World Health Organization

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

Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
WHOPIR
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Hetero Labs Limited (Unit 1)
Corporate address of manufacturer	Hetero Labs Limited Hetero Corporate, 7-2-A2 Industrial Estates Sanath Nagar, Hyderabad 500 018 Telangana, India
Inspected site	
Name & address of manufacturing site	Hetero Labs Limited (Unit 1) Survey No 10, I.D.A, Gaddapotharam Village, Jinnaram Mandal, Sangareddy Dist 502319 Telanagana, India
Synthetic Unit/Block/ Workshop	Unit 1
Desk assessment details	
Date of review	19 October 2022
APIs covered by this desk assessment	See full list of APIs under section c) below
List of documents submitted	The following documents were requested: a) A list of all regulatory inspections performed in the last 5 years and their outcomes, including "non-compliant" inspections; b) Current full inspection report(s), including deficiency letters, for inspections performed by a competent stringent regulatory authority in the past three years with a certified translated copy where this is not in English; c) Proof of CAPA implementation and final decision by the competent stringent regulatory authority related to observations or deficiencies noted in the latest inspection report or to any warning letter or equivalent regulatory action (production-line specific); d) A copy of the manufacturing authorization and GMP certificate granted by the local national authority together with a certified translation, where this is not in English; e) A site master file whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format;

	f) The list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN), including all types of chemicals and products (e.g., pesticides, herbal medicines, chemicals or veterinary products, etc.); g) The most recent product quality review(s) (PQR)(s) of the concerned product(s); PQR(s) or equivalent documentation covering all required subsections and trend results, including statistical evaluation; h) The completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s); i) The list of any recalls in the past three years related to any product manufactured on site with quality defects; j) A 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; k) Master batch manufacturing and packaging record(s) of the WHO product(s) of interest; l) 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; m) Description of any recent or foreseen out-of-stock situations; n) A list of notifications of upcoming inspections by competent national regulatory authorities in the next 6 months.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USA FDA	Dates of inspection:	2 to 12 August 2021
	Type of inspection:	GMP for APIs
	Block/Unit/Workshop:	Unit 1
	APIs covered:	Various sartans
	Note	The company submitted several rounds of corrective actions to USA FDA. The bulk of the CAPAs are related to “Sartans” and impurities including control of the process and validation of analytical procedures. The observations made by USFDA were more specifically relating to specific products that have not been submitted for WHO Prequalification and related impurities.
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	October 2019 (Desk review) – GMP compliant 20-24 February 2017 (Onsite) – GMP compliant	
Brief summary of	Production and control of APIs	

manufacturing activities	
General information about the company and manufacturing site	According to the last WHO on-site inspection report, the site is located in Survey No.10, IDA, Gaddapotharam village, Jinnaram Mandal, Sangareddy district-502319, Telangana, India. There were 13 Production blocks (A, B, C, D, E, F, G, H, I, J, K, L, M) for pharma related production: Blocks E, G and M were for intermediates production. Blocks F, I, K and L were for oncology APIs. Penicillin, beta lactam antibiotics and hormonal APIs were not produced on this site.
Focus of the last WHO inspection	October 2019 Desk review, based on inspection reports for USA FDA, Health Canada, OGYEI Hungary, PMDA Japan. February 2017 Onsite inspection:
Areas inspected	Blocks A, B, C, D and H and ancillary areas were covered during the 2017 WHO Onsite inspection.
Out of scope and restrictions (last WHO inspection)	Manufacturing blocks that were not used for WHO APIs were not inspected.
WHO APIs covered by the last WHO inspection	Lopinavir Stavudine Tenofovir disoproxil fumarate Emtracitabine Lamivudine Abacavir sulfate Zidovudine Efavirenz Atazanavir monosulphate Abacavir sulfate Sofosbuvir Dolutegravir sodium Daclatasvir dihydrochloride Darunavir
Additional products to be covered by this desk assessment:	See section c
Abbreviations	**Meaning**
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:

A copy of the manufacturing authorization issued by the local authority, was submitted.

b) Site master file (SMF):

A SMF (effective 22 July 2022) was submitted and was found acceptable.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
The site listed 121 APIs being manufactured on site by chemical synthesis, from many different classes. There are no penicillins or beta-lactam antibiotics or steroidal hormones manufactured on site.
The list of APIs for the WHO is the following:
-Sofosbuvir
-Lopinavir
-Tenofovir Disoproxil fumarate
-Emtricitabine,
-Abacavir (sulfate)
-Dolutegravir (sodium)
- Daclatasvir (dihydrochloride)
- Darunavir (ethanolate)
-Dolutegravir (sodium)
-Velpatasvir
-Nevirapine *Anhydrous*,
-Efavirenz

