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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	Micro Labs Limited (Bommasandra)
Corporate address of manufacturer	Micro Labs Limited 31 Race Course Road, Bengaluru – 560 001 India
Inspected site	
Name & address of manufacturing site	Micro Labs Limited Plot No: 43-45, K.I.A.D.B Jigani – Bommasandra Link Road Anekal Taluk Bengaluru – 560 105 Karnataka, India
Desk assessment details	
Date of review	19-22 July 2021
APIs covered by this desk assessment	• WHOAPI 329 Dolutegravir sodium • WHOAPI 273 Ethambutol hydrochloride
List of documents submitted	1. A copy of the manufacturing authorization 2. The most recent version of the SMF, including legible printouts of the water system and HVAC system (i.e. clean areas for processing APIs), pipeline and instrumentation drawings 3. A list of all the APIs (medicinal or other) manufactured on site. Buildings for the manufacture of WHO PQ APIs and if there are any shared facilities and equipment for these APIs 4. Copies of inspection reports by a stringent regulatory authority 5. CAPAs and proof of CAPAs implementation related to the above-mentioned inspection reports 6. A copy of the procedure on batch codification 7. A list of solvents being recovered, the relevant procedure and controls on recovered solvents. 8. A copy of any warning letter or equivalent regulatory action issued by any authority to which the site provides or has applied to provide a product. 9. The most recent PQRs of WHO PQ APIs. PQRs or equivalent documentation covering all required subsections and trend results 10. A confirmation by the senior QA representative that a full self-inspection or external audit dedicated to prequalified APIs has been performed and all

	matters dealt with 11. A list of any recalls carried out in the last 3 years 12. Master batch manufacturing records of WHO PQ APIs as well as one completed BMR corresponding the latest production of each of the above-mentioned APIs.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
USFDA, USA	Dates of inspection:	11-16.02.2019
	Type of inspection:	Surveillance inspection
	Block/Unit/Workshop:	N/A
	Type of APIs covered:	Celecoxib, Olmesartan
USFDA, USA	Dates of inspection:	27-28.11.2018
	Type of inspection:	Pre-approval laboratory operations for Irbesartan
	Block/Unit/Workshop:	QC laboratory, Production Block B
	Type of APIs covered:	Irbesartan
USFDA, USA	Dates of inspection:	27.02-02.03.2017
	Type of inspection:	Post-approval
	Block/Unit/Workshop:	ML15
	Type of APIs covered:	Losartan, Celecoxib, Dorzolamide, Irbesartan, Bepostatine, Telmisartan, Olmesartan, Rasagiline, Bromfenac, Ticagrelor, Nitropruside, Darunavir, Isoproteranol, Dabigatran, Mirabegron, Levomilnacipran, Tofacitinib, Apixaban, Dolutegravir (none of these APIs were manufactured and exported to USA since 2015)
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The site was last inspected by WHO PQT during 8-10 December 2015 and it was found to be in compliance with GMP. In addition, a desk assessment was conducted in April 2018 based on the USFDA inspection carried out in March 2017 and it included review of batch records and other quality system documentation. Based on the desk assessment the site was deemed compliant with WHO GMP.	
Brief description of	Manufacturing, packaging, quality control of APIs No toxic or hazardous substances including beta lactams, cytotoxic or	

manufacturing activities	contraceptive hormones are manufactured on site
General information about the company and manufacturing site	The manufacturing site in Bommasandra industrial area was established in 2007 and it is located approximately 25Km from Bangalore. The site is engaging in the manufacture, quality control and packaging of APIs and their intermediates. At the time the site was inspected in 2015, it consisted of four manufacturing blocks, a hydrogenation block and a solvent recovery plant and 46 APIs were included in the list of approved APIs manufactured on-site. According the most recent SMF there are six manufacturing blocks and 82 approved APIs.
Focus of the last WHO inspection	The inspection focused on the production and control of Lumefantrine, Artemether and Ethambutol Dihydrochloride. The inspection covered all GMP systems for APIs including but not limited to premises, equipment, documentation, materials, validation, sanitation and hygiene, quality control and utilities.
Areas inspected	Quality management, personnel, buildings and facilities, process equipment, documentation and records, materials management, production and in-process controls, packaging and labelling, storage and distribution, laboratory controls, validation, change control, rejection, returns, recalls, complaints, contract manufacture.
WHO APIs covered by the last WHO inspection	• APIMF217 Lumefantrine, • API259 Artemether • APIMF273 Ethambutol Dihydrochloride.
Additional products covered by this desk assessment:	• WHOAPI 329 Dolutegravir sodium

