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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, Bioanalytical and Statistical Site	ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies P. O. Box: 925161 Amman 11190, Jordan 31.95804904 latitude, 35.8690225161 longitude, 31°57'28.977 N, 35°52'8.481 E
Corporate address of Organization	Same as above
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	HA665 Sofosbuvir 400 mg tablets Randomized, four- way, four- period, fully replicated, single oral dose, open-label, crossover, bioequivalence study to compare Sofosbuvir 400 mg Tablets produced by European Egyptian Pharmaceutical Industries, versus invotor (400 mg Sofosbuvir tablets) in healthy subjects under fed condition.
Inspection details	
Dates of inspection	21, 22 and 23 September 2016
Type of inspection	Initial
Introduction	
Brief summary of the activities	The inspection focused on the bio-equivalence study conducted for the product HA665-Sofosbuvir 400 mg tablets, from the sponsor EEPI. The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO additional guidance for organizations performing in vivo bioequivalence studies, including bioanalysis, clinical phase, and biochemical/haematological testing .
General information about the company and site	ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies, a Contract Research Organization (CRO), was established by ACDIMA in 2000 to provide bioequivalence testing services to the pharmaceutical industry and headquartered in Amman, Jordan.
History	The site was previously audited and accredited by the Jordan Food and Drug Administration (JFDA), Jordan Ministry of Health and Turkish Ministry of Health as follows: - JFDA, Bioanalytical Lab Accreditation – 20/09/08 - JFDA, Bioanalytical Lab Accreditation – 21/10/11 - JFDA, Clinical Site Accreditation – 22/05/12 - JFDA, Medical Lab Accreditation – 23/07/12 - Jordan Ministry of Health, Medical Lab Accreditation – 2012 - JFDA, Bioanalytical Lab Accreditation – 15/01/15 - JFDA, Clinical Site Accreditation – 13/06/15 - JFDA, Medical Lab Accreditation – 21/08/15 - Turkish Ministry of Health, 10-14/09/15

Brief report of inspection activities undertaken - Scope and limitations	
Out of scope	Not applicable

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
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)

1. Organization and management

As per the company's presentation, the Arab Company for Drug Industry and Medical Appliances (ACDIMA) was instituted in 1976 with a total capital of USD 300,000,000, invested by 17 governments of Arab Countries. In its establishment doctrine, ACDIMA's Board of Directors approved a strategy that aims at boosting investments in diversified pharmaceutical projects of on-demand feasibility and unique value.

The CRO was started in 2000 with the headquarter in Amman, Jordan.
According to the opening meeting presentation the facility has a capacity of 60-bed dormitories and 10-bed clinical ward, a dedicated screening area with physical examination and sample collection rooms, a secure pharmacy with temperature control, a dining room and recreation lounge, multiple dosing and phlebotomy stations room.

The in-house medical laboratory providing full medical screening tests, was equipped with the following instruments: Beckman Coulter® AC.T diff TM Hematology Analyzer, Roche Cobas® c111 Chemistry Analyzer & c311 with AVL 9180 Electrolyte Analyzer, Human® Semi-automated Chemistry Analyzer, Linear® ELISA reader and washer, Human® Coagulometer.

The bioanalytical facility was equipped with LC-MS/MS systems: AB Sciex API 4000, AB Sciex API 4500, AB Sciex API 6500, Automated 96-well auto-samplers, Watson™ LIMS for secure data processing & warehousing, refrigerated centrifuges, Milli-Q^{TM} water, microbalance & ultra-microbalance. All study samples are stored in controlled freezers (-20°C and -70°C) and continuously monitored with 24-hour mobile-call and e-mail alarms and supported by a standby generator.

2. Computer systems

Watson LIMS was implemented and used to process HPLC-MS/MS data. The software validation master plan was reviewed and was dating from after the study (15.01.2016). It was an overarching plan, that described the main lines of what should be covered and the steps to be followed.
The user and functional requirements specification stated that the analyst administrator role will be permitted to overwrite existing quantitation tables and to access the audit map editor. The analyst administrator was readily available and working in the laboratory.
The User and Functional Requirement Specifications stated many relevant and adequate requirements, including the following:
-"The Analyst software must be capable of detecting alterations to raw data files performed outside of the normal mechanisms provided by the application itself"
OQ and PQ protocols were available for review.

