NAFDAC Bioavailability and Bioequivalence Studies Regulations, 2024

Comments are Welcomed from Stakeholders within 60 Calendar Days (ending 7th December 2024) Please send all comments/input/feedback to regulatoryaffairs@nafdac.gov.ng

NAFDAC Bioavailability And Bioequivalence Studies Regulations

Arrangement of Regulations

Regulation

NAFDAC Bioavailability And Bioequivalence Studies Regulations

[ ] Commencement

In exercise of the powers conferred on the Governing Council of the National Agency for Food and Drug Administration and Control ('the Governing Council') by Section 30 of the National Agency for Food and Drug Administration and Control Act, Cap. N1, LFN, 2004 and Section 12 of the Food, Drugs and Related Products (Registration, Etc.) Act. Cap. F33. LFN, 2004 and of all the powers enabling it in that behalf, the Governing Council with the approval of the Minister makes the following Regulations: -

PART 1
OBJECTIVE AND APPLICATION

1. **Objective**
   The objective of these Regulations is to provide regulatory framework for the conduct of investigation of bioavailability and bioequivalence studies and data obtained to support registration of generic drug and related products manufactured, imported, exported, advertised, sold, displayed for sale, distributed, or used in Nigeria.

2. **Application**
   These Regulations shall apply to conduct of bioavailability and bioequivalence studies and data obtained to support registration of generic drug and related products manufactured, imported, exported, advertised, sold, distributed, displayed for sale, or used in Nigeria.

PART II
APPLICATION FOR CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES, GENERAL CONSIDERATIONS, STUDY CONDUCT

3. **Application for conduct of bioavailability (BA) and bioequivalence (BE) studies**
   (1) Manufacturers of drug and related products shall submit an application to the Agency for the approval of the protocol for conducting bioavailability and bioequivalence studies before the commencement of the studies.
   (2) The protocol shall comply with the Agency's Guidelines on Good Clinical Practices.
   (3) Pursuant to regulations 3 (1) and (2) of this regulation, bioavailability and bioequivalence studies of generic drugs may be waived where the application satisfies the requirement for Biowaiver as outlined in the BA and BE Guidelines and any other regulatory requirements of the Agency.
   (4) The Application as specified in regulation 3 of this regulation shall be accompanied with
      (a) the fees as specified by the Agency from time to time.
      (b) relevant product dossier.

(c) Bioequivalence Trial Information Form (BTIF), Bio waiver application Form (BAF) and the Quality templates.
(d) other requirements as may be prescribed by the Agency.

(5) For BE, the study protocol shall be approved by the Agency before commencing the study.

(6) The report of the study upon completion shall be submitted to the Agency within the time frame as may be prescribed by the Agency.

4. **General Considerations**

(1) Studies for
(a) bioequivalence shall be conducted to determine if a generic product is equivalent to a reference product in terms of the rate and extent of active ingredient absorption
(b) bioavailability shall be conducted to determine the extent and rate of active ingredient absorption from a pharmaceutical product.

(2) The design to be adopted shall be the preferred study design in accordance with the requirements specified in the relevant Guidelines.

(3) Healthy volunteers shall be for BE studies as study population.

(4) Notwithstanding regulations (4) (3) of this regulations, where patients may used as study population, the use of the patient shall be in accordance with the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.

(5) The dosage regimen used in
(a) BE studies shall follow the recommendations as approved by the Agency
(b) BA studies shall be clearly defined in the study protocol.

(6) Blood samples for purposes of BA or BE Study shall be collected for up to 72 hours following administration for oral products.

(7) Blood samples collection time shall be adequate to ensure completion of gastrointestinal transit and Active Pharmaceutical Ingredient (API) absorption.

(8) The study report from BA or BE study shall be submitted to the Agency using the NAFDAC Bioavailability and Bioequivalence Trial Information Form (BTIF) and other template as may be prescribed by the Agency.

(9) Active pharmaceutical ingredients with long elimination half-lives shall have the ideal interval between administration of the products as prescribed in the Guidelines on the investigation of bioavailability and bioequivalence of drugs.

