World Health Organization

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

Part 1: General information

Name of QC Laboratory (physical and chemical analysis)	PROXY Laboratories B.V.
Physical address	Archimedesweg 25, 2333 CM Leiden, The Netherlands
Name of QC Laboratory (microbiological analysis)	MicroSafe Laboratories
Physical address	Darwinweg 24 2333 CR Leiden, The Netherlands
Date of inspection	7-9 January 2014
Type of inspection	Routine inspection
Type(s) of testing included in the inspection	Physical, chemical, microbiological testing
Summary of the testing activities performed by the QC Laboratory	

Type of Analysis	Finished products	Active pharmaceutical Ingredients
Physical/ Chemical analysis	pH, density, refractive index, optical rotation, viscosity, water content, conductivity, residual solvents, limit tests, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass, content)	pH, refractive index, optical rotation, viscosity, melting point, distilling range, loss on drying, water content, osmolarity, conductivity, heavy metals, residual solvents, limit tests, acid value, iodine value, peroxide value, ester value, hydroxyl value, saponification value, sulphated ash, residue on ignition, total organic carbon, solubility
Identification	HPLC (UV-VIS, PDA, RI, ELSD, conductivity detection), LC/MS,	HPLC (UV-VIS, PDA, RI, ELSD, conductivity detection), LC/MS,

	GC (FID, MS), TLC, UV-VIS spectrophotometry, IR, basic tests	GC (FID, MS), TLC, UV-VIS spectrophotometry, IR, basic tests
Assay, impurities and related substances	HPLC (UV-VIS, PDA, RI, ELSD, conductivity detection), LC/MS, GC (FID, MS), TLC, UV-VIS spectrophotometry, AAS, FTIR, CE, volumetric titrations	HPLC (UV-VIS, PDA, RI, ELSD, conductivity detection), LC/MS, GC (FID, MS), TLC, UV-VIS spectrophotometry, AAS, FTIR, CE, volumetric titrations
Microbiological tests	Sterility test, microbial limit tests, bacterial endotoxins test (LAL), microbial assay of antibiotics, preservative efficacy test	Sterility test, microbial limit tests, bacterial endotoxins test (LAL), microbial assay of antibiotics

Part 2: Summary

General information about the company and site

PROXY Laboratories B.V. (PROXY) offers quality control services for the testing of raw materials, intermediates and finished products and tests to monitor water systems and stability studies. Services include analytical method development and analytical method validation. PROXY also has a small production facility to perform small-scale contract manufacturing for aseptic filling of small batches of (medicinal) products. Since the last inspection PROXY and MicroSafe, a contract laboratory for microbiological analyses for customers, have been merged and all microbiological testing has been transferred to MicroSafe. MicroSafe is also based at the Bioscience Park in Leiden.

PROXY history:

- PROXY laboratories was founded on March 30th 2001
- Acquisition of (the assets of) MicroSafe in March 2012
- Merger between PROXYLABS Holding and Bactimm Farma Holding in December 2012 and founding of Sinensis Life Sciences B.V.

The merger between the laboratories and the foundation of Sinensis do not have a regulatory impact, since the legal entities remain the same.

MicroSafe laboratories history:

- MicroSafe laboratories were founded in Leiden 1993
- Laboratory was cGMP & GLP compliance certified by the Dutch authorities since 1994

- In July 2005 the laboratory became a part of the Millipore Bioprocess Division
- Laboratory was transferred to the new facilities in 2007
- On March 14, 2012 MicroSafe was acquired by PROXY Laboratories
- December 17, 2012 MicroSafe and Proxy Laboratories became part of Sinensis Life Sciences

MicroSafe is not a legal entity, but a second site of PROXY Laboratories.

History of WHO and/or regulatory agency inspections
The Proxy Laboratories were inspected by the WHO team on 24 to 26 July 2010. This was the first WHO inspection at MicroSafe Laboratories.

List of regulatory audits

Auditor	Location	ate(s)
WHO-prequalification	PROXY	24-26 July 2010
OESO-GLP Inspectorate	MicroSafe	14-16 September 2010
SHE-inspectorate	PROXY	5 October 2010
Dutch Health Inspectorate	MicroSafe	20 October 2010
Dutch Health Inspectorate	PROXY	14 December 2010
OESO-GLP Inspectorate	PROXY	12-14 January 2011
US-FDA	PROXY	9-15 September 2011
SHE-inspectorate	PROXY	1 December 2011
Dutch Health Inspectorate	PROXY	16 February 2012
OESO-GLP Inspectorate	MicroSafe	9-16 October 2012
Dutch Health Inspectorate	MicroSafe	4 September 2013
US-FDA	PROXY	14-18 March 2013
Dutch Health Inspectorate	PROXY/MicroSafe	12 September 2013
OESO-GLP Inspectorate	PROXY	7-9 October 2013
SHE-inspectorate	PROXY/MicroSafe	18 November 2013
Dutch Health Inspectorate	PROXY	7-8 January 2014
WHO-prequalification	PROXY/MicroSafe	7-9 January 2014

Focus of the inspection
The inspection focussed at the WHO good practices for pharmaceutical quality control laboratories (GPPQCL). This was WHO and Dutch inspectorate joint inspection.

