World Health Organization

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

<table>
<tr><th>Part 1</th><th>General information</th></tr>
<tr><td colspan="2">Laboratory information</td></tr>
<tr><td>Name and address of QCL</td><td>Laboratórios Basi – Indústria Farmacêutica, S.A. (Basi)
Parque Industrial de Mortagua. Lote 15 Mortagua, 3450-232, Portugal</td></tr>
<tr><td>Laboratory units/divisions</td><td>Quality Control Unit</td></tr>
<tr><td colspan="2">Desk assessment details</td></tr>
<tr><td>Start and end dates of review</td><td>29 May 2019 – 05 June 2019</td></tr>
<tr><td>Tests covered by this desk assessment</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>Water content, Conductivity, Residual solvents, Uniformity of dosage units (mass, content), Potentiometric determination of pH, Relative density, Optical rotation, Potentiometric titration, Viscosity, Thin-layer chromatography, Gas chromatography, Liquid chromatography, Loss of drying, Infrared spectrophotometry, Total organic carbon in water for pharmaceutical use, Flame photometer, Disintegration of tablets and capsules, Disintegration of suppositories and pessaries, Dissolution test for solid dosage forms and suspensions, friability of uncoated tablets, Tablet hardness,</td><td>Clarity and degree of opalescence of liquids, Degree of coloration of liquids, Potentiometric determination of pH, Relationships between reactions of solutions, Approximate pH and colour certain indicators, Relative density, Optical rotation, Viscosity, Melting point, Potentiometric titration, Thin-layer chromatography, Gas chromatography, Liquid chromatography, Loss of drying, water content, conductivity, Infrared spectrophotometry, Total organic carbon in water for pharmaceutical use, Residual solvents sulphated ash, Density, refractometry, Acid value, Iodine value, Saponification value,</td></tr>
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		Resistance to crushing of tablets, Particulate contamination subvisible particles, Osmolarity.	Limit tests.
	Identification tests	HPLC (UV-VIS, DAD, IR), GC (FID, MS), TLC, UV-VIS spectrophotometry, FT-IR (NIR), Flame photometer, Classic test.	HPLC (UV-VIS, DAD, IR), GC (FID, MS), TLC, UV-VIS spectrophotometry, FT-IR (NIR), Flame photometer, Basic test.
	Assay, impurities and related substances	HPLC (UV-VIS, DAD, IR), GC (FID, MS), TLC, UV-VIS spectrophotometry, FT-IR (NIR), Potentiometry, Volumetric titrations, Gravimetry, Flame photometer	HPLC (UV-VIS, DAD, IR), GC (FID, MS), TLC, UV-VIS spectrophotometry, FT-IR (NIR), Potentiometry, Volumetric titrations, Gravimetry, Flame photometer
	Microbiological analysis	Sterility test, Microbial enumeration tests, Tests for specified micro-organisms, Microbial assay of antibiotics, Efficacy of antimicrobial preservation.	Sterility test, Microbial enumeration tests, Tests for specified micro-organisms, Microbial assay of antibiotics, Efficacy of antimicrobial preservation.
	Baterial endotoxin testing (BET)	Baterial endotoxin test (LAL – Lymulus amebocyte lysate)	Baterial endotoxin test (LAL – Lymulus amebocyte lysate)
	Stability testing	According to ICH Quality Guideline Q1A (R2) • 25°C ± 2°C/60% RH ± 5% RH • 30°C ± 2°C/65% RH ± 5% RH • 30°C ± 2°C/75% RH ± 5% RH • 40°C ± 2°C/75% RH ± 5% RH Photostability testing, Any other required particular T/RH conditions.	According to ICH Quality Guideline Q1A (R2) • 25°C ± 2°C/60% RH ± 5% RH • 30°C ± 2°C/65% RH ± 5% RH • 30°C ± 2°C/75% RH ± 5% RH • 40°C ± 2°C/75% RH ± 5% RH Photostability testing, Any other required particular T/RH conditions.

List of documents submitted	• GMP Certificate_HIMP_EN.pdf • GMP Certificate_HMP_EN.pdf • GMP Certificate_VMP_EN.pdf • GMP Certificate_VMP_PT.pdf • LIF_8.pdf • LIF_A_8.pdf • LIF_B_8.pdf • LIF_B_8_List of Tests to Prequalify.pdf • List of Equipment and Status_Q_Pulse_PT-EN.pdf • Authority Inspection Report_2017_Certified Translation_EN.pdf • Authority Inspection Report_2017_Original_PT.pdf • CAPAs.docx • Audits Conformation.pdf	
Any documents missing?	All requested documents received.	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
INFARMED	Dates of inspection:	3 – 5 May 2017
	Type of inspection:	Renewal of Good Manufacturing Practices Certificate of Medicinal Products for Human Use.
	Unit/Division inspected:	Warehouses, Production and packaging areas, (physical-chemical and microbiological) Quality control laboratory, Sample room, Stability chambers, Water production system, Air treatment system.
	Tests covered:	Not listed in report
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	An onsite of inspection has not been performed by WHO. The last desk review was conducted 31 January 2013 (Inspection number INSP-2018-0155). WHO concluded that upon review of the evidence provided the laboratory was compliant with WHO Guidelines and requirements. WHO recommended that a detailed QC joint inspection be conducted with INFARMED in the future.	

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<tr><td>Brief summary Of activities</td><td>The GMP certified laboratory carries out quality control operations (physical/chemical and microbiological analysis) and batch release activities (Medicines, cosmetics, food supplements, medical devices, etc.) as well as analytical method development and validation, stability studies according to ICH guideline, compatibility studies and preservatives effectiveness determination, along with the preparation of the related technical documents.</td></tr>
<tr><td>General information about the QCL</td><td>Basi laboratories was founded in 1956. In 2009 a new facility was constructed in the Industrial park of Mortágua. In 2011 the laboratory was GMP certified by the Government agency accountable to the Health Ministry, named INFARMED – National Authority of Medicines and Health Products, IP to perform Chemical/Physical and Microbiological testing, certification and batch release.

The laboratory participates in several proficiency testing schemes including EDQM – PTS Physio-Chemical Studies and KNMP proficiency Programme for HPLC, potentiometric titration, pH, melting point, relative density and refractive index methods.

At the time of this desk review there were 40 employees.</td></tr>
<tr><td>Focus of the last WHO inspection</td><td>Not Applicable</td></tr>
<tr><td>Areas inspected</td><td>Not Applicable</td></tr>
<tr><td>Out of scope and restrictions (last WHO inspection)</td><td>None identified in previous 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, viscosity, water content, conductivity, residual solvents, limit tests, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass content).</td><td>pH, density, optical rotation, viscosity, melting point, loss on drying, water content, conductivity, residual solvents, sulfated ash, refractometry, acid value, iodine value, peroxide value, saponification value, limit tests</td></tr>
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	Identification tests	HPLC (UV-VIS, DAD), GC (FID, ECD), TLC, UV-VIS spectrophotometry, FT-IR, basis tests	HPLC (UV-VIS, DAD), GC (FID, ECD), TLC, UV-VIS spectrophotometry, FT-IR, basis tests
	Assay, impurities and related substances	HPLC (UV-VIS, DAD), GC (FID, ECD), TLC, UV-VIS spectrophotometry, FT-IR/NIR, potenciometry, volumetric titrations, gravimetry	HPLC (UV-VIS, DAD), GC (FID, ECD), TLC, UV-VIS spectrophotometry, FT-IR/NIR, potenciometry, volumetric titrations, gravimetry
	Microbiological analysis	sterility test, microbiological limit test, microbial assay of antibiotics and efficacy of antimicrobial preservation	sterility test, microbiological limit test, microbial assay of antibiotics and efficacy of antimicrobial preservation
	Bacterial endotoxin testing (BET)	bacterial endotoxin test (LAL – Lymulus amebocyte lysate)	bacterial endotoxin test (LAL – Lymulus amebocyte lysate)
	Stability testing	According to ICH Quality Guideline Q1A (R2): • 25°C ±2°C/60% RH ±5% • 30°C ±2°C/65% RH ±5% • 40°C ±2°C/75% RH ±5% photo-stability testing, any other required particular T/H conditions	According to ICH Quality Guideline Q1A (R2): • 25°C ±2°C/60% RH ±5% • 30°C ±2°C/65% RH ±5% • 40°C ±2°C/75% RH ±5% photo-stability testing, any other required particular T/H conditions
Additional tests covered by this desk assessment:	No new tests have been identified.		

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:

Basi holds an Industrial Operating License (number 110-E/2013 and 18042/2019-1) and a certificate of Good Manufacturing Practice (GMP) compliance (permit No. F016/S1/MH/001/2019) and Manufacturers Authorization (permit No. F016/001/2019). Permits were granted by the Portuguese National Authority of Medicines and Health Products, IP (INFARMED) on 9th October 2019.

b) Laboratory information file (LIF):

The Laboratory Information file (LIF_8.pdf) was provided. This document was set out in accordance with WHO requirements. It contained general information on the laboratory, quality management system, document control, personnel, premises, equipment, materials, type of subcontracting and contact details, validation of analytical procedures, internal and external audits, stability and Microbiological testing.

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

The following inspections have been recently performed at the site:
2019:

1. Food and Drugs Authority - Ghana – Inspection;
2. Republic of Yemen – Ministry of Public Health & Population– Inspection;
3. Libyan Ministry of Health-Inspection

2017:

1. Uzbekistan Health Authority – Inspection;

d) Qualification, validation and calibration status of equipment:

The laboratory has a documented qualification, validation, calibration and maintenance process. Maintenance is controlled within validated software called Q-pulse by the Maintenance department. It is documented that equipment is validated or re-qualified based on a risk assessment whenever the equipment or utilities have been modified or relocated. The laboratory have a 4 step process for qualification (design, installation, operational and performance qualification).

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:

A statement was provided and signed by José Filipe Campos de Silva (2 May 2019) that the site was frequently audited by clients and is subjected to self-inspection. A list of second party audits is listed above.

f) Additional documents submitted:

Not Applicable

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 ***Laboratórios Basi – Indústria Farmacêutica, S.A. (Basi) Parque Industrial de Mortagua. Lote 15 Mortagua, 3450-232, 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-eighth 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-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/

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. Fiftieth 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. 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