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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, Bioanalytical and Statistical Site	RA Chem Pharma Limited, Clinical Research & Biosciences Division, Plot-No.26&27, Technocrat Industrial Estate (TIE), Balanagar, Hyderabad, Telangana State-500037, INDIA *GPS coordinates were 17.47 decimal degrees latitude and 78.44 longitude, as obtained on site from "GPS-coordinates.net" by the inspector*
Corporate address of Organization	RA Chem Pharma Limited, Plot-No.26&27, Technocrat Industrial Estate (TIE), Balanagar, Hyderabad, Telangana State-500037, INDIA
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	HA663 Sofosbuvir 400 mg tablets, Study #: 039-15-WHO A randomized, open-label, balanced, two-treatment, three-period, three-sequence, partial replicate, single oral-dose, crossover, reference scaled average bioequivalence study of Sofosbuvir 400 mg Tablets of Hetero Labs Limited, India Comparing with that of the innovator (Sofosbuvir) 400 mg Tablets in healthy, adult, human subjects under fed conditions.
Inspection details	
Dates of inspection	16-19 July 2016
Type of inspection	Initial
Introduction	
Brief summary of the activities	Bioanalysis, Clinical phase, pharmacokinetic/statistical analysis, X-rays
General information about the company and site	Operations were started in 2007. The company is also called CRBio (it has a website at www.crbio.co.in).
History	They were inspected by MoH Turkey in 2009. In 2011, they were reinspected by MoH turkey. They were inspected by USFDA in 2012. The site moved in 2013. According to opening meeting, there was an approval by US FDA in 2014. In 2015, there were two US FDA inspections in June 15-19, 2015 (no 483) and October 12-16, 2015 (there was a 483 issued).
Brief report of inspection activitiesundertaken - Scope and limitations	
Out of scope	Clinical laboratory (outsourced)

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
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
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
IEC	(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
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
ULOQ	upper limit of quantification
URS	user requirements specifications

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

1. Organization and management

The company stated that they performed approximately 60 studies per year.

The company had a master index of SOPs, that included 258 SOPs in total. It was signed and dated 15 July 2016 (the day before the inspection).

All of the SOPs had an effective date, version number and effective date and were managed by the SOP on SOPs, effective 22 August 2014, addendum 01 dated 13 May 2016.

The study was to determine the bioequivalence of Sofosbuvir 400 mg tablets of Hetero labs limited, India. The total number of samples was 25 per subject, including 1 ambulatory visit. Periods 1 to 3 were conducted on 27 October, 6 November and 16 November 2015. There were 60 subjects randomized and 59 assayed, with 54 included in the pharmacokinetic and statistical analysis. They received a high fat, high calorie breakfast. Only 5 adverse events were reported of raised triglyceride levels.
Protocol deviations were all related to late blood sampling due to subjects reporting late or not reporting at all

There were separate quality assurance teams for bioanalysis and for clinical activities.
Batch failure investigation, however, was not tracked or trended, thereby not allowing to see any trends in performance over time. These go in the validation folder for each individual study. There was no logbook of OOS. The personnel training SOP, dated 9 August 2013, stated that repeated mistakes by the same personnel were identified by internal department IQC/QA, but there was no process for this in reality. As the internal standard response was highly variable for a number of subject samples, there may have been issues with the company's methodology and procedures. Issues raised during the inspection were resolved in the company CAPAs.

The US FDA 483 from the inspection performed in October 2015, and the associated CAPAs, were reviewed on Day 1. The EIR for the clinical inspection was reviewed for the inspection that started June 15, 2015 and ended on June 19, 2015.

2. Computer systems

The validation master plan was requested but there was none available.
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 also considered insufficient, but this was resolved in the CAPAs.

The validation of the system for verification of participation (Sentinel software, also called "CTVR") in other studies was reviewed and was lacking validation of the ability to retrieve the correct subject from the finger print. It only included verification of access with passwords by authorized users and that they are able to perform the tasks in the given modules. This was resolved in the CAPAs.

