World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Quality Control Laboratory

Part 1	**General information**		
Inspected laboratory details			
Name of Laboratory	APTYS PHARMASERVICES		
Address of inspected laboratory site	Biopôle Clermont-Limagne F-63360 Saint Beauzire France		
Inspection details			
Dates of inspection	8-9 October 2018		
Type of inspection	Initial		
Introduction			
Brief description of testing activities	**Type of Analysis**	**Finished Products**	**Active pharmaceutical ingredients**
	Physical/Chemical analysis	pH, density, water content (Karl Fischer), friability, disintegration, tablet hardness, dissolution, viscosity, dimensions, uniformity of dosage (mass, content), extractable volume, average volume.	pH, water content (Karl Fisher), loss on drying, viscosity, residual solvents, limit tests, solubility, conductivity
	Identification tests	HPLC (UV-VIS detection, RI), RI, FTIR, UV-VIS spectrophotometry, TLC, chemical reaction (basic tests).	HPLC (UV-VIS detection, RI), RI, FTIR, UV-VIS spectrophotometry, TLC, chemical reaction (basic tests).
	Assay, impurities and related substances	HPLC (UV-VIS detection, RI), AAS, ICP, UV-VIS spectrophotometry, gravimetric analysis, volumetric titrations, Potentiometry	HPLC (UV-VIS detection, RI), AAS, ICP-MS, UV-VIS spectrophotometry, gravimetric analysis, volumetric titrations, Potentiometry
	Microbiological	Subcontracted	Subcontracted

	analysis		
	Stability Testing	Under ICH conditions	Under ICH conditions

General information about the laboratory	APTYS PHARMASERVICES was established in 2002 as a private contract research and development organization. The laboratory obtained ISO 9001:2008 certification in 2011 and ISO 9001:2015 in 2018. The laboratory has been granted GMP license issued by the French authority ANSM but have not as yet been inspected or certificate issued. APTYS PHARMASERVICES provides the following services: • Custom-made formulation and complex generic development – including design, production of prototypes and controls of liquid, semi-solid and solid dosage forms. • Quality control and ICH stability, analytical development and validations • Production assistance – including scale-up and technology transfer. Customer support for design, installation and qualification of a production plant. The laboratory does not perform microbiological, bacterial endotoxin or sterility testing.
History of inspections	WHO: it is the first on-site inspection by WHO Laboratory was inspected by: • Bureau Veritas ISO certification 2018
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	All areas within the facility
Restrictions	None encountered
Out of scope	Not applicable

Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GMP	Good manufacturing practices
HPLC	High performance liquid chromatography (or high-performance liquid chromatography equipment)
KF	Karl Fisher titration
LIMS	Laboratory information management system
MB	Microbiology

MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometry or spectrophotometer

Part 2	**Summary of the findings and comments (where applicable)**

1. Organization and Management

APTYS PHARMASERVICES had a well-defined organization and management structure. Laboratory responsibilities, authority and interrelationship of personnel were specified in job descriptions and organization charts. The total number of personnel accounted to twelve (12) at the time of inspection.

Senior Management is involved and committed to the Quality Management System and its application. They have ensured availability of managerial and technical personnel with appropriate authority and resources needed to carry out their duties as defined in their job descriptions. The personnel have ability to identify the occurrence of departures from the quality system as well as initiate actions to prevent or minimize such departures. Procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures are in place.

Summary of roles and responsibilities are specified in signed job descriptions. An Organogram defines the relationships between management and technical personnel. The Deputy Responsible Pharmacist should have a complete understanding of the activities of the Quality Department.

2. Quality management system

There was an established, implemented and maintained Quality Management System (QMS) according to the requirements established in ISO standard 9001:2015. The laboratory obtained ISO 9001:2008 certification in 2011 and ISO 9001:2015 in 2018 from Bureau Veritas Certification. The quality manual was accessible to all staff. The laboratory had displayed the quality policy.

