

**Training on Assessment of Registration Dossiers Involving Bioavailability/
Bioequivalence Data**

**Addis Ababa, Ethiopia
August 31–September 3, 2010**

Trip Report

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Background

The U.S. Agency for International Development (USAID) and the U.S. Pharmacopeia (USP) have been providing technical assistance to Ethiopia since 2005, first through the USP Drug Quality and Information (DQI) program and, currently, through the Promoting the Quality of Medicines (PQM) program. The President's Emergency Plan for AIDS Relief (PEPFAR) has generously provided funding for a number of activities intended to build the capacity of the Ethiopian Food, Medicines, and Health Care Products Administration and Control Authority (EFMHACA) to assist in ensuring the quality of the country's essential medicines.

In FY10, PQM received funding from USAID/Ethiopia Mission (PEPFAR program) to provide technical support to EFMHACA to strengthen their regulatory capacity, especially in medicines registration, and assist the national quality control (QC) laboratory in achieving ISO 17025 accreditation. PQM's support to EFMHACA has primarily focused on training laboratory staffs in basic and advanced quality control procedures and developing quality systems in the QC laboratory. This training focused on medicines registration, including dossier review.

Purpose of Trip

- Train staff of the EFMHACA Registration and Licensing Directorate on assessment of bioavailability/bioequivalence (BA/BE) data.

Source of Funding

These activities were funded by USAID/Ethiopia Mission, President's Emergency Plan for AIDS Relief (PEPFAR) program. The Quality Safety Medicines (QSM) Division of the World Health Organization (WHO) provided the trainers and training modules.

Overview of Activities

The training workshop was conducted during the week of August 31–September 3, 2010, at the Hotel HZ in Addis Ababa, Ethiopia. The workshop was officially opened by Mr. Yehulu Denekew Alameneh, EFMHACA Director General; Mrs. Sefanit Mengistu, Director of EFMHACA's Product Registration and Licensing Directorate presented a welcoming address.

A total of 11 staff attended the training workshop ([Annex 1](#)), which covered both theoretical content through PowerPoint presentations and practical application through the review of dossiers.

The training followed the prepared Agenda ([Annex 2](#)) and included the following topics:

- Principles of interchangeability testing
- Design of BE studies
- Regulatory requirements for bioequivalence and existing guidelines
- Statistical and analytical considerations
- Most frequent deficiencies in submitted data and good clinical practices (GCP)
- Selection of comparators
- Biowaivers and the Biopharmaceutical Classification System: Theory, practical implications, and regulatory requirements
- Biowaivers and the Biopharmaceutical Classification System: Examples

Trainees also performed practical hands-on bioequivalence testing using artemisinin-based combination medicines.

Conclusion

The training was valuable and successful. The trainees were awarded certificates of participation; they also submitted evaluations of the course. The trainers submitted written recommendations for consideration by the EFMHACA Product Registration and Licensing Directorate regarding future steps in the assessment of bioequivalence (see [Annex 3](#)).



**Bioequivalence Data Assessment Training for FMHCA Organized by
Ethiopian Food, Medicine and Health Care Administration and Control Authority
In collaboration with
PEPFAR/Ethiopia, USP PQM, and World Health Organization
August 31-September 3, 2010 ♦ KZ Hotel ♦ Addis Ababa, Ethiopia**

LIST OF PARTICIPANTS

No.	Name of Participants	Education Level	Place of Work	Position	Address (E-mail/Tel No.)
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AGENDA

Date/Time	Subject	Presenter	Moderator
Tuesday 31/08/2010 08:30-09:00	Registration of Participants	Organizers	
09:00-09:05	Welcome Address	Mrs. Sefanit Mengistu, Director Product Registration and Licensing Directorate, FMHACA	Mrs. Sefanit Mengistu
09:05-09:20	Opening Remark	Mr. Yehulu Denekew Alameneh Director General, EFMHACA	Mrs. Sefanit Mengistu
09:20-09:35	Keynote Address	Mrs. Elina USAID/Ethiopia	Mrs. Sefanit Mengistu
10:35-11:00	Tea Break	Organizers	
11:00-02:00	<ul style="list-style-type: none"> • Principles of interchangeability testing • Design of BE studies 	Dr. Alfredo Garcia WHO	Dr. Milan, WHO
12:30-02:00	Lunch Break	Organizers	
02:00-03:30	Regulatory requirements for bioequivalence and existing guidelines	Dr. Alfredo Garcia	Mr. Eshetu Wondemagegnehu, PQM

