailability and therefore, bioequivalence of each formulation. The reports should be based on raw quantitative and qualitative data. The reports will require the compilation of summary tables and graphs that should be presented as described in the WHO guidance on bioavailability/bioequivalence. Sections of the clinical study report (E3) that are not applicable for comparative bioavailability studies should be stated as such and should appear in the table of contents for the clinical study report with the words "not applicable".

Bio-equivalence study report should contain at least the following items:

4.1.1 Information on the investigators and study administrative structure. This should include the geographic location of the study facility(ies) or clinical research organization (CRO) conducting the studies as well as the name, address,

telephone, and fax numbers of individuals responsible for the performance of the study.

4.1.2 Description of study design. The most appropriate study type is two-period randomized crossover study. If other study types were used (e.g. parallel group design), these should be justified by the applicant. In general, single-dose study with sufficiently long period for blood samples collection is acceptable.

4.1.3 Information about investigators, study site, study dates.

4.1.4 Data about preparations used: manufacturer, place of manufacture, batch number. Reference preparation in bio-equivalence study should be well known preparation used in most countries of the world. The best acceptable reference is innovator preparation or product from WHO list of international comparator products if listed.

4.1.5 Characterization of study subjects. Bio-equivalence study should be normally performed in healthy volunteers. If patients were used, this should be justified by the applicant. Number of subjects should not be smaller than 12. Study report should contain inclusion and exclusion criteria, listing of demographic data of all subjects.

4.1.6 Description of study procedures. Administration of test products, meals, and times of blood sampling or urine collection periods should be described in the clinical report.

4.1.7 Description and validation of drug determination methods in investigated material. Analytical method should be validated over the measured drug concentration range. Validation should contain methodology and results of sensitivity, specificity, accuracy, precision and repeatability determination. Analytical methods should be validated based on Unites States Food and Drug Administration's (USFDA) Bioanalytical Method Validation: Guidance for Industry or European Medicines Agency's (EMA) Guideline on bioanalaytical method validation.

4.1.8 All measured drug concentrations should be presented.

4.1.9 Calculation methodology of pharmacokinetic parameters. Preferred is non-compartmental analysis. If modelled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.

4.1.10 Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference ratios of pharmacokinetic parameters. The main parameters to assess the bio-equivalence are area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{max}) ratios. The 90% confidence interval for the AUC-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. The 90% confidence interval for the C_{max}-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75-133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.

4.2 Supporting documentation

Supporting documentation should include but not limited to the following:

4.2.1 Protocol and protocol amendments
4.2.2 Sample case report form (unique pages only)
4.2.3 List of IECs or IRBs (plus the name of the committee Chair) – Representative written information for patient and sample consent forms
4.2.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
4.2.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer.
4.2.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.
4.2.7 Randomisation scheme and codes (patient identification and treatment assigned)
4.2.8 Audit certificates (if available)
4.2.9 Documentation of statistical methods. The statistical report should be provided in this appendix. See also ICH E3 Annex VIII (Guidance for section 11.4.2 - Statistical/Analytical Issues and Appendix 6.1.9).
4.2.10 Publications based on the study
4.2.11 Important publications referenced in the report
4.2.12 Discontinued patients
4.2.13 Protocol deviations
4.2.14 Patients excluded from the efficacy analysis
4.2.15 Demographic data
4.2.16 Compliance and/or drug concentration data (if available)
4.2.17 Individual efficacy response data

Examples of tables and figures which may be included in this appendix are as follows:

4.2.17.1 Individual and mean measured plasma concentrations of the test at each sampling time
4.2.17.2 Individual and mean measured plasma concentrations of the reference at each sampling time
4.2.17.3 Cumulative AUC of the test
4.2.17.4 Cumulative AUC of the reference
4.2.17.5 Individual and mean linear concentration-time profiles for the test and reference
4.2.17.6 Individual and mean semi-logarithmic concentration-time profiles for the test and reference
4.2.17.7 Adverse event listings (each patient)
4.2.17.8 Listing of individual laboratory measurements by patient.
4.2.17.9 Case Report Forms
4.2.17.10 CRFs for deaths, other serious adverse events and withdrawals for AE
4.2.17.11 Other CRFs submitted
4.2.18 Individual Patient Data Listings (US Archival Listings)
4.2.19 Analytical Study Report
4.2.20 Analytical Validation Report