# A cGMP FACILITY DEDICATED TO THE BIOPRODUCTION OF LENTIVIRAL BASED THERAPEUTIC VACCINES AND OTHER T-CELL BASED THERAPIES

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## BACKGROUND

THERAVECTYS is a privately-owned, fully integrated discovery and clinical development biotech company originating from the Pasteur Institute. The company capitalizes on over 15 years of fundamental research in the field of lentiviral vectors and owns over 20 patent families, either developed in-house or exclusively licensed from worldwide renown institutions from which the company has secured exclusive worldwide rights for the use of lentiviral vectors in vaccination and immunotherapy applications.

Based on its lentiviral vector technology platform, THERAVECTYS develops therapeutic vaccines and immunotherapies to fight cancers and infectious diseases, including a proprietary and differentiated CAR T-cell technology platform.

The company has recently completed the first-ever vaccination clinical trial conducted with lentiviral vectors confirming both the safety & immunogenicity of the lentiviral vector platform.

## THERAVECTYS' TECHNOLOGY

The lentiviral vectors have the unique ability to transduce enables dividing cells - such as T-cells - but also non-dividing cells - such as dendritic cells in a stable manner.

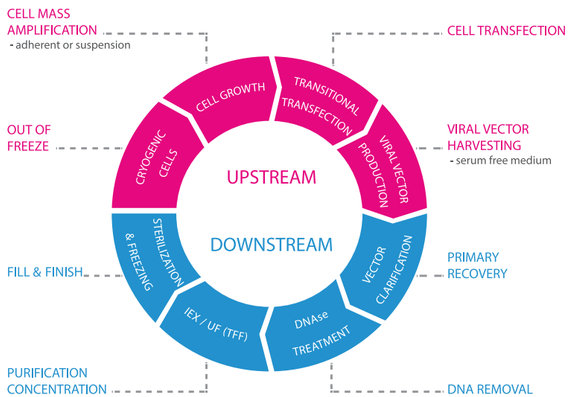
The transgene encompassed in the lentiviral vector are under the regulation of a proprietary patented human promoter (beta-2 microgobulin) that is overexpressed in APC but also in T-cells and NK cells.

This integrative, non-replicative, non-pathogenic and self-inactivating recombinant lentiviral vectors derived from the HIV-1 NL4-3 strain has been successfully used in a therapeutic clinical trial against HIV and will be used to initiate two additional phase I/II in oncology including one CAR T-cell trial.

## BIOPRODUCTION PROCESS

THERAVECTYS designed an innovative manufacturing process combining high production yields, impurity profiles compatible with direct injections into humans and high immunogenicity.

The process is spread out over 3 weeks, starts by an expansion and transient transfection of HEK293SF cells (USP step, 18 days) and encompasses 2 purification steps (DSP, 2 days), followed by a sterilizing filtration before filling. The bioproduction process will be using state-of-the-art bioreactors (from 20 to 1.000 L) and semi-automated single-use dowstream and fill-and-finish equipements. The expected batch size will be between 200 up to 5.000 vials, and fully compliant with phase III clinical trial requirements.




## QUALITY CONTROLS

THERAVECTYS has developed proprietary, specific and validated assays to control the quality of its lentiviral vector batches such as RCL (replication-competent lentivirus), lentiviral vector titration by qPCR, residual DNA characterization etc.

Upon approval of our proposed QC plan by the European Regulatory Agency, the French and the Belgian regulatory agencies have granted THERAVECTYS with the approval to launch its first clinical trial.

Additionally, the QC plan has also received a positive feedback from the FDA during a pre-IND meeting late 2014.

While some of the QC methods remain to be adapted to the targeted indications (transgene expression, provirus sequence integrity, etc.), most of them are applicable to any lentiviral vector-based vaccine candidates Additional QC have been recently developed and implemented (MOI, integration profile...) to support THERAVECTYS' adoptive T-Cell clincial developments.

**MAIN STEP PRODUCTION TESTING & RELEASE CONTROLS DETAILS:**

| TEST | BULK | DRUG SUBSTANCE | DRUG PRODUCT |
|---|---|---|---|
| **SAFETY** | | | |
| Mycoplasma | ELISA | | |
| Mycobacteria | Culture | | |
| Adventitious Virus | Culture | | |
| RCL | | Culture + Detection | |
| **DOSAGE / ACTIVITY** | | | |
| Infectious Titer | qPCR | | |
| Physical Titer | | P24 | |
| Immunogenicity | | | ELISPOT |
| Transgene expression | | | FACS or WB |
| **IDENTITY** | | | |
| Transgene Identity & Integrity | | | Sequencing |
| Enveloppe Identity | | | Seroneutralisation |
| **PHYSICOCHEMICAL PROPERTIES** | | | |
| pH | | EP/USP | |
| Osmolality | | | |
| Appareance | | | EP/USP |
| Extractible volume | | | EP/USP |
| **PURITY** | | | |
| Endotoxin | EP/USP | | |
| Total Protein | | BCA | |
| HCP | | ELISA | |
| Residual DNA | | Picogreen | |
| Residual Benzonase | | ELISA | |
| **MICROBIOLOGY** | | | |
| Bioburden | EP/USP | | |
| Sterility | | | EP/USP |
| **SEALING** | | | |
| Container integrity | | | Vacuum testing |

## A cGMP BIOPRODUCTION FACILITY

In January 2015, only 12 months after the initiation of the works of its plant, THERAVECTYS has been granted the status of a GMP pharmaceutical manufacturing establishment by the French National Agency for Medicines and Health Products Safety (ANSM).

The new facility will be used to fulfill the company's internal clinical development program needs, in addition to those of strategic pharmaceutical partners. In the coming months, THERAVECTYS will produce cGMP lentiviral vectors for its first phase I/II clinical trial in oncology (adult T leukemia/lymphoma induced by HTLV-1) and for its differentiated CART-cell-based immunotherapy upcoming clinical trial.

## MAIN PLANT CARACTERISTICS

| CONTAINMENT | SURFACE |
|---|---|
| **Biosafety level 1:** Vectorology Platform | 410 m² |
| **Biosafety level 2:** Immuno-monitoring Platform | |
| **Biosafety level 2+:** R&D Production Platform & Process Development Platform | |
| **Biosafety level 3:** QC laboratory for cell culture | |

| CLEAN ROOM CLASSIFICATION *(In accordance with EN ISO 14644-1)* | CONTAINMENT | SURFACE |
|---|---|---|
| **Grade D :** First Airlock | **Biosafety level 3:** production unit | 340 m² |
| **Grade C:** Preparation, USP & DSP | | |
| **Grade A in B:** Fill & Finish | | |
| **Non classified:** Secondary packaging & storage areas | | |

With a total surface area of 750 m2, including 340 m2 multiple grade cleanrooms (A, B and C), THERAVECTYS' manufacturing facility will integrate both production and quality control activities.

The site has been designed to optimize operation and product workflows.

## NEXT STEPS

THERAVECTYS has continued to improve its industrial processes to strengthen its trade secrets and Intellectual Property (IP).

Major accomplishments include the development of a stable cell line to increase production yield, the implementation of an improved lyophilization process leading towards a more stable final product, as well as the design and the validation of new, specific and proprietary quality controls.

These achievements, and the company's unique and unrivaled expertise, offer a significant competitive advantage in the field of immunotherapy.