World Health Organization

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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 Ltd. Unit 3
Corporate address of manufacturer	Hetero Corporate 7-2-A2 Industrial Estates Sanath Nagar, Telangana Hyderabad, 500 018 India
Inspected site	
Name & address of manufacturing site	Hetero Labs Ltd. Unit 3, Survey No.120, 128, 150 (PART), 150/1, 151/2 &158/1, N. Narasapuram, Nakkapally (M), Visakhapatnam, Andhra Pradesh, 531 081, India
Synthetic Unit/Block/Workshop	Production blocks E, I, P, J Intermediate Drying section - I
Desk assessment details	
Date of review	5 October 2022
APIs covered by this desk assessment	1. Lamivudine API intermediate used in Dolutegravir (sodium)/Lamivudine/Tenofovir Disoproxil fumarate tablet, film-coated 50mg/300 mg/300 mg 2. Emtricitabine intermediate 3. Dolutegravir intermediate
List of documents submitted	a. A list of all regulatory inspections performed in the last 5 years and their outcomes; b. The full inspection reports, 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 including APIs manufactured on-site; g. The most recent product quality review (PQR) of the concerned API covering all required subsections and trend results, including statistical evaluation; h. The completed batch manufacturing and packaging records, including the analytical part, for the most recently validated/ released batch of relevant product; 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 has been performed and all matters dealt with; k. Master batch manufacturing and packaging records of the WHO product 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.	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USA FDA	Dates of inspection:	19 to 23 November 2018
	Type of inspection:	Pre-approval for intermediate
	Block/Unit/Workshop:	Not mentioned
	APIs covered:	Imatinib Mesylate API intermediate by chemical synthesis
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	18 October 2017 Compliant with GMP for APIs	
Brief summary of manufacturing activities	Unit III had several production blocks for the production of intermediates. Block E was dedicated to Lamivudine anhydrous. Activities in various blocks included hydrogenation, and other steps and stages in the production, drying and control of intermediates and APIs	

General information about the company and manufacturing site	Production, packaging, labelling and control of intermediates and APIs. The company Hetero Drugs Ltd has several manufacturing sites. Unit III was established in 2008 and produces and controls key starting materials, intermediates and APIs. A full description was provided in the 80 page (plus annexes) Site Master File dated effective September 2022.
Focus of the last WHO inspection	Pharmaceutical Quality system Documentation system Production system Facilities and equipment system Laboratory control system
Areas inspected	Generally, all areas of WHO GMP were covered during the inspection. This included, but was not limited to quality system, reprocessing, reworking, complaints, premises, equipment, materials, production system, computerized systems and others. The report was available and the WHOPIR was already archived.
Out of scope and restrictions (last WHO inspection)	N/A
WHO APIs covered by the last WHO inspection	Sofosbuvir API intermediate Lamivudine API intermediate Atazanavir API intermediate
Additional products to be covered by this desk assessment:	General GMP for APIs, see also above Emtricitabine API intermediate Dolutegravir API intermediate
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 license and GMP certificate were provided.

b) Site master file (SMF):

A detailed, 80 page SMF, with annexes (meeting the guideline for SMFs) were submitted. The document was dated September 2022 and found acceptable.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:

A list consisting of 8 pages, was provided – listing the chemical intermediates / substances produced on site.

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

Drug Control Administration (DCA), Andhra Pradesh, India. June 2022

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

Product quality review reports were submitted for Dolutegravir, Lamivudine and Emtracitabine intermediates. (Note: No batches of Emtracitabine were manufactured during the period January to December 2021). The PQR reports were acceptable and represented the required sections for review including complaints, trending of data, hold time, recalls etc. In general, results were tabulated and graphically presented including control limits or calculation of process capability index.

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

Batch records and parts of an analytical report were submitted for Dolutegravir and Lamivudine intermediate. These were generally acceptable and no comments were made.

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

Declared that the company has ceased manufacturing Emtracitabine intermediate.
Parts of the master documents were submitted for dolutegravir (process I), lamivudine and (dolutegravir process II)

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

The company declared that there were no recalls in the last 3 years

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 declared that a self-inspection programme was followed.

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 declared that no warning letter (or similar) had been received to date.

k) Out-of-stock situations:

The company had no recent out-of-stock product and did not foresee any out-of-stock situation in the near future.

l) Additional documents submitted:

N/A

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 Ltd., Unit 3,*** located at ***Survey No.120, 128, 150 (PART), 150/1, 151/2 &158/1, N. Narasapuram, Nakkapally (M), Visakhapatnam, Andhra Pradesh, 531 081, 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 o***r ***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)