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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research site - **Inspected site**	PT Equilab International (Indonesia) Jl. RS.Fatmawati Persil 33 Jakarta 12430 Indonesia
Name and Address of Bioanalytical Research Site	**Not inspected**
Name and address Statistical Site	**Not inspected**
Corporate address of Organization	PT Equilab International (Indonesia) Jl. RS. Fatmawati Persil 33 Jakarta 12430 Indonesia
WHO product number covered by the inspection / Product names / Study numbers / Study titles	**WHO application no: RH090** Bioequivalence study of 150 mg medroxyprogesterone acetate injection
Sponsor	PT Tunggal Idaman Abdi
Inspection details	
Dates of inspection	15 – 19 March 2021
Type of inspection	Initial – Real-Time Remote Assessment
Introduction	

Brief summary of the activities	PT Equilab International is an independent Contract Research Organization (CRO) in Indonesia. PT Equilab International provides the following services: a. Bioavailability/Bioequivalence (BA/BE) Study, b. Clinical Trial, c. Pharmaceutical Analysis, d. Medical/clinical laboratory to the customer.
General information about the company and site	PT Equilab International was the first independent BA/BE Center which officially started in 2003 in Indonesia. The company had completed about 600 BA/BE studies so far for local and international customers. The clinical Research Unit (Clinical Trial Division) was launched in 2007. The organization was divided in five departments, i.e. QA, Method development & Validation, Bioanalytical laboratory, Clinical Research Unit and Commercial & support.
History	PT Equilab International was audited and inspected by the National Accreditation Body (Komite Akreditasi Nasional), BPOM RI, NPRA, and UK MHRA. The company was additionally audited by WHO consultants for technical assistants in 2011 & 2013.
Brief report of inspection activities undertaken	The following scope and study-related clinical activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, IMP accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment qualification and maintenance, employee training, computer controls, and a tour of the facility.
Scope and limitations	
Out of scope	This site was only responsible for the clinical part of the application. The bioanalytical and statistical activities were, therefore out of the scope of this inspection.

Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original and accurate

BE	bioequivalence
BDL	below detection limit
CAPA	corrective actions and preventive actions
CC	calibration curve
CPU	clinical pharmacology unit
CRA	clinical research associate(e)
CRF	(electronic) case report form
CRO	contract research organization
CTM	clinical trial manager
CoA	certificate of analysis
CSC	Clinically significant criteria
CSR	clinical study report
CSV	computerized system validation
DQ	design qualification
ECG	electrocardiogram
GAMP	good automated manufacturing practice
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HPLC	high-performance liquid chromatograph
HR	human resources
LC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	international Conference on Harmonization
ICU	intensive care unit
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NPRA	national pharmaceutical regulatory agency
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system

	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	UPS	uninterruptible power supply
	URS	user requirements specifications
	WI	Work instruction

Part 2	**Summary of the findings and comments (where applicable)**

General section

1. **Organization and management**

A presentation was provided explaining the activities of the organization in detail. It was noted that new hygienic measures were implemented to limit the spread of the COVID-19 virus.

The site was certified in accordance with ISO 17025:2017 for competence of testing and calibration laboratories and ISO 15189:2012 for the competence of the clinical laboratory. The site was also assessed for GCP compliance by UK MHRA and GCP – GLP compliance by NPRA Malaysia every 3 years since Aug 2013. An NPRA certification was issued on 19 Aug 2019 which had a 3-years validity.

The Organizational chart depicting key positions signed and dated 1 Jan 2021 was available.

The personnel list was maintained by HR, alongside their position and qualification. The quality department had a Quality Manager, Quality Assurance Officer, and QA administration staff who reported to the Operations Manager, Ms. Lucia Rat Handayani. There were 60 employees, together with one consultant for the clinical laboratory and one consultant for the clinical trial.

If the capacity of the site were exceeded, it was noted that the company might subcontract the work as per the applicable procedure.

A delegation list with details about activities was available for the study in the scope of inspection. Randomly selected job descriptions, including a description of their

responsibilities were reviewed. Every job description was signed and dated by the staff member to whom it applied.

An agreement on the Implementation of Bioequivalence Study was provided. Two addendums were also available respectively dated 18 Apr & 28 Sep 2016. The provisions for indemnity and subject injury reimbursement, confidentiality & publication property, as well as the retention time for the whole report and raw data (both hard and electronic) were specified in the agreement. The retention time for the study documentation was defined as 10 years with notification prior to destruction.

The general working hours were from 8 am to 5 pm unless more shifts were required depending on on-going studies. The first post-dose sample of the study in the scope of inspection was administered after 0.5 day and an overnight stay was not required as per the study design.

The observations made with respect to the Organization and management were adequately addressed in the respective CAPA plan provided by the CRO.

2. Computer systems

A documented inventory of all computerized systems on the network, with a clear identification of those which were GxP regulated was submitted.

The User Requirement Specifications of these software systems, together with the respective CSV protocol and report were provided. A quality statement to confirm that the computer system validation protocol had been checked and audited for compliance to SOPs for Computerised System and Qualification and Validation was signed and dated by amongst others, the operations manager.

A Computer System Risk Assessment for each software system was also carried out. A documentation which was provided to record the respective change control for the subject database in a software system, was reviewed.

The method of access control was specified and a list of people who had access to database, together with the respective role allocation was maintained in the applicable SOP. Secure and unique, individual-specific identifiers and passwords were used. Access to each component of the system by the different users, was appropriately defined, controlled and documented by using an adequate audit trail.

SOP for Computer system validation guidance was available to describe the implementation of a computer system validation. Both periodic validation and re-validation of computerized systems were described in the SOP.

The following SOPs were also available:

- Validation Master Plan
- Software Validation
- Computer Software Validation List
- User Requirement Specification
- Computer System Risk Assessment

A system for the implementation of regular updates to the software programs, based on a risk assessment on the potential impact that it could have on current data and on qualification or validation status was available and reviewed.

PT Equilab International established and maintained procedure for identifying, collecting, indexing, accessing, archiving, storing, maintaining, protection, back-up, retrieval, retention time, and destroying of quality and technical records in accordance with SOP for Control of Records Procedure. In addition, the back and restoring process was described in WI for Back up data. The backup was properly done and periodically restored.

SOPs were in place for usage of each software program that was used to perform clinical activities of a BE study. However, none of the available software systems were applicable at the time of the conduction of the study in the scope of inspection. A migration report was provided by the vendor responsible for Subject Database Software system on 3 Jul 2020. The documentation was in local language. It was noted that all information related to the subjects enrolled in the studies which took place prior to the development of this software system was transferred to the current software system in use. A random check was performed to verify the successful migration of data.

The deficiency related to the Computerized systems was sufficiently addressed in the CRO's respective CAPA plan.

3. Quality management

The CRO's Quality management was reviewed to determine whether appropriate and technically valid SOPs were established and followed in a proper manner.

An adequate CRO Master File was provided.

A Quality Assurance programme was available with designated personnel, performing audit and quality control activities in accordance with the applicable requirements, independent of the work they were assuring, including study specific audits.

The quality manual was reviewed. It was stated that when external laboratories or facilities were used, it would be ensured that the requirements related to the respective facilities and environmental conditions were met. However, the details were not provided in the quality manual.

A master list of SOPs was available and the structure of the QMS was acceptable overall.

SOP for Internal Audit and Quality Assurance Audit was reviewed. According to the SOP, the internal audits covered data input errors in the subject database.

Two external companies were subcontracted to perform activities related to the study in the scope of inspection, i.e. companies for waste management and bioanalytical activities. The bioanalytical activities started on 5 May 2018. However, the Laboratory responsible for the bioanalytical part of the study was audited on 11-12 Apr 2019 since the company was already listed by the WHO. 11 findings were identified in the audit report. The audit report and the respective CAPA plan was reviewed and found satisfactory.

Form for Corrective action and Preventive action was completed to address the non-conformity related to the ISR batch 1 results which did not meet the acceptance criteria. The CAPA plan was finalized on 30 Mar 2017. However, the bioanalytical part of the study was completed by another CRO and the respective results were provided in the WHO application RH090.

The deficiency related to the QMS was adequately addressed in the CRO's respective CAPA plan.

4. Archive facilities

Enough and appropriately secure storage space was designated to be the temporary archiving facility on the 1st floor.

SOP for Control of records was available to describe the management of the archive facility.

An agreement between PT Equilab International and an external archive facility was signed on 27 Aug 2019 to provide a long-term archiving of study documentation.

All documents consisting of project records and facility records stored in the archive room. Access to the archive storage was controlled and restricted to archivist staff, QA personnel and GA staff. Access to the archive room was accompanied by the archivist or Quality section staff and the purpose to access should be stated in Logbook Archive Room.

Quality Assurance administration staff or archivist were responsible for taking and replacing the records from the archive, and the purpose for taking the records were stated in the Logbook.

The archive room's temperature and humidity were monitored three times a day on weekdays and recorded in Monitoring Room Light, Temperature and Humidity Form. Pest control monitoring by third party was recorded in Monitoring Control form. All activities for temperature, humidity and pest control monitoring were recorded in Logbook of Archive Room. The activities were reviewed and confirmed.

The preventive measures were implemented in accordance with the respective SOPs, i.e.

- SOP for Control of Records which contained the procedure of archiving process.
- SOP for Business Continuity Planning and Disaster Recovery Planning which contained the procedure of backup records
- WI for Work instruction for Pest Control

The length of time for which study documentation, including raw data, was kept in the archive at the site was specified as 10 years, in the contract between the sponsor and the CRO.

All data, including both paper and electronic versions, were organized to ensure they were easy to retrieve and traceable. The archive processes were tested through the successful recall of requested documents and records during the conduct of the inspection and found effective.

The observation made with respect to the Archive facility was adequately addressed in the respective CAPA plan.

5. Premises

During the Real-time remote assessment, a virtual tour of facility was conducted and led by the PI & study physician.

The laboratory of PT Equilab International was equipped with a clinical site with total 75 beds on the 3rd (30 beds) and 4th floors (45 beds), an ICU (which was a joined room with the physical exam room), a pharmacy, a bioanalytical laboratory, a medical/clinical laboratory, operational supporting room and archiving room. The details of the building were described in the CRO Master File.

The premises were clean, had adequate lighting and humidity control where necessary.

The premises were equipped with smoke detectors, fire extinguishers and emergency exit with appropriate setup to ensure adequate safety for subjects and personnel. Adequate safety measures were also taken to limit the spread of COVID-19 virus. Synchronized clocks were located throughout the facility to document the exact time study activities occur. Facilities for changing and storing clothes and for washing and toilet purposes were clean, well ordered, easily accessible. Toilets were lockable and alarmed. The toilet doors were designed to ensure that they could be opened from the outside, should there be a medical emergency.

Entry to the facility was restricted and controlled. The entries to the restricted sections, including archiving and drug storage facilities were accessed by a card with magnetic coding that was read electronically when touched a scanner and used in place of a key to doors (cardkey). Some doors could be simply locked by keys. The provisions to ensure emergency evacuation was made. Any entry to and exit from the facility with restricted access were recorded. A list of personnel authorized to access any respective restricted area was provided.

Monitoring of room temperature and humidity of the premises was carried out by using a hygro-thermometer. The temperature was also monitored by an applicable software system for data recording in temperature monitoring. The digital thermometer used for monitoring of temperature in refrigerators and freezers were connected to an alarm system. An email notification would be sent to the responsible staff in case of temperature excursions when out of the respective acceptable range. The CRO's Security would also be alarmed. The system was tested during the inspection.

The facility was powered by a continuous commercial electricity supply. There was a Diesel Generator (DG) for power generation in case of electricity supply disruption, with an applicable SOP for usage and maintenance and the respective logbook, Additionally, a UPS for use at the site in case of power failure incidents was available. The maintenance service was provided by authorized personnel. The equipment was managed in accordance with WI for Operating and maintenance of generator set & WI for UPS test. The logbook for testing of generator was provided and reviewed.

Clinical Pharmacology Unit

Appropriate measures were in place to prevent subjects from exiting the facility. Adequate gowning and ID-signs were given to subjects once admitted into a study. Bracelets were used to identify subject's ID. In case of running concurrent studies, each study group was distinguished by gowns in different colours.

ICU

The ICU was inspected during the virtual tour. The usage of the defibrillator was demonstrated.

Pharmacy

Pharmacy temperature and humidity condition were monitored by both hygro-thermometer & digital temperature record software system.

The pharmacy was visited during the inspection and the handling of medicinal products, including reconciliation of retained samples from the studies in the scope of inspection was verified to be compliant.

The deficiency related to the Premises was adequately addressed in the CRO's CAPA plan.

6. Personnel

The clinical staff were appropriately qualified, trained and experienced to support and run the clinical trial and to be able to respond effectively to reasonably foreseeable emergencies.

All newly hired employees were trained on SOPs and given on-the-job training with respect to their job description and assignments as scheduled in the training plan. Records of training and assessment of knowledge of GCP and any other relevant area or technique were maintained. Study specific training was recorded in the clinical plan. For the study in the scope inspection, protocol version 4.0 was applicable.

A training plan for retraining of existing staff and a training matrix were also available.

Study personnel were delegated study activities based on their job description after completion of specific protocol training. Delegation list signed by PI for clinical activities was verified.

Each employee was required to document his/her training details in the individual training record. A training file that contained CV, JD, training plan, training record, training evaluation sheets and professional certifications was available for each employee. The training documentation of randomly selected permanent & contracted staff was reviewed.

Clinical section

7. Clinical phase

There was enough space to accommodate the study subjects. The facility was generally equipped with 75 beds. However, due to COVID-19 restrictions, the capacity of the CPU was reduced.

The duration of the clinical phase of study in the scope of inspection was approximately 4 months and 3 weeks. The day of drug administration, the subjects were instructed to come to PT Equilab International. Pregnancy tests were performed for each subject before the study drug intake. After a 10-hour overnight fast, a 10-mL blood sample (control) were drawn by vein puncture immediately before drug administration.

Alarm bells were in place in the accommodation facilities so that subjects could alert CRO staff in case of need. The alarms were randomly checked.

The study site had rooms and/or areas, as appropriate, for the subjects' registration and screening; obtaining informed consent of individual subjects without compromising privacy; subjects' housing; subjects' recreation; restricted access rooms for handling of pharmaceutical products and blood, dining hall; room for emergency medical care (ICU) with emergency or first-aid equipment and appropriate medication for use in emergencies. The records and handling of the medications for use in emergencies were inspected.

An agreement was signed on 8 Aug 2019 between a hospital and PT Equilab International to make provisions for the urgent transportation of subjects to the hospital for their emergency care, if required. The site was also equipped with an ambulance.

An inventory list of equipment used in the clinical facility was provided. All equipment was appropriately labelled with equipment unique ID, date of calibration and next calibration.

The adequate function and performance of emergency-use equipment was verified at appropriate intervals. The documentation for periodic verification of defibrillator, and oxygen regulator was reviewed.

The rationalization of the sample size was discussed with the CRO. It was noted that the sample size was determined by Concept Foundation based on recommendation from WHO's Prequalification Programme's "Guidance on Bioequivalence Studies for Reproductive Health Medicines" & "Additional guidance on submission requirements for medroxyprogesterone acetate depot injection products using the CTD format".

The deficiencies related to the clinical phase were adequately addressed.

8. Clinical laboratory

PT Equilab International had an in-house clinical laboratory which was accredited in accordance with SNI ISO 15189:2012, for screening the health of the subjects. Certificate of accreditation issued by Komite Akreditasi Nasional was available.

If clinical laboratory needed to sub-contract the other tests, PT Equilab International had collaboration with the reference clinical laboratory.

A list of laboratory normal ranges and clinically significant criteria (CSC) dated 14 Jan 2016 was available.

The procedure for labelling of samples for use in screening procedures and clinical laboratory was described in the respective SOP for Pre-examination process. The labels were provided manually.

Individual reports were created by the laboratory for each subject and attached to the CRFs. For the measurement of alcohol in the human breath and detection of hCG hormone in urine for pregnancy test, a Breath Alcohol Detector & a Pregna Strip™ kit were respectively used. The tests were based on chemical reaction to produce a colour change as an indicator for positive or negative result. A photo of the results was provided and available.

Data integrity requirements applied to the software systems used for the generation of laboratory results related to the study were inspected and verified during the inspection.

The deficiency related to the clinical laboratory was sufficiently addressed.

9. Ethics

The study, including the protocol, informed consent and other required documentation were approved by an Independent Ethics Committee, i.e. Health Research Ethics Committee Faculty of Medicine Universitas Indonesia; Cipto Mangunkusumo Hospital before the study was conducted.

The minutes of the meeting dated 1 September 2014, 8:10-9:00, were reviewed. The meeting took place at the Ethic Committee Room, Medicine Faculty, University of Indonesia. The members of Ethic Committee had expressed concerns about the safety of subjects and required clarification and justification with the references. The concerns were addressed by the CRO.

The subjects were informed that the treatment for all adverse events in the study including adverse effect or uncomfortable reaction that occurred during study, until seven days after last blood sampling, would be covered by Sponsor.

There was no Insurance Company to cover for wellness of bioequivalence study subjects in Indonesia. Thus, for the Bioequivalence study in the scope of this inspection, the Sponsor was responsible for all indemnity and medical expenses related to adverse events or uncomfortable reaction that occurred during the study, until seven days after last blood sampling in accordance with the Formulir UB-1(section VIII Pernyataan Sponsor). The form was stamped and signed on 25 Jul 2016.

The ICF was available in both English and the applicable local language.

The deficiencies related to the Ethics Committee were adequately addressed.

10. Monitoring

The study was monitored/audited by the following third parties:

- Study Monitoring by Quintiles Indonesia
- Study Audit by Nick Dance and David Frank from Qudos - UK dated 1-3 August 2017, and the respective CAPA Follow up Audit by Nick Dance and David Frank from Qudos-UK dated 24-25 January 2019

The monitoring visits by Quintiles Indonesia were recorded on a visit-log form. The correctness of the report and validity of the statements that the monitoring was carried out in accordance with the protocol, SOP's, applicable regulatory requirements and monitoring checklist were verified. The audit report prepared by Qudos – UK and signed by Lead auditor on 2 Mar 2018 was reviewed.

The deficiency related to the Monitoring was sufficiently addressed.

11. Investigators

The CV of the PI was reviewed. The PI did not possess any specialization in gynaecology; however, he was qualified as a general physician. He had been PI or Clinical Research manager for 35 clinical trials.

12. Receiving, storage and handling of investigational drug products

All the information concerning the receipt, storage, handling and accountability of investigational products and the respective reference drug, at every stage of the trial was recorded on the template for Study Drug Checklist, test result of analysis of drugs and the comparator product, the certificate of analysis, the respective CRA & QA quality control,

shipment condition together with the data-logger documentation. A note to file was issued to justify a short temperature excursion during the shipment.

Details of the pharmaceutical products used in the study including dosage form and strength, lot number, expiry date and the Indonesian registration number were properly documented.

The responsibility for storage, delivery, return and keeping records of the investigational products was designated to a suitably qualified pharmacist within the CRO. Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor in a restricted area, accessed only by authorized personnel. The pharmacy area was accessed by keycard and the study medication was kept in securely locked cupboards.

The generation of randomization list was delegated to an external consultant in accordance with an agreement and the working instruction for Preparation of investigational Product part 1.1 Randomization Process, and the respective method mentioned in the textbook Dixon WJ and Massey _ Randomization.

Dispensing of the study drugs were performed in accordance with the applicable requirements which was documented on the template for Line clearance in drug dispensing. A drug dispensing report was also provided for 150 subjects, dated respectively 12 Apr & 24 Aug 2016. A quality control was carried out and reported by the CRA and QA on a separate template for Document review.

The study drugs were labelled with the project code, compound name, period and subject number, and randomization code.

Samples of the product in the original container were retained for confirmatory testing at the time of inspection in accordance with the agreement with the sponsor.

The deficiencies related to the handling of IMP were sufficiently addressed in the CRO's CAPA plan.

13. Case report forms

Case report forms were randomly selected and reviewed with respect to the screening & subjects' eligibility, lab-results, ECGs, reporting of adverse events & usage of concomitant medication and deviations of blood sample collection times.

14. Volunteers, recruitment methods

Subject candidates were invited based on data in Subjects Database Excel sheets and subject database software system (implemented since 2020) with a phone call and recorded in Volunteer Recruitment form. During the invitation through phone call or text message, subject candidates were briefly informed about the study e.g. drug to be investigated, study duration, and date of study implementation. New subjects were recruited through word of mouth. For the study in the scope of inspection, the midwives with offices in the region were asked to identify and inform potential volunteers to be considered for recruitment and screening. Illiterate volunteers were not accepted.

At the time of inspection, an external cross participation verification was not feasible due to the absence of an appropriate system to fit the purpose. However, the CRO had made an agreement with a vendor/developer to build up a proper software system. Subsequently, a meeting between the CRO and the respective authorities took place. The minutes of the meeting was available dated 3 Feb 2021 by which the authorities were informed that Equilab had found the vendor for subject software database (ceksubject.com). The filter on NIK (Nomor Induk Kependudukan) number from subject's National ID Card would be enabled to track the subjects' latest study participation. Every CRO would be given a password to maintain the confidentiality of the data.

Volunteers underwent the screening process after giving the consent for screening as prescribed in SOPs respectively for Clinical bioequivalence / bioavailability study implementation and Subject information and Informed Consent. During screening, the volunteer's medical information was verified and documented in respective forms as defined in relevant SOPs. Volunteers' data was maintained in the volunteer medical journal at the time of study. During screening activities, volunteers undertook study specific ECG, protocol specific haematology, biochemistry, serology and urine tests 14 days prior to their first dosing day.

Volunteers selected in the pre-screening and reporting for study participation underwent the study informed consent process. Informed consent presentation was given in groups in the local language by the PI followed by a One-on-One presentation with the Clinical Research Physician to resolve medical/general study related queries. Volunteers could proceed for study specific activities only after having obtained their consent for study participation. Sufficient time was given to the volunteers to take a decision on their study participation. Randomly selected signed consent documents were reviewed and verified to be signed and dated by the volunteer and PI.

The study volunteers were divided in 5 groups and the study's duration was 11 months and two weeks. Pregnancy tests and alcohol breath test were performed for each subject before the study drug intake.

A deficiency related to the recruitment and ICF was identified which is discussed in detail in Part 3 of this report.

15. Food and fluids

This section is not applicable for this study.

16. Safety, adverse events, adverse event reporting

Adverse events were documented in the CRF in the section for Adverse Event Reporting according to the applicable SOP for both adverse events occurring during the study and post-study.

Concomitant medication was also captured on the form if relevant. The logbook for usage of medicines in emergency for the period of studies was available.

