

**Prequalification of Medicines Programme
WHO PUBLIC INSPECTION REPORT (WHOPIR)
Quality Control Laboratory**

Part 1: General information

Name of QC Laboratory	Pharmacie et Aide Humanitaire Centre Humanitaire Médico-Pharmaceutique (PAH-CHMP)		
Physical address	4, voie militaire des Gravanches, F 63100 Clermont-Ferrand, France		
Date of inspection	26-27 September 2013		
Type of inspection	Routine		
Type(s) of testing included in the inspection	Physical and chemical testing		
Summary of the testing activities performed by the QC Laboratory	Type of analysis	Finished products	Active pharmaceutical ingredients
	Physical/ Chemical analysis	pH, density, disintegration, dissolution, uniformity of dosage units (mass, content), friability, dimensions, limit tests	pH, density, acid value, iodine value, limit tests, neutralizing capacity, heavy metals
	Identification	FTIR, TLC, HPLC, spectrophotometry, basic tests	FTIR, TLC, HPLC, spectrophotometry, basic tests
	Assay, impurities and related substances	HPLC (UV-Vis, PDA detection), UV spectrophotometry, FTIR, volumetric titrations	HPLC (UV-Vis, PDA detection), UV spectrophotometry, FTIR, volumetric titrations

Part 2: Summary
General information about the company and site

The Centrale Humanitaire Médico-Pharmaceutique (CHMP) was founded in 1990 by “Pharmaciens Sans Frontières” as a non-profit-association, supplying medicines and various medical supplies. The CHMP control laboratory was established in 1994, after its separation from Pharmaciens Sans Frontières at the request of the local authority, and its main task was to test the quality of medicinal products. CHMP included its own purchasing and distribution center, as well as a purchasing agency in Nairobi. The CHMP was officially recognized by ANSM in 2011 as a pharmaceutical humanitarian establishment. The purchasing activity at Clermont-Ferrand was stopped in 2012 and CHMP was united with the consortium of

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Pharmaciens et Aide Humanitaire (PAH) to create “PAH CHMP” (CHMP being dissolved and taken over by PAH to take their current name). Currently, the laboratory collaborates with procurement agencies in Africa and international organizations as an independent quality control laboratory. It provides training to various institutions for them to develop their pharmaceutical systems and QA staff is involved in the audits of several pharmaceutical companies. It is a member of several networks, including LEEM and the EDQM network for a collaborative study on International Chemical Reference Standards (ICRS) on behalf of the WHO.

The CHMP laboratory performed tests on the following pharmaceutical dosage forms:

- Tablets
- Capsules
- Injections
- Syrups/Oral Solutions
- Dry powder for injections
- Ointments/Creams
- Gels
- IV infusions

Tests were performed on products coming from many pharmaceutical manufacturers that are currently registered in the WHO Prequalification Programme (e.g., Agila, Cipla, Guilin, Mylan, Ranbaxy, Strides) and had also been mandated with some market monitoring tests by WHO PQ.

Microbiological analyses were contracted out to an external laboratory called “ICARE”, which is operates under a pharmaceutical manufacturing licence and is subjected to inspections by the Agence Nationale de Sécurité du Médicament (ANSM).

Recent changes at the site included the implementation of a laboratory information management system (LIMS), in place since 2013. A green chemistry project had been set in place as well.

The laboratory participates in the control of medicines suspected to be falsified and in the control of essential generic medicines (through LEEM). It participates in a pharmaceutical information system in Benin through ESTHERAID.

There are currently 4 laboratory technicians and 1 director of Quality and Development, a responsible/supervisory pharmacist and a pharmacist responsible for quality management. Some of the administrative staff was providing their services on a volunteer basis.

History of WHO and/or regulatory agency inspections

The most recent inspection of CHMP was performed on 9-10 September 2008. The first WHO inspections were performed in 2004 and in February 2006.

Focus of the inspection

The inspection focussed on covering all relevant sections of the WHO good practices for pharmaceutical quality control laboratories (GPPQCL).