3. Quality management

With regards to bioanalytical activities:
An Audit report, dated 17 November 2015 done by a QA auditor for the sofosbuvir analysis. It only covered "bulk spikings, forms, chromatograms and logbooks". No subject numbers were given. It was in the form of a questionnaire. It stated "is there a validated method? List the applicable method validation report number and addendums" but this was not done. Only "Yes" was written. It was the only in process audit performed and it was done on the bulk spikings (without specifying which bulk spikes were there specifically)

Root cause was not identified by QA for all of the failures they were not even mentioned in the QA report and only a small portion of all subjects data were considered – no explanation was given on why the others were omitted.

Recommendations were made for QA to take a better look at the issues with their studies, especially in case of significant problems.

With regards to clinical activities: quality management was acceptable for clinical activities in the most part.

Deficiencies were resolved in the company CAPAs.

4. **Archive facilities**

The archive facilities were on site. They were protected from fire hazards and pests. Documents were adequately retrievable. Data backups were also stored on CDs in that room. Logs were kept of room entry and of documents taken and returned. This was acceptable.

5. Premises

The facilities had three floors with a total of 114 beds and 2 ICUs with 6 beds. There were 7 LC MSMS in the laboratory.
The ground floor housed volunteer registration, informed consent and screening as well as the bioanalytical laboratory.
The first floor housed the pharmacy and IT.
The second floor housed CPU I and II, QA, archives, PK and statistical analysis.
The third floor housed CPU III, IV and V.

Hematology and biochemistry screening tests were outsourced but X-rays and ECGs were performed in-house.

Equipment was inspected in both the clinical and bioanalytical premises.
In the clinical premises.
-ECG: inspectors verified that the ECG equipment was functional. It was accompanied by a log book entry. ECGs were accessible four weeks after recording. Inspectors verified traceability by taking a random database number from the log book and checking that there was a corresponding ECG on the appropriate date and at the appropriate time labeled with the subject's initials.
-X-Ray: adequate protection was provided to employees and subjects with usage of protective shields.

Facilities inspected included:
Bed rooms, toilets (incl. alarms), dining rooms (incl. scales for food weighing), phlebotomy rooms, intensive care units.
RA Chem had a contract in place with a nearby hospital in case of SAEs. It was verified that mock runs had taken place and that SOPs existed.

6. Personnel

According to the SOP,, effective from 9 August 2013, all employees were to be trained on relevant SOPs. Induction training was to be given to any new employee. The induction training was shown. There was no mention of the specific contents of the training. The SOPs an employee was trained on were to be listed in a logbook for personnel training.
The training logbook was reviewed.

The training records for the PI was reviewed along with his job description. He had joined on 3 March 2014 and had signed it then. It was signed and dated. Issues raised regarding contents of the training were resolved in CAPAs.

Clinical section

7. Clinical phase

T-licenses (2 licenses) were verified:
The BE study protocol was dated 11 May 2015. Other documents reviewed included:
-Medical screening record, ICF, CRFs of 3 periods, and volunteer information of selected subjects.
-SOPs: measurement of vital signs and clinical examination, line clearance, dispensing, meal management.

8. Clinical laboratory

Medcis pathlabs was used to perform hematology and biochemistry tests. It was certified by NABL and CAP. It was not covered during this inspection.

9. Ethics

Inspectors checked that the content of the ICF was proper:
-Potential side effects were informed
-Subjects could stop participating the study at any time with no reason
-Pro-rated compensation: there was a proportionate compensation without specifying a detailed rate.

The registration of the ethics committee was verified on the CDSCO website as of 2013. The trial was in 2015 and it was still covered according to statements made during the inspection.

The approval letter of the IEC, including attendance, was reviewed and was found acceptable.

10. Monitoring

The sponsor representative performed 3 on site visits.

11. Investigators

The training and CV of the investigator was recorded in a folder, and was shared with the ethic committee as part of the submission for trial approval. The investigator was signing the delegation log prior to the study having begun.

12. Receiving, storage and handling of investigational drug products

Product accountability was verified for the test and reference. The procedures used by the pharmacist for line clearance and handling of the test and reference were witnessed.
The new pharmacist's credentials were verified and deemed acceptable.

13. Case report forms

Issues were raised with regards to CRFs. They were resolved in the company CAPAs.

14. Volunteers, recruitment methods

Inspectors verified the following:
-screening of volunteers as per the requirement in the protocol:

This was verified for randomly selected subjects 7, 11,43,51,58

-All the inclusion requirements were screened in the medical screening record, and the values met the acceptance criteria.

-All the criteria both of inclusion and exclusion were checked on the beginning day of study period 1.

