World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Quality Control Laboratory (QCL)

Part 1	**General information**		
Laboratory information			
Name and address of QCL	INFARMED I.P. Direção de Comprovação da Qualidade Av. Brasil, Nº 53, Edifício Tomé Pires, 1749-004 Lisboa, Portugal.		
Desk assessment details			
Start and end dates of review	8 – 14 March 2019		
Tests covered by this desk assessment	**Type of Analysis**	**Finished Products**	**Active pharmaceutical ingredients**
	Physical/Chemical analysis	pH, density, optical rotation, limit tests, degree of coloration of liquids, clarity and degree of opalescence of liquids, loss on drying, water content, residual solvents, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass, content)	pH, optical rotation, melting point, loss on drying, limit tests, sulphated ash, degree of coloration of liquids, clarity and degree of opalescence of liquids, loss on drying, water content, residual solvents
	Identification tests	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, FTIR, NIR, RAMAN, Chemical identification tests*	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, FTIR, NIR, RAMAN, Chemical identification tests*
	Assay, impurities and related substances	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS

		spectrophotometry, potentiometry, volumetric titrations, FTIR	spectrophotometry, potentiometry, volumetric titrations, water content, residual solvents, FTIR
	Microbiological analysis	Sterility test, Total Microbial Counts, Test for Specified Microorganisms, Microbial assay of antibiotics	Sterility test, Total Microbial Counts, Test for Specified Microorganisms, Microbial assay of antibiotics
	Miscellaneous	Bacterial endotoxins: Gel Clot and Kinetic chromogenic	Bacterial endotoxins: Gel Clot and Kinetic chromogenic

List of documents submitted	• Anexo_Tecnico_ed_17_05_01_2018.pdf • Scope of Assessment_MJA0817.pdf • Cert_IPAC_2008.pdf • Cert_EDQM_2018.pdf • List_Equipment_annex6.pdf • List_Comput_stsyem_annex7.pdf • LIF_OMS_26_2018.pdf • AUDIT_REPORT_MJA_08_17.pdf • CAPA_MJA 08_17_Evidences_mai_2018.docx	
Any documents missing?	All the requested documents were supplied	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
European Network of Official Medicines Control Laboratories	Dates of inspection:	05/12/2017 to 07/12/2017
	Type of inspection:	Reassessment audit
	Unit/Division inspected:	INFARMED I.P (Direção de Comprovação da Qualidade) Parque de Saude de Lisboa – Avenida do Brasil, 53, 1749-004 Lisbon, Portugal
	Physical areas covered:	Biology and Microbiology Laboratory and Pharmaceutical Chemistry and Technology Laboratory
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Onsite inspection:16-17 July 2015 (INSP-2015-0272) Inspection closed 5 January 2016 It was concluded that the laboratory was operating in compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories (GPPQCL).	

<table>
<tr><td>Brief summary of activities</td><td>The inspection focused on the WHO good practices for pharmaceutical quality control laboratories (GPPQCL) and all laboratory areas were inspected.</td></tr>
<tr><td>General information about the QCL</td><td>INFARMED I.P. – National Authority of Medicines and Health Products, is a Government agency under the Portuguese Health Ministry, which regulates, authorises, assesses and monitors all activities relating to human medicines and health products for the protection of Public Health.

INFARMED was established in 1994 and has been responsible for assessing the quality of medicinal products, active pharmaceutical ingredients and health products (including cosmetics and medical devices) presently marketed in Portugal. INFARMED also participates in the quality control of medicines approved by Centrally Authorized Procedure in coordination with the European Medicines Agency (EMA). INFARMED is the official Control Authority for Batch Release and issues the European Batch Release for Blood Derived Products, which encompasses both the analyses of samples and the review of the production documentation of specific batches.</td></tr>
<tr><td>Focus of the last WHO inspection</td><td>The focus of the inspection was on WHO good practices for pharmaceutical quality control laboratories (GPPQCL).</td></tr>
<tr><td>Areas inspected</td><td>Inspection of Chemical, Physical and Microbiological activities.</td></tr>
<tr><td>Out of scope and restrictions (last WHO inspection)</td><td>None as per the last WHO inspection report.</td></tr>
<tr><td>WHO Prequalified tests covered by the last WHO inspection</td><td>
<table>
<tr><th>Type of Analysis</th><th>Finished Products</th><th>Active pharmaceutical ingredients</th></tr>
<tr><td>Physical/Chemical analysis</td><td>pH, density, optical rotation, osmolarity, limit tests, degree of coloration of liquids, clarity and degree of opalescence of liquids, loss on drying, water content, residual solvents, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass, content)</td><td>pH, optical rotation, melting point, loss on drying, osmolarity, limit tests, sulphated ash, degree of coloration of liquids, clarity and degree of opalescence of liquids, loss on drying, water content, residual solvents</td></tr>
<tr><td>Identification tests</td><td>HPLC (UV-VIS, DAD, fluorescence,</td><td>HPLC (UV-VIS, DAD, fluorescence,</td></tr>
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		RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, FTIR, Chemical identification tests	RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, FTIR, Chemical identification tests
	Assay, impurities and related substances	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, potentiometry, volumetric titrations, FTIR	HPLC (UV-VIS, DAD, fluorescence, RI, ELSD, MS), GC (FID, MS), TLC, UV-VIS spectrophotometry, potentiometry, volumetric titrations, water content, residual solvents, FTIR
	Microbiological analysis	Sterility test, Total Microbial Counts, Test for Specified Microorganisms, Microbial assay of antibiotics	Sterility test, Total Microbial Counts, Test for Specified Microorganisms, Microbial assay of antibiotics
	Miscellaneous	Bacterial endotoxins: Gel Clot and Kinetic chromogenic	Bacterial endotoxins: Gel Clot and Kinetic chromogenic
Additional tests covered by this desk assessment:	None		

Abbreviations	**Meaning**
API	Active pharmaceutical ingredient
CAPA	Corrective and preventive action
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometer
GC	Gas chromatograph or gas chromatography
GLP	Good laboratory practices
GPPQCL	Good practices for pharmaceutical quality control laboratories
HPLC	High performance liquid chromatograph
QA	Quality assurance
QCL	Quality control laboratory
SOP	Standard operating procedure

Part 4	Summary of the assessment of additional supporting documentation

a) Authorization granted by the local authority (if any) or ISO 17025 certificate:

Certification granted by Council of Europe – European Directorate for the Quality of Medicines and Healthcare – OMCL Network Quality Management System – Attestation number (EDQM/MJA-135), in accordance with ISO/IEC 17025 with the relevant texts of the European Pharmacopoeia, the Quality Management Guidelines and the Terms of Reference of the General European OMCL Network.

Accreditation Certificate issued by IPAC – Portuguese Accreditation Institute stating INFARMED comply with the accreditation criteria for Testing Laboratories according to ISO/IEC 17025. Issued 2008-07-30 number L0460. Re-assessment certificate issued by IPAC 2018-01-05 (Anexo Técnico Edição 17 L0460).

b) Laboratory information file (LIF):

The Laboratory Information file was provided in document LIF_OMS_26_2018.pdf. The file was arranged in accordance with the WHO guidelines. A summary of processes was available within this document and found to adequately address WHO requirements.

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

- IPAC (National Accreditation Body) 29-30 October 2018
- European Network of Official Medicines Control Laboratories – 5-7 December 2017.
- IPAC (National Accreditation Body) 13-14 November 2017
- IPAC (National Accreditation Body) 14-15 November 2016

d) Qualification, validation and calibration status of equipment:

The facility had in place a documented procedure for the preventive maintenance of equipment and the premises. There were documented procedures in place for the IQ/OQ/PQ of equipment (SOP GRL/26). An equipment list was provided with each item of equipment was assigned a unique identifier.

e) Confirmation by the quality manager that a full self-inspection dedicated to the tests submitted for prequalification has been performed and all matters dealt with:

Within the LIF the facility conducted annual internal audits that covered the main functional areas of the laboratory including management requirements.

- Management requirements – 8 June 2018
- Microbiology – 5 September 2018
- Pharmaceutical Chemistry and Technology – 8 May, 30 August and 5 September 2018.

From the internal audit information provided it was concluded that the facility had adequately covered the critical areas of the quality management system.

f) Additional documents submitted:

INFARMED regularly participates, every accreditation cycle, in commercially available proficiency testing schemes (PTS). For areas where there are no PTS available the laboratory has established a policy to guarantee external quality control by participating in collaborative studies, performing comparisons between the results of the OMCL and the manufacturer's and internal comparison of results for the same samples by different analysts and the use of blind samples.

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspections and on the GPPQCL evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site ***INFARMED I.P. – Direção de Comprovação da Qualidade***, located at ***Av. Brasil, Nº 53, Edifício Tomé Pires, 1749-004 Lisboa, Portugal*** is considered to be operating at an acceptable level of compliance with WHO GPPQCL guidelines.

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 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 GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

2. 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

3. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report. Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO GMP Guidelines*** or ***TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six 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/

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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

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

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
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

8. 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 TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

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 2.
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

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
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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***
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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. 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

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***
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. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5. ***Short name: 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. Fifties 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