Inspected Areas

The inspection covered the following sections of the WHO GPPQCL text:

- Organization and management
- Quality management system
- Control of documentation
- Records
- Data-processing equipment
- Personnel
- Premises
- Equipment, instruments and other devices
- Contract
- Reagents
- Reference substances and reference materials
- Calibration, verification of performance and qualification of equipment, instruments and other devices
- Traceability
- Incoming samples
- Analytical worksheets
- Validation (verification and transfer) of analytical procedures
- Testing
- Evaluation of test results
- Certificate of analysis
- Retained samples
- Safety

2.1. Organization and management

The organization of the CHMP was defined in an organization chart, signed and dated July 2013, which named the technical and quality assurance staff under each of their functions. Overall, the laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were adequately defined.

2.2. Quality system

The Quality Manual dated 2 January 2013 was reviewed. It was a high level general document covering all activities and processes.

The quality management system of CHMP was based on WHO good practices for pharmaceutical quality control laboratories, ISO 9001 (2008) and ISO 17025. It consisted of an autonomous quality assurance function that managed quality audits and self-inspections.

Quality Management System (QMS) processes were clearly described and well documented, as well as their interactions, through policies, procedures, instructions, plans, programmes and records.

Internal audits: Internal audits were performed on an annual basis by an external consultant. The frequency of the internal audits was specified as annually in the procedure PMAQ/05 and was defined in a pre-established schedule. An internal note was sent 1 week prior to the internal audit to the divisions that would be subjected to the audit.

Corrective and preventive actions (CAPA): Corrective and preventive actions implementation and effectiveness were followed in tracking tables that were maintained for internal audits and for OOS, for internal deviations, another one for change controls.

Change controls: Change controls were managed using procedure PDIR/PO2 and could be initiated by any member of personnel through form No. PDIR/PO2/E1.

Deviations: Deviations were filed when quality system requirements were not satisfactorily fulfilled. A separate procedure was in place for dysfunction with equipment or premises. The example of the report on the flooding that occurred in the laboratory in August 2013, was reviewed. The laboratory also had a separate procedure in place for variations which were filed for changes to analytical procedures.

Management review: Trending was performed on an annual basis and was seen for 2011 and 2012.

2.3 Control of documentation

Procedure No. PMAQ/PO on documentation management explained the management of the different types of documents being used, distributed and issued by the laboratory.

Procedures were valid for 3 years but were reviewed more frequently if changes were found to be required.

Each procedure had a section for recording the reading and acknowledgement of the procedure at its implementation.

Changes in documents were tracked and a history of changes was available with each standard operating procedure.

Obsolete documents were removed from circulation, stamped obsolete and then stored in the laboratory's archive. This was traced through a table at the end of each procedure.

Master lists of QMS documents (procedures, instructions and forms) were available and generally up to date.

Documents were kept for 5 years in the laboratory's archives. See "Part 5" for observations regarding the archives.

2.4 Records

Training records, calibration and validation records, analytical reports, sample inward registers and maintenance logs were all part of the controlled documentation system and were kept in an appropriate manner.

Inward samples testing registers, contained all of the necessary details such as sample number, denomination, common international denomination, pharmacopeia reference, dosage, dosage form, manufacturer, lot number, date of expiry, date of receipt, customer, methods used and results. This information was maintained in LIMS and in Excel spread-sheets during the transition period between the previous system and the LIMS. Registers were reviewed for both 2012 and 2013 and various examples were reviewed.

2.5 Data-processing equipment

Electronic chromatographic data was backed up every evening. Date and time was server controlled. Data integrity checks were performed and the systems in place to ensure data integrity were deemed acceptable further to CAPAs.

2.6 Personnel

Training was defined in 2 procedures, procedure No. P RH/PO1 which focussed more on continuous training and procedure No. PLCQ/PO29 which focused on initial training upon arrival of a new employee.

Evaluation questionnaires for the different methods for which analysts were declared to be competent were reviewed and were found to be satisfactory in that they truly assessed the analysts understanding of requirements attached to each method in use.

A summary of practical training evaluations specific to each analyst's post was available. This area was considered to be acceptable overall.

