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20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Pharmaceutical Product (FPP) Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	Aspiro Pharma Limited	
Corporate address of manufacturer	Survey No. 321, Biotech Park, Phase III, Karkapatla village, Markook Mandal, Siddipet, Telangana, 502281, India	
Inspected site		
Name & address of manufacturing site	Survey No. 321, Biotech Park, Phase III, Karkapatla village, Markook Mandal, Siddipet, Telangana, 502281, India.	
Production Block/Unit	NA	
Desk assessment details		
Date of review	15 October 2020	
Products covered by this desk assessment	Remdesivir Powder for solution for injection 100mg/vial (CV001)	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA, USA	Dates of inspection:	10-21 October 2019
	Type of inspection:	Pre-approval inspection (initial inspection)
	Block/Unit:	NA
	Type of products/Dosage forms covered:	Sterile manufacturer of human drug products produced by aseptic processing and lyophilization (Pantoprazole Sodium for injection and Succinyl Choline Chloride injection)
Health and Youth Care Inspectorate, The Netherlands	Dates of inspection:	11-14 February 2020
	Type of inspection:	Initial inspection
	Block/Unit:	NA
	Type of products/Dosage forms covered:	Aseptically prepared dosage form (lyophilizates) and terminally sterilized (small volume liquids)
Ministry of Health Brazilian Health Regulatory Agency	Dates of inspection:	03 February 2020
	Type of inspection:	Desk assessment
	Block/Unit:	Not applicable

(ANVISA), Brazil	Type of products/Dosage forms covered:	Steriles: Terminally Sterilized Emulsions; Aseptically Processed Powders; Lyophilized Powders; Terminally Sterilized Small Volume Parenteral Solutions; Aseptically Processed Small Volume Parenteral Solutions
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	WHO had not previously inspected Aspiro Pharma Limited.	
Brief description of manufacturing activities	Not applicable	
General information about the company and manufacturing site	Not applicable	
Focus of the last WHO inspection	Not applicable	
Areas inspected	Not applicable	
Out of scope and restrictions (last WHO inspection)	Not applicable	
WHO products covered by the last WHO inspection	Not applicable	
Additional products covered by this desk assessment:	Not applicable	
Abbreviations	**Meaning**	
AHU	Air handling unit	
API	Active pharmaceutical ingredient	
BMR	Batch manufacturing record	
BPR	Batch production record	
CAPA	Corrective and preventive action	
CC	Change control	
GMP	Good manufacturing practices	
NC	Non conformity	
NRA	National regulatory agency	
PQR	Product quality review	
PQS	Pharmaceutical quality system	
QA	Quality assurance	

QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure

Part 4	**Summary of the assessment of supporting documentation**

a) Manufacturing authorization and GMP certificate granted by the local authority:

The Drugs Control Administration (DCA), Government of Telangana, India has issued a GMP certificate as stipulated under the provisions of Schedule "M" of the Drugs and Cosmetics Rules, 1945. Also, the DCA issued a Drug Manufacturer Licence in Form 28 (36/MD/AP/2013/F/G) dated 5 Feb 2014 with validity 4 February 2024.

The DCA also issued an approval dated 21 June 2020 in Form 28A (21/MD/TS/2014/F/G/L) for Remdesivir Injection 100 mg / 20 mL, Remdesivir for Injection 100 mg / vial.

Remdesivir is the loan license product contract given by the Hetero for manufactured at Aspiro Pharma Limited. The Loan License Manufacturing Authorization was provided to WHO.

b) Site master file (SMF):

The manufacturer has submitted the site master file (APL-SMF-12 effective date 20 December 2019) which provided a high-level overview of the manufacturing activities carried out at the site. In general, the SMF appear to be adequate.

c) List of regulatory inspections performed in the last 3 years and their outcome:

S. No.	Name of the Regulatory Agency	Dates of Audit	Inspection outcome
1.	State Service of Ukraine on Medicines and Drugs Control, Ukraine (PIC/S) **(Desktop Assessment)**	Recertified in July 2020	GMP certificate received
2.	Agencia Nacional de vigilancia Sanitaria (ANVISA), Brazil **(Desktop Assessment)**	Recertified in February 2020	GMP certificate received
3.	EU- Dutch, The Netherlands	11-14 February 2020	GMP certificate received