Inspected Areas
The inspection covered the following sections of the WHO GPPQCL text
- Implementation of CAPAs (corrective actions and prentive actions) from previous WHO inspection
- 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 worksheet
- Validation of analytical procedures
- Testing
- Evaluation of test results
- Certificate of analysis
- Retained samples
- Safety

2.1. Organization and management

At the national level, Laboratory was legally authorized to perform the tests mentioned above. The Laboratory had managerial and technical personnel with the authority and resources needed to carry out their duties. The organization and management structure of the Laboratory was defined.

2.2 Quality system

Quality assurance (QA) documents (SOPs) were approved and available for the laboratory employees to perform different procedures and tasks.

One of the pillars of the quality system was the Out of the Ordinary (OOO) system. This system contained the procedures for handling of changes, non-conformances, Out of Specification (OOS) and complaints. Part of the OOO system was a periodic OOO Board meeting that investigated escalated serious and complex issues. Each PROXY employee was authorized to submit issues to the Board. In this Board the operational and QA managers and relevant specialists participated. Of all four elements of the OOO system annual quality reviews were performed, which have been looked at by the inspectors.

<u>Complaints</u>

Responsibilities regarding complaints were laid down in a specific document. The handling of complaints was described in SOP. Complaints were trended by the following categories:

- analytical method
- batch identification
- mistake in conclusion
- mistake in client project code
- mistake in product name
- mistake in test result
- mistake in sample date
- mistake in specification

- client request more information on CoA
- miscellaneous CoA
- mistake in sample identification
- external issues
- other complaints

Self-inspection

The self-inspection approach was laid down in the document audit policy. QA Manager was responsible for resolution of self-inspection observations. The following QS system elements were covered by the self-inspection:

- supplier system
- QS
- sample flow
- equipment system
- training system
- good distribution practice system
- archive system
- good laboratory practice system
- human resources system

Self-inspections of different elements were carried out quarterly.

2.3 Control of documentation

There were procedures in place to generate and approve SOPs, records and analytical work books as well as procedures for issuing certificates of analysis (CoA). Distribution of the documents was controlled. Documents were protected from editing. Access to the original electronic files (in Word format) of the documents was granted to QA staff only.

The QA documents control system at Proxy and MicroSafe were paper based; the procedures, forms, and logbooks were generated digitally, but control was maintained in a paper system. Electronic documents as "read only" were available for all employees.

Documents were released after 2 weeks of approval. Two weeks were given to the relevant employees to read the document and to be trained on document/new version of the document.

Paper documents were archived for 15 years.

2.4 Records

All original observations, including calculations and derived data, calibration, validation and verification records and final results were retained. Records included data recorded by analysts in analytical worksheets. The records for each test contained sufficient information to permit the tests to be repeated and/or the results to be recalculated. The records included the identity of the personnel involved in preparation, testing of the samples and reviewing the test results. All laboratory analysis package including laboratory journals (in case the analysis was not performed in accordance with compendia method) initially were "buddy checked" and afterwards submitted to reviewers.

2.5 Data-processing equipment

Back up of electronic data was carried out regularly. Laboratory explained that there are two types of back up "cold" and "hot". Cold back up was carried out every week and hot every day. Back up data was stored on separate server on 2 different disks.

2.6 Personnel

Training

The high level training approach was described in the training policy. Underneath a number of detailed descriptions were laid down in SOP's, such as the SOP for introduction training. According to the general policy every employee started with the same basic training, but in the specific introduction training SOP 4 different levels were defined of which the supervisor of the new employee decided up to which level training was required.

Technicians who perform manual integration of HPLC peaks had to be qualified and re-qualified every year by independently performing manual integration and comparing the results obtained by colleague technicians. Also for some other defined tests technicians have to be re-qualified by performing a qualification twice per year.

The training system allowed for disqualification and requalification of an employee for analytical tests if required.

