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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	CAD Middle East Pharmaceutical Industries LLC
Corporate address of manufacturer	King Khalid International Airport Road Industrial Estate Riyadh 11496 P.O. Box 26721 Kingdom of Saudi Arabia
Inspected site	
Address of inspected manufacturing site if different from that given above	King Khalid International Airport Road Industrial Estate Riyadh 11496 P.O. Box 26721 Kingdom of Saudi Arabia
Unit / block / workshop number	Alpha Block
Manufacturing license number	01-01-00007
Inspection details	
Dates of inspection	2-5 May 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	CAD Middle East Pharmaceutical Industries LLC (hereafter referred as CAD) facility has one manufacturing block with six independent suites to handle multi-products at a time in different production suites. The manufacturing building has six independent production suites to manufacture various APIs and its intermediates. Each suite has 3 reactors of various materials of construction to satisfy the multi-purpose manufacturing criteria, filtering and drying system dedicated to that. Several polymorphic forms of Sofosbuvir have been observed during development and the manufacturing process should consistently produce Sofosbuvir as the most thermodynamically stable polymorphic form. It has been clarified in the site master

	file/dossier submitted to WHO (APIMF) that the manufacturing process has been designed to exclusively obtain the form-α. First batch of API Sofosbuvir was produced in the year 2014 (trial batches). Validation batches were completed in March/April 2015. These processes were validated at suite 6 (small capacity). Since then, several changes in the process and the batch size were implemented and accompanied by revalidation. In 2016 and 2017 there was no production of the final API Sofosbuvir so far. However, four batches of the intermediate SOFO-1 were produced in 2017. Batches SOF1172001, SOF1172002 and SOF1172003 were produced in February and March 2017, used for process validation and afterwards shipped to PHARCO Egypt. Batch SOF1173004 was stored at the warehouse and is planned to be used during production of Sofosbuvir at the CAD site. According to the information given, PHARCO has established a second API manufacturer which makes use of SOFO-1 produced by CAD.
General information about the company and site	CAD is a limited liability company established in 2006; it is one of the economic offset companies (governmental program). CAD is specialized in the manufacturing of Active Pharmaceuticals Ingredients (APIs) and it is located within the industrial zone of King Khalid International Airport (KKIA) north of Riyadh – the capital of Saudi Arabia. The Manufacturing site is constructed on 35,500 square meters (about 250 m in length x 150 m in width). According to the CAD policy, company will follow all international GMP guidelines, including WHO, EU and ICH.
History	This was the first WHO-PQ inspection. The Saudi FDA inspected CAD on 11/Jan/2015. The license number issued was 901/2013. There were no inspections / certifications from other authorities.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients: • Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation

	• Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories)
Restrictions	None
Out of scope	Areas related to Sofosbuvir API were covered whereas other APIs were out of scope
WHO product numbers covered by the inspection	Sofosbuvir API (for Sofosbuvir 400 mg Film-Coated Tablets, HP003)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology

MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

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

Brief summary of the findings and comments

1. Quality management

In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. The Quality Unit was divided into quality assurance (QA) and quality control (QC) with management responsibilities shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key staff.

The traceability of records and documentation system were satisfactory.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Personnel

Personnel met during the inspection were suitably qualified through qualifications, experience and training in general. From the discussion and review of documents, it appeared that there was not sufficient number of personnel on site, in particular in the quality assurance department as procedures were not timely reviewed.

Department	No. of Persons
Human Resources and Administration	10
Finance	6
Technical & Operations	1
Engineering	20
Research & Development	9
Production	33
QA, QC and Regulatory Affairs	22
Supply Chain Management	4
Warehouse	5
Health, Safety & Environment	4
Information Technology	6
Business & Development / Marketing & Sales	4
Total Employees	**124**

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing being conducted. Suitable sanitation and change room facilities were provided.

The SOP on training procedure was discussed which was applicable to employees and workers. The training was coordinated by HR department, and training on GXP, HSE and general areas was provided by respective departments as well as by external experts. An annual training calendar for the current year was discussed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Buildings and facilities

The manufacturing' building external dimension is 62.88 meters in length, 31.02 meters in width, and 17.50 meters in height. The building constructed with RCC and brick walls and it is divided into two floors in addition to a third floor for plant utilities and a basement. The ground floor is at 1.40 meter level, the first floor is at 6.90 meter level, the second floor at 11.85 meter i.e. the technical area, is at 1.40 meter (all referenced to the street level). This building contains six manufacturing compartments / suites to manufacture APIs / Intermediates. Each suite has three reactors, filtering and drying system dedicated to that suite.

The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Manufacturing areas provided acceptable space for the placement of equipment.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

4. Process equipment

Equipment used in the manufacture of Sofosbuvir appeared to be of appropriate design and size for its intended use, cleaning and maintenance. Manufacture and material transfer took place in closed systems wherever possible. All equipment viewed appeared to be clean and well maintained.

Equipment was required to be cleaned according to documented procedures. Equipment usage logbooks were available. Records were maintained and equipment status was indicated by sign on each of equipment.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Documentation and records

Documents related to the manufacture of API were prepared, reviewed, approved and distributed according to written procedures. Document control was the responsibility of QA, as checked whilst reviewing the responsibilities of the QA department. Specifications were established for raw materials, intermediates and APIs. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. The Company had a policy to archive all logbooks and other documents.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Materials management

Warehouse building consisted of physically separated raw material and finished product storage area. Both warehouses were equipped with dedicated HVAC systems to maintain the temperature within the required limits. Warehouse was equipped with receiving bay and dedusting area. Both areas were well designed and separated from the storage areas in the warehouse. Vacuum cleaner with identification tag and status label was available in the de-dusting area. Protection against the entry of insects or other animals and pest control measures were ensured. Insect and rodent traps etc. were installed, as appropriate. High-rack storage systems, three levels high, for storage below 30 °C were present. Further, for heat sensitive materials cold storage (2 – 8 °C) and freezer (< -10 °C) were available.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Production and in-process controls

The alpha manufacturing block was subdivided into 6 suites with following details:

- Suite 1 and 3 used for production of intermediate SOFO-1 (Stage-I)
- Suite 2 and 4 used for synthesis of crude Sofosbuvir (Stage-II)
- Suite 5 and 6 used for Stage-III (final stage). The Suite 6 has a smaller capacity and primarily used for the development of small batches.

