World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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, CN-12075, Italy
Inspected site	
Name & address of manufacturing site	Huvepharma Italia s.r.l. Via R. Lepetit 142, Garessio, CN-12075, Italy DUNS: 436233369
Synthetic Unit/Block/Workshop	Buildings 1, 2, 5, 6, 7 and ancillary areas
Desk assessment details	
Date of review	11 October 2022
APIs covered by this desk assessment	

PQT Number	**API**	**Prequalification status**
APIMF084, WHOAPI-084	Artesunate	Prequalified
APIMF207	Artemisinin	Prequalified
APIMF235, WHOAPI-235	Artemether	Prequalified
MA056	Artesunate API in Amodiaquine (hydrochloride)/Artesunate Tablet 67.5mg/25mg	Prequalified
MA057	Artesunate API in Amodiaquine (hydrochloride)/Artesunate Tablet 135mg/50mg	Prequalified
MA058	Artesunate API in Amodiaquine (hydrochloride)/Artesunate Tablet 270mg/100mg	Prequalified

	MA087	Artemether API in Artemether Solution for injection 80mg/ml	Prequalified

List of documents requested

a) A list of all regulatory inspections performed in the last 5 years and their outcomes;
b) Current full inspection report(s), 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 and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary 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(s) (PQR)(s) of the concerned product(s); PQR(s) or equivalent documentation covering all required subsections and trend results, including statistical evaluation; proprietary information for vaccines is not required – delete as appropriate;
h) The completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s);
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(s) has been performed and all matters dealt with;
k) Master batch manufacturing and packaging record(s) of the WHO product(s) 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) A table to specify which parts of the manufacturing process for the

	concerned product(s) were covered by the inspection of the competent SRA authorities performed in the last 5 years	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered and comments**	
AIFA, Italy	Dates of inspection:	8 to 12 October 2018
	Type of inspection:	General inspection
	Block/Unit/Workshop:	Not specified
	APIs covered:	Not specified
AIFA, Italy	Dates of inspection:	14 to 18 October 2019.
	Type of inspection:	General inspection
	Block/Unit/Workshop:	Warehouse, utilities, bock 1,2, 5, 6, 7, finishing block 2,5,7, QC block 21. Block 3 and 4 discontinued.
	APIs covered:	General GMP inspection of the site
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Desk review on 10 to 11 June 2019 Operating at an acceptable level of compliance with WHO GMP guidelines.	
Brief summary of manufacturing activities	Production and control of intermediates and APIs, salt formation, purification, crystallization, primary and secondary packaging, labeling	
General information about the company and manufacturing site	The factory started activities in 1894. It was previously owned by Aventis, Sanofi Aventis. It is now Huvepharma Italia s.r.l. The company is dedicated to production and control of intermediates and APIs for human and veterinary use, through mainly chemical synthesis. No biotechnology or fermentation products are manufactured. The company also manufactures for Sanofi and Solvay and others	
Focus of the last WHO inspection	Desk review of Italian authority inspection report	
Areas inspected	Inspection report review	
Out of scope and restrictions (last WHO inspection)	N/A	
WHO APIs	APIMF084 Artesunate	

covered by the last WHO inspection	APIMF207 Artemisinin APIMF235 Artemether
Additional products to be covered by this desk assessment:	See above

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 valid manufacturing authorization and GMP certificate were provided.

b) Site master file (SMF):

A detailed SMF dated 10/06/2022 was submitted, containing various annexes. It was generally found acceptable

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

See list provided.

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

AIFA, Italy. 8 to 12 October 2018. General inspection. 12 Major deficiencies. Closed and approval obtained 28 May 2019

AIFA, Italy. 14 to 18 October 2019. General inspection. 6 Major deficiencies. Closed and approval obtained 20 March 2020

FDA, USA. 7 January 2021. Review of AIFA inspection report. Approved

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

Artemisinin PQR: May 2021 to April 2022 (Building 6)
No batches were produced during this period. Therefore no deviations, no complaints, no rejected batches, no returns. The stability data showed no cause for concern

Artemether PQR: March 2021 to February 2022 (Building 7)
No batches were produced during this period. Therefore no deviations, no complaints, no rejected batches, no returns. The stability data showed out of specification results in accelerated conditions. No CAPA was taken as the material is sensitive to these storage conditions.

Artesunate PQR: December 2020 to November 2021 (Building 2)
Seventeen batches were produced during this period, two batches were rejected. Nine deviations were reported. Three OOS and 5 OOT results were reported in the period. The company investigated the incidents, performed a risk assessment and considered the process validated and under control.

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

Artemether.	February 2020
Artesunate.	May 2021
Artesunate.	June 2021
Artemisinine.	May and June 2022

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

Master documentation for the following products were submitted and considered generally acceptable:

Artemether.	February 2020
Artesunate	April 2021
Aretsunate (Puro)	June 2021
Dihydroartemsinine	April 2021
Artesunate	March 2020

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

The company declared that there had been no recalls in the past 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 declared that a self-inspection procedure was in place.

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 there had been no warning letter or similar action, issued or taken against them.

k) Out-of-stock situations:

The company declared that there had been no out-ot-stock situation and that none was foreseen.

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 ***Huvepharma Italia s.r.l. (buildings 1, 2, 5, 6, 7)*** located at ***Via R. Lepetit 142, Garessio, CN-12075, Italy*** 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 or 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-conditioning 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)