OVERVIEW OF BIOEQUIVALENCE AND REGULATORY SUBMISSION

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Drug Evaluation and Research

Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternative and if their bioavailabilities (rate and extent of absorption) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

- Pharmaceutical equivalence
  - Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, same route of administration and are identical in strength or concentration.
- Pharmaceutical alternative
  - Same molar amount of the same API(s) but differ in dosage form (*e.g.,* tablets *vs.* capsules), and/or chemical form (*e.g.,* different salts, different esters); and
  - Deliver the same active moiety by the same route of administration.

Pharmaceutical Equivalence (is it enough ?)

- Pharmaceutical equivalence by itself does not necessarily imply therapeutic equivalence this is because pharmaceutically equivalent FPPs may differ in formulation (excipient, drug particle size, mechanism of release) and in manufacture (equipment, Process and site), this in turn will result in differences in disintegration, dissolution and impact product performance.

- Therapeutic equivalence
  - The drugs are Pharmaceutically equivalent
  - They have the same safety and efficacy profiles after administration of same dose

Products that require Bioequivalence study

- Solid oral FPPs
  - immediate- and modified-release FPPs
- Complex topical formulations
  - emulsions, suspensions, ointments, pastes, foams, gels, sprays, and medical adhesive systems
- Complex parenteral formulations
  - depot injections, nasal/inhalational suspensions

Products that do not require Bioequivalence study

- Parenterally administered products as an aqueous solution.
- Solution for oral use (e.g. Syrups, elixirs and tinctures), optic or ophthalmic products.
- Powders for reconstitution as an aqueous solution.
- Pharmaceutically equivalent products that are gases.
- Pharmaceutically equivalent topical products prepared as aqueous solutions.
- Aqueous solutions for nebulization or nasal drops intended to be administered with essentially the same device, contain the same API(s) in the same concentration and contain the same excipients in similar concentrations.

Establishing Bioequivalence

- Comparative pharmacokinetic studies
  - *In vivo* comparative bioavailability studies
  - Comparison of performance of FPPs based on rate and extent of absorption of API from each formulation
    - Area under the concentration-time curve (AUC)
    - Maximal concentration (Cmax)
    - Time to maximal concentration (Tmax)

- Comparative *in vitro* methods
  - Biopharmaceutics Classification System (BCS) – Apply for Biowaiver using the Biowaiver application form.
  - Additional strengths biowaivers

Establishing Bioequivalence (cont..)

FPPs being tested

- Comparator product
  - NAFDAC/WHO list of comparator product.
- Test product
  - Bio-batch of sufficient size
    - Representative of product proposed for market
    - Support future scale-up
    - Full characterization in dossier

Fixed Dose combination product (FDC)

- The generic FDC product should be compared with the pharmaceutically equivalent comparator FDC product.
- In certain cases, (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator.

Waiver request for a bioequivalence study

- A manufacturer may request a waiver of the requirement for submission of an in vivo bioequivalence study for an immediate release oral dosage form.(BCS 1 & 3)
- A biowaiver is the term used to describe a regulatory drug approval process whereby the efficacy and safety part of a dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

Waiver request for a bioequivalence study (cont.)

- For solid oral dosage forms, biowaivers may be possible based on the Biopharmaceutics Classification System (BCS) or on the proportionality of the formulation of a product to the formulation of another strength of that product (an additional strengths biowaiver).

Submission of Bioequivalence report

- Generic products must satisfy the same standards as those applied to the innovator products. The manufacturer of a generic product must demonstrate that its product:
  - Satisfies the same standards as those applicable to the innovator product
  - Provide assurance that it is clinically interchangeable with, i.e. therapeutically equivalent or bioequivalent to, the innovator product.

Submission of Bioequivalence report (cont..)

- Bioequivalence study report should be submitted to NAFDAC in the CTD format (Module 5.3.1.2 and 5.3.1.4)
- Filled NAFDAC Bioequivalence Trial Information Form (BTIF) (can be found on the NAFDAC website www.nafdac.gov.ng)

Submission of BCS Biowaiver application

- BCS Biowaiver application can be submitted to the agency using the BCS biowaiver form.
- Additional strength application can be submitted using the additional strength biowaiver form (can be found on the NAFDAC website www.nafdac.gov.ng.)

References

- NAFDAC Guideline on Registration Requirements to Establish Interchangeability of Generic Pharmaceutical Products.
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, WHO Technical Report Series, No. 992, Annex 7 with a new Appendix 2.