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	Divi's Laboratories Limited
Corporate address of manufacturer	Divi's Laboratories Limited, 1-72/23 (P)/ Divis/303 Divi Towers Cyber Hills, Gachibowli Hyderabad, 500 032 Telangana India
Inspected site	
Name & address of manufacturing site	Divi's Laboratories Limited, Unit 1 Lingojigudem village, Choutuppal Mandal, Yadadri Bhuvanagiri District, Telangana, 508 252 India
Synthetic Unit/Block/Workshop	Unit 1
Desk assessment details	
Date of review	26 July 2022
APIs covered by this desk assessment	APIMF451, WHOAPI-451 Molnupiravir. Also used in CV009 finished product.
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 API and FPPs manufactured on-site. The list should include proprietary names and International Non Proprietary 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 (PQR) of the concerned Molnupiravir API covering all required subsections and trend results, including statistical evaluation; h. The completed process validation protocol and report, 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; o. Table to specify which parts of the manufacturing process for the concerned API were covered by the inspection of the competent SRA authorities performed in the last 3 years	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USA FDA	Dates of inspection:	11 to 15 November 2019
	Type of inspection:	Routine
	Block/Unit/Workshop:	Unit 1
	APIs covered:	Dextromethorphan Base and HBr Diltiazem HCl Fosphenytoin sodium Iopamidol Levetiracetam Nabumetone Niacin Naproxen Naproxen Sodium

		Proguanil HCl Quetiapine Fumarate Telmisartan Tamsulosin HCl Valacyclovir HCl Zolpidem tartrate
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Not inspected previously	
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:
The manufacturing license is valid until 31/12/2027.
The GMP certificate granted by local authority is valid until 18/12/2024.

b) Site master file (SMF):
Submitted. Generally acceptable.

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

Divi's Laboratories Limited, Unit-1
Lingojigudem
Annexure-5
List of API's manufactured at Unit-1 with INNs

S. No.	Name of the API	In-house code	INN Names
1.	Alexidine Dihydrochloride	Laura	Alexidine dihydrochloride
2.	Atovaquone	Sheldon	Atovaquone
3.	Carvedilol	Corsa	Carvedilol
4.	Dextromethorphan hydrobromide	Sigma	Dextromethorphan Hydrobromide
5.	Dextromethorphan base	Sigma base	Dextromethorphan
6.	Diltiazem hydrochloride	Aztec	Diltiazem hydrochloride
7.	Hydroxychloroquine sulfate	Surya	Hydroxychloroquine
8.	Iopamidol	Welcome	Iopamidol
9.	Iopromide	Lumina	Iopromide
10.	Levetiracetam	Oscar	Levetiracetam
11.	Levetiracetam process-B	Oscar-U	Levetiracetam
12.	Phenprocoumon	Pfizer	Phenprocoumon
13.	Molnupiravir	Venkatesha	Molnupiravir
14.	Nabumetone	Hovione	Nabumetone
15.	Naproxen	Merck	Naproxen
16.	Naproxen sodium	SN	Naproxen Sodium
17.	Niacin	Rover	Nicotinic acid
18.	Proguanil hydrochloride	Intel	Proguanil Hydrochloride
19.	Quetiapine fumarate	Excel	Quetiapine fumarate
20.	Tamsulosin hydrochloride	Anchor	Tamsulosin hydrochloride
21.	Telmisartan	Premier	Telmisartan
22.	Valacyclovir hydrochloride	Voltas	Valaciclovir
23.	Valacyclovir hydrochloride (Hydrous form)	Voltas hydrate	Valaciclovir

Divi's Laboratories Limited, Unit-1
Lingojigudem
Annexure-5
List of Intermediates manufactured at Unit-1

S. No.	Name of the Intermediate	In-house code	INN Names
1.	A-Wing	Johnson	None
2.	B- Wing	Recordati	None
3.	Sulphazine	Nexen	None
4.	R-Amine (R)-(-)-5-(2-aminopropyl)-2-methoxy benzene sulphonamide	Eagle	None
5.	Free Amine Pivalate Ester	Hyline-VII	None
6.	Cytosine Menthyl Ester	Apollo	None
7.	EF-9	Altima	None
8.	D-11	Acura	None
9.	PMB-pyrrolidine chloro benzamide	Fluence	None

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

Authority	Inspection type	Date	Outcome
EMA inspection (MHRA and JAZMP Slovenia	Onsite GMP inspection	13-16 December 2016	Approved
USFDA	Onsite GMP inspection	14-16 May 2018	Approved
USFDA	Onsite GMP inspection	11-15 November 2019	Approved
USFDA	Request for GMP records	February-April 2021	No comments received from USFDA
Drug Control Administration & CDSCO India	Onsite GMP inspection	30 April, 1-2 May 2019	Approved
Drug Control Administration & CDSCO India	Onsite GMP inspection	25-26 October 2021	Approved

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
The PQR was planned between July and September 2022 and therefore was not submitted.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
Annexure 6 submitted contains the records for the "Process Performance Qualification" (as referred to by the company) with three batches included for the validation. This process validation was done with three batches, and records reflected the different stages in API manufacturing. The protocols and reports were authorized. No deviations were recorded during validation, samples were placed on stability. According to the company, the validation is valid for one year. Analytical reports were not included in Annexure 6.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
The Master Batch Production Record for "Venkatesha" was submitted in Annexure 8. Different stages had different product numbers such as, PD/VNK/RPF/03/I (Stage I), effective 01/09/2021 and stage V, PD/VNK/RPF/03/Vc, effective 13/07/2021. Sieving and packaging master was effective from 14/01/2022.

h) Recalls in the past three years related to APIs with quality defects:
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:
Declaration was submitted, that self-inspections are conducted every 6 months. There was however no statement that the matters had been dealt with.

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):
None were issued to date.

k) Out-of-stock situations:
No out-of-stock situation is foreseen by the company.

l) Additional documents submitted:
N/A

Part 5	Conclusion – Desk assessment outcome

Based on the GMP evidence received and reviewed, it is considered that a desk assessment may be performed in lieu of a WHO Inspection. The site ***Divi's Laboratories Limited (Unit 1)*** located at, ***Lingojigudem Village, Choutuppal Mandal, Yadadri Bhuvanagiri District, Telangana, India*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

The WHOPIR will remain valid for three 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)