Trinidad and Tobago

Requirements for Bioequivalence Studies

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Generic Drug Products Requirements to the Innovator Product

- Must conform to the same **standards**
  - quality
  - safety
  - efficacy.
- Same **basic and technical data** required for assessment.
- Must shown to be **pharmaceutically equivalent**
  - Data about the therapeutic equivalence may be required.

Generic Drug Products

- Requirements to assess equivalence:
  - Comparative bioequivalence
  - Comparative pharmacodynamic studies in humans
    - when the quantitative analysis of the API(s) and/or the metabolites in plasma, blood or urine cannot be made with a high degree of accuracy
  - Comparative clinical trials
  - In vitro dissolution tests.

Regulatory Basis

- Food and Drugs Act Chapter 30:01 (Act No. 8 of 1960)
  - Amended by: 39 of 1968 /156 of 1972 /*31 of 1980 /16 of 1986 /12 of 1987 /6 of 1993 /16 of 1998/ 6 of 2005
  - http://rgd.legalaffairs.gov.tt/Laws/Chs.%2028-31/30.01/30.01%20aos.htm
- Annex 3: Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability
  - (WHO, 1999) www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf

Other Guidelines

- Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
  - (FDA, 2003)
  - http://www.fda.gov/cder/guidance/5356fnl.htm
- Note for Guidance on Investigation of Bioavailability and Bioequivalence
  - (EMEA, 2001)
  - http://www.emea.europa.eu/pdfs/human/ewp/140198en.pdf

Other Guidelines

- Conduct and Analysis of Bioavailability and Bioequivalence Studies
  - Part A: Oral Dosage Formulations used for Systemic Effects, 1992;
  - Part B: Oral Modified Release Formulations, 1996
  - (Health Canada, 1996)
  - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/bio-b_e.html

Concerns

1. Analytical Method
2. Plasma Level-Tissue Curves and AUC
3. Independence
4. Compliance

1 Analytical Method

- HPLC with UV detector
- LC-MS
- Method validation details to be provided
  - sensitivity
  - selectivity
  - precision
  - inter- and intra-day variability
  - minimum detectable amount
  - percent recovery (when an extraction is involved)

1 Analytical Method

- Submit representative chromatograms
  - to determine quality of chromatography
    - peak width
    - retention time
    - resolution of analyte
      - from an internal standard
      - other materials in the sample

1 Analytical Method

- For derivatization procedures
  - internal standard that is also derivatized
- Provide calibration curves
- For chiral HPLC columns
  - chromatogram must show the resolution of isomers.

2 Plasma Concentration-Time Curves and AUC

- Minimum of eighteen (18) volunteers
- Plasma sample collection
  - a period long enough to characterize the elimination phase
  - Generally three half-lives
- Plasma profile of both test and reference sample submitted for each volunteer.

2 Plasma Concentration-Time Curves and AUC

- Statistical analysis required:
  - ANOVA test on log transformed AUC
  - Both $AUC_{o\text{-}t}$ and $AUC_{o\text{-}\infty}$
  - Table of C_{max}, t_{max}, AUC for test/standard

3 Independence

- Study center should be independent
- Chief analyst/investigator’s qualification and experience
  - Bioequivalence study
    - Study design and protocol
  - Data interpretation

4 Compliance

- Annex 3: Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability
  - (WHO, 2005) http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf

4 Compliance

- WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI- Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964,
  - amended by the
    - 29th WMA General Assembly, Tokyo, Japan, October 1975
    - 35th WMA General Assembly, Venice, Italy, October 1983
    - 41st WMA General Assembly, Hong Kong, September 1989
    - 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
    - and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
    - Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
    - Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004
      - (WMA, 2004)
      - http://www.wma.net/e/policy/pdf/17c.pdf