3. Quality management

The majority of recent documents were signed off, dated, checked and stamped.

A set of SOPs was implemented at the site .

The following SOPs were requested from the list of SOPs and reviewed:
-"Source documents review and data queries management"
-"Source documents review, verification and auditing", version 1, dated from 21/03/2016
-"Management review meetings", version 01.

Some of the above SOPs were not found to be sufficiently detailed. See sections below for more detail.

The quality management system (QMS) was not adequate in terms of analyzing OOS/recurring incidents or deviations . Analyzing OOS/recurring incidents was not done except during internal audits: an internal audit is not intended for these activities. The management review meetings Version 1, effective since 17/07/2016, was not sufficiently specific and therefore minutes from the last management meeting and CAPA were requested, as well as its schedule.

For the Sofosbuvir study, only one deviation was recorded for incorrect samples sorting for subject No.22. It described the deviation as "Upon routine analysis batches review by Team Leader, Quality control for Sofosbuvir study encoded (BC-SOF-15/431) it was found that the samples sorting in LIMS sequence in Run #17 (Subject #22) was wrong." It was classified as minor and closed by taking data directly from the Analyst software and importing it to Microsoft Excel instead. Another deviation (No. SP04-042-D.01) was reviewed. It stated that 3 samples which had been selected for ISR analysis were not analyzed due to a technical error.

An OOS was reported after assessors reported that the CV for low QC was found above the acceptance criteria of 15%. After excluding the QC sample, the concentration from the original QC batch 29 from subject 26, there was a CV of 14.17% only and therefore it was considered acceptable.

The OOS/OOT investigation was followed by CAPAs which included training and a quiz to help prevent issues from reoccurring.

Document control was acceptable as the majority of recent documents were signed off, dated, checked and stamped, but older documents were lacking and the list of SOPs was not signed nor dated.

4. Archive facilities

The document archival room was visited. It was situated at basement in the main building. It was equipped with a fire extinguisher system, temperature and humidity monitoring. A min/max thermometer was available and temperature was recorded twice a day. The site did not record the temperatures during the weekends and the bank holydays. The logbooks were maintained for entry and exit, document storage and retrieval. All data were kept for a period of 10 years according to the company's policy.

5. Premises

The company had sufficient space to accommodate the personnel and activities required to perform the studies. The site has adequate facilities, including laboratories, and equipment.

Conditions of the pharmacy where the investigational products are stored was found to be appropriate, with entry and exit restricted by access control. A min/max thermometer was available and temperature recorded twice a day.

The availability and state of equipment for emergency care such as defibrillators, suction machine, oxygen cylinders, etc. were verified and found to be adequate. All the emergency drugs were checked for expiration date and found to be adequate.

Toilet facilities and panic/alarm buttons were verified to function as well as the camera surveillance systems.

6. Personnel

Personnel was generally well trained and competent in their respective areas. Training records were reviewed for a few randomly selected staff members and the level of documented training and accreditation was deemed satisfactory.

Clinical section

7. Clinical phase

Subjects were admitted in the building via a separate entry. Bracelets and batch numbers were provided to each subject; following number allocation, subjects were invited to the room were the Co-Investigator was providing information regarding the study. After all questions raised by the subjects were answered by the Co-Investigator the ICF was signed by the subject, Co-Investigator and a witness.

Following ICF signature, subjects were entering the screening procedures room where BMI, weight and height were measured. If the subject was considered eligible he was invited to the room where physical examination, medical history, concomitant medication were recorded. An ECG was performed by the study nurse, urine and blood samples are collected as well. Subjects were afterwards going home and called by the site personnel if eligible.

Number of screened subjects: 68 subjects
Number of withdrawn subjects- During screening: 32 subjects
-Number of withdrawn subjects due to selection criteria- During screening: 20 subjects
-Number of withdrawn subjects due to personal reason- During screening: 12 subjects
Number of subjects enrolled in the study: 36 subjects
Number of subjects withdrawn during the study: 5 subjects

8. Clinical laboratory

Upon request, the inspector was provided with the ACDIMA medical laboratory accreditation certificate. It was noted that the approval certificate was issued on 28 August 2012 by the Jordanian Ministry of Health.