-The requirements of exclusion were recorded in the CRF.

-The volunteer management system was acceptable overall. Random participation checks were done by selecting volunteers from the WHO trial.

It was verified that volunteers were receiving pro-rated payment for their participation after the trial or after their participation ended.

15. Food and fluids

The breakfast composition, calorie counts were in line with WHO recommendations for caloric intake from the WHO Multi-Source Guideline (Ref. 2) but as stated above, breakfast was missing from the CRF for period 3.

16. Safety, adverse events, adverse event reporting

It was verified that the reported AEs were traceable to the source documentation or CRFs. It was verified that no AEs existed in source documentation without being mention in the study report.

It was verified that the reported protocol deviations were accounted for in source documentation or CRFs, and that no protocol deviations were mentioned on source without being reported.

Bioanalytical section

17. Method development

The method was stated to have been taken from the literature further developed from there. Different extraction trials were performed in different solvents. Experiment details were retained in a method development book.

18. Method validation

The original report was dated Dec 14 2015 (first subject analyzed Nov 19 2015). The supplementary method validation (addendum) was performed on 15 and 16 December 2015 and included long term stability, extended precision and accuracy. This validation was not performed due to problems noted during the analysis but was treated as part of the standard validation package.

The injection reproducibility experiment failed on 30 October 2015. A partial blockage was suspected by the analyst and a call was made for the engineer to attend to the instrument who came on 2 November 2015. The response was found to be stable then.

Preparations were verified. The stock solution of CC and QC was prepared and weighed separately. The concentration of stock solution of CC and QC was recalculated by inspectors. The potency of both the reference standard Sofosbuvir (RS) and Sofosbuvir D_6 (IS) used in calculation was consistent with their potencies in the COAs and the results were correct. IS was weighed by the supplier and sealed in a vial, and the printed weighing result was provided by the vendor along with the vial. RA Chem transferred the whole vial of IS and used the weight without a double check.

The anticoagulant was K_2EDTA and the blank plasma was the same as in the study.

The COAs of the RS and IS were reviewed. There were two stock solutions with the same solution ID (MV-025-15-DS-01) in the initial method validation and this was raised as a deficiency and resolved in the company CAPAs.

19. Sample collection, storage and handling of biological material

In the bioanalytical report, the list of missing samples was described and reviewed by inspectors.

20. Analysis of study samples

According to the opening meeting presentation, for a total of 4147 samples assayed, 229 were repeated corresponding to 5.5%. 19 repeats were due to poor chromatography. 7 repeats due to failing CC, 201 repeats due to IS variation, and 2 repeats due to suspected interchange A total of 14 runs had failed and were repeated. The average run spanned approximately 5h50min and included 102 injections.

The chromatographic data was reviewed in detail for several subjects. Investigations performed for the study were reviewed.

The SOP on Handing of columns and the usage logbook for the columns were reviewed. Several tailed peaks were observed in the chromatography by the inspector, which indicated a reduced column efficiency. The company stated that they change for a new one when observing a column cannot elute acceptable peaks.

The SOPs for Chromatography, Method validation, Repeats, Batch Acceptance, and incurred sample reanalysis were reviewed. Issues were raised which were resolved in the company CAPAs.

21. Data processing and documentation

The company described having implemented a new SOP starting 2 November 2015 on handling of high internal standard variability.

22. Good laboratory practices

Ultra deep and deep freezers were adequately qualified, calibrated and maintained. They were equipped with alarm systems and temperature monitoring. The alarm checks were not verified due to time constraints.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

The statistical calculation for subject sample size was verified and considered acceptable.

On Day 4, due to unacceptable ITSD variation (See attached graphs), the company was requested to redo the statistical analyses by excluding some of the subjects. The study result still indicated that the study was passing the BE criteria.

24. Study report

An amendment to the study report was considered necessary due to the issues with IS variation.

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, *RA Chem* located at Plot-No.26&27, Technocrat Industrial Estate (TIE), Balanagar, Hyderabad, Telangana State-500037, India, is considered to have an acceptable level of compliance with WHO GCP and GLP.

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 5

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 TRS No. 996, Annex 9
   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 TRS No. 992, Annex 7
   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 TRS No. 850
   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. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
   Short name: WHO TRS No. 996, Annex 5
   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.
   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