Job descriptions:

Job descriptions (responsibilities) were available for all personnel. The following job descriptions were reviewed and assessed to be accurate:

- Manager QA/ QP.
- Responsible persons for receiving samples, chemicals, manufacturing materials and reference standards. Those responsibilities were shared by three trained technicians.

Job descriptions were kept in personal binders.

2.7 Premises

Archives

Archive facilities ensured secure storage and retrieval of all documents. Access to the archives was restricted to the designated personnel. There were separate archives for:

- analytical data (projects)
- equipment binders, training files and GLP studies
- current QS documents
- most recent GLP studies

Chemistry section:

The Analytical laboratory facilities were acceptable in size and suitable for performing of analyses. Surfaces and finishing were suitable for easy maintenance. Premises were kept clean and tidy to ensure safe work. Temperature and RH was routinely controlled and recorded in the different areas.

Microbiology section:
The Microbiological laboratory facilities were located on 4th floor and were of a suitable size and construction and were designed to suit the functions and operations to be conducted in them. Surfaces and finishing were smooth. Premises were kept clean and tidy. There was general warehouse for storage reagents, media and materials.

The following tests were carried out in "clean" room:
- Limulus amebocyte lysate (LAL)
- Bioburden (BB) for WFI
- incubation of sterility test

The following tests were carried out in one room what was separated in 2 similar rooms containing 2 LAF boxes:
- microbial enumeration tests
- growth promotion test
- incubation of environmental monitoring tests
- microbial bacteria tests
- preparation for organisms identification testing
- preparation of master strains passages

Separate room was used for antibiotics testing. Tests were performed in LAF box.

Sterility tests were performed in a Class A barrier isolator placed in a Class C cleanroom. The isolator was sterilised by VHP. The standard program of the isolator included a leakage test. The gloves were replaced at least once every three months. Before entering the sterility testing room there were several change rooms. Pressure differentials between change rooms and sterility testing room were monitored.

Isolator qualification was carried out by contractor annually for:
- HEPA filters integrity
- air velocity
- viable and non-viable particles
- pressure differentials
- gloves integrity

A separate air handling unit (AHU) was installed to supply the air to the Microbiological laboratory sterility testing room including change rooms. Rooms were supplied with 100% fresh air. Final HEPA filters were installed in the respective rooms.

Area classification had been carried out by a contractor. Tests performed were in accordance with ISO 14644 standard annually for:
- viable and non-viable particles
- air velocity
- air changes per hour
- HEPA filters integrity test.

2.8 Equipment, instruments and other devices of physical/chemical and microbiological laboratories:

Each item of equipment and instrument used for testing, verification and calibration was uniquely identified. IQ, OQ and PQ were carried out. Labels attached to the equipment and instruments showed calibration date and calibration due date. Critical equipment including incubators, fridges, freezers and stability chambers were connected to an emergency power system. Alarms of critical equipment and air pressure cascades for the sterility test suite and changing rooms were monitored. Excursions passing the pre-set limits lead to an alarm being raised to mobile phones.

The microbiological laboratory autoclave was only used to sterilise equipment parts used for tests, not for waste. Waste was removed by a contractor. Pre-sterilized disposable equipment, like filters, syringes and needles were used in the microbiological laboratory.

2.9 Contracts

N/A

2.10 Reagents

Purchases

Solvents and reagents were purchased from reputable, approved suppliers and were accompanied by the certificates of analysis (CoA). The material safety data sheets were available for laboratory technicians.

Evaluation of suppliers

Approved supplier's list was shown to the inspector. Approved suppliers lists were available for:

- equipment
- service providers
- non – GMP materials
- materials, disposables etc. used in manufacturing process
- media and microbial cultures
- consumables:
    - chemicals
    - reagents
    - reference materials

Solvents and reagents

Solvents and reagents were properly labelled with date of receipt, date of opening the bottle/package and expiry date. If expiry date was not specified on the CoA expiry date was defined by the laboratory technicians responsible for receipt of reagents. Two ways of setting the expiry date was applied:

- maximum 5 years from the date of manufacture or
- maximum 5 years from the date of receiving

Defined expiry dates were generated from the laboratory experience.

Water
Milli-Q water was used for TOC analysis and purified water (PW) for other analysis. PW was generated by reverse osmosis. PW was tested once per 3 months in accordance with PhEur. Milli-Q water was tested once per month.

Microbiological laboratory used commercially purchased water for injection or water for irrigation. CoAs were available for both kinds of water.

Reagent solutions prepared in the laboratory
Preparation of reagents and volumetric solutions in the laboratory was adequately documented. Reagents and solution labels contained required information.

Culture Media
Microbiological laboratory used commercially purchased "ready to use" culture media. Growth promotion tests of media were carried out for every batch. Before release (growth promotion tests) media were stored in separate quarantine area.

2.11 Reference substances and reference materials
Mainly Pharmacopoeia reference standards were used. If Pharmacopoeia reference standards were not available, customers supplied laboratory with working standards. Working standards were dispensed in glove box (if required also under nitrogen). Working standards were qualified against primary standards and dispensed in aliquots. Inventory and usage of each reference and working standard was recorded into individual log books.

2.12 Calibration, validation and verification of equipment, instruments and other devices
The planning of the maintenance and calibration of most of the laboratory equipment was indicated on a planning board. For individual equipment a laboratory technician was made responsible to perform the in-house maintenance and calibration in a timely matter. Maintenance and calibration programmes were adequate and also the documentation was assessed to be under control. The laboratory itself was quite large, well organized and was equipped with a large numbers of instruments to perform all the different tests. Temperature monitoring of critical equipment was carried out continuously via BMS system and T mapping studies of fridges, freezers, incubators and stability chambers were carried out annually.

All laboratory equipment had the following binders:
- calibration
- maintenance and defects
- cleaning

Some examples of the equipment calibration were checked.

Excel datasheets
For a number of tests Excel sheets were used for calculation. A dedicated SOP was presented on the use of Excel spread sheets, calculators and rounding. The approach of controlling spread sheets had been looked at. Each test, if applicable, had its own approved and controlled spread sheet, containing fixed calculation factors, which cannot be changed by a technician.

The software of the HPLC's has been evaluated as per US Food and Drug Administration Code of Regulations part 11.The audit trail was fully traceable and back up of raw data was maintained for 15 years.

Proxy Information Management System (PIMS) was in – house developed and validated system. Some validation documentation was spot checked. PIMS was use as inventory system, except for equipment.

2.13 Traceability

The reference material(s), equipment(s), reagent(s), culture media, analyst(s), calculation(s) were suitably recorded in the analytical test report and traceability was deemed suitable and sufficient.

2.14 Incoming samples

Sample receipt area was inspected. At arrival samples were logged in the PIMS and recorded on a paper format. The PIMS was used for fast tracking of information, but the paper forms were leading. At arrival samples were checked for damage and contents. Documents supplied together with the samples were reviewed and also checked. Labels had unique Project number (identity number) which was traceable till the Certificate of Analysis (CoA). Project number was generated by the PIMS. Most of the samples were stored at room temperature; some were stored at 2 – 8 °C and a few at -20°C.

After the samples have been logged in, the paper form went to Operational QA, where all relevant documentation, such as analytical test records and copies of the relevant part of the pharmacopoeia, were collected.

Sample submission forms were available to the public at Proxy Laboratories web page.

According with laboratory policy samples should be analysed within 10 working days.

2.15 Analytical worksheet

Separate analytical worksheets (WS) were used for different tests. WS were signed by technician who performed the tests and reviewer. WS were paper based documents and were issued by Operational QA. WS were prepared based on analytical test methods.

2.16 Validation of analytical procedures

The methodology of performing assay validation studies had been looked at on the basis of two specific examples. Therefore a specific analytical method validation protocols and reports were reviewed. The studies were performed according to ICH Q2 guidelines and were assessed as being adequate

2.17 Testing

The samples were tested in accordance with the work plan of the laboratories. After logging the incoming samples to the registers, samples were forwarded to the laboratories for testing. Two types of sterility tests were performed - direct inoculation and membrane filtration.

2.18 Evaluation of test results

Investigation of out of specification results (OOS)
SOP "OOS" was based on US FDA guideline. SOP was supplemented with flow chart and check list. Customers were informed about all OOS cases. A specific OOS investigation report was reviewed and found to be appropriately carried out.

2.19 Certificate of Analysis (CoA)
After all tests have been performed the completed records together with the report form with the test results, and if applicable copies of logbook pages, were returned to Operational QA. They perform a review of all laboratory documentation and prepare a CoA. CoA was checked by the QA personnel and approved by the Manager QA.

2.20 Retained samples
Samples were retained as per customer's requests. In case customer did not specify sample retention time sample was retained for 2 weeks. In case of OOS result, sample was retained for 4 weeks.

2.21 Safety
Safety and eye showers were available. Smoking, eating and drinking was not allowed in the laboratory. Staff was wearing laboratory protective clothing and glasses.

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, ***PROXY Laboratories B.V.*** located at Archimedesweg 25 and Darwinweg 24, 2333 CM Leiden, The Netherlands was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories for the scope activities listed below:

- Physical/Chemical and microbiological 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.