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:
Valid manufacturing license and GMP certificate were provided in support of the on-site manufacturing activities

b) Site master file (SMF):
The most recent version of the SMF was provided. Review of the SMF did not give rise to any observations

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
A list of 82 APIs was provided along with the license to manufacture for domestic market and export.

d) List of all regulatory inspections performed in the last 5 years and their outcomes:

Regulatory Authority	Inspection date	Inspection scope	Outcome
USFDA, USA	11-15.05.2015	APIs registered with USFDA	Satisfactory
WHO, Geneva	08-10.12.2015	Follow up	Satisfactory
USFDA, USA	27.02-02.03.2017	Post-approval	Satisfactory
MFDS, Korea	14-16.11.2018	Pre-approval	Satisfactory
USFDA, USA	27-28.11.2018	Pre-approval laboratory	Satisfactory
USFDA, USA	11-16.02.2019	GMP surveillance	Satisfactory

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
The company provided annual PQRs for Dolutegravir Sodium for the period 2017-2020. The 2020 PQR was reviewed in detail. No batches were rejected, recalled or returned during the review period. No complaints were received for any batches in 2020. Critical process parameters for each stage of manufacturing as well as in process controls were found to be within the acceptable limits. Yields for each stage of production met product specifications. Review of facilities, equipment and utilities indicated that they were qualified and where appropriate calibrated.

The annual PQRs for Ethambutol Hydrochloride for the period 2017-2020 were provided. No batches were manufactured in 2020. The most recent PQR indicates that supplier agreement was in place and reviewed. Documentation in relation to manufacturing and quality control were reviewed, and no changes were applied. No recalls or complaints were registered. No changes to documentation took place. Review of facilities, equipment and utilities indicated that they were qualified and where appropriate calibrated.

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

The BMRs of Dolutegravir Sodium for each manufacturing stage were provided and did not give rise to any observations.

No batches of Ethambutol Hydrochloride were manufactured in 2019 or 2020. The most recent batch record dates back to 2018. This BMR was reviewed and did not give rise to any observations.

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

Master BMRs and BPRs for Dolutegravir Sodium and Ethambutol Hydrochloride were provided and did not give rise to any observations.

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

The company provided a written declaration that no PQ API batches have been recalled in the last three 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 provided a declaration stating that both internal and external audits (Corporate QA) have been conducted according to the company's system.

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):

No warning letter or equivalent regulatory action has been taken against the site and APIs manufactured on-site

k) Out-of-stock situations:

No out of stock situation has taken place or is foreseen for the near future

l) Additional documents submitted:

The company provided the following additional documentation which was reviewed:

1. SOP Batch numbering system.
2. Confirmation that no recovered solvents are used in the manufacture of Dolutegravir Sodium
3. Confirmation that no recovered solvents are used in the manufacture of Ethambutol Hydrochloride.
4. HVAC and Water distribution layouts

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 ***Micro Labs Limited*** located at ***Plot No: 43-45, K.I.A.D.B Jigani – Bommasandra Link Road, Anekal Taluk, Bengaluru – 560 105, Karnataka, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This compliance status shall be valid until **July 2022** or when another inspection is conducted by WHO or by a stringent regulatory authority.

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 WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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 TRS 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-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/

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

5. 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**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 961, 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 3.
   Short name: WHO TRS No. 957, Annex 3
   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.
   Short name: WHO TRS 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.
    Short name: WHO TRS 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. ***Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***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

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. ***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

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. ***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

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production 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

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 guidance 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 Multisource guidance or 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

24. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

25. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

26. 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
https://www.who.int/publications-detail/978-92-4-000182-4

27. 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