(10) Where multiple dose studies in patients are required, the design shall follow the provisions under "Consideration for multiple dose studies" as prescribed in the Guidelines on the investigation of bioavailability and bioequivalence of drugs.

(11) Pharmacokinetic assessment, safety and tolerability assessment shall be in line with the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.

5. **Participants**

(1) The minimum number of participants for the BA and BE studies shall be as prescribed by the Agency

(2) The proposed statistical plan shall be stated in the study protocol.
(3) The error variance associated with the primary parameters to be studied shall be a tool to determine the number of participants to be used in a BE Study.
(4) The applicant shall provide a detailed description of the test and reference drug products, used and to be used, including their composition, strength, and route of administration.

6. **Study Conduct**
(1) Participants to be used in implementing a BE study shall be appropriately screened and selected based on the inclusion and exclusion criteria defined in the study protocol.
(2) In a case of cross-over study, a participants shall be given the test product and the reference product in randomized order, and an adequate wash-out period allowed following the administration of each product.
(3) In parallel design study, the interval between the administration of the test product and the reference product shall not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured.

PART III
STUDY REPORTING, DROPOUTS AND WITHDRAWALS, EXCLUSION OF PARTICIPANT DATA, MONITORING OF PARTICIPANTS DURING THE STUDY, INVESTIGATIONAL PRODUCT, CHOICE OF COMPARATOR PRODUCT

7. **Study Reporting**
(1) The study report shall
(a) be submitted in accordance with the Agency's BTIF.
(b) include the study protocol, the statistical analysis plan, the results of the study, and a discussion of the results and where applicable, module 5 of the Common Technical Document or electronic Common Technical Document (CTD/eCTD).
(c) provide comprehensive documentation of its protocol, conduct, and evaluation in compliance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) rules.
(d) be prepared using the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guideline or a similar guide as approved by the Agency.

8. **Dropouts and withdrawals**
(1) The applicant shall have sufficient number of study participants to account for possible dropouts or withdrawals.
(2) Further to regulation (8) (1) of this regulation, replacement of study participants following a dropout or withdrawals during the study shall not be allowed.
(3) Dropouts or loss due to Serious Adverse Event (SAE) shall be reported to the Agency.

9. **Exclusion of participant data**
   (1) Criteria for the exclusion of participants shall be clearly presented in the protocol in line with the provisions of the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.
   (2) The age of the participants shall be between 18 and 55 years.
   (3) The weight of participants shall be within the normal range with a body mass index (BMI) between 18 and 30 kg/m2.
   (4) Participants shall
      (a) not have any history of alcohol or drug abuse problems
      (b) be non-smokers.
   (5) Suitability of participants shall be determined using; standard laboratory tests, medical history, and physical examination.
   (6) Further medical investigations and other consideration shall be followed as specified in the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.

10. **Monitoring of participants during the study**
   (1) The applicant shall be responsible for the monitoring of participants.
   (2) Further to regulation (10) (1), the monitoring shall include safety and providing medical care.

11. **Investigational product**
   (1) The product
      (a) being tested in bioequivalence studies for registration purposes shall be the same as the planned commercial product in terms of composition, quality characteristics including stability, and manufacturing methods including equipment and procedures.
      (b) to be used in BE studies shall comply with the requirements of Good Manufacturing Practice (GMP).
      (c) sample shall follow the procedures and considerations specified in the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs

12. **Choice of comparator product**
   Innovator product to be used shall be as may be prescribed by the Agency.

PART IV
STUDY STANDARDIZATION, WASH-OUT INTERVAL, SAMPLING TIMES, STATISTICAL ANALYSIS, QUALIFICATION FOR A BIOWAIVER, PROHIBITION

13. **Study standardization**
   Applicant shall ensure:
   (1) that the proposed facility to be used for BE implementation is adequate and equipped to ensure Standardization of Trial Participants
   (2) compliance with participants standardization process or requirements as specified in the Agency's Guidelines for Investigation of Bioavailability and Bioequivalence including

specifications for before administration of test or reference products for immediate and modified release.