The documentation relating to the movement of samples from the clinic to the laboratory was reviewed for a selection of subject samples. The data were complete allowing traceability and reconstruction of these key activities.

The medical laboratory results (hematology, biochemistry, urinalysis & serology (Hepatitis B & C, HIV)) were evaluated by the Co-investigator. Individual printed laboratory reports for each subject were sign and dated by the Co-investigator. Results of laboratory test were generated by "MABS" software and approved by a specialized medical technologist in addition to the clinical Co-investigator.

9. Ethics

The study protocol ID: 472-2015 V.02, February 2015 was approved by the Institutional review board (IRB) of ACDIMA BioCenter on 28/02/2015 and JFDA on 10/03/2015, before the study conduct.
Consent process was carried out by the Co-investigator (delegated by the Principal Investigator). The subjects were signing and dating the consent form, along with one witness and the Co-investigator.
All informed consents were verified by the inspector, the following was noted: For several volunteers the Co-investigator signature date was not on the same day as the subject's signatures. A "Note to File" was created explaining that the Co-investigator was present during the inform consent process, however signature was provided a few days later. The clinical coordinator assisting during the process was signing the Informed Consents on the same day as the subjects.

10.Monitoring

The monitoring of the study reviewed during the inspection was performed by the Sponsor.
The following monitoring visit reports were provided to the inspector:
- Site Qualification Report, visit date 1-30 Oct 2014
- Site Monitoring Report, visit date 17-18 Jun 2016
- Site Close-Out Report, visit date 17-18 Jun 2016

11.Investigators

Both investigators participating to the study had appropriate qualifications, trainings and sufficient experience in the conduct of BE studies, as confirmed by their CVs (CVs - Appendix 7 to the study protocol).

12.Receiving, storage and handling of investigational drug products

The test product was Sofosbuvir 400 mg Tablets manufactured by European Egyptian Pharm Ind., batch number: 5105008, Manufacturing date: 02/2015, Expiry date: 15/02/2017.
An inspector visited the area where test and reference products were stored. Conditions were found to be appropriate: the products were stored in the pharmacy accessible only to authorized personnel; the min/max thermometer was available and temperature was recorded twice a day.

Inspectors asked for evidence demonstrating the date when the test product and the comparator product were analyzed since the assessment team pointed out that the CoAs were not dated. This information was stated to be the sponsor's responsibility; inspectors agreed with the CRO on this point.

13.Case report forms (CRF)

Paper CRFs were used to record data on each subject during the course of the trial. Data collected on each volunteer were captured and consistent with the protocol.
CRFs for selected subjects were verified by the inspector and found to be appropriate. Screening and follow-up laboratory results, as well as ECG copy and alcohol and drug of abuse tests results were attached to the CRF. CRF and CRF's attachments were signed and dated by the Co-investigator.
Errors noted for some of the CRFs were appropriately reported and clarified via Notes to File. The "Note to Files" describing the inconsistencies were signed and dated by the Co-investigator.

14.Volunteers, recruitment methods

The company is using the "National Database" for Clinical Studies hosted by the JFDA to control participation in trials accommodating a pool of more than 4,000 subjects starting 2004. As soon as a subject has been identified a copy of the credential is done and verification against JFDA database is completed in order to ensure that the subject has not participated in a similar study within the last eighty days**.**

15.Food and fluids

Subjects were not allowed to have meals and fluids other than those served by the study team.
Meals were administered according to the study schedule:
Day 1: Standardized dinner was served 12 hours before dosing.
Day 2: Standardized breakfast was served 30 minutes before dosing. Standardized lunch was served 6 hours after dosing, a snack at 8 hours after dosing. All meals were identical in all periods and served at approximately the same time.

Fluid restrictions were placed only in day 2 of the study. Subjects were not allowed to have fluids one hour before dosing and four hours after except for 120 ml, 1 hour before dosing, 240 ml of water with the product on dosing and 120 ml of water 2 and 3 hours after dosing. Otherwise, subjects were allowed to drink water as desired.