S. No.	Name of the Regulatory Agency	Dates of Audit	Inspection outcome
4.	Saudi Food & Drug Authority (SFDA), Saudi Arabia	17-18 October 2019	GMP certificate received
5.	USFDA, USA	10-21 October 2019	GMP certificate received
6.	Ethiopian Food and Drug Administration (EFDA), Ethiopia	20-23 September 2019	GMP certificate received
7.	GMP inspection- National Drug Authority, Uganda	16-17 September 2019	GMP certificate received
8.	Tanzania Medicines & Medical Devices Authority (TMDA), Tanzania	12-13 September 2019	GMP certificate received
9.	Ministerio De Salud DIGEMID (Direccion General de Medicamentos, Insumos y Drogas), Peru	26-30 August 2019	GMP certificate received
10.	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), Colombia	Renewal inspection on 05-09 August 2019	GMP certificate received
11.	ZAZIBONA (Zambia, Zimbabwe, Botswana, Namibia), SADC	26-28 June 2019	GMP certificate received
12.	Ministry of Health, Indonesia.	Certified: 06 August 2019	GMP certificate received
13.	Ministry of Health of the Republic of Kazakhstan, Kazakhsta	11-12 July 2018	GMP certificate received
14.	Ministry of Health Pharmacy and Poisons Board (PPB), Kenya	06-07 June 2018	GMP certificate received
15.	Republic of Yemen	Certified: 16 May 2018	GMP certificate received
16.	Ministry of Industry and Trade of the Russian Federation, Russia	09-12 April 2018	GMP certificate received
17.	Agencia Nacional de vigilancia Sanitaria	20-24 November 2017	GMP certificate

S. No.	Name of the Regulatory Agency	Dates of Audit	Inspection outcome
	(ANVISA), Brazil		received
18.	State Service of Ukraine on Medicines and Drugs Control, Ukraine (PIC/S)	07-11 August 2017	GMP certificate received
19.	Ministry of Health, Cambodia	Certified: 28 July 2017	GMP certificate received

d) List of all the products and dosage forms manufactured on-site:

The manufacturer has provided a list of all the products manufactured on-site. The list contains a total of 29 finished pharmaceuticals (injectable: lyophilized, liquid) products of different therapeutic areas. Basically, the site produces medicinal products of different therapeutic areas on the same manufacturing facility using shared equipment and utilities.

A retrospective risk assessment was performed for Remdesivir injection. The manufacturer has also provided a procedure on the preparation and review of permitted daily exposure for being a multipurpose facility. This procedure was prepared by Cliwis, service provider. The effective implementation of this procedure and other controls should be verified during on-site GMP inspection.

Aseptic process simulation details:
The manufacturer has provided the following batch manufacturing records:

- Aseptic process simulation Batch No APS020004, batch Size 300L (6000 vials)
- Aseptic process simulation Batch No APS020003, batch Size 300L (6000 vials)
- Aseptic process simulation Batch No APS020002, batch Size 300L (6000 vials)
- Aseptic process simulation protocol and report of Line 2 (Batch No APS020005, 50L Batch size)
- Aseptic process simulation protocol and report of Line 1 (Batch No APS020002, APS020003 and APS020004, 300L Batch Size)

In general, the submitted documents appear to be satisfactory. An on-site inspection will assist in verifying the expected GMP compliance for sterile products.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):

The manufacturer has provided the process evaluation report (PER) for Remdesivir injection 100mg/vial instead of product quality review (PQR). It was clarified that the Remdesivir is a new product with no product manufacturing during 2019. It was clarified that Remdesivir manufacturing started in the month of May-2020 at Aspiro Pharma Limited. As per the SOP No. APL-QASOP027 (Title: Product Quality Review), PQR shall be prepared annually based on a rotational schedule for all products manufactured and a trend analysis shall be carried out for each manufactured product throughout the review period. The Process Capability index (CpK) shall be carried out with a minimum of 20 batches.

At the time of the WHO dossier submission, only 7 batches of product were manufactured during 2020. Taking this in consideration, details of only 7 batches were evaluated and documented in the PER report. At 2020 year-end, PQR shall be prepared for Remdesivir injection.

The PER provided the following product details:

Product Code (31000488), Batch size 95 L (6209 vials), 24-month tentative shelf life and 7 batches produced for domestic market. The manufacturer has two manufacturing lines wherein Line-1 is for 300L batch size and Line-2 is for 95L batch size. The following summarises the process evaluation report:

