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Prequalification Team Inspection services
WHO INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	Clinical parts of studies, in the scope of the inspection, were performed at contracted CROs. Details provided in the section for WHO product umbers
Name and Address of Bioanalytical Research Site	**Mylan Laboratories Ltd,** Clinical Research Centre, Saradhi Chambers, A4-Rukminipuri, Near Poulomi Hospital, Dr A.S Rao Nagar, Sainikpuri-ECIL Main Road, Hyderabad-500 062, India
Name and address Statistical Site	Biostatistics of the studies, in the scope of the inspection, was performed at another sites. Details are provided in the section for WHO products, covered by inspection.
Corporate address of Organization	Mylan Laboratories Ltd, Clinical Research Centre, Saradhi Chambers, Plot No. A4-Rukminipuri, A.S Rao Nagar, Hyderabad-500 062, India
WHO products – CRO Study numbers - covered by the inspection/ Product names/ Study numbers	1- Study no. C14349; Tablets 50 mg: Clinical Facility & Pharmacokinetic/Biostatistics Department: Aizant Drug Research Solutions Pvt Ltd 2- Study no. 017-16, Tablets 800 mg with co-administration of another product Clinical Facility & Pharmacokinetic/Biostatistics Department: AXIS Clinical Ltd (Lab) 3- Study no. 551-15; Injectable suspension 150 mg/mL: Clinical Facility & Pharmacokinetic/Biostatistics Department: Lambda Therapeutic Research Ltd 4- Study no. 186-16; Tablets 100 mg Clinical Facility & Pharmacokinetic/Biostatistics Department: AXIS Clinicals Ltd (Lab). 5- Study no. 905-06; Tablets 200 mg + 50 mg Clinical Facility & Pharmacokinetic/Biostatistics Department: Lotus Labs Pvt. Ltd 6- Study no. C10165; Tablets 300 mg/100 mg Clinical Facility & Pharmacokinetic/Biostatistics Department: Aizant Drug Research Solutions Pvt. Ltd.

Inspection details	
Dates of inspection	4-8 September 2017
Type of inspection	Routine inspection
Introduction	
Brief summary of the activities	Bio-analytical facility at CRC was started in July 2006 and expanded in 2008 into the current facility to suit the growing portfolio and bioequivalence needs. Hence the Bio-analytical Laboratory is the main functionary division and performs the respective activities.
General information about the company and site	The company was originally operated under the name of Matrix Laboratories. In-house Bio-analytical facility was initiated in July 2006. Subsequent to Acquisition of 100% stake of Matrix by Mylan, Matrix became a subsidiary of Mylan in 2007. From January 2012, Matrix was fully transformed as Mylan Laboratories Ltd.
History of inspections	The CRO was subject to various numbers of authorities' inspections since September 2007. A full overview of all inspections performed, was presented by the CRO. WHO has performed a total of 8 inspections of the facility since January 2008. The most recent one was performed in July 2016.
Brief report of inspection activities undertaken	
Scope and limitations	
Out of scope	Clinical activities, pharmacokinetic and statistical calculations, screening tests.

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
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report

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
HPLC-MS/MS	liquid chromatography–mass spectrometry
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
(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
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
URS	user requirements specifications

Part 2	Brief summary of the findings and comments (where applicable)

General section

1. Organization and management

The centre was generally in compliance with the national requirements and adequately equipped by LCMS/MS instruments, operating with applicable software.

The CRO had provided the organization chart depicting key positions and the names of responsible persons. The CRO Master file was also available.

Bio-analytical methods were developed and validated using in-house resources and expertise.

A list of studies submitted to WHO-PQ assessment team was provided to the WHO-inspectors.

The organization initiated the preparation of protocol, preceded with approval and implementation, followed by procurement of the test product. Reference and test products were directly imported from the USA after obtaining the required licenses from CDSCO and other applicable authorities.

Once the clinical part was completed, the samples were shipped to the Mylan CRC Bioanalytical lab, where data was produced, the study report completed, reviewed and quality controlled by Pharmacokinetic department, before submitting to the respective authorities.

The Quality management system was designed to meet regulatory requirements

2. Computer systems

Computer system qualification was reviewed. Issues raised during the inspection were resolved in the company CAPA.

Operational qualification and risk assessment for computerized systems were considered insufficient, but this was resolved in the CAPAs.

Two different software were linked to the chromatography instruments, providing chromatograms and pertaining data, in addition to software processing the statistical data. A full list was provided.

Windows XP has been upgraded to Windows 7 and implemented to all LC-MS/MS instruments.

Additionally, new software was acquired to provide regression calculation and respective data processing. The software was implemented on 1 September 2017.

Privileges such as modification of audit trail settings, disable/enable/clear audit trails were not allocated to the IT administrator.

Change controls were raised for the LC-MS/MS (total 13) after the upgrade of Windows XP to Windows 7.

Observations made in relation to this section were all addressed by the CRO and the CAPA was reviewed and accepted.

3. Quality management

The quality management system was designed to meet the regulatory requirements.

A full list of SOPs was provided in the CRO Master File with the inspectorate requesting an updated list of SOPs.

The quality management system was studied by review of SOPs in connection with the respective procedures.

The SOP on the development of bioanalytical method and project initiation was available which provided guidance on method development.

List of SOP deviations for one of the studies was provided and reviewed.

It was verified that QA personnel were independent of the work they were quality assuring, including: conducting or monitoring of the trial; conducting bioanalysis and performing reporting and pharmacokinetic and statistical analyses.

4**. Archive facilities**

Archiving procedures and the corresponding SOP were reviewed. Handling of requests was properly done. The described practice was in line with the procedure and requirements. Any documentation retrieved from archive should be returned within 15 days. Procedures were in place in case the documentation was not returned within 15 days.

The company had a total of three archiving facilities. All the archiving facilities were managed by Mylan, equipped by superior fire fighter systems. Paper documentation was kept in the cabinets which were also gas proof, since the sprinkles were chemically functional. Archiving facilities were located on the upper floors to avoid early destruction of documentation in case of flood.

5. Premises

A facility walk through was carried out.

The premises consisted of 4 stories, a front desk area, meeting rooms, drug and sample storage (with freezers) area equipped by temperature and/or humid monitoring devices, spacious laboratories for performing bioanalytical tasks, including instruments used for chromatography (LCMS/MS) – labelled with sufficient information such as ID numbers, installation date, calibration date and expiration date.

All instruments used during the study experiments were verified for their presence.

Access to the restricted area was enabled by biometric method (finger print), which was verified.

The rooms for preparation of samples were sufficiently equipped by pipettes, balances, centrifuge devices, etc. A log-book was provided for record of usage of each instrument.

A daily calibration of balances was carried out and the balances were connected to printers for daily documentation of calibration. This was verified.

Specific calibration certificates for instruments were verified.

6. Personnel

CVs and Job descriptions and training records were requested and reviewed.

The last training plan for updated regulatory guideline, and the pertaining list of personnel trained were reviewed.

When an employee resigned from the CRO, a clearance form was completed by all departments. The form should be completed by the employee before he/she left the CRO. The process was verified and found to be compliant.

Clinical section

7. Clinical phase

The clinical phase of the studies was not inspected, since the clinical phase of the studies within scope of this inspection were contracted to other CROs.

8. Clinical laboratory

This part was conducted at various CROs or at specialized clinical laboratories.

9. Ethics

This area was not inspected.

10. Monitoring

Monitoring plan and reports of one of the studies were requested and reviewed.

The follow up response on this report, specifically for the medical assessment of the subjects were reviewed.

An assessment of abnormal laboratory measurements for study subjects in one of the studies and corresponding justification was provided and submitted to the WHO assessors on 2 Jul 2017.

Issues raised in relation with this section were addressed sufficiently and CAPA was provided and accepted.

11. Investigators

This part was not in the scope of this inspection.

12. Receiving, storage and handling of investigational drug products

Receipt, storage, handling and accountability of investigation drug products were recorded properly. The shipment documentation and import licence of study medication were reviewed and verified.

Drug products were stored in a dedicated area with restricted access, manged by trained personnel. The temperature and humidity of the room was monitored digitally and individual access was logged.

The storage area was inspected.

13. Case report forms

This part was not inspected.

14. Volunteers, recruitment methods

This part was not inspected.

15. Food and fluids

This part was not inspected.

16. Safety, adverse events, adverse event reporting

This part was not inspected.

Bioanalytical section

17. Method development

The development of bioanalysis methods for studies under consideration was reviewed.

Equipment used for method development was verified.

Literature used in method development was requested. During the inspection, it was identified that a method was used with no supportive literature available.

Observations made in relation with this section were all addressed and CAPA provided and accepted.

18. Method validation

There was a log for summary of method validation experiments, to record whether the experiment/process of validation passed or failed.

Method validation of four studies in the scope of the inspection where randomly reviewed to verify the reliability of the method used in the sample analysis.

During the inspection, source documentation and raw data for validation of bioanalytical method and analysis of subject plasma samples, as well as audit of the electronic data, audit trails for electronic data capture and handling of data related to the PK study were reviewed. The preparation and results from calibration standards (CC), quality control samples (QC), internal standards pertaining solutions and reagents and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from analytical runs, including their respective parameters.

Observations made in relation with this section were all addressed and CAPA provided and accepted.

19. Sample collection, storage and handling of biological material

Samples sent by courier to CRO, were received at the Mylan CRC site. All the samples would be checked and stored in the dedicated freezer at -70 °C degrees.

Samples were received blinded containing the following information: Project number, sampling time point, subject number, period and sequence number of sample and suffix digit, indicating the aliquot number.