2.7 Premises

Laboratory facilities were considered to be acceptable in size and suitable for storage and performing of the analyses. All the surfaces and finishing were suitable for easy maintenance. Premises were kept clean and tidy to ensure safe work. Temperature was continuously controlled. Both temperature and humidity were continuously monitored by electronic means.

2.8 Equipment, instruments and other devices

The laboratory was equipped with:

- 1 Agilent HPLC system (with possibility of refrigeration down to 4°C for the auto-sampler)
- 1 Waters HPLC system (with auto-sampler) equipped with a diode array detector, operated by Empower II.
- 2 dissolution testing equipment (6 vessels).
- 1 disintegration apparatus.
- 1 friability testing equipment.
- 2 balances (analytical, with a lower range of 10 mg).

- 1 FTIR equipment
- 1 spectrophotometer (Shimadzu).
- 1 sonication bath.
- 1 pH meter, trimetric Karl Fisher (3 in 1) equipment.
- Purit® water purification equipment for dissolution media water.
- 2 refrigerators, 1 not in use as it is a back-up.
- dessicators for reference standards.
- Class A glassware (pipettes, volumetric flasks, etc.)
- 1 laboratory glass washer
- 2 water hot baths

Residual solvent testing was not performed.

The equipment and associated accessories were found to be adequately maintained, each labelled with their unique registration numbers and in good order. Files were available containing general data, maintenance, qualification and calibration data.

2.9 Contracts

Microbiological testing was sub-contracted as well as balance and standard weight standardization and balance calibration and maintenance. A valid contract was shown between PMC Milliot and CHMP PAH for this activity.

2.10 Reagents

Evaluation of suppliers

Most of the reagents and solvents were from well-known brands such as Sigma.

Solvents

Flammable solvents were kept in small quantities in a cabinet inside the laboratory and larger supplies were kept in a separate stone/cement building, equipped with spark-proof lighting.

Reagents

Reagents were maintained under controlled conditions in the laboratory. Reagents storage was found to be in good order in that area. Consumption of the reagents was recorded on stock cards and in general was traceable and adequately organized.)

Reagent solutions prepared in the laboratory

2.11 Reference materials

Only primary reference standards were used. They were stored either under controlled room temperature or under refrigerated conditions (2-8°C or -15-26°C). They were labelled with their opening date and the expiry date was recorded.

2.12 Calibration, validation and verification of equipment, instruments and other devices

Mechanical performance verification of the dissolution equipment was performed once a year by an external contractor.

The laboratory performed in house testing using USP Prednisone tablets once a year as well. There was no consideration of whether verification could be necessary on a more frequent basis.

Certified standard weights were recertified once per year by a company called PMC Milliot.

The equipment and instruments were calibrated according to a master schedule. Most were seen to have done within the pre-set dates. The calibration/verification status was clearly visible on the corresponding labels but the target recalibration date was not always visible. Since this information was easily retrievable, this was not considered to be a significant issue.

Excel datasheets

Excel data sheets were in process of being replaced by automatic calculations in LIMS. At the time of the inspection, calculations were performed in duplicate using both Excel and LIMS.

2.13 Traceability

Traceability was deemed to be acceptable and sufficient in that each analysis was retraceable to the unique sample number, to the reference standard that was used, equipment, reagents and to its raw electronic data through laboratory notebooks and the appropriate registers.

2.14 Incoming samples

The laboratory does not perform their own sampling but does provide instructions on how the sampling should be performed to organizations performing sampling for them.

Samples were assigned a unique number. If different samples bearing the same batch number but sampled from a different source were received, each one was assigned an individual batch number.

Samples were given a label with date and time of receipt from which 24 hours are given to record the sample in the system. The sample is received in a temperature/humidity controlled area in which temperatures are monitored continuously since September 2013.

Retention samples were required to be kept until 1 year after the date of expiry, however often these were not retained as the quantity of sample received is usually sufficient for 1 set of tests only.