Suite no. 5 consisted of personnel airlock G27, material airlock G28, main production room G30, dryer room G29 and washing room G31. Points of use for purified water were designed appropriate. Hoses needed for material transfer were stored in dry status after purging with solvents and drying with nitrogen.

These suites were not dedicated for production of Sofosbuvir. The process validation batches of Sofosbuvir were produced in 2015 using above mentioned suites. In 2017, only Stage-1 was produced and material was dispatched to Pharco Pharmaceuticals Egypt.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

At the time of the inspection, there was no packaging taking place. It was observed that there was no designated area specified for packaging activities, and a weighing balance was placed in the centrifuge area.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Storage and distribution

See description in chapter 6 (Materials management).

10. Laboratory controls

Quality control department and microbiology department were situated in the administration building. Instrumentation room and wet laboratory were on the first floor. Laboratories were found well equipped and organized.

According to the information in the site master file (SMF), there should also be an in-process control laboratory, well equipped with instruments like Karl-Fischer Titrator, pH Meter, Moisture Analyser and Analytical Balance. However, this was not available at the moment. There were only plans to implement this laboratory at the production building. Empty room was shown.

Microbiological laboratory area was on the second floor. The microbiology laboratory was well equipped with instruments like Bio-Safety Cabinet (BSC), Incubators, Air Sampler, Microscope, Sterilizing Autoclaves, Colony Counter, pH Meter, and Scientific Refrigerator. Passing of personnel airlock was necessary for access to the area. Other rooms in the microbiological laboratory area were incubator room, washing room, media preparation room and BSC room (BSC with class D surrounding). Microbiological testing was conducted for water samples, environmental control samples, and APIs upon requirement.

Chambers for stability testing and store for retained samples were on the second floor too.

Reference samples of raw materials and final APIs are retained and stored in a dedicated retained sample room. Room entry logbook was available. More than 20 retained samples of Sofosbuvir were on storage.

Several examples together with the laboratory tests for SOFO-1 from the year 2017 were checked. Documentation for the preparation of standards and samples for HPLC were found complete, including the printouts generated from the printer connected with every scale. Equipment usage logbooks were available.

Equipment was found in good condition. Equipment installed was compared with the listing in the current SMF. Listing and equipment numbers were found in accordance with the equipment in the laboratory except in-process labs.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Validation

Validation policy was described in the Validation Master Plan (VMP) with the validation approach described. The VMP for API and intermediate manufacturing facility of CAD Middle East was discussed. The process validation was performed using prospective and concurrent approach.

Tentative qualification and validation plan for the year 2017 was available. Document gave an overview about performance verification (e.g. HVAC system), periodic review (HVAC and nitrogen system), Re-qualification (every 5 years) as well as for plans in the area of process, cleaning and method validation. There were no plans together with Sofosbuvir production and analysis.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

12. Change control

Change control procedure was available. There were definitions for permanent changes, temporary changes (reviewed and approved in advance with defined change duration or time period for implementation on temporary basis). Further, minor (minimal potential to have an advance effect) and major changes (substantial potential, requires the submission of a supplement and approval by the regulatory prior to distribution) were described. Detailed guideline for change classification was part of the procedure. Alternative change control form was used for changes in the non-GMP area. Changes should be initiated by filling the change control

request form. Logbooks were maintained product wise and by QA. Change control logbooks for Sofosbuvir were available and were checked for period from 2015 to 2017.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Rejection and re-use of materials

The SOPs "Reprocessing of APIs and Intermediates" and "Reworking of APIs and Intermediates" was shown and checked in detail. Reworking SOP was applicable for all failed APIs and Intermediates recommended for reworking. According to the SOP, R&D department is responsible to prepare the reprocessing / reworking procedure. Production department should prepare the BMR.

According to the information given, there was no reworking / reprocessing for this API.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Complaints and recalls

Complaints were handled according to with responsibilities defined and complaints classified with definitions of each. Handling of product complaints procedure was discussed. The complaints were classified into critical, major and minor. An action will be taken to freeze all stocks for critical complaints. It was however noted that the procedure did not specify use of risk management tools for the investigation of complaints including impact assessment. The procedure was cross referenced to recall procedure. There was no complaint received in 2016 and 2017 for any products.

Handling of product recall procedure was discussed. The procedure described in which situations recall will be initiated, in particular, outcome of a complaint, regulatory authority, and degradation of product etc. The recalls were classified into high, medium and low class. The procedure did not clearly stipulate who is responsible for recalling products. From the product recall form used for dummy recall, it was noted that QA initiated dummy recall whereas CEO approved the dummy recall exercise.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Contract manufacturers (including laboratories)

All manufacturing activities and product analysis activities were carried out on CAD site only. This information was also provided in the SMF. There are plans to have external laboratory for analysis of some tests.

PART 3
Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, *Sofosbuvir manufactured at CAD Middle East Pharmaceutical Industries LLC, King Khalid International Airport Road, Industrial Estate, Riyadh 11496 P.O. Box 26721, Kingdom of Saudi Arabia* was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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 manufacturer, 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 GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile 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 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. 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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf