### Part 1
#### General information

<table>
<thead>
<tr>
<th>Laboratory details</th>
<th>Laboratory information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the laboratory</td>
<td>Laboratoire National De Controle Des Medicaments (LNCM Morocco) (National Laboratory of Medicine Control)</td>
</tr>
<tr>
<td>Corporate address of Laboratory</td>
<td>Rue Lamfadel Cherkaoui, B.P. 6206 10 000 Rabat, Maroc</td>
</tr>
</tbody>
</table>

#### Inspected Laboratory

| Address of inspected Laboratory if different from that given above | Same as above. |

<table>
<thead>
<tr>
<th>Summary of activities performed at the laboratory</th>
<th>Type of Analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physical / Chemical analysis</td>
<td>pH, water content, loss on drying, melting point, viscosity, density/specific gravity, optical rotation, conductivity, residue on ignition, weight, volume, particles in injections, friability, tablet hardness, dimensions, disintegration, dissolution, uniformity of dosage units</td>
<td>pH, water content, loss on drying, melting point, viscosity, density/specific gravity, optical rotation, conductivity, residue on ignition, weight, volume.</td>
</tr>
<tr>
<td></td>
<td>Identification</td>
<td>HPLC, TLC, GC, spectrophotometry (UV-VIS, IR, fluorescence and atomic absorption)</td>
<td>HPLC, TLC, GC, spectrophotometry (UV-VIS, IR, fluorescence and atomic absorption)</td>
</tr>
<tr>
<td></td>
<td>HPLC (UV-VIS, DAD,</td>
<td>HPLC (UV-VIS, DAD,</td>
<td></td>
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</tbody>
</table>

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| Assay, impurities and related substances | HPLC, TLC, GC, spectrophotometry (UV-VIS, IR, fluorescence and atomic absorption) | HPLC, TLC, GC, spectrophotometry (UV-VIS, IR, fluorescence and atomic absorption) |
| pH, water content, loss on drying, melting point, viscosity, density/specific gravity, optical rotation, conductivity, residue on ignition, weight, volume, particles in injections, friability, tablet hardness, dimensions, disintegration, dissolution, uniformity of dosage units |
| Microbiological analysis | Not applicable | Not applicable |

**Inspection details**

**Dates of inspection** 26-28 March 2018

**Type of inspection** Routine inspection

**Introduction**

This was the fourth WHO-PQ inspection of LNCM, Morocco. The laboratory was previously inspected in 2012, 2014 and November 2016. The last WHO-PQ inspection was concluded as non-compliant due to non-compliances identified in the area of data integrity and microbiology. At the opening meeting, the WHO Inspection team was informed that the laboratory was certified by the European Directorate for the Quality of Medicines in 2007.

**Scope and limitations**

**Areas inspected** The inspection focused on the implementation of the corrective and preventive actions addressing the critical and major observations following the WHO
### November 2016 inspection.

#### Restrictions
None

#### Out of scope
Based on the request received from the LNCM, Morocco, the microbiology laboratory was not included in the scope of this inspection.

#### Key persons met
- Omar Bouazza, Director of Directorate of medicines and pharmacy
- Bouchra Meddah, Head LNCM
- Maria Slimani, Quality Management Unit
- Mohamed Aymaz, Metrology Unit
- Aziz Alami, Metrology Unit
- Ali Hajjami, Information Technology Unit
- Saadia Issmaili, Head of Chemical Service
- Leila Hakkou, Head of Biological Assay
- Ahmed Rami, Head of Safety and Environment and deputy of RMQ
- Khadija Ait hammarik, Quality Sample Unit
- Imane Haouch, Quality Assurance Service
- Mohamed Talbi, corresponding of Quality of chemical Service
- Hari Ramanathan, Senior Technical Manager / USP

#### Abbreviations
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>BDL</td>
<td>below detection limit</td>
</tr>
<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
</tr>
<tr>
<td>CC</td>
<td>change control</td>
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<tr>
<td>CFU</td>
<td>colony-forming unit</td>
</tr>
<tr>
<td>CoA</td>
<td>certificate of analysis</td>
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<tr>
<td>DQ</td>
<td>design qualification</td>
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<tr>
<td>EM</td>
<td>environmental monitoring</td>
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<tr>
<td>FAT</td>
<td>factory acceptance test</td>
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<tr>
<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<tr>
<td>FPP</td>
<td>finished pharmaceutical product</td>
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<tr>
<td>FTA</td>
<td>fault tree analysis</td>
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<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<tr>
<td>GC</td>
<td>gas chromatograph</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<tr>
<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectrophotometer</td>
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<tr>
<td>IQ</td>
<td>installation qualification</td>
</tr>
<tr>
<td>KF</td>
<td>Karl Fisher</td>
</tr>
<tr>
<td>LAF</td>
<td>laminar air flow</td>
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<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
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</table>
Part 2  Brief summary of the findings and recommendations

Brief summary of the findings and comments

1. Organization and management

The National Laboratory of Medicines Control (LNCM) is a division of the Directorate of Medicines and Pharmacy, a public department, under the authority of the Ministry of Health of Morocco. The National Laboratory was established to assist the Ministry of Health to verify the quality of medicines and other health products, and to ensure that medicine and other health products meet international standards for quality.

In general, the laboratory has sufficient managerial and technical personnel to carry out its duties. An organization and management structure of the laboratory were presented at the opening meeting. The total number of staff accounts 74 at the time of the inspection.

The laboratory is headed by Pr. Bouchra Meddah, and comprises of six sections:

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Physico-chemical testing,
Biological testing,
Quality assurance
Testing of health products,
Metrological unit
Quality management.

An organogram showing the structure of the laboratory is part of the quality manual.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Quality management system


Generally, the Quality management system was well established, documented and implemented. A quality manual defining the quality management system was available. The scope of this quality manual was applicable to all of its activities carried out by the laboratory.

The activities of the laboratory were systematically and periodically (once a year) audited internally. It was claimed that since the last WHO PQ inspection, the quality manager is not auditing her division but instead is auditing other areas. The audit schedule for 2017 and 2018 was in place. List of internal auditors was available and total of three auditors were qualified. Qualification of internal auditors included practical and theoretical training. Before an internal auditor was qualified as a lead auditor, he/she was required to observe one internal audit.

Proficiency testing scheme (PTS) for 2016 and 2017 was discussed. The PTS for dissolution test was performed in 2016, whereas HPLC, GC, dissolution, osmolality, and IR tests were performed in 2017 as part of the PTS program.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Control of documentation

The laboratory has established and maintained a manual system of procedures to control all documents. A master list identifying the current version status and distribution of the document was annexed to the quality manual. Each controlled document had a unique identifier, version number and date of implementation. The Director of LNCM designed one person as « Quality Document controller » for the Laboratory, in order to master the all quality documents in LNCM; creation, edition, dissemination, use, revision, suppression etc.
The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

4. Records

The laboratory did not use analytical worksheets or lab notebooks for recording of results, instead photocopies of the monograph and manufacturer’s specifications were used to record the observations. The analytical record of Artesunate/Lumefantrine 20 mg/120 mg tablets was reviewed. The raw data, including calculations and derived results, was checked and were found to be recorded on loose uncontrolled forms.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Data processing equipment

A data integrity procedure was available. The procedure provided responsibility of various personnel, back up, verification of audit trail, access control, administration system, ethical requirement, lifecycle data using ALCOA principle. The information technology (IT) personnel were responsible for the verification of audit trails whereas the quality manager was responsible for ensuring audit trail is switched on or not. It was noted that audit trails were so far not verified to ensure no unjustified changes were made by the analysts before accepting results of the testing. Date/time of computerized systems is verified by IT personnel on monthly basis.

The laboratory was in the process of installing a computer network to connect HPLC instruments. Two new HPLC systems have already been connected to the server using Agilent Open Lab software. The laboratory indicated that it is planned to network the remaining HPLC and GC instruments.

The privileges given to various personnel were reviewed. It was noted that only two roles were currently in use for OpenLab as well as for the standalone computer systems. Four IT administrators have open ended privileges whereas analysts have privileges for the following areas:

- Edit content of project
- Edit integration parameters
- Edit system suitability parameters
- Edit users own running sequences
- Edit method overriding parameters
- Review audit trail
- Manual control (in run)
- Manual control (only when instrument idle)
- Abort of any running samples
- Reprocess data
- Perform manual compound identification
- Perform manual integration

WHO Inspection report:
The SOP addressing management of password and user account, was reviewed. Access to computerized systems was password protected.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Personnel

The laboratory had personnel employed with the necessary education, training, technical knowledge and experiences for the various assigned functions. This was verified, when reviewing the testing of Artesunate/lumefantrine tablets.

The inspectors reviewed the identified training needs for 2018, the training plan and the training records for 2017. These documents and the applied principles were found to be adequate.

The laboratory participated in the WHO proficiency testing scheme.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Premises

Premises used for Physico-chemical testing were in general suitably for its purpose. The facilities for the Physico-chemical laboratory were found to be of suitable size and design to suit the functions and to perform the operations to be conducted.

Separate rooms were available for the weighing and preparation of samples and for the storage of reference substances including at storage requirements of 2-8°C. Different rooms housed different analytical instruments such as HPLC, polarimeter/densimeter, KF titrators, pH meter, conductivity meter, osmolality meter, UV spectrometer and dissolution apparatuses. A safety cabinet for the handling of cytotoxic substances was available.

The environmental conditions of storage facilities were monitored and controlled.

The refrigerators to store reference standards are connected to data loggers and alarms systems which in turn are connected to mobile phones. Monitoring was done daily.

The area for microbiological testing was under reconstruction and thus not inspected.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Equipment, instrument and other devices

WHO Inspection report:
The laboratory facilities for Physico-chemical testing’s were adequately equipped with suitable instruments. Instruments that were shown to be defective or outside specified limited were taken out of service and were clearly labelled as such. The equipment, instruments and other devices used for the performance of tests, calibration, validated and verifications were found suitable. They were qualified and/or calibrated regularly.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Contracts

Not inspected due to time constraints.

10. Reagents

The reagents used in the laboratory were of appropriate quality and correctly labelled. ELGA filtration system was used for the filtration of water used for reagents and buffer. It was claimed that water is tested every day for pH and conductivity.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Reference substances and reference materials

The SOP for the handling of reference standard was revised following the last WHO inspection. The procedure requires that reference standards should be verified upon receipt as well as before use. The batch validity of compendial standards was checked before use. The suitability of working substances submitted by the manufacturers was evaluated based on the information given on the certificate of analysis.

The compendial reference substances and working standards submitted by manufacturers were used by the laboratory for analysis. A logbook was kept as an inventory, containing the name of the substance, date of reception, lot number, internal code, supplier, intended use, place of storage and end of use date.

At the end of each month, standards that were obsolete and expired were discarded. The disposal was recorded.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

12. Calibration, verification of performance and qualification of equipment, instruments and other devices

An annual schedule for the calibration/qualification of Physico-chemical instruments was available for 2018. The FTIR was calibrated twice a year as the instrument was recently changed.

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The internal procedure for the calibration and verification of balances was inspected. The balance calibration for Mettler Toledo was reviewed. Calibration of balances is outsourced. Calibration of balance performed by the contractor was requested. It was noted that this balance was last calibrated in November 2017.

Calibration procedure of dissolution apparatus was inspected. The dissolution apparatus was calibrated once every year by internal and external party. It was noted that the dissolution of reference tablets was not tested as part of the instrument qualification.

HPLC calibration was performed by in-house personnel annually. An SOP was in place. In addition, the SOP on control of HPLC procedures described tests to be performed before each analysis. Tests such as precision of peak area, retention time, carry over test for impurity, signal to noise ratio for impurity, similarity factor for assay and impurity and response factor were performed prior to each analysis.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Traceability

The traceability of analytical results to primary reference substances was verified. When performing tests according to pharmacopoeias the laboratory used the specified official standard and verified batch validity using information obtained from the websites of the corresponding pharmacopoeias and accompanying leaflets.

When tests were performed that were part of the authorized dossiers, the laboratory requested information from the manufactures whether the provided reference substances were primary or secondary standards. In case secondary standards (working standards) were supplied the information whether these standards are traceable to primary standards was also requested.

The calibration of analytical instruments was traceable to certified reference materials or national standards. This was verified when the calibration of analytical balances was reviewed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Incoming samples

Upon reception, samples were registered in a logbook and a sample form. A test request accompanied each sample submitted. It was noted that the pages of the logbook of the Physico-chemical laboratory for incoming samples were not consecutively numbered. Prior to testing, the samples were stored either in a refrigerator or in an air-conditioned storage room at temperature 15°C to 25°C.
The temperature of the refrigerator was monitored using LabGuard devices and software. The temperature sensor was placed in a position that was identified as worst case following a temperature mapping study performed by an external company.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Analytical worksheet

The laboratory did not use analytical worksheets to record observations following the analysis of samples. Analytical report of Levonorgestrel tablets was reviewed. It was noted that specification provided by the manufacturer in their submission dossier was copied and referred. For products manufactured by Moroccan manufacturers, complete test was performed as claimed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

16. Validation of analytical procedures

LNCM did not validate analytical methods as the laboratory claimed that only compendial methods and methods received from manufacturers are used which can be considered as validated. The specificity, repeatability, linearity and accuracy of the method were verified during the analysis of a sample. When methods of manufacturers were used the validation of these methods in dossiers of manufactures was evaluated. In addition, the specificity and repeatability of the method was verified. The laboratory refers to the EDQM guideline for validation and verification of analytical methods. An SOP on validation and verification of analytical methods was in place.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

17. Testing

The samples were tested according to the test request applying either compendial provisions or methods which were part of the authorized dossiers. Deviations from the test procedures were approved and documented.

Due to the construction of the Microbiology section, all microbiological tests are currently done by another unit of the laboratory and was not inspected.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

18. Evaluation of test results
The SOP on handling of OOS results was reviewed. The OOS procedure stipulated that the sample has to be retested in case the OOS investigation is inconclusive. The number of retests is predefined and limited (maximum two retests). The decision, whether the result of the retest confirms the doubtful result or not, was based on the evaluation if the results were “similar”. However, no criteria, e.g. statistical tests, or procedures were given to evaluate the similarity. The lab informed the inspectors that these criteria are currently under investigations. Similarly, OOS procedure did not provide guidance on how hypothesis testing has to be performed to discount potential laboratory errors. The flow chart was found ambiguous as it did not provide information once OOS was confirmed as invalid.

The laboratory has started to maintain a logbook of OOS after the last WHO inspection. In 2017, the logbook contained only valid OOS as the laboratory deemed that it is not required to maintain a log of all results that were subject to an OOS procedure. The corresponding investigations reports were stored in a separate folder.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

19. Certificate of analysis

Not inspected due to time constraints

20. Retained samples

Not inspected due to time constraints.

21. Safety

In general, this section was found to be satisfactory.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

PART 3

Conclusion

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, as well as the corrective actions taken the **LNCM, Rabat, Morocco**, located at **Rue Lamfadel Cherkaoût, B.P. 6206 10 000 Rabat, Maroc**, was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

WHO Inspection report:
This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

**PART 4**

**List of GMP guidelines referenced in the inspection**

   
   **Short name: WHO TRS No. 957, Annex 1**
   

   
   **Short name: WHO TRS No. 986, Annex 2**
   

   
   **Short name: WHO TRS No. 961, Annex 2**
   
   [http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)

   
   **Short name: WHO TRS No. 970, Annex 2**
   

   
   **Short name: WHO TRS No. 929, Annex 4**
   
   [http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1)

   
   **Short name: WHO TRS No. 961, Annex 5**
   
   [http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
   
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

   
   Short name: WHO TRS No. 957, Annex 2

   
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    
    Short name: WHO TRS No. 961, Annex 9
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

    
    Short name: WHO TRS No. 981, Annex 2
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

*Short name: WHO TRS No. 992, Annex 5*


*Short name: WHO TRS No. 996, Annex 5*

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf