

Good Laboratory Practices/Good Clinical Practices Audits: Equilab and San Clin EQ

Bandung & Jakarta, Indonesia

July 8-12, 2013

Trip Report

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Promoting the Quality of Medicines

Implemented by U.S. Pharmacopeia

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PROMOTING THE QUALITY OF MEDICINES

Executive Summary

PQM conducted follow-up, final audits on Good Laboratory Practices and Good Clinical Practices at Equilab International and San Clin EQ as part of the overall strategy towards prequalifying locally-manufactured anti-tuberculosis medicines in Indonesia.

Confidential audit reports were drafted and submitted to each contract research organization (CRO) and will be followed up routinely by PQM Indonesia. The audit reports should be consulted for detailed audit findings and recommendations.

After addressing audit report findings, San Clin EQ and Equilab International could potentially be recommended to local manufacturers as CROs to conduct bioavailability/bioequivalence (BA/BE) studies towards submission of product dossiers to the World Health Organization (WHO) for Prequalification.

It is anticipated that a WHO Prequalification team will evaluate a CRO in the event that a local manufacturer submits a product dossier for prequalification using either company as its CRO for BE studies.

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About PQM

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID’s response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical assistance to developing countries, PQM helps build local capacity in medicine quality assurance systems, increase the supply of quality medicines to priority USAID health programs, and ensure the quality and safety of medicines globally. This document does not necessarily represent the views or opinions of USAID or the United States Government. It may be reproduced if credit is given to PQM and USP.

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- Mr. Edwin Toledo, Senior GMP Specialist, U.S. Pharmacopeia's Promoting the Quality of Medicines, for arranging the audits

ACRONYMS

ADE	Adverse Drug Event
ATB	Anti-tuberculosis medicines
BA/BE	Bioavailability/Bioequivalence
BPOM	Badan Pengawas Obat dan Makanan
CAPA	Corrective and Preventive Actions
CRF	Case Report Form
CRO	Contract Research Organization
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
OECD	Organization for Economic Co-operation and Development
PD	Product Dossier
PQ	Prequalification
PQM	Promoting the Quality of Medicines Program
QA	Quality Assurance
SOP	Standard Operating Procedure
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

With financial support from the United States Agency for International Development Indonesia Mission (USAID/Indonesia), the Promoting the Quality of Medicines (PQM) program has been providing technical assistance directly to selected local manufacturers to improve their good manufacturing practices (GMP) and product dossier compliance, working toward World Health Organization (WHO) Prequalification (PQ). PQM is also providing support to capacitate two contract research organizations (CROs)—namely Equilab International in South Jakarta and San Clin EQ in Bandung—to conduct bioavailability and bioequivalence (BA/BE) studies for anti-tuberculosis medicines (ATBs) according to Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) for acceptance into the WHO PQ program. Currently, there are no WHO-approved CROs in Southeast Asia that can conduct BA/BE studies for products in the WHO PQ process. The PQM program intends to support these local CROs to serve as recognized centers for conducting BA/BE studies for both market authorization and for WHO PQ in Indonesia and the rest of Southeast Asia.

During the current calendar year, PQM anticipates that a number of local manufacturers in Indonesia will be conducting pilot and full BA/BE studies at these CROs. Products which are not eligible for bio-waivers under WHO guidelines will need to submit BE data as part of their product dossier application.

Purpose of Trip

PQM will conduct follow-up, final GLP and GCP audits at Equilab International and San Clin EQ as part of the overall strategy towards prequalifying locally-manufactured ATBs.

Source of Funding

The trip was funded by USAID/Indonesia and Core TB funds.

Overview of Activities

San Clin EQ

July 8-10, 2013

The following table summarizes the final PQM audit of San Clin EQ's clinical and bioanalytical facility. The audit was conducted to assess the firm's capabilities and future potential in terms of compliance with international standards on GCP and GLP in conducting BA/BE studies. This audit was performed using WHO Guidelines for Good Clinical Practice, Organization for Economic Co-operation and Development Principles of Good Laboratory Practice, Additional guidance for organizations performing in vivo bioequivalence studies, WHO Technical Report Series, No. 937, 2006, Annex 9, USA FDA guideline on Bio analytical method Validation, EMA guideline for Bio analytical method validation, and the EMA Q&A on dispensing of investigational medicinal products in clinical trials.



A summary of the assessment is provided in the table below. All acronyms used in tables in this trip report are explained in the Acronyms list included on page 5.