Date/Time	Subject	Presenter	Moderator
03:30-04:00	Tea Break	Organizers	
04:00-05:30	<ul style="list-style-type: none"> • Statistical and analytical considerations • Introduction to the case studies (1) 	Dr. Alfredo Garcia	Mr. Eshetu Wondemagegnehu
Wednesday 01/09/2010 08:30-04:30	BE case studies (1) <ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study writing assessment report 	Dr. Alfredo Garcia Dr. Henrike Potthast WHO	Dr. Milan, WHO
04:30-05:00	Tea Break	Organizers	
05:00-12:30	BE case studies (2) <ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study writing assessment report 	Dr. Alfredo Garcia Dr. Henrike Potthast	Dr. Milan, WHO
12:30-02:00	Lunch Break	Organizers	
02:00-03:30	<ul style="list-style-type: none"> • Presentation of BE data in product dossier • BE study and assessment report writing practical issues 	Dr. Henrike Potthast	Dr. Milan, WHO
03:30-04:00	Tea Break	Organizers	
	<ul style="list-style-type: none"> • Most frequent deficiencies in submitted data and GCP • Selection of comparators 	Dr. Henrike Potthast	Dr. Milan, WHO
04:00-05:30	<ul style="list-style-type: none"> • Most frequent deficiencies in submitted data and GCP • Selection of comparators 	Dr. Henrike Potthast	Dr. Milan, WHO
Thursday 02/09/2010 08:30-10:00	BE case studies (3) <ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study • Writing assessment report 	Dr. Alfredo Garcia Dr. Henrike Potthast	Dr. Milan,WHO
10:00-10:30	Tea Break	Organizers	
10:30-12:30	BE case studies (4)	Dr. Alfredo Garcia	Dr. Milan, WHO

Date/Time	Subject	Presenter	Moderator
	<ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study • Writing Assessment report 	Dr. Henrike Potthast	
12:30-02:00	Lunch Break	Organizers	
02:00-03:30	Biowaivers, Biopharmaceutical Classification System <ul style="list-style-type: none"> • Theory and practical implications • Regulatory requirements 		Mr. Eshetu Wondemagegnehu
03:30-04:00	Tea Break	Organizers	
4:00 -05:30	Biowaivers, Biopharmaceutical Classification System <ul style="list-style-type: none"> • Examples: Introduction to case studies 	Dr. AlfredoGarcia Dr. Henrike Potthast	Mr. Eshetu Wondemagegnehu
Friday 03/09/2010	BCS case studies (1) <ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study • Writing assessment report 	Dr. AlfredoGarcia Dr. Henrike Potthast	Dr. Milan, WHO
10:30-11:00	Test Break	Organizers	
10.40-12.30	BCS case studies (2) <ul style="list-style-type: none"> • Work in small groups guided by tutors • Assessment of model BE study • Writing assessment report 	Dr. Alfredo Garcia Dr. Henrike Potthast	Dr. Milan, WHO
12.30-13.30	Lunch Break		
13.30-15.20	Artemisinin-based combination therapy medicines: BE testing	Dr. Henrike Potthast	Dr. Milan, WHO
	Panel discussion		
15.20-15.40	Coffee/tea break		
15.40-16.30	Closing ceremony		EFMHCACA



Recommendations to EFMHACA Product Registration and Licensing Directorate Future Steps in Assessment of Bioequivalence

These recommendations were provided by the trainers who participated in the Bioequivalence Data Assessment training for Ethiopian Food, Medicines, and Health Care Products Administration and Control Authority (EFMHACA) assessors conducted in Addis Ababa the week of August 31–September 3, 2010. They reflect the trainers' current understanding of the regulatory requirements and assessment practices of bioequivalence (BE) in Ethiopia. These recommendations should not be considered complete, nor are they systematically organized. Before taking any regulatory action, the trainers suggest that EFMHACA review the recommendations with full knowledge of their applicability to local conditions.

A. Regulatory requirements

Observations

Regulatory requirements concerning proof of interchangeability by BE currently do not correspond to the standards recommended by the World Health Organization (WHO) or those covered by regulatory guidelines in developed countries. Requirements are not comprehensive or detailed enough to properly instruct manufacturers about the BE data that must be submitted and, subsequently, assessed.

- 1) Article 5 of the existing guidelines should be reworked to clarify requirements for documentation of BE, particularly regarding:
 - a) For which products BE studies are required (concept of interchangeability—generic medicines);
 - b) Which comparators should be used (prioritize registered innovators);
 - c) Conducting BE in compliance with defined standards of good clinical practices (GCP) should be required;
 - d) Structure and format of the BE study report should be defined—optimally to follow International Conference on Harmonisation (ICH) guidelines—to facilitate the work of assessors; having a better-defined structure for the study report will also make possible to improve assessment tools (e.g., checklist, assessment report, etc.). General BE waivers for certain formulations (e.g., inhalation and nasal preparations) should not be given. Conditions for granting a biowaiver should be revised according to current scientific knowledge;
 - e) Classes of medicines for which biowaivers are applicable according to the Biopharmaceutical Classification System (BCS) should be outlined.

- 2) The guidelines should be compatible with existing pharmaceutical legislation, or legislation should be revised to provide the necessary legal support for regulatory requirements and actions. It may be beneficial to either adopt or modify guidelines already available from WHO or stringent regulatory bodies (e.g., European Union, U.S. Food and Drug Administration, Health Canada) that define BE requirements. The in vivo and in vitro requirements for different dosage forms and routes of administration (e.g., prolonged or delayed release dosage forms, locally acting products, etc.) are diverse and should align with international requirements. It is also recommended that the Medicine Regulatory Authorities (MRAs) of neighboring countries agree on the harmonized text of the guidelines.
- 3) In order to protect public health, regulatory requirements for BE should not differentiate between countries of origin for individual medicines. A plan should also be put in place that addresses what should be done during the interim period if critical medicines are made unavailable by immediate application of these new requirements.
- 4) Any new requirements should be communicated directly to representatives of the pharmaceutical industry and should be made public before being implemented.
- 5) An implementation plan should be developed, and confirmed by EFMHACA management, that outlines the gradual implementation of the new standards with provisions on how to proceed in the interim period. Optimally, the implementation plan would also be made public.
- 6) Implementation of revised BE requirements should correspond to implementation of internationally recognized regulatory requirements in other related fields, especially as concerns good manufacturing practices (GMP). BE requirements should be strengthened to follow implementation of GMP compliance.

B. Assessment practices

Observations

Although the assessment of BE studies is well structured and the assessors have sufficient practical experience, the current process of conducting and documenting the assessment does not meet internationally accepted standards. Assessors must expect the BE study to fully meet the established requirements; so, first, the standards for registration must be raised to conform to international standards.

- 1) The existing assessment tool (checklist) should be amended to include relevant aspects of BE studies, which should be the focus of assessors. Once updated, that assessment tool can also be used to document assessment outcomes, to serve as a simple assessment report, and to ensure the quality of the assessment. Templates for assessment reports are publicly available, for example through WHO, or, for instance, a Bioequivalence Trial Information Form could serve as a model for an assessment tool.
- 2) It may be useful to first apply upgraded BE requirements to medicines, which are critical to the public health and for which concerns about bioavailability could cause problems. These medicines should be identified and made publicly available.
- 3) It may be practical to establish a simple database (e.g., associated with a database of registered medicines) of submitted and assessed BE studies; this would eliminate the need to

re-assess studies that are submitted repeatedly and prevent divergent assessment outcomes. Association with a database of registered medicines could prove helpful for informing health professionals about medicines that have been assessed as therapeutically interchangeable.

- 4) Regarding medicines for which the BE has been already assessed by WHO or a stringent authority, it may be useful to compare EFMHACA results of a BE assessment with publicly available sections of similar assessment reports from WHO, the European Medicines Agency, U.S. FDA, or other websites.
- 5) Review the outcomes of GCP inspections organized by WHO or other MRAs, which are publicly available, and consider organizing GCP inspections abroad, in case of problematic studies. Cooperating with other MRAs that have respective submissions for registration may also prove beneficial. While training inspectors and organizing studies abroad is demanding, verifying the authenticity and credibility of BE data is an essential step in responsible decision-making when protecting the public health. Taking this step would also contribute to improving the quality of data submitted by the applicants.
- 6) Assessors should participate in a regular training program to stay current in the field and to prevent the turnover of trained assessors. Experienced assessors, who should lead the assessment of BE studies and who would have developed special knowledge in this area, could be proposed to WHO for participation in prequalification assessments. They could then organize internal trainings for colleagues to pass on that knowledge. EFMHACA may also benefit from having their inspectors participate in WHO-organized GMP inspections according to an established scheme.

Addis Ababa, September 3, 2010

Participating trainers:

Dr. Henrike Potthast, Federal Institute for Drugs and Medical Devices of Germany (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM))

Dr. Alfredo Garcia Arieta, Spanish Agency for Medicines and Health Products (Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS))

Dr. Milan Smid, World Health Organization (WHO)

Dissemination list:

- **Mrs. Sefanit Mengista**, Director, Product Registration and Licensing Directorate, EFMHACA
- **Dr. Fatoumata Nafo-Traore**, WHO Representative for Ethiopia
- **Mr. Bekele Tefera**, Essential Drugs and Medicines/National Program Officer (EDM/NPO), WHO Country Office-Ethiopia
- **Regulatory Support Team**, Quality and Safety of Medicines (QSM), WHO Headquarters