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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Solara Active Pharma Sciences Limited
Corporate address of manufacturer	3rd & 4th Floor Batra Centre No 28, Sardar Patel Road, Guindy, Chennai – 600032, Tamil Nadu, India Tel : 00914443446700, 00914422207500 Fax: 00914422350278 info@solara.co.in
Inspected site	
Name & address of manufacturing site	Solara Active Pharma Sciences Limited 120A & B, 36, 120P & 121 Industrial Area, Baikampady, New Mangalore - 575011, Karnataka, India N 12.95182° E 74.82561° D-U-N-S: 676159823
Synthetic Unit/Block/ Workshop	Plant-1 for intermediate manufacturing Plant-2 & Plant-3 for API manufacturing
Manufacturing license number	Form 25 KTK/25/500/2005 (VIDE ref. No DCD/MFG/SR-156/18-19, valid till March 30, 2023
Desk assessment details	
Start and end dates of review	24 January – 29 January 2021
APIs covered by this desk assessment	**Active Pharmaceutical Ingredient** Sofosbuvir Artemether Oseltamivir monophosphate Artesunate (non-micronised) Artesunate (micronised) Lumefantrine Zidovudine Praziquantel

List of documents submitted	1. FDA US EIR, dates of inspection 17 – 21 February 2020 2. WHO inspection report, dates of inspection February 12 - 15, 2018 3. MFDS, Korea GMP certificate 4. US FDA EIR Form 483 and its complete responses submitted with FDA; dates of inspection July 23-27, 2018 5. List of APIs manufactured on site 6. List of regulatory inspection 7. Copy of manufacturing authorization (Manufacturing license) issued by Drugs Control Department Form 25 KTK/25/500/2005 (VIDE ref. No DCD/MFG/SR-156/18-19, valid till March30, 2023 8. Copy of GMP certificate issued by Drugs Control Department No DCD/SPL1/CR-660-2020-21, GSC No: DD011S200000031 valid till September 23, 2021 9. SMF, annexes and drawings 10. PQRs for the following products covering the period between January 2019 – December 2019: i. Sofosbuvir ii. Artemether iii. Artesunate (Micronized) iv. Artesunate (Non-micronized) v. Lumefantrine vi. Praziquantel 11. BMRs and analytical raw data: i. Artemether ii. Artesunate (Non-micronized) iii. Artesunate (Micronized) iv. Praziquantel 12. Information about recovered solvents 13. Master BMRs and BPRs: i. Sofosbuvir ii. Artemether iii. Oseltamivir monophosphate iv. Artesunate (Non-Micronized) v. Artesunate (Micronized) vi. Praziquantel vii. Lumefantrine viii. Zidovudine 14. Declaration: recalls 15. Declaration: self-inspection 16. Declaration: sartans 17. Declaration: recovered solvents 18. Declaration on Nitrosamines 19. Declaration: warning letters 20. Declaration: out-of-stock 21. Declaration: upcoming inspections 22. Information: table to specify which parts of the manufacturing process for the concerned products were covered by the inspection of the competent SRA authorities performed in the last 3 years
Any documents missing?	None

Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
US FDA, USA	Dates of inspection:	17 – 21 February 2020
	Type of inspection:	Compliance Program Active Pharmaceutical Ingredient (API) Process Inspection
	Block/Unit/Workshop:	Plant -1, Plant - 2 and Plant - 3
	APIs covered:	1. Albendazole 2. Artesunate 3. Colchicine 4. Hydralazine Hydrochloride USP 5. Methoxsalen USP 6. Oseltamivir Phosphate USP 7. Praziquantel 8. Succinyl Choline Chloride USP
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Last WHO PQT on-site inspection was carried out 12 -15 February 2018. At the time of the inspection the name of the site was "Sequent Scientific Ltd". <u>Initial conclusion of the inspection:</u> Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report a decision on the compliance of Sequent Scientific Ltd, located at120 A&B, 36, 120P & 121, Industrial Area, Baikampady, New Mangalore -575011, Karnataka, India with WHO good manufacturing practices for active pharmaceutical ingredients will be made after the manufacturer's response to the observations has been assessed. The manufacturer is expected to respond to all deficiencies and for each include a description of the corrective action implemented or planned to be implemented, and the date of completion or target date for completion. In addition, for deficiencies classified as "major", supporting documentation should be submitted with the response as objective evidence of completion of corrective actions. The acceptability of corrective actions will be assessed through evaluation of the response to each observation and will be followed up during the next inspection. CAPAs were evaluated by inspectors and the inspection was closed 1 May 2018 <u>Final conclusion:</u> The actions taken, or proposed to be taken, to correct the deficiencies have been reviewed by the Prequalification Inspection Group. In general, they are considered acceptable and their satisfactory implementation will be verified during future inspections. The Prequalification Inspection Group has recommended that the manufacturing of the APIs: • Artemether– manufactured at Plant-2 & 3 • Oseltamivir monophosphate – manufactured at Plant-2 & 3 • Artesunate non micronized – manufactured at Plant- 3 • Artesunate micronized - manufactured at Plant- 3 • Lumefantrine - manufactured at Plant- 3	

	• Zidovudine – manufactured at Plant 2 • Praziquantel - manufactured at Plant- 3 • Sofosbuvir – manufactured at Plant-2 & 3 • Ledipasvir– manufactured at Plant-2 & 3 can be considered to be compliant with the standards of Good Manufacturing Practices (GMP) for APIs published by the World Health Organization (WHO), for the scope of activities listed below: • Manufacture and packaging of intermediates and active pharmaceutical ingredients
Brief summary of manufacturing activities as of February 2018	Manufacturing, packaging, labelling, testing and storage of intermediates and active pharmaceutical ingredients
General information about the company and manufacturing site as of February 2018	Sequent Scientific Limited was incorporated in 1995 and is engaged in the development and manufacture of API and intermediates used in finished pharmaceutical products. Sequent have facilities at Mangalore and Mysore in Karnataka, at Tarapur and Mahad in Maharashtra and at Vizag in Andhra Pradesh, India. The Mangalore facility is ISO: 14001 certified and has 3 production blocks: • Plant-1 used for manufacturing of intermediates • Plant-2 and Plant-3 used for the manufacture of APIs.
Focus of the last WHO inspection	Artemether– manufactured at Plant-2 & 3 Oseltamivir monophosphate – manufactured at Plant-2 & 3 Artesunate non micronized – manufactured at Plant- 3 Artesunate micronized - manufactured at Plant- 3 Lumefantrine - manufactured at Plant- 3 Zidovudine – manufactured at Plant 2 Praziquantel - manufactured at Plant- 3 Sofosbuvir – manufactured at Plant-2 & 3 Ledipasvir– manufactured at Plant-2 & 3
Areas inspected	Pharmaceutical Quality System Documentation system Production System Facilities and Equipment System Laboratory Control System Packaging and labelling system
Out of scope and restrictions (last WHO inspection)	APIs out of scope of PQ
WHO APIs covered by the last WHO inspection	Artemether– manufactured at Plant-2 & 3 Oseltamivir monophosphate – manufactured at Plant-2 & 3 Artesunate non micronized – manufactured at Plant- 3 Artesunate micronized - manufactured at Plant- 3 Lumefantrine - manufactured at Plant- 3 Zidovudine – manufactured at Plant 2 Praziquantel - manufactured at Plant- 3

	Sofosbuvir – manufactured at Plant-2 & 3 Ledipasvir– manufactured at Plant-2 & 3
Additional products to be covered by this desk assessment:	None

Abbreviations	**Meaning**
APQR	Annual product quality review
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
EIR	Establishment inspection report
GMP	Good manufacturing practices
PW	Purified water
SOP	Standard operating procedure

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

a) Manufacturing authorization and GMP certificate granted by the local authority:
Licence: Form 25 KTK/25/500/2005 (VIDE ref. No DCD/MFG/SR-156/18-19, valid till March30, 2023
GMP certificate: No DCD/SPL1/CR-660-2020-21, GSC No: DD011S200000031 valid till September 23, 2021

b) Site master file (SMF):
SMF submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
In total 48 APIs are manufactured on-site within the following Therapeutic categories:

1. Antipsoriatics
2. Anthelmintic
3. Antimalarial
4. Phosphorus supplementation
5. Psychostimulants
6. Antihyperparathyroid
7. Antiretroviral
8. Aesthetic
9. Anti-inflammatory
10. Antihypertensive
11. Antiviral
12. Selenium Supplement
13. Chemo Adjuvant
14. NSAID
15. Anti-psoriasis
16. Antifungal
17. Muscle relaxant
18. Anaesthesia

19. Hyperammonaemia
20. Hepatitis B
21. Anticoagulant
22. Hepatitis C
23. Antiprotozoal
24. Cardiovascular Agent
25. Amyotrophic Lateral Sclerosis (ALS)
26. Anti-gout
27. Anxiolytic
28. Nutritional supplements
29. Food Supplement

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

S. No	Name of regulatory Authorities (National)	Inspection dates	Inspected Substance
1.	Drug control department for the state of Karnataka, India	August 2018	GMP Inspection and Marketing Authorisation (Manufacturing licence)
		August 2020	GMP Inspection
2.	Central Drug Standard Control Organization, India	August 2018	GMP Inspection and Marketing Authorisation (Manufacturing licence)
		January 2019	GMP Inspection
		August 2020	GMP Inspection

S. No.	Name of regulatory Authorities (International)	Inspection dates	Inspected Substance
1.	USFDA, USA	23rd to 27th July 2018	Hydralazine Hydrochloride, Oseltamivir Phosphate, Praziquantel, Albendazole, Mesna, Colchicine
		17th to 21st February 2020	Albendazole, Artesunate, Colchicine, Hydralazine Hydrochloride USP, Methoxsalen USP, Oseltamivir Phosphate USP Praziquantel, Succinyl choline chloride USP

2.	EDQM	06th to 08 September 2017	Succinyl choline chloride. (Suxamethonium chloride)
3.	AEMPS, Spain	06th to 08th September 2017	Succinyl choline chloride. (Suxamethonium chloride)
4.	KFDA, Korea	16th to 18 July 2018	Oseltamivir Phosphate

e) Most recent product quality reviews (PQR)s of the concerned WHO APIs:
Reviewed: PQRs contained required information and CAPAs.
1. Praziquantel
2. Artemether
3. Artesunate

Checked:
1. Lumefantrine
2. Sofosbuvir

Note: the company declared that Oseltamivir phosphate and Zidovudine APIs have not been manufactured for the past 5 years, therefore no PQRs submitted.

f) Batch manufacturing records including the analytical part, for the most recently released batch of relevant APIs:
Reviewed:
i. Artemether
ii. Artesunate (Non-micronized)
iii. Artesunate (Micronized)
iv. Praziquantel

Note: the company declared that Oseltamivir phosphate and Zidovudine were not manufactured for the past 9 years with Sofosbuvir and Lumefantrine last manufactured in 2016, therefore BMRs and analytical raw data were not submitted.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Checked:
i. Sofosbuvir
ii. Artemether
iii. Oseltamivir monophosphate
iv. Artesunate (Non-Micronized)
v. Artesunate (Micronized)
vi. Praziquantel
vii. Lumefantrine
viii. Zidovudine

h) Recalls in the past three years related to APIs with quality defects:
Declaration submitted: no recalls related to APIs with quality defects

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 submitted that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with accordingly.

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):
Declaration submitted: no warning letter, or equivalent regulatory action, issued by any authority

k) Out-of-stock situations:
Declaration submitted: no out-of-stock situation

l) Additional information submitted:
1. Declaration: no "Sartan" products being manufactured at Solara Active Pharma Sciences Limited, located at 120 A & B, 36, 120P & 121 Industrial Area Baikampady, New Mangalore, Karnataka
2. Declaration: recovered solvents are used only in the manufacture of Artesunate, Praziquantel and Lumefantrine. The recovery solvents / reagents are not employed in other listed products.

Part 5	Conclusion – Desk assessment outcome

Based on the previous WHO inspection and desk assessment 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 ***Solara Active Pharma Sciences Limited, Plants 1&2&3***, located at ***120A &B, 36, 120P & 121 Industrial Area, Baikampady, New Mangalore - 575011, Karnataka, 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 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. 1015), 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