Note: a detailed confidential audit report was submitted to San Clin EQ

Item	Description
Institution Evaluated	PT San Clin EQ, Jl. Leuwigajah No. 174 Cimahi, Bandung, West Java, Indonesia
Specific Objectives	<ul style="list-style-type: none"> • Determine level of compliance with international GLP and GCP standards following CAPA plan implementation from 2011 audit • Determine readiness of San Clin EQ to conduct BE studies as part of the PQM technical assistance program for ATBs in Indonesia
Partners	<ul style="list-style-type: none"> • San Clin EQ and PT Sanbe Farma (San Clin EQ's parent company)
Auditors/ Evaluators	<ul style="list-style-type: none"> • Dr. Andre van Zyl, PQM Consultant • Mr. Christopher Raymond, Chief of Party-Consultant, PQM Indonesia
Key Personnel: QA and Lab Management	<ul style="list-style-type: none"> • Mr. Metta Bodhiloka Susilo, General Manager • Ms. Eva Sumiyami, Technical Manager • QA and Clinical staff and employees
Agenda	See <i>Annex 1</i> for a detailed Agenda
Areas/Topics Evaluated	<ul style="list-style-type: none"> • Site visit/walk-through for Clinical part of BA/BE (Day 1): SOPs, CRF, personnel documentation, study protocols, monitoring, pharmacy, etc. • Bioanalysis (Day 2): lab equipment inspection, method development and validation, equipment calibration, reference standards, sample analysis, chromatograms, etc. • See <i>Annex 1</i> for details
Key Findings	<ul style="list-style-type: none"> • Progress made from previous audit/CAPA from 2011; renovations and improvements in clinic layout, no major deficiencies in facility • <i>Please refer to the full audit report for detailed findings</i>
Conclusion	<ul style="list-style-type: none"> • San Clin EQ has adequate facilities and procedures complying with GCP and GLP to conduct BA/BE studies as part of the PQM technical assistance program for ATBs in Indonesia. • After addressing audit report findings, San Clin EQ should be ready to operate under the appropriate GCP and GLP environment to conduct BE studies for local manufacturers in Indonesia.
Next Steps	<ul style="list-style-type: none"> • San Clin EQ will address CAPA and audit findings by October 2013 and regularly report to PQM on progress • PQM will provide San Clin EQ with reference standards and comparator products for upcoming BE studies conducted on behalf of local manufacturers receiving technical assistance from PQM. • San Clin EQ will be evaluated by a WHO PQ team in the event that a PD is submitted by a local manufacturer for prequalification using San Clin EQ as the CRO for BE studies.



Equilab International

July 10-12, 2013

The following summarizes the final audit of Equilab International's clinical and bioanalytical facility. The audit was conducted to assess the firm's capabilities and future potential in terms of compliance with international standards on GCP and GLP in conducting BA/BE studies. This audit was performed using WHO Guidelines for Good Clinical Practice, OECD Principles of Good Laboratory Practice, Additional guidance for organizations performing in vivo bioequivalence studies, WHO Technical Report Series, No. 937, 2006, Annex 9, USA FDA guideline on Bio analytical method Validation, EMA guideline for Bio analytical method validation, and the EMA Q&A on dispensing of investigational medicinal products in clinical trials.



Note: a detailed confidential audit report was submitted to Equilab International

Item	Description
Institution Evaluated Location	PT Equilab International Jl. RS. Fatmawati Persil 33 Jakarta 12430, Indonesia
Specific Objectives	<ul style="list-style-type: none">• Determine level of compliance with international GLP and GCP standards following CAPA implementation from 2011 audit• Determine readiness of Equilab International to conduct BE studies as part of the PQM technical assistance program for ATBs in Indonesia
Partners	<ul style="list-style-type: none">• PT Equilab International• Dexa Medica (parent company of Equilab International)• BPOM Indonesia
Auditors/ Evaluators	<ul style="list-style-type: none">• Dr. Andre van Zyl, PQM Consultant• Mr. Christopher Raymond, Chief of Party-Consultant, PQM Indonesia• Ms. Rusri Diyana, SubDit BA/BE, BPOM Indonesia• Ms. Sri Darmayani, SubDit BA/BE, BPOM Indonesia
Key Personnel: QA and Lab Management	<ul style="list-style-type: none">• Ms. Effi Setiawati, General Manager• Clinical and bioanalytical lab staff
Agenda	See <i>Annex 1</i> for a detailed Agenda
Areas/Topics Evaluated	<ul style="list-style-type: none">• Site visit/walk-through for Clinical part of BA/BE (Day 1): SOPs, CRF, personnel documentation/training and qualifications, study protocols, monitoring, pharmacy, etc.• Bioanalysis (Day 2): lab equipment inspection, method development and validation, equipment calibration, reference standards, sample analysis, chromatograms, etc.• See <i>Annex 1</i> for details.

Key Findings	<ul style="list-style-type: none"> • Some deficiencies and observations were noted • <i>Please refer to the full audit report for detailed findings</i>
Conclusion	<ul style="list-style-type: none"> • Equilab International has most procedures in compliance with GCP and GLP to conduct BA/BE studies as part of the PQM technical assistance program for ATBs in Indonesia. Some improvements are still needed in the physical facility. • After addressing audit report findings, Equilab International could potentially be recommended to local manufacturers as a CRO to conduct BA/BE studies towards submission of PD to WHO PQ.
Next Steps	<ul style="list-style-type: none"> • Equilab International will address CAPA and audit findings by October 2013 and regularly report to PQM on progress • PQM will provide Equilab International with reference standards and comparator products for upcoming BE studies conducted on behalf of local manufacturers receiving technical assistance from PQM • Equilab International's facility (building) is being purchased by Dexa Medica this year, and they plan to make improvement renovations and move the clinical areas to the ground floor for ease of access in the case of emergencies. • Equilab International will be evaluated by a WHO PQ team in the event that a PD is submitted by a local manufacturer for prequalification using Equilab International as the CRO for BE studies.



Agenda

Day 1

Opening meeting:	
Attendance list	
Confirmation of the scope of the review	
CRO presentation	
Documentation review:	
Investigator brochure	
Protocol preparation	
Protocol amendments	
CRF	
Information to subjects	
ICF	
Advertising and subject recruitment	
Financial aspects of the trial	
Insurance	

Agreements	
IRB agreement	
IEC composition	
Agenda	
Meetings	
CVs	
Minutes	
Approvals	
DRA approvals	
CVs and qualifications of investigators	
Laboratory used	
Accreditation	
Normal ranges	
Labels on samples of IMP	
Handling of IMP	
Shipping records for IMP	
Decoding procedure	
Master randomisation	
Pre trial monitoring	
Trial initiation monitoring	
Updates during trial (Brochure, protocol, ADE)	
IRB and DRA approval of updates	
Updates to normal values	
Monitoring reports	
Source documents and CRFs	
ADE reporting, also to DRA	
Report to DRA and IRB	
Trial:	
Subject screening log	
Subject identification code list	
Subject enrolment list	
IMP accountability log	
Signature sheet	
Post trial:	
IMP accountability	
Destruction of IMP	
Completed subject identification	

list	
Audit certificate	
Close out report monitoring	
Treatment allocation and decoding	
Final report by investigator	
Clinical report	
Site visit:	
Screening	
Clinical examination	
CPU	
Pharmacy	
Dosing	
Sample collection	
Waste	
Archives	

Day 2

Activity for review	
BAL	
Opening meeting <ul style="list-style-type: none"> • Introductions • Attendance Record 	
Personnel <ul style="list-style-type: none"> • Organization, responsibilities • CVs signed and dated • Training 	
Laboratory walk through: <ul style="list-style-type: none"> • Samples inward record • Allocation of staff for activities • Training • Equipment • Balances • Pipettes • HPLC • LC MSMS 	
Freezers	

<ul style="list-style-type: none"> • Qualification • Mapping • Sample movement • Data loggers 	
Reference standards	
Fridges	
Equipment and instruments: <ul style="list-style-type: none"> • Qualification • Maintenance • HPLC, LC MSMS • Columns 	
Documentation review:	
Method development and validation <ul style="list-style-type: none"> • SOP • Report • Full validation • Partial validation • Cross validation • Reference standard used 	
Parameters <ul style="list-style-type: none"> • Accuracy • Precision • Recovery • Selectivity • Calibration curve • Stability 	
Stability <ul style="list-style-type: none"> • Short term • Long term • Bench top • Freeze thaw • In injector 	
Stock solution preparation	
Plasma selection and pooling <ul style="list-style-type: none"> • Sensitivity and selectivity • Anticoagulant effect 	

<p>Routine testing</p> <ul style="list-style-type: none"> • Chromatograms • Electronic data • Conditions • Audit trail • Back calculations • Electronic data review 	
<p>Repeat analysis</p> <ul style="list-style-type: none"> • SOP - authorization • Codes 	
<p>Incurred sample re-analysis</p>	
<p>Documentation review:</p> <ul style="list-style-type: none"> • SOPs and records in the lab • Qualification protocols and reports • Maintenance logs for equipment • Use logs for equipment and parts (e.g. columns) • Reference standards: preparation, storage, use • Sample stability source data • Manual calculations for the concentrations 	
<p>Review of CAPAs</p>	
<p>Closing meeting</p>	