14. **Wash-out interval**
    (1) A formulation shall have a washout period between doses.
    (2) The washout period as specified in regulation (14) (1) shall
        (a) be long enough to allow the previous dose to be eliminated from the body.
        (b) follow the consideration as prescribed in the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.

15. **Sampling times**
    Sampling time, frequency and schedule shall be accordance with the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.

16. **Statistical analysis**
    (1) Statistical analysis shall be conducted during the bioequivalence trial.
    (2) The statistical methods for testing bioequivalence shall be specified clearly in the protocol before data collection.

17. **Qualification for a biowaiver**
    (1) Classification of a drug and related products shall be
        (a) based on the Biopharmaceutics Classification System (BCS).
        (b) used to determine if a biowaiver is appropriate for a drug product as shall be approved by the Agency.
    (2) The decision to waive bioequivalence testing in favor of in vitro methods shall depend on a risk-benefit analysis of the drug's solubility and intestinal permeability, dissolution profiles in various media, excipients used in the formulation, and potential risks to public health and individual patients.
    (3) Qualification for a biowaiver shall also be based on dose-proportionality of formulations as specified in the Agency's Guidelines on the investigation of bioavailability and bioequivalence of drugs.
    (4) An appropriate reference product shall be selected based on the purpose of the studies. The formulation, manufacturing, and quality data of test product shall be available and as approved by the Agency.

18. **Prohibition**
    Generic drug and related products shall not be manufactured, imported, exported, advertised, sold, distributed, displayed for sale, or used in Nigeria except bioavailability and bioequivalence studies has been conducted on it in accordance with the provisions of these Regulations.

PART IV
OFFENCES AND PENALITIES

19. **Offences and Penalties**

(1) Any person who contravenes any of the provisions of these Regulations commits an offence and liable on conviction. In the case of: -

(a) an individual, to imprisonment for a term not exceeding one year or to a fine not exceeding N800,000:00 or both,

(b) a body corporate, to a fine not exceeding N5,000, 000:00.

(2) Where an offence under these Regulations is committed by a body corporate, firm or any other association of individuals, every: -

(a) director, manager, secretary or other similar officer of the body corporate;

(b) partner or officer of the firm;

(c) trustee of the body concerned;

(d) person concerned in the management of the affairs of the association; or

(e) person who was purporting to act in a capacity referred to in paragraphs (a) to (d) of this regulation, commits an offence and liable to be proceeded against and punished in the same manner as if he had himself committed the offence, unless he proves that the act or omission constituting the offence took place without his knowledge, consent or connivance.

20. **Forfeiture after conviction**

(1) A person convicted of an offence under these Regulations shall forfeit to the Federal Government:-

(a) any asset or property constituting proceeds derived from or obtained, directly or indirectly, as a result of the offence; and

(b) any of the person's property or instruments used in any manner to commit or to facilitate the commission of the offence.

(2) In this section, "proceeds" means any property derived or obtained, directly or indirectly, through the commission of the offence.

PART V
MISCELLANEOUS

21. **Enforcement of the Regulations**

The Agency is exclusively responsible for the enforcement of these Regulations.

22. **Interpretation.**

In these regulations—

"Agency" means the National Agency for Food and Drug Administration and Control.

"Bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are no intended to be absorbed into the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

"Cross Over Study Design" means a type of Clinical Trial where each Participants receives multiple treatment such as e.g test and reference product in a specific order. Participants are switched from one treatment to another after a washout period

"Healthy volunteers" means individuals who are between 18- 65 years old (Sometimes 65 years old), in good Physical and mental health, have no history of severe allergies, are non-smokers or light smokers, have a body mass index (BMI) within normal range (18.5- 30), are willing to provide informed consent and have not participated in another clinical trial recently. Health volunteers are also referred to as health participants.

23. **Citation.**

These Regulations shall be cited as the NAFDAC Bioavailability and Bioequivalence Studies Regulations 2024.

MADE at Abuja this ……. day of …….2024.

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Dr. Mansur Kabir

Chairman of the Governing Council

National Agency for Food and Drug Administration and Control (NAFDAC)