2.15 Analytical worksheet

Analytical reports were written-up, checked, signed and dated by the analyst, then checked and signed by QA. Excel-based analytical worksheets were briefly reviewed. The data contained in these worksheets were completed by making reference to laboratory notebooks, reference standard and reagent registers. LIMS is soon to be fully implemented.

2.16 Validation of analytical procedures

The decision on how procedures should be validated was described in flowcharts. The first step was to evaluate the specificities and difficulties in applying any new method. If possible, the method was requested from the manufacturer. All of the possible different scenarios were adequately described in the flowchart (i.e., whether the method validation data is available if it is a manufacturer's method, etc...). Feasibility studies were performed whenever a method was not available in the pharmacopeia. Method transfer was not routinely done but was undergoing discussion for artesunate/amodiaquine from Guilin (it is noted that Guilin did not share their method with PAH CHMP when this was requested – this would be necessary due to reproducibility issues).

2.17 Testing

Results of analytical reports, including OOS report of products from prequalified manufacturers were reviewed as examples of how testing was performed.

1. Efavirenz 200 mg capsules from Ranbaxy, Lot No. 2338899. The methods used for impurities were the USP pending monograph V1. It was within specification limits.
2. Lamivudine/Zidovudine/Nevirapine 150 mg/300 mg/200 mg tablets from Ranbaxy, manufactured on September 2011, received on February 15, 2012 at the laboratory, had a no n-conforming test result.
3. Abacavir sulfate 20 mg/mL oral solution from Cipla Ltd, Lot No. G20344, was found to be OOS with an unknown impurity result of 1.8% , with a retention time of 10.5 (eluting before the abacavir peak) and a pH of 4.8, when tested according to the international pharmacopoeia. This result was transmitted to CAMEG Burkina Faso, and was not disputed by the company.
4. Lamivudine/zidovudine 150 mg/300 mg “Avocomb” was seen, lot No. 2348476 from Ranbaxy Laboratories. It was found to be compliant.
5. Tenovofir/Efavirenz/Emtricitabine 300/600/200 mg tablets (lot No. 10911724) from Matrix Laboratories, were found to be OOS (sample No 2012/EXT/2012). Disintegration took more than the specification limit of 30 minutes.
6. Phenoxymethylpenicillin from NCPC North Best Co Lot 120812 was found to be OOS (2012/EXT/201).

A new laboratory analyst (PhD in analytical chemistry) was received in April 2013 and presented changes performed to the manner in which sequences are established.

System suitability calculations were performed in line with the pharmacopoeial monograph requirements but this verification was not documented (see observation under “Part 5”). The procedure for sequences was improved in 2013.

The procedure on sequences No. PCQ/P05/12 was reviewed and was considered acceptable.

2.18 Evaluation of test results

Test results were evaluated by the analyst in charge of the analysis and QA.

The laboratory had a colour identification system in place for analytical reports: red meant that the testing was still in process, yellow meant that it was undergoing QA review while green meant that the results and analytical report had been reviewed and found acceptable.

OOS investigations: The SOP on the management of OOS, PMAQ/03 was reviewed and was considered acceptable further to CAPAs.

There was a procedure in place for working with the manufacturers once they were informed by the client of the OOS and disputed the result.

2.19 Certificate of Analysis

Although not examined in detail due to time constraints, this area was found to be generally acceptable.

2.20 Retained samples

Retained samples were kept in the laboratory's drug distribution center warehouse. These could be tracked in LIMS through the general sample inventory.

2.21. Safety

All analysts received safety and security training. Safety and eye showers were available and tested on an annual basis. The solutions for the eye showers were replaced when expired. Material safety data sheets were available. Chemical fumehoods were verified every year. One of the fumehoods was being refurbished at the time of the inspection.. This area was considered to be acceptable overall.

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, a decision on the compliance of ***Pharmacie et Aide Humanitaire Centre Humanitaire Médico-Pharmaceutique (PAH-CHMP)*** was considered to be operating at an acceptable level of compliance with WHO recommendations for Good Practices for Pharmaceutical Quality Control Laboratories for the scope activities listed below:

- Physical/Chemical analysis of finished pharmaceutical products and active pharmaceutical ingredients

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.

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