The shipment received for randomly selected studies was reviewed:
Samples provided for 24 subjects, each subject 29 samples x 2; were received, with a total of 1392 samples. The inspection noted that only 1310 samples were received. Date of receipt was noted. Temperature data logger was calibrated for a period of one year.

The freezer ID used for sample storage was verified. The blood sample labelling was verified.

The sample aliquots are equipped by a digital detector to monitor the temperature during the transport of the samples.

Documentation on the shipment of randomly selected study was reviewed and verified.

The bio-analyst would determine which subject samples need to be analysed and the request would be sent to the custodian on a requisition form. Samples would be provided from the freezer and verified on the form by two persons, and sent to the lab in frozen condition.

Observations made in relation to this section were all addressed by the CRO and the CAPA was reviewed and accepted.

20. Analysis of study samples

4 Studies in the scope of the inspection were selected to verify the data provided for analysis of study samples.

Sample analysis runs were randomly selected and compared with the data generated in the report for further verification of results of calibration standards and respective calibration curve, QC, IS RT, back calculation using respective slope and intercept, preparation of CC and QC, sample processing record

The missing samples were documented. It was also verified that respective subjects were excluded, in case the whole batch was missing.

The procedure for running the subject sample analysis was reviewed.

In the analysis of the samples, the accuracy of LQC was reviewed to verify that it met the criteria - 67 % of the total QC must be within 85 – 115 %.

The source data in the analyst software system was also reviewed. No observations made.

Reanalysis of subject samples where the results were above the upper limits was reviewed. Therefore, the QC solution was 50-50 diluted and a reanalysis performed.

Observations made in relation to this section were all addressed by the CRO and the CAPA was reviewed and accepted.

20. Repeats, reinjection and reintegration of samples

Re-assay and reinjection of clinical samples and reporting of final concentration procedure was discussed. The procedure defined that re-assay was basically reprocessing e.g. sample preparation, extraction and analysis of a sample, whereas reinjection was defined as a repeated injection of the same processed sample on one or more occasions. Different codes (Code A to Q) were assigned if samples were re-analysed.

The list of repeats, reintegration and reinjection of samples for all four studies was requested and reviewed.

Repeat analysis of selected studies was discussed to ensure that the repeats were rationalized according to the applicable requirements and procedures. The reasons for repeats were: Acquisition error, QCS failure, concentration above ULOQ, ISTD variation, QC failure (did not meet the applicable criteria).

Examples of reinjection were also verified. Reinjection was due to high back pressure which resulted to RT shifting, columns resulted to tailing or bad chromatography of analyte or ISTD.

21. Data processing and documentation

The data processing and documentation was reviewed.

An investigation was performed as to why a large number of subjects had pre-dose over 5 % Cmax in one of the studies in the scope of the inspection. It was also demonstrated that the exclusion and inclusion of these objects would not have considerable impact on the result of the analysis. The results were submitted to the WHO assessors.

22. Good laboratory practices

QC and QA were applied to all steps related to the study sample analysis.

Deep freezers were adequately qualified, calibrated and maintained. They were equipped with alarm systems and temperature monitoring.
Temperature mapping of the freezers and refrigerators were not inspected.

Periodic calibration certificates for balances and other measuring devices such as pipettes were reviewed and verified, as well as the pertaining SOPs to ensure proper maintenance of the devices.

Equipment and devices were properly marked with unique identification number, together with the calibration date and next calibration date where applicable.

Chemicals, reagents and solutions were labelled to be identified with correct concentration and date of expiry, as well as storage condition. Information concerning source, preparation date and stability was available on specific forms and templates used according to the QMS.

In case of maintenance and/or repair, a bioanalytical instrumentation maintenance report would be completed. Instrument could either be repaired by in-house engineer or a service person, ordered by in-house engineer. A report would be provided by the service-provider.

The process for water quality and pertaining documentation were reviewed.

The SOP for disposal of biomedical waste was reviewed. The previous version was also reviewed to verify that it was also applied to 2015 studies.

The log book for disposal and receive of the chemical was reviewed. Disposed biomedical was handled according to the procedure.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

This part was not inspected.

24. Study report

Bioanalytical study reports for following studies were provided.

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 and GLP at CRO Mylan Laboratories Ltd.

All the non-compliances observed during the inspection that were listed in the full 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. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9
   Short name: WHO BE guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth report*. World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO multisource guidance
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.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
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
   Short name: WHO TRS No. 996, Annex 5 WHO GDRMP guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan 1998.
Short name: WHO GLP
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1
http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1

9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

10. US FDA Code of Federal Regulations Part 11
http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP". http://www.who.int/tdr/publications/documents/glp-handbook.pdf

13. 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 TRS No. 961, Annex 9
http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
Short name: WHO TRS No. 957, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf

15. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

16. WHO Good Clinical Laboratory Practices (GCLP)
http://www.who.int/tdr/publications/documents/gclp-web.pdf