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	Huvepharma Italia S.r.l	
Corporate address of manufacturer	Via R. Lepetit 142, Garessio, 12075 San Donato Milanese, Italy	
Inspected site		
Name & address of manufacturing site	Via R. Lepetit 142, Garessio, 12075 San Donato Milanese, Italy	
Synthetic Unit/Block/Workshop	N/A	
Desk assessment details		
Date of review	10-11 June 2019	
APIs covered by this desk assessment	APIMF084 Artesunate APIMF207 Artemisinin APIMF235 Artemether	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA	Dates of inspection:	15-19.02.2016
	Type of inspection:	Comprehensive
	Block/Unit/Workshop:	Building 2, Building 4, Building 7
	Type of APIs covered:	Antimalarials, Antiepileptics, Bile Acid Sequastrants
AIFA, Italy	Dates of inspection:	21-25.09.2015
	Type of inspection:	Routine
	Block/Unit/Workshop:	All production areas (7 production buildings, 5 warehouses)
	Type of APIs covered:	Antimalarials, Anticholinergics, Antimuscarinics, Selective Dopamine Blockers, Antiepileptics, Bile Acid Sequastrants

Part 3	Summary of the last WHO inspection
Date and conclusion of most recent WHO inspection	The site has never been inspected by WHO Prequalification Team
Brief description of manufacturing activities	N/A
General information about the company and manufacturing site	The site in Garessio is authorized by the Agenzia Italiana del Farmaco (AIFA) to manufacture APIs and their related intermediates. The site became operational in 1984 as part of "Gruppo Lepetit SpA" until December 2000 when it changed hands to "Aventis Bulk" and subsequently Sanofi-Aventis, and Sanofi SpA. Since April 30, 2016 the name changed to Huvepharma Italia S.r.l. due to an acquisition by Huvepharma Bulgaria. There is no change regarding the site legal address. The facility is dedicated to the production of active pharmaceutical ingredients for human and/or veterinary use, related intermediates and food flavours. The APIs and other products manufactured at this site are made up exclusively from chemical synthesis and are intended to be used in oral dosage forms. No sterile APIs or intermediates are manufactured on site. No biotechnology or fermentation activities are carried out on site.
Focus of the last WHO inspection	N/A
Areas inspected	N/A
Out of scope and restrictions (last WHO inspection)	N/A
WHO APIs covered by the last WHO inspection	N/A
Additional products covered by this desk assessment:	APIMF084 Artesunate APIMF207 Artemisinin APIMF235 Artemether

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 most recent manufacturing authorisation and GMP certificate issued by AIFA were provided. Both documents were verified in EudraGMDP and are publicly available

b) Site master file (SMF):

The most recent version of the SMF was provided. The document provides an overview of the QMS including facilities and equipment as well as operations and activities. 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 7 APIs manufactured on site was provided. In addition, one more API was contract manufactured on site

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

The site was inspected by the following authorities during the review period:

Date of GMP inspection	Regulatory Agency Country	Type of Inspection
21-25 September 2015	AIFA Italy	General Inspection
15-19 February 2016	FDA USA	General Inspection
17 May 2018	Italian Ministry of Health - Veterinary Division, Office V, Italy	Pre-Approval Inspection

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
No PQR for Artemether API was provided since only 3 validation batches had been manufactured in 2013. No batches of Artesunate and Artemisinin API had been manufactured during the review period.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
No WHO PQ APIs have been recently manufactured. The 2013 copy of Artemether validation report was provided and it did not give rise to any comments.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Detailed Master BMRs for the manufacture of Dihydroartemisinin and Artemether were provided. The company has not recently manufactured WHO PQ APIs

h) Recalls in the past three years related to APIs with quality defects:
No recall was carried out during the review period.

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:
A confirmation letter on self-inspection programme signed by the Site Quality Manager, was provided

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 regulatory action has been issued for the site by any NRA during the review period

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 ***Huvepharma Italia S.r.l*** located at ***Via R. Lepetit 142, Garessio, 12075 San Donato Milanese, Italy*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIR will remain valid until **June 2021**, 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 2.
   Short name: WHO TRS No. 957, Annex 2
   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