Food, Medicine and Health Care Administration and Control Authority

Bio-equivalence Study Registration Requirements in Ethiopia (Four Countries Experience)

Mengistab W. Aregay (Bpharm, MSc. in Health Monitoring and Evaluation)
Deputy General Director of FMHACA

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Ethiopian Food, Medicine and Health Care Administration and Control Authority
Outlines

• Introduction
  – Overall
  – Food, Medicine and Health Care Administration and Control Authority

• Medicine Registration Requirements

• Bio-Equivalence study

• Challenges related to BE study

• Efforts underway to overcome challenges

• Acknowledgements
II. Introduction – Ethiopia – Geography
Introduction - Ethiopia

• Demographic
  – Ethiopia is the second most populous country in Africa with a population of ~ 80 million
  – It is least urbanized with 83.3% live in rural

• Political and administration set up
  – Federal Government structure constructed of
    • Nine regional states and
    • Two city administration
Introduction - Ethiopia

- **Policy and legal frame work**
  - The National health Policy
  - The National medicine policy
  - Food, Medicine and Health Care Administration and Control proclamation No 661/2009
  - Resulting in Improved access to PHC and Essential Medicines

- **Economic situation**
  - Ethiopia is one of the least developed countries
  - Agriculture led industrial economy
  - It is implementing a sustainable development and poverty reduction program (SDPRP) including MDGs with vision of becoming one of mid income countries within 2 decades
Introduction- mandate of the Authority

• Reform has been undertaken in the health sector

• Accordingly the Authority is mandated to regulate
  • Safety and Quality of Food;
  • Safety, efficacy, quality and proper use of medicine
  • Ethical practice and competency of health professionals;
  • Quality of health and controllable health related services
  • ports of entry and exist (export and import permits)
    • Food and medicine and their raw and packaging materials.
Responsibilities of the Authority

a) Regulatory Standards Setting need to be approved
b) Inspection & Licensing
c) Food and medicine Quality Assessment & Registration
   – Market authorization – dossier evaluation and GMP Inspection
   – Laboratory testing
   – Clinical trail authorization and monitoring
   – Post-marketing surveillance
     • ADR monitoring
     • Lab base Post marketing
d) Provision and control Regulatory Information
e) Medico Legal
   – Development and revision of laws.
   – Taking administrative measures
Medicine Registration Requirements

I. Requirements for Abbreviated New Drug

1. Agency Agreement

2. Certificate of pharmaceutical products

3. Chemical and pharmaceutical documentation

3.1 Quality of Raw Material(s)

   – Active Pharmaceutical Ingredient(s)
     • Properties of API(s)
     • Sites of Manufacture of API(s)
     • Route(s) of Synthesis of API(s)
     • Specification of API(s)
     • Stability testing of the API(s)

   – Specification of Excipients
     • a list of tests and limits for results for each excipient,
Requirements for Abbreviated New Drug

3. Chemical and pharmaceutical documentation

3.2 Finished Product
   - Formulation Development
   - Data on Composition

3.3 Data on Packaging Materials (Container & Closures)

3.4 Data on Manufacturing and Packaging Procedures

3.5 Analytical Report
   - Quality specifications (release and stability) and analytical procedures for the dosage form.
   - Declaration of Pharmacopoeia- USP, EP, BP, Ph.Int. and other pharmacopoeia accepted by the Authority
Requirements for Abbreviated New Drug

3. Chemical and pharmaceutical documentation

3.6 Stability Report - Test Condition -
   – Accelerated studies and Real time studies
   – Analytical method and stability specification

4. Summary of pharmacology, toxicology and efficacy of the product


6. Labeling Requirements
   – General requirements for package labeling
   – Package leaflet
   – Label of the immediate container

7. Sample of Actual Products and/or Reference Standard Substance / Active ingredient
Bio-Equivalence study as registration Requirement
Medicine Registration BE – study report

General

• Bioequivalence report is required for those oral dosage forms of drugs which are known to pose bioavailability problem.

• The study should be against innovator or marketing leading registered medicine with the Authority.

• Assessment of equivalence will normally require
  – an in vivo study, or
  – justification that such a study should not be required in a particular case.
General

– An in-vitro test can be used if the product is in the same solid dosage form but in a different strength and is proportionally similar in its active and inactive ingredients as another product made by the same manufacturer and of known bioavailability.

– Bioequivalence studies are preferred where a drug produces meaningful concentrations in accessible biologic fluid, such as plasma.