Management Review:
Although the size of the company is small and management reviews take place frequently, addressing all required matters with due attention. The site had an established management review process and addressed all issues raised.

Quality Risk Management:
The laboratory had a procedure in place for the identification of risk and a process of monitoring such risks. The laboratory had successfully addressed issues identified during inspection.

Data Integrity:
A SOP was implemented detailing the scope, responsibilities, procedure and audit trails involved. A thorough understanding of the key role it plays in pharmaceutical analyses of Inactive (IPI) and Active Pharmaceutical Ingredients (API) as well as Final Pharmaceutical Product (FPP) analyses providing a COA for release of batches to market by the License Holder was available within this document. The scope included but was not limited to sample receipt records; QC practises, issuing and use of note books, documented results and printed records, reviewed results, computerised system details and retrieval of it; software program functionalities and disaster recovery. Identified issues were successfully closed during the CAPA review.

Internal Audits:
The laboratory had in place an internal audit process and an annual schedule that was planned at the beginning of each calendar year. The plan for 2018 was reviewed and audits were currently on schedule. Due to the small size of the company resources were limited and further consideration was required when planning audits and areas of high risk to be prioritized. Gap analysis audits were scheduled. Audit reports were available with listed findings. The laboratory had successfully addressed issues identified during inspection.

Corrective and Preventive Action:
The laboratory had a SOP in place, ensuring that adequate Corrective and Preventative Actions take place. Identified issues were successfully closed during the CAPA review.

3. Control of documentation

The laboratory had an established document control. Due to the small size of the laboratory all documents were available electronically with only a selected few hard copies in the laboratory at the workstations. Documents were reviewed on a three-yearly cycle and revision dates were recorded in an excel spreadsheet. Limited information on revision dates was available on the documents. A master list of documents was available.

There was a process in place for the archiving of documents and records. The original copies of documents and laboratory notebooks were stored in a locked cabinet in the office of the QA and QC managers and in a cabinet in the store room/stability chamber. All documents and records were scanned, and electronic data stored on external drives.

Changes made to documents was communicated with Personnel
Laboratory notebooks were printed by an external company. All laboratory books contained a unique serial number as well as an internal unique identifying number. The laboratory had successfully address issues identified.

4. Records

Analytical data were recorded in laboratory notebooks and were fully traceable to samples, instruments, test procedures and reference standards. Records related to laboratory activities such as instrument qualification, calibration, raw data, test results and reports were stored. The laboratory had successfully address issues identified during inspection.

5. Data processing equipment

Within the laboratory there were several HPLC instruments, UV & IR Spectrophotometer, and a micro-analytical balance that were linked to computers or provided printouts. Each analyst had their own login for the computers within the laboratory. Administration rights were restricted, preventing analysts to alter time and date stamps on the computer. All equipment was well maintained with appropriate log and maintenance records available. Identified issues were successfully closed during the CAPA review.

6. Personnel

The personnel met during the inspection were experienced, skilled and knowledgeable in the tasks they were performing. An organizational chart was available clearly identifying roles and responsibilities. A process was in place for regular performance reviews, including review of training requirements and job description for all staff. A process was in place to train Personnel on the core functions every three years and all records were available.

Generally, the laboratory had sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions. Personnel performing specific tasks were appropriately qualified in terms of their education, training and experience, as required.

7. Premises

The laboratory premises were clean and tidy and provided adequate room for laboratory activities. The laboratory environment was appropriate for performing different tests. The laboratory consisted of several rooms with a separate stability chamber containing a number of refrigerators, freezers and incubators at different temperatures and humidity. The main laboratory housed the HPLC instruments, a glass washing area, pH meter, balance and chemical storage. A second smaller room was dedicated to chemical tests including dissolution and UV spectrophotometry. A microbalance was housed in this room on a separate stand-alone bench. Log books were available for each piece of equipment.

