PHAGOPROD

Phage therapy, that is the therapeutic use of bacteriophages for the treatment of pathogenic bacterial infections, is a highly promising answer to the antibiotic resistant scourge (1,270,000 deaths directly attributable to antibiotic resistance worldwide in 2019[1], 10 million forecasts by 2050[2]).

In this promising field, Pherecydes Pharma has developed phages products obtained by purification and amplification of natural phages against strains such as P. *aeruginosa*, S. *aureus* and E. *coli*. These treatments are specific to each patient, which means that only the active phages against the strains will be administrated to the patient. As part of this personalized medicine treatment, an in vitro diagnostic test is performed to determine the patient's strain susceptibility to the phage. This diagnostic test is called phagogram and was developed by Pherecydes Pharma.

In this context, Phagoprod has been defined to implement, optimise and scale-up the GMP manufacturing and diagnostic processes currently developed at the laboratory scale. Thus, the final objective is to achieve large-scale commercial exploitation of Pherecydes Pharma's products, first at the EU level, then at the US level.

To this end, Phagoprod project was designed with 2 major milestones:

- the GMP upgrade of a manufacturing and Quality control plant running at an industrial level and

- a medical biology laboratory for diagnostic running at an industrial level.

This project is important for society to keep and develop Pherecydes Phama's expertise in phage production, quality and phage therapy.

Regarding the diagnosis site

The Diagnostic site is integrated into the new Pherecydes facilities built in Nantes. The plan and set up of the Diagnostic site have been carefully designed, monitored and controlled under the guidance of consultants. To support them, CERIS, an architectural firm specialized in pharmaceutical sites has been appointed by Pherecydes Pharma. In addition, Nantes Metropole, which hosts the laboratory is supported by AIA architects which specializes in hospital and clean room installation. All these actors finalized the construction plans in April 2018. Regular site construction monitoring meetings are held with Nantes metropole, AIA, CERIS and Pherecydes Pharma (Q4-2018) and minor modifications/adaptations are implemented as the construction progresses.

From 2021, a dedicated team has been recruited to carry out the implementation of the Diagnostic laboratory, with the support of expert consultants (5QBD-Biotech). It requires an important amount of work, on the phagogram test itself and on the QMS (Quality Management System). The 2 main achievements are:

- The development and validation of the IVD test (Phagogram) in accordance with the IVD Directive 98/79/CE

- (ii) the design and implementation of a QMS compliant with the ISO 15189 (Medical Biology Laboratory).

Indeed, to comply with the Directive 98/79/CE, a file, called "Technical documentation", must be available,

[1] The Lancet

[2] Rapport de Jim O'Neill, 2016

containing the following topics:

(a) The analytical evaluation of the IVD - In Vitro Diagnostic -;

(b) The set-up of a QMS - Quality Management System - ;

(c) The Risk Analysis.

Afterwards, the "self-certification" according to the Dir 98/79/CE can be carried out, by May 2022.

The phagogram 1.5 was developed by the Diagnostic manager (PhD, PharmD), who joined in May 2021, together with the Expert technician (transferred from Pherecydes R&D Department) in liaison with the CSO and Quality Director. The analytical performance of the phagogram was performed Q4-2021, showing its reproducibility and robustness.

The GMS design was defined in Q4-2021, by the expert consultant 5QBD-Biotech, in conjunction with the new QA engineer (who joined in Sept 2021) and the diagnostic team.

Regarding the production site

An agreement has been signed with MB Pharma to bring its production site up to GMP standard.

Pherecydes reviewed and supervised the organization of the quality control laboratories set-up, including the choice of equipment and machineries in line with GMP compliance. Throughout the years of the project, Pherecydes Pharma has written documentation required for the regulation such as the detailed definition project, the user requirement specifications for the equipment, the validation master plan, the master standard operational procedures that explain how Pherecydes Pharma wants to manage the site and the quality on the site (deviation, change control, preventive actions and corrective actions, training management, audit...)

Most equipment was bought and transferred to our production site (MB Pharma).

The equipment qualification, training and qualification of the MB Pharma team, choice of GMP raw material, including buffer solution, aseptic process validation, and documentation writing were performed in 2019/2020, to ensure that MB Pharma could produce batches that meet GMP/ICH requirement.

A strong collaboration has developed over the years between Pherecydes Pharma and MB Pharma teams, through discussions, meetings, audits, improvement plans. The production plan and process robustness were enhanced with the arrival of a new Industrial Operation Director in March 2021 in Pherecydes Pharma.

All GMP batches produced in 2020 and 2021 (10 batches in total) have all been confirmed by the MB Pharma's QP (Qualified Person), demonstrating the CDMO's capability to produce GMP/ICH compliant batched, in a consistent manner.

The project resulted in three major innovations:

- The capacity to produce GMP batches of phages

MB pharma is now able to produce phages under GMP conditions which represents a real breakthrough in Europe. From now on, Pherecydes can rely on MB Pharma for the production of batches for its clinical trials.

- A semi-automated, operator diagnostic in place

In December 2021, the Phagogram 1.5 was finalised and "validated" according to the performance evaluation carried out in Q4-2021. A Semi-automated system will be developed for the next generation of Phagogram (2.0), planned for 2023/2024, through the collaboration with the CEA Leti that started in Q4-2021 (a program funded by the French agency BPI).

- A Medical biology laboratory status granted

In December 2021, the QMS was designed with the main forms to trace the diagnostic activity. The risk analysis has been completed at 75%. The IVD performance evaluation has also been completed.

The implementation of the QMS, with all documentation work was performed in Q1/Q2-2022. The formalizing of this performance evaluation of the IVD was also completed Q1/Q2-2022, as well as the finalization of the Risk analysis.

The Diagnostic team continues to grow to meet clinical needs. The hiring of technicians (2) and Diagnostic assistant (1) has also been undertaken in Q1-2022. Training and qualification are planned for Q1/Q2 2022.

The self-certification, after all the work performed and formalized in the “Technical Documentation” is planned by the end of May 2022.