The deficiency related to the adverse even reporting was adequately addressed.

17. Sample collection, storage and handling of biological material

The specification of the samples (plasma EDTA), sampling method, volume and number of samples were stated in the clinical trial protocol and in the information provided to the volunteers.

Collection, preparation, shipping and storage of samples were documented. The second aliquots of the study samples were separately shipped to the Bioanalytical site. Blood sample collection time-point deviations were properly reported. The storage and transfer of the samples were recorded in a logbook for operation and maintenance of Deep Freezer in accordance with the applicable SOP.

All storage conditions (e.g. freezer temperature) were specified in the study protocol, controlled, monitored and recorded throughout the storage period.

Sample storage room

There was no controlled access to the sampling room. After the last sampling of the day, the samples were transferred to the bioanalytical department. There was only one freezer in the range of -20 °C in the sampling room. For the storage of samples in -70 °C, the samples should be transferred to the freezer located in the bioanalytical zone.

18. Data processing and documentation

QA maintained Document Control and Distribution as per the applicable SOP. Master documents of Quality Manual, Site Master File, Study Protocol, SOP/Work Instructions,

Records (Forms, Templates and Logs) were maintained by the QA department. Logbooks used for recording of data were properly bound.

The issuance of templates was described in the SOP for Control of Records. Duplication of blank templates, as many as quantity requested by the authorized personnel would be made and controlled by QA. The records were documented in the respective logbook. However, this procedure was not applicable at the time of the study in the scope of this inspection.

A document to record the date and time of obtaining of study specific ICF was available and served as volunteers' screening list. A separate volunteers' enrolment list was also available.

All the computerized systems used for the clinical activities were equipped with adequate audit trail function.

19. Good laboratory practices

An equipment inventory used for clinical activities was available signed and dated by the QM on 26 Feb 2021.

All Equipment was identified by a unique identification / serial number and labelled in accordance with the respective SOP.

The calibration certificates and/or qualification documentation of randomly selected equipment, as well as temperature mapping of randomly selected Deep Freezer used for the study in the scope of inspection were verified.

An alarm system was installed to control the temperature of the critical storage areas, such as freezers and refrigerators. The alarm system was connected to the software system for data recording in temperature monitoring.

The annual temperature mapping of the freezer, applicable to the study period, was carried out in accordance with the respective procedure.

The deficiency related to the equipment was adequately addressed.

20. Study report

The study procedures and results, as well as the protocol deviations were randomly selected to verify the accuracy of the clinical study report version 3.0, dated 30 Aug 2018. Both PI and QA of PT Equilab International and the Bioanalytical site had signed and approved the report.

All monitoring and audit reports were available before release of the final study report.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	The CRO master (CROMF) file was reviewed. The company's master file provided introductory information of the organization and covered all information required by the guidelines for the preparation of a contract research organization master file (WHO Technical Report Series, No. 957, 2010, Annex 7).
Annexes attached	Not applicable

Part 3	**Conclusion**

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, the study was considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at ***PT Equilab International (Indonesia)***; located at ***Jl. RS. Fatmawati Persil 33, Jakarta 12430, Indonesia***.

All the non-compliances observed during the inspection that were listed in the complete report as well as those reflected in the WHOPIR, were addressed by the CRO, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	**List of guidelines referenced in the inspection report**

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP
   https://www.who.int/tdr/publications/documents/gclp-web.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
Short name: WHO GCP Annex 3
https://apps.who.int/iris/bitstream/handle/10665/37340/WHO_TRS_850.pdf?sequence=1

4. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
Short name: WHO TRS 1010, Annex 9
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

5. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009.
Short name: OECD GLP
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
Short name: WHO Ethics Committee Guidance
https://www.who.int/ethics/publications/9789241502948/en/

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
Short name: WHO storage and transport guidance or ***TRS 961 Annex 9***
https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf;jsessionid=B7F180F317E8BE2DB4289C7BF9A561FF?sequence=1

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