– Where a drug does not produce measurable concentrations in accessible biologic fluid, 
  • comparative clinical trials or 
  • pharmacodynamic studies may be necessary.
Medicine Registration BE – study report

- **Bio Equivalence Studies are a must for**
  
  a. Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:

  b. Non-oral and Non-parenteral products designed to act by systemic absorption (such as trans-dermal patches, suppositories)

  c. Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption

  d. Fixed combination products with systemic action
Medicine Registration BE – study report

• **Equivalence Studies are not necessary for**

  a) Parenteral preparations (e.g. Intravenous, Intramuscular, subcutaneous, Intrathecal administration) as aqueous solution

  b) Ophthalmic or otic products prepared as aqueous solutions and contain the same active substances in the same concentration and essentially the same excipients in comparable concentration

  c) Topical preparations

  d) Gases

  e) Solutions for oral use which contain the active substance(s) in the same concentration as the innovator product and do not contain an excipient that affects gastro-intestinal transit or absorption of the active substance.
**Medicine Registration BE –study report**

- **Equivalence Studies are not necessary for**
  
  f) Powders for reconstitution as a solution and the solution meets the criteria indicated in (a) or (e) above.

  g) Inhalation and nasal preparations-special invitro testing should be required to document comparable device performance

  h) Other dosage forms where absorption from the site of administration is not a requirement for their efficacy.

* The Country has also daft list of medicines that are eligible for bio-waver for BE as per BCS (WHO and USFDA)
Medicine Registration BE – study report

The report on in-vivo bioequivalence studies should include but not limited to the following information and data:

1. Study protocol
2. Summary of the study
3. Objective
4. Subjects
   - individual volunteers involved in the study
   - Inclusion criteria.
   - Number (minimum 12), sex, race, age, weight and screening tests done prior to commencement of the study.
   - Exclusion criteria.
Medicine Registration BE – study report

• The report on in-vivo bioequivalence studies should include

5. Materials

• Product name, formulation type and complete composition of the drug used in the study both for the test and reference product.

• Certificate of analysis for reference and test product and comparative dissolution data should be submitted where applicable.

6. Study Design – mainly cross over design

  – Description of the test procedure including:
    a) Number of treatment group
    b) Treatment periods
    c) Type of test
6. Study Design

• Description of the test procedure including:
  
  d) Doses, route of administration
  
  e) Administration schedule (fasting state, with or after meal), etc.
  
  f) Sampling times and method for collection of samples
  
  g) Storage condition (from time of collection to analysis)

7. Chemical Analysis

  – Method used to determine plasma (or other biologic fluid) concentrations of the drug and
  
  – during and pre study validation data.
Medicine Registration BE – study report

• The report on in-vivo bioequivalence studies should include

8. Result

– All results (raw data) should be presented clearly
– Sufficiently detailed statistical and/or any other procedures for calculating the parameters used
– Clinical findings
– Plasma concentrations of the drug in the formulations compared:
  • Mean area under the plasma concentration time curve (AUC)
  • Mean peak plasma concentrations (Cmax)
  • Mean time to reach peak plasma concentrations (Tmax)
  • Steady state plasma concentration.
Medicine Registration BE – study report

9. Subjects

• Number, sex, age and weight of volunteer(s) who have completed the study.
• For those who have not completed the study, the reasons

10. Discussion and Conclusion

NB. Representative chromatograms obtained from pre study and within study analytical validation from analysis of subjects samples should be attached.
Medicine Registration BE – study report

• Acceptable criteria

1. At confidence Interval the log transformed T/R of AUCo-t, AUCo – oo and Cmax should be 80% to 125%

2. AUCo-t/AUCo-oo not more than 20% for both test and reference

3. Bio-analytical method validation, lower level of quantification and Upper level of quantification RSD not more than 15%

4. LLOQ and ULOQ in relation to the usual to the actual sample measured

5. Reference product must be innovator product and market leading product
Medicine Registration BE – study report

• Requirement for Local manufacturers

• Local manufacturers are required to provide only comparative dissolution test

• This due to lack of access to affordable BE centre
Challenges related to BE study

1. In availability of affordable bio-equivalent centers
   - Sub-Saharan African Countries including Ethiopia have no access to affordable BE Centers.

2. Lack of list of reliable BE centers

3. No Inspection of BE study

4. In availability of complete list of comparator products
Efforts underway to overcome challenges

1. Establishment of BE centre for East Africa
   • With help of GTZ and WHO establishment of a BE Centre in Ethiopia that serves to Manufacturers in Kenya, Uganda, Tanzania and Ethiopia is on process

1.1 Rational for establishment of BE centre for East Africa
   – High prevalence of HIV/AIDS, Malaria and TB with high mortality in Sub-saharan Africa and
   – high consumption of medicines for such diseases – including ARV, Anti-malaria and Anti-TB medicine
   – Most of the patients in East Africa and COMESA are not able to pay for medicine such as ARV, Anti-malaria and Anti-TB medicine
Efforts underway to overcome challenges

1.1 Establishment of BE centre for East Africa- Rationale

- These medicines are mostly distributed through international funds like Global fund for HIV/AIDS, Malaria and TB (GFHTM), Bill and Melinda Gates Foundation, Clinton foundation, PEPFAR

- GF and others accept only such drugs that are prequalified by WHO

- Market in Africa are different from industrialized countries, markets most of them are regulated health program financed externally

- Local production could cover a growing share of this market
Efforts underway to overcome challenges

1.1 Establishment of BE centre for East Africa- Rationale

• Local manufacturers need to improve the quality of products and upgrade GMP standards and have to show the efficacy and safety of the generic products to get WHO-prequalification.

• Such centres cost at least $50,000 to 200,000 for a BE study (South Africa and India are cheapest and EU and US most expensive)

• These prices are too high for comparatively small local companies in Sub-Saharan Africa

• Hence they need to have access to affordable BE centre
Efforts underway to overcome challenges

1. Establishment of BE centre for East Africa-

1.2. Technical feasibility and demand for a regional BE centre

• Technical feasibility was conducted to investigate the issues
  – Establishment of a BE centre/clinical partner in East Africa
  – It long term economic feasibility and
  – The financial requirement to initiate this project

• For this purpose
  – a fact finding mission to four countries – namely Ethiopia, Kenya, Tanzania and Uganda was carried out (about 74 stakeholders interviewed) and
  – three Workshops were conducted in Addis Ababa- Nairobi -Addis Ababa – Nairobi - Addis Ababa
Efforts underway to overcome challenges

1.2. Technical feasibility and demand for a regional BE centre

- Participation of stakeholders
- all important stakeholders including regulators, academics, research institutes, clinical partners and representative of manufacturers from the four countries participated in the workshops and process

- Establishment of a BE Centre (laboratory/clinical partner) in the region was unanimously welcomed provided BE studies

- Many countries were prepared to host and contribute in kind by offering space in the existing premises, buildings, installations and infrastructure
Efforts underway to overcome challenges

1.3 Legal form of BE centre

• Three options for the ownership/operation of the regional BE centre were explored (establishment)

1. BE centre under one of the country drug regulatory authorities technical feasible but impartiality is not guaranteed and some authorities did not wish to have – ruled out

2. BE centre under complete private ownership – but would require large investments involving premises, buildings, installations, equipment, instrument etc.
• Even though this could good model for sustainability – rule out

3. BE centre under public and private partnership- this model was considered to be realistic as investment is not required for premises, buildings, installations, or equipment and selected
Efforts underway to overcome challenges

1.3 Legal form of BE centre

• The BE centre should
  – be independent in its decision
  – financially autonomous after 2 years of the initial phase

• The responsibility of the BE centre include
  – Planning, study protocols, organization of the studies, bio-analytics, quality assurance and medical report, pharmacokinetic data evaluation, statistics, and data management, audit and
  – The clinical report (clinical trail at hospital and research institutes) could be outsourced

• Ethiopia has been selected to host the BE centre and the BE centre is hosted in Addis Ababa, with a clinical affiliate in Nairobi, Kenya
Efforts underway to overcome challenges

1.3 Legal form of BE centre

- The BE centre will implement the Clinical and laboratory parts of BE studies needed for WHO pre-qualification of essential drugs against HIV/AIDS, Malaria or TB

- Initial cost for 2 years will be covered by the project Management of BE

- Steering Committee is to be formed in the proposed BE centre in Ethiopia with private sector representation from participating companies in the region and public sector to overview the whole project
Efforts underway to overcome challenges

1.3 Legal form of BE centre

- **WHO** has been /will be involved indirectly from the beginning to assure the quality

- The BE centre will implement –after creation and acceptance by WHO through collaborative studies -at least 6 studies per year; and later up-to 12 per year

- **Board composed of (established)**
  - 4 Pharmaceutical companies from
  - School of pharmacy, AAU
  - Clinical partners in Ethiopia and Kenya
  - GTZ
  - WHO

- **Advisory Board (Established)**
  - Observers to Advisory board
Status of the establishment of the BE Centre

• Space secured in School of Pharmacy, medical school and A.A.U
• Memorandum of understanding signed among partners.
• Management Board as well as Advisory board established
• Finance almost mobilized
• It is believed that it will start by the year 2011
Efforts underway to overcome challenges

2. Efforts by the Authority

• Training on BE assessment has been given to experts with technical and financial assistance of USP/PQM and WHO

• Revision of the Registration guidelines including BE Study will be carried out

• Revision of list if medicines eligible for biowaver on basis of BCS- WHO and US FDA

• compilation complete list of comparator and BE Centers
Acknowledgements

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• WHO for its technical assistance
• GTZ for the technical assistance
• USP/PQM for technical and financial assistance for BE training
It is possible to collaborate, harmonize and make a difference in assuring safety, efficacy, Quality and Proper use of medicine in Africa

Thank You!!!