8. Equipment, instruments and other devices

The equipment within the laboratory contained unique identification number, calibration dates and next due dates. External maintenance records were available. There was a Planning qualification 2018 excel spreadsheet that listed all internal and external qualification of equipment. All temperature sensitive equipment and room temperature and humidity monitoring was in place with parameters being measured at 5 minute intervals.

All external calibration reports were signed by the QC manager and verified before being released for use within the laboratory.

Temperature mapping had been performed in the stability chambers. This was conducted by an external company. This was conducted annually and last performed 30/1/2018. All records were available. Mapping was conducted at the same time as the general maintenance or the stability chambers.

A procedure was available for the cleaning of glassware within the laboratory.

Identified issues were successfully closed during the CAPA review.

9. Contracts

A newly established process had been implemented for the auditing of external contractors and Technical Quality Agreements. The laboratory had successfully address issues identified during inspection.

10. Reagents

Due to the small size of the laboratory, weekly inventories were performed to review stock levels. Deliveries were received via the reception area, technicians were informed of the delivery and orders or samples were placed into the laboratory for further processing. A data base of deliveries was available.

11. Reference substances and reference materials

Reference standards were stored in the laboratory in a cabinet. All references were labelled for use with an expiry. Once expired references were destroyed. Temperature sensitive references were stored in the stability chambers. As there were currently no samples in this chamber it was not an issue. However, it was raised by the inspectors that temperature fluctuations of the stability chamber when retrieving reference samples was not best practice.

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

Equipment was calibrated and qualified with all records available. Labels indicating equipment calibration status were affixed to all equipment and instruments. The laboratory had successfully address issues identified during inspection.

13. Traceability
Test results were traceable to analyst, analytical instruments, equipment (including HPLC columns), reagents, reference substances and test procedures. Identified issues were successfully closed during the CAPA review.

14. Incoming samples
The laboratory had a central electronic registry dealing with receiving and distribution of the samples. A process was in place for the reception of goods. The laboratory corrected issues raised during the inspection and successful implementation will be verified at next inspection. Identified issues were successfully closed during the CAPA review.

15. Analytical worksheet
Analytical worksheets were generally neatly competed with limited corrections of entries and results.

16. Testing
The samples were tested in accordance with the methodology requested by the contacting organization. Test results were recorded in laboratory notebooks. The laboratory participated in an appropriate proficiency testing scheme.

17. Evaluation of test results
The laboratory had a process in place for the review of results. All results were compiled into a laboratory notebook and signed by the QC manager daily.
Identified issues were successfully closed during the CAPA review.

18. Certificate of analysis
CoA`s were signed by the responsible analyst, head of the laboratory and approved by the coordinator of the division.

19. Retained samples
Retained samples were appropriately stored in the stability chamber area. The samples were kept until the end of analysis. Samples were returned to the customer upon request, otherwise they were destroyed at the end of the study and Destruction Certificates were in place.

20. Safety
Laboratory personnel were observed wearing appropriate PPE when in the laboratory. There was hand washing facilities within the laboratory area. Only electronic MSDS were available, there were no hard copies, or a register of chemicals stored within the laboratory. The facility was clean, shelves and cupboards were clearly labelled with contents. A laboratory technician was assigned the responsibility of safety.

Part 3	Conclusion – Inspection outcome

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, ***APTYS PHARMASERVICES***, located at ***Biopôle Clermont-Limagne F-63360 Saint Beauzire, France*** was considered to be operating at an acceptable level of compliance with WHO GPPQCL Guidelines.

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 manufacturer, 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.

Part 5	List of WHO Guidelines referenced in the 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 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

3. 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/
4. 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

5. 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 GDRMP guidance or ***WHO TRS No. 996, Annex 5***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

6. 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/

7. 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/

8. 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 3.
   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

9. 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

10. 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

11. 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

12. 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

13. 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/

14. 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/

15. 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/

16. 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

17. 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

18. 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

19. 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. 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