16.Safety, adverse events, adverse event reporting

At each contact with the subject, the Co-investigator was seeking information on adverse events by questioning and, as appropriate, by examining the subjects. Information on all adverse events was recorded immediately in the source document, and also in the appropriate adverse section of the CRF.
The test and reference product were well tolerated. Nineteen adverse events were reported, out of which one was moderate and the others were mild. According to the Co-investigator assessment these were unlikely related or unrelated to the study drug administration.
No significant or serious adverse events were reported during the study conduct.

Bioanalytical section

17. Method development

Method development was stated to be recorded in a logbook. Testing was stated to have started on 19/03/2015. There was no information on where the method was taken from or on the reasons for selecting the method. There were no preparation records. This could not be seen to constitute method development and it did not appear to be an original record.

18. Method validation

Over 125 methods for analysis have been validated. The bioanalytical unit was equipped with AB Sciex API 4000, 4500 and 6500, Automated 96 well auto-samplers, Watson LIMS, refrigerated centrifuges.

The SOP entitled "Bioanalytical method validation", version V04, valid since 03/07/16, was reviewed. It was shown to the inspector in response to a question regarding pre-dose samples. This SOP, was, however not found to adequately cover pre-dose samples as these cannot be considered as true blanks. The company should correct their understanding of the purpose of the pre-dose samples.

19. Sample collection, storage and handling of biological material

The extraction procedure was pre-written in standard forms (using liquid/liquid extraction). The following instructions were found:
"-Pipette 250 µL of human plasma.
-Take the blank sample apart and spike with 25 µL of diluent to compensate addition of IS solution.
-Spike each sample with 25 µL of IS working solution
-Add 4 mL of the diethyl ether
-Vortex for 60 seconds
-Centrifuge for 5 minutes at a speed of 4000 rpm at 5°C.
-Freeze the samples and decant the upper organic layer.
-Evaporate the organic layer under nitrogen stream at 40°C".
The time of start and end of extraction was written as the same for the CCs, QC and subjects; it appeared as if they were all done at exactly the same time. The date and time on the auto-sampler was also identical.
There was no documentation of sub-batches if any or whether aliquots 1 or 2 were processed; it was stated to be aliquot 1.

Blood samples were collected in tubes containing lithium heparin. Plasma samples were then harvested in Eppendorfs (2 aliquots). They were centrifugated at each time point and documented.

20. Analysis of study samples

Inspectors proceeded to reviewing the electronic chromatographic data. The chronological order of the runs was verified. The randomization of subjects to the different runs was also explained and was considered acceptable.

Results, projects and instrument audit trails were reviewed on the two instruments reported to have been used for Sofosbuvir in the bioanalytical laboratory. It was noted that in September 2014, the audit trail system was changed to "GXPAuditMap". This is acceptable.

Issues were observed regarding high internal standard variation. This was resolved in the company CAPAs.

21. Data processing and documentation

The data was reprocessed as per inspector's request to reduce smoothing from 10 to not more than 4. The new data, created with a smoothing of 3, was reviewed but this had an impact on calibration curves. It is not clear if the runs would still be passing or not since this was not properly done during the course of this inspection. A few chromatograms/integrations were no longer deemed sufficiently accurate to get optimal results.

The calculated plasma concentrations for each time point and randomly selected subjects were reviewed.

22. Good laboratory practices

All equipment was appropriately labelled. Mobile phases and washing/storage solutions were also appropriately labelled with the expiry and preparation dates.

GLP audits were performed on a daily basis following a checklist, as per the SOP version 5, dated 20/03/2016, and covered reagents, solutions, chemicals, logbooks, cleanliness, tidiness, equipment being maintained, calibrated and working properly, as well as environment, freezer and refrigerator temperatures, and safety measures. A different and more detailed checklist was used on a monthly basis.

Calibrations were done every 3 months by the supplier of the balances, Mettler Toledo, using standardized weights from Mettler Toledo Switzerland. Daily calibration was performed by the analytical team.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

This area was not covered due to time constraints.

24. Study report

This area was not covered due to time constraints.

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 *BC-SOF-15/431* was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *ACDIMA Jordan*, located at *P. O. Box: 925161 Amman 11190, Jordan*.

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