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

AIFA, Italy. 28 January 2019 to 2 February 2019. Acceptable
AEMPS, Spain. 28 January 2019 to 2 February 2019. Acceptable
OGYEI, Hungary. 18 March 2019 to 22 March 2019. Acceptable
WHO. PQT, Geneva. 2 September 2019 to 1 October 2019. Acceptable
NDA, Uganda. 12 September 2019 to 13 September 2019. Acceptable
CDSCO, India. 17 September 2019 to 19 September 2019. Acceptable
CDSCO, India. 4 November 2019 to 6 November 2019. Acceptable
DCA, India. 4 November 2019 to 6 November 2019. Acceptable
CDSCO, India. 23 June 2021 to 25 June 2021. Acceptable
DCA, India. 23 June 2021 to 25 June 2021. Acceptable
FDA, USA. 2 August 2021 to 12 August 2021. OAI
DCA, India. 17 August 2022 to 18 August 2022. Await report
CDSCO, India. 17 August 2022 to 18 August 2022. Await report
PMDA, Japan. 23 August 2022 to 25 August 2022. Await report

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

The company submitted several product quality review reports for the period of January to December 2021. A few were randomly selected for review.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
The company submitted batch manufacturing records (and certificates for analysis) for several products. A few were randomly selected for review. See comments below.

Daclatasvir dihydrochloride
Dolutegravir sodium
Abacavir sodium
Lopinavir
Emtracitabine
Sofosbuvir
Darunavir ethanolate
Abacavir sulfate

Batch production records were generally found acceptable.

Copies of analytical reports for various products, (as above) were submitted. Spot checks were done. The reports were generally found acceptable and no significant observations were made.

Declaration:
The company provided a declaration stating that the following products had not been manufactured during the previous 3 years:
Velpatasvir
Tenofovir disoproxil fumarate
Lamivudine
Efavirenz

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

The following master records were submitted. These were spot checked and found acceptable in general.
Daclatasvir dihydrochloride
Dolutegravir sodium
Abacavir sulfate
Lopinavir
Emtricitabine
Sofosbuvir
Darunavir ethanolate
Abacavir sulfate
Velpatasvir
Tenofivir disoproxil fumarate
Lamivudine
Efavirenz
Nevirapine

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

Losartan Potassium. 99 Batches were recalled on 30 October 2021 due to the presence of Azido impurity. The recall is completed.

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

The company provided a declaration that a self-inspection is conducted every six months.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):

The company provided a declaration stating that there no warning letter (or equivalent had been issued to the company.

k) Out-of-stock situations:

The company issued a declaration that no out of stock situation had been experienced, or was foreseen.

l) Additional documents submitted:

The following inspections were anticipated:
ANVISA, Brazil. September 2022
COFEPRIS, Mexico. October 2022
Health Canada, Canada. October 2022

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 site ***Hetero Labs Limited Unit 1***, located at ***Survey No 10, I.D.A, Gaddapotharam, Jinnaram Mandal, Sangareddy Dist. 502319, Telanagana, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIR will remain valid for 3 years, 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 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 ***TRS No. 957, Annex 2***
   untitled (digicollections.net)

2. 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 WHO TRS No. 986, Annex 2***
   https://digicollections.net/medicinedocs/documents/s21467en/s21467en.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://digicollections.net/medicinedocs/documents/s23457en/s23457en.pdf

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
Short name: WHO TRS No. 1033, Annex 3
9789240020900-eng.pdf (who.int)

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
https://digicollections.net/medicinedocs/documents/s21440en/s21440en.pdf

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 TRS No. 1010, Annex 8**
https://digicollections.net/medicinedocs/documents/s23455en/s23455en.pdf

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
https://digicollections.net/medicinedocs/documents/s20108en/s20108en.pdf

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 TRS No. 961, 957), Annex 1
https://digicollections.net/medicinedocs/documents/s18681en/s18681en.pdf

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 3.
Short name: WHO TRS No. 957, Annex 3
https://digicollections.net/medicinedocs/documents/s22358en/s22358en.pdf

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
https://digicollections.net/medicinedocs/documents/s19959en/s19959en.pdf

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***
https://digicollections.net/medicinedocs/documents/s18677en/s18677en.pdf

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***
https://digicollections.net/medicinedocs/documents/s18683en/s18683en.pdf

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***
https://digicollections.net/medicinedocs/#d/s21438en

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
https://digicollections.net/medicinedocs/documents/s18682en/s18682en.pdf

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
https://digicollections.net/medicinedocs/#d/s20177en/

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
https://digicollections.net/medicinedocs/#d/s20175en/

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. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***
https://digicollections.net/medicinedocs/documents/s23697en/s23697en.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***
Essential Medicines and Health Products Information Portal (digicollections.net)

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***
9789240020900-eng.pdf (who.int)

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. 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

24. 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

25. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditionning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://digicollections.net/medicinedocs/documents/s23699en/s23699en.pdf

26. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
9789240020900-eng.pdf (who.int)

27. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**
9789240001824-eng.pdf (who.int)