1. 9 batches of Remdesivir API (Specification No RSM146-02) were procured, tested and used to produce 7 batches of finished product. Trend analysis for water content, total impurities, assay, acetone, isopropyl alcohol, acetonitrile, dichloromethane, di-isopropyl ether, ethyl acetate, tetrahydrofuran, 2,2-dimethoxypropane, isopropyl acetate, toluene was performed, and graphical presentation was part of the PER.
2. 6 batches of Betadex Sulfobutyl ether Sodium NF (Specification No RMS100-03, RMS148-00) were procured, tested and used to produce 7 batches of finished product. Trend analysis for water content, pH, assay, beta cyclodextrin (betadex), 1,4-butane sultone, sodium chloride, 4-Hydroxybutane-1-sulfonic acid, Bis (4-Sulfobutly) ether disodium, Average Degree of Substitution was performed, and graphical presentation was part of the PER.
3. Summary of critical process parameters of in-process (compounding stage) test parameters and trend analysis chart for pH, stirring speed, temperature,
4. Filtration stage (pre-filtration bubble point (primary filter), pre-filtration bubble point (secondary filter), pressure applied during filtration, post-filtration bubble point (primary filter) and post-filtration bubble point (secondary filter)
5. Filling, stoppering and lyophilization stage (filling machine speed 20 vial per minute and filling duration NMT 24 hours)
6. Bulk manufacturing stage
7. Manufacturing yield
8. Review of finished product results

The manufacturer is required to submit the PQR of Remdesivir injection as soon as it is available for review. The effective implementation of the PQR procedure and related aspects should be verified during an on-site GMP inspection.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s):

Remdesivir injection is manufactured for domestic and export markets. It was clarified that there is no difference in the formulation, composition and manufacturing process of Remdesivir produced for different markets. However, some differences in the specification and STP for Domestic and Export markets for Remdesivir injection were highlighted by the manufacturer.

The following batch manufacturing record, packaging record and analytical records were provided:

- The batch manufacturing record of RED020002 (Product Code: 31000493)
- The batch packaging record of RED020002A (Product Code: 440521)
- Certificate of analysis and test request form for chemical and microbiology testing for Batch No RED020004 (Product Code: 31000493)

g) Master batch manufacturing and packaging record(s) of the product(s) of interest:

The following Master batch and packaging records were provided:
- The Master batch manufacturing record for Product Code: 31000493
- The Master packaging record for Product Code: 440521

h) Recalls in the past three years related to products with quality defects:

No product recalls were received from the past three years.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with:

The manufacturer confirmed that as per SOP#APL-QASOP15 a periodic self-inspection program is conducted by senior quality assurance representatives. It is a continuous process and is performed for all dug products manufactured on site. In addition, the CDSCO-DCA performed an inspection in May and July 2020 for Remdesivir for injection.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:

The manufacturer has confirmed that there is no warning letter or equivalent regulatory action, issued by any authority to the site or to any product manufactured and distributed from Aspiro Pharma Limited located in Biotech Park, Phase III, Karkapatla village, Markook Mandal, Siddipet, Telangana, 502281, India.

k) Out-of-stock situations:

The manufacturer has confirmed that Aspiro Pharma Limited do not foresee any out-of-stock situations in the manufacturing and distribution of the commercial drug products.

l) Additional documents submitted:

From the information provided by the manufacturer, Aspiro Pharma Limited have 2 manufacturing lines: Line-1 and line -2. It was confirmed that Line-2 is covered in the inspection conducted by the USFDA (October 2019) whereas Line-1 and 2 were covered in the inspection of EU- Dutch (February 2020). Remdesivir for injection is manufacturing on both Lines (Line-1 and Line-2).

The manufacturer has confirmed that Aspiro Pharma Limited do not have any notifications of upcoming inspections by competent national regulatory authorities in the next 6 months.

Part 5	Conclusion – Desk assessment outcome

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The ***Aspiro Pharma Limited, Survey No. 321, Biotech Park, Phase III, Karkapatla village, Markook Mandal, Siddipet, Telangana, 502281, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This WHOPIR will remain valid for **1 year**, provided that the outcome of any inspection conducted during this period is positive.

Part 6	List of guidelines referenced in this inspection report

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

2. 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. ***Short name: WHO GMP for APIs*** or ***WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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

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

5. 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

7. 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.
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

8. 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.
Short name: WHO GPPQCL guidelines **or** ***WHO TRS No. 957), Annex 1***
http://www.who.int/medicines/publications/44threport/en/

9. 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.
Short name: WHO TRS No. 957, Annex 2
http://www.who.int/medicines/publications/44threport/en/

10. 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.
Short name: WHO TRS No. 961, Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. 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.
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

13. 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. ***Short name: WHO TRS No. 943, Annex 3***
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

14. 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.
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

15. 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.
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. 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. ***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

17. 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. ***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

18. 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.
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. 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.
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. 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. ***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. 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 GDRMP guidelines or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

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

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf