



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Quality Control Laboratory

Part 1: General information

Name of the QC Laboratory	Health Concepts International		
Physical address	113 Thailand Science Park, Paholyothin Rd., Klong 1, Klong Luang, Pathumthani Thailand 12120		
Contact person and email address.	Ms Navaporn Tagontong Laboratory Manager and Senior Analyst Pharmacist navaporn@hc-intl.com		
Date of inspection	Monday, 7 March – Tuesday, 8 March 2016		
Type of inspection	Initial inspection		
Type(s) of testing included in the inspection	Chemical, physical		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Physical/Chemical analysis	pH, dissolution, uniformity of dosage units,	pH
	Identification	HPLC, UV-VIS Spectrophotometer	HPLC, UV-VIS Spectrophotometer
	Assay, impurities and related substances	HPLC (UV-VIS, DAD detection), UV-VIS spectrophotometer, determination of related substances and impurities by comparison with reference standards	HPLC (UV-VIS, DAD detection), UV-VIS Spectrophotometer, Determination of related substances and impurities by comparison with reference standards

General information about the company and site

Health Concepts International laboratory (HCI) is a subsidiary of the Concept Foundation. It was established in 2001 and testing was started in 2003 with support of the Concept Foundation. It provides quality testing of a hormonal suspension injection for a manufacturer in Indonesia; independent product testing for the International Planned Parenthood Federation (IPPF) and Marie Stopes International (MSI). HCI

has performed testing for Concept Foundation and UNFPA to ensure the quality of products, particularly misoprostol, supplied to specific countries. It has experience testing misoprostol tablets and mifepristone tablets on a routine basis and levonorgestrel and ethinyl estradiol as part of ISO qualification. HCI provides services to Concept Foundation as part of the development of generic formulations of depot medroxyprogesterone acetate, in particular in the development of methods for dissolution profiles.

History of WHO and/or regulatory agency inspections

This was the first WHO inspection of the laboratory. It had not yet been inspected by stringent regulatory authorities.

HCI obtained ISO/IEC 17025: 2005 certification by the Bureau of Laboratory Quality Standards from the Ministry of Public Health (BLQS) in Thailand in 2007 for testing in the context of MPA analysis, Ethinyl estradiol assay and content uniformity. The last audit was in 2014 and in 2015 submitted a self-declaration. The accreditation (No. 1103/50) expires on 29 April 2017.

A mock inspection was performed by NIDQC in Vietnam in 2015 for WHO Prequalification.

Focus of the inspection

The inspection focussed on the quality management system and on chemical and physicochemical tests as the areas of quality control testing which were requested to be prequalified by the WHO.

Inspected Areas

The following areas of the WHO good practices for quality control laboratories were covered in this inspection:

- 2.1 Quality system
- 2.2 Control of documents
- 2.3 Records
- 2.4 Data-processing equipment
- 2.5 Personnel
- 2.6 Premises
- 2.7 Equipment, instruments and other devices
- 2.8 Reagents
- 2.9 Reference substances and reference materials
- 2.10 Calibration, verification of performance and qualification of equipment, instruments and other devices
- 2.11 Traceability
- 2.12 Incoming samples
- 2.13 Analytical sheet
- 2.14 Validation of analytical procedures
- 2.15 Testing
- 2.16 Evaluation of results
- 2.17 Certificate of analysis

- 2.18 Retained samples
- 2.19 Safety

(please note that the sections below have a different numbering than those of the WHO good practices for quality control laboratories.)

2.1. Organization and management

The Organization Chart dated 29 January 2016 was reviewed. The Managing Director was Peter Hall. The Laboratory Manager supervised 3 staff members, the QA/QC Pharmacist (Quality System Management), the Senior Laboratory Analyst and Laboratory Analyst. Housekeeping, accountants finance manager and secretarial services were also provided for. The Concept Foundation provided regulatory and financial support, for official test methods published in Pharmacopoeia and HR.

2.2. Quality management system

The draft quality manual, Version 026-03-16 was reviewed. It contained a detailed revision history.

The laboratory implemented a data integrity procedure on 27 January 2016. It described data integrity principles and referred to ISO/IEC 17025 clause 4.13.2 Technical records and 5.4.7 Control of data and WHO Technical Report Series no. 957 Annex 1 clause 4.2 and 5.2(b), (d), and (e).

The following SOPs were reviewed:

- OOS procedures: SOP-PQC-002 (version 006-10-15)
- Complaints, non-conformity, CAPAs: SOP-HCI-004 (version 011-09-15)
- Risk management: SOP-HCI-006 (version 007-04-15)
- Data integrity: SOP-PQC-009 (version 000-01-16) See observations under “Part 5”.
- Training: SOP-HRD-001 (version 012-09-15).

2.3. Control of documentation

Microsoft Word and Excel files were password protected.

2.4. Records

In the quality manual, audit trails were defined as “enabled to control changes to information stored in computerized system. In case Audit trail is not available, change to raw data is controlled by level of authority of software program. Supervisor/laboratory manager will be informed to approve the change, record of justification and information of changes in the printed raw data.”

Records were requested for the recent analyses of a hormonal contraceptive injection and bulk, that was tested for assay by LD, job number 003/16, completed on 2 March 2016, NB053, p. 197-199, NB058, p. 20-30, Sample registration number S-02-24-16-001,-002,-003,-004.

Laboratory notebooks were printed in the most part. The applicability/completion of all of the described measurements could not be verified.

2.5. Data-processing equipment

Back-ups were performed automatically once a day through Concept Foundation. Agilent LC solutions were used on the two HPLC instruments seen at the laboratory. Different versions were in use.

Peak areas were exported into an Excel spreadsheet automatically by the Agilent software on the System 031 which used the 2014 version of the software.

2.6. Personnel

Staff received training for dissolution testing by the USP. Performance was monitored through a control chart for internal quality control. Repeatability of standard was verified through percentage agreement and percentage RSD. This was nevertheless stopped in October 2015. Out of limits were not graphed in one instance, but were nevertheless indicated in writing.

Personnel qualification files were maintained. A list of test results obtained by each analyst during PT/Inter-laboratory comparison was available.

In case of new SOPs or changes in SOPs, a training is foreseen within seven days after distribution of the SOP.

2.7. Premises

Premises were well adapted to the laboratory work being performed. Housekeeping was generally excellent.

2.8. Equipment, instruments and other devices

The laboratory was equipped with two HPLCs, a dissolution tester, pH meters, one analytical balance, ovens and UV-visible spectrophotometer equipment. Equipment was maintained and re-qualified once a year by ISO/IEC 17025 certified calibration laboratory or system owner (Agilent).

2.9. Contracts

There was a contract with a Agilent for annual maintenance and requalification.

2.10. Reagents

The management of reagents was acceptable overall. The type and amount of reagents in use was limited to the analyses being undertaken by the laboratory.

2.11. Reference substances and reference materials

USP standards are ordered from the USP Pharmacopoeia except for certain methods where they order EDQM standard, if the client requires it. The standard used will generally depend on customer requirements. Reference standards were tracked in a protected Excel spreadsheet register. All reference standards seen were stored under appropriate storage conditions.

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

Dissolution

An Erweka dissolution tester DT 72x was available at the laboratory. Full performance verification was last performed in 2015. Erweka requalification was performed every 6 months or before performing testing if the equipment was not used for a long period of time.

HPLC

Calibration, installation, design and operational qualification was performed by Agilent for the HPLCs. This was documented in a standard binder from the company's local service provider.

For the computerized systems used to operate the HPLCs, time and date was locked and could only be changed using the administrator password. The Windows activity log was not considered as part of the system to ensure data integrity.

There were folders with similar names in different places, for instance, the raw data folder under "Result" on the D drive, was also found on the Desktop.

Balances

Calibration and performance verification records were maintained. This area was considered acceptable overall, since the balance was removed from the laminar airflow, which had caused issues with its stability.

Chromatographic columns

There were approximately 11 columns available. There was no documentation of the tests performed upon receipt.

UV-Visible

An Agilent spectrophotometer was used.

2.13. Traceability

Traceability was acceptable and ensured through the regular updating of spreadsheets for registration, receipt and testing of samples.

For electronic data, measures were taken to improve traceability in the corrective and preventive actions.

2.14. Incoming samples

The list of incoming samples was maintained in an Excel spreadsheet that was password protected. It included the recording of registration number (sequentially assigned), product name, dosage form, batch number, manufacturing date, expiry date, manufacturer, contact person, date of receipt, destroy date, received by, total received sample quantity, description from visual inspection, storage conditions, and records of who recorded the entry, date, who verified the entries and the date. The last samples that had been received were:

-A combined injection of MPA 50 mg/L, EC 10 mg/mL, batch number CI-412, registration number S-02-24-16-001, -002, -003,-004, tested for a from manufacturer in the ASEAN area, was received on 24-Feb 2016. Test results were obtained on 25-26 February 2016. Results were to be found in NB058 P. 15-19. The laboratory told inspectors that some samples were currently under OOS investigation. This was indicated in the spreadsheet entitled “Registration 2016 Test Info”, which included more detailed information on testing, including the sample label number and the number of retained sample units, the start of testing date, page of book where the analysis was recorded, and description of any OOSs or method transfer, or training in the remarks section. For the hormonal contraceptive injection assay, there was an OOS under investigation for Job Number 008/16. Training and method transfer was done on the samples just prior to this (Job number 006/16 and 007/16 for content uniformity and assay).

- from BDN for HPLC testing of gemfibrozil and 2,5-dimethylphenol, on 25 February 2016 and were indicated to be stored in the refrigerator between 2-8oC as part of proficiency testing.

HCI recently tested 100 samples of misoprostol samples with support from Concept Foundation and from UNFPA. It took approximately three months to perform the analyses.

2.15. Analytical worksheet

Worksheets were printed and included blanks for pasting weighing slips and details of the samples, reagents and reference standards. Some of the information appeared to be retyped and was pasted in laboratory notebooks belonging to each analyst.

2.16. Validation of analytical procedures

When methods were provided by a manufacturer and already validated, the laboratory verified specificity.

Method validation was performed when testing a new product for example, tablets of mifepristone 200 mg and misoprostol 200 µg.. Validation of stability was performed.

Method verification for levonorgestrel and ethinyl estradiol assay, dating from 21 December 2015, was reviewed. It included specificity, repeatability, intermediate precision and reproducibility. All parameters passed testing requirements. The USP method had recently been fully adopted, rather than using an in-house method. Reproducibility was verified through comparison of tests results with those of another laboratory, called the Center of Analysis for Product Quality, Faculty of Pharmacy, Mahidol University (MUPY-CAPQ).

The method validation report for the related substances method for misoprostol method SOP-PQC-112 for Agilent 1260, was reviewed. Specificity, accuracy, linearity and range, LOD, LOQ were performed. This validation was also performed using the reference standard of A type misoprostol (the principal degradation product of misoprostol, which has the same molecular structure as misoprostol, with the exception of the loss of a water molecule through an acid-base catalysed reaction

leading to the formation of a double bond conjugated with the ketone function on the pentacarbon ring).

Note: method transfer was performed when switching from one HPLC to another.

Method uncertainty was defined for misoprostol in the assay and content uniformity for Agilent 1260 method. The detailed report was reviewed and concluded uncertainty of 0.00701 mg/tablet for assay of misoprostol and 0.00674 mg/tablet for content uniformity of misoprostol.

Method uncertainty was stated to have been done for all methods. It was also reviewed for the levonorgestrel assay for the SOP-PQC-104 determination of levonorgestrel and ethinylestradiol, with 0.002 mg/tab for levonorgestrel and 0.001 mg/tab for ethinylestradiol.

2.17. Testing

The laboratory specializes in the testing of the following products:

- Medroxyprogesterone acetate and estradiol cypionate injectable suspension, MPA 50 mg/mL and EC 10 mg/mL (identification, assay, content uniformity, pH, identification of methylparaben and propylparaben, assay of methylparaben, assay of propylparaben, based on in-house method SOP-PQC-101 based on USP 37/NF32: 2014 and in-house method SOP-PQC-102 based on journal of analytical and bioanalytical chemistry Vol. 376, p. 440-443)
- Medroxyprogesterone acetate injectable suspension, MPA 150mg/mL (identification, assay and content uniformity of medroxyprogesterone acetate and assay of methylparaben and propyl paraben and pH, based on in-house method SOP-PQC-115 based on USP 37/NF32: 2014, SOP-PQC-102 based on Journal of analytical and bioanalytical chemistry Vol. 376, 2003, p. 440-443, and in-house method SOP-PQC-101 based on USP 37/NF 32: 2014)
- Medroxyprogesterone acetate injectable suspension (identification, assay, content uniformity by in-house method SOP-PQC-115 based on USP 37/NF32:2014)
- Levonorgestrel tablets (levonorgestrel 0.75 mg (identification, assay, content uniformity by In-house method SOP-PQC-103 based on USP 37/NF 32:2014)
- Levonorgestrel and ethinylestradiol tablet (levonorgestrel 0.150 mg and ethinylestradiol 0.030 mg) (identification of the 2 APIs, assay, content uniformity by in-house method SOP-PQC-104 based on USP 37/NF 32:2014)
- Mifepristone tablets 10, 25 and 200 mg (identification, assay and content uniformity by in-house method SOP-PQC-111 based on USP pending monograph 1.1:2008)
- Misoprostol tablet 200 mcg (identification of misoprostol, assay of misoprostol, content uniformity of misoprostol, related substances A-type misoprostol by in-house method SOP-PQC-112 based on USP Pharmacopoeial Forum Volume 26 (5) September-October 2000)

2.18. Evaluation of test results

They performed proficiency testing in collaboration with BDN Thailand as well as inter-laboratory comparison.

OOS's were being recorded adequately in the most part. The OOS investigation performed for the pH for the hormonal contraceptive injection, was reviewed. The investigation appeared thorough and contained a logical explanation/root cause for the OOS pH value (ie., that the samples were more than 30 days old and that the manufacturer had already indicated to them that pH would be outside the release specification after 30 days of storage).

2.19. Certificate of analysis

This area was acceptable overall.

2.20. Retained samples

Samples were retained for a period of 6 months to 1 year after the expiry date, depending on customer requirements. The area where samples were stored was temperature and humidity controlled.

2.21. Safety

Before analysts did tests, they had to familiarize themselves with the MSDS sheets. There were safety procedures in place, in any case, to prevent/remediate accidental exposure. All persons entering the laboratory were required to wear mask, gloves, overshoes and head covers.

Emergency eye showers and body showers were available in different areas of the laboratory.

The laboratory was equipped with chemical fume-hoods and was well ventilated.

Organic solvents were stored in a flammable chemical cabinet but it was not equipped with air extraction. The laboratory was equipped with smoke detectors and detectors.

Steroid chemical waste was placed in bottles labelled with their content. This waste was managed by the site waste management system.

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 and planned, ***Health Concepts International Ltd (HCI), 113 Thailand Science Park, Paholyothin Rd., Klong 1, Klong Luang, Pathumthani, Thailand 12120***, was considered to be operating at an acceptable level in 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 as well as those reflected in the WHOPIR, were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

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