# Generic Project Plan for Cell and Gene Therapy (CGT) Products from Greenfield to Manufacturing License

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## INTRODUCTION

Advanced therapy medicinal products (ATMPs) are supposed to play a significant role for personalized medicine in the future. In particular, cell and gene therapy products (CGT) are crucial in this development. Some products are already in the market launch, many new products will come soon. A well-structured project management plan for design, construction and start-up is seen as a useful tool for obtaining a manufacturing license. Using a PM software tool, all the requirements are specified that need to be considered and evaluated in time. Such a generic project plan is provided by Valicare in order to work out and adapt the necessary requirements of our customers.

## INDIVIDUALIZED THERAPY

ATMPs offer new therapeutic approaches for previously untreatable diseases. From cancer therapy to the treatment of autoimmune diseases, to specific (stem cell-dependent) injuries, individualized therapeutic approaches can provide not only mitigation, but also cure. Thereby, ATMPs will play a central role.

## ADVANCED MEDICINE

Unlike conventional medicine, the development and production of ATMPs is based on complete cells or their biomolecules. It is a heterogeneous group of preparations. By definition, ATMPs are used as gene therapeutics, somatic cell therapeutics or bio-engineered tissue products. All ATMPs have in common that their starting materials are substantially modified.

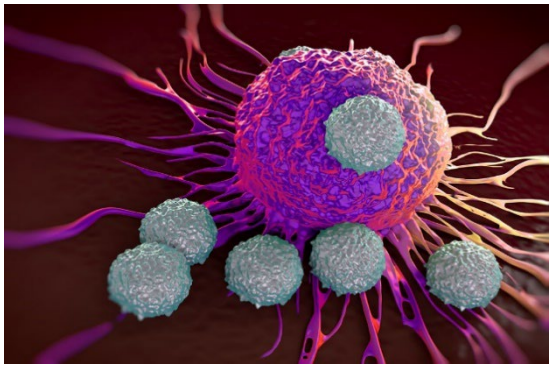

**Figure 1. T cells are attracting a tumor cell.**

Gene therapeutics (manipulated nucleic acids) are used to correct genetic defects or inborn errors of metabolism genetically. On the other hand, cells are isolated, stimulated, expanded, and/or genetically modified specifically for cure or for attacking abnormal cells that are harmful. Currently, the most prominent example are CAR-T cells used for the therapy of lymphomas and leukemia (see Fig. 1).

## DEVELOPMENT GOES ON

Even if there are already many achievements, the development is progressing; many clinical trials are registered with the aim of expanding the therapeutic field, improving of treatment success, and getting side effects under control. The pipeline of investigative CGT is filled and pushing into the market.

### *Development potential is strong*

Usually, the development takes place in R&D facilities, especially in clinical departments or start-ups. This is favorable, because in this context, there is as much flexibility as possible, and processes can be developed with a maximum of this flexibility. In order to obtain a manufacturing license, many processes have then to be specified and validated. GMP requirements such as a pharmaceutical quality system, qualified suppliers as well as qualified premises and equipment must be met.

### *Manufacturing space is limited*

Qualified premises and equipment are the basic prerequisite for obtaining a manufacturing license. Thus, many developers use external providers who manufacture investigational medicinal products. However, due to the boom in this new therapy field and the enormous number of clinical trials, manufacturing capacity runs low now. Therefore, the consideration of establishing a plant on the green field has become more prominent.

### *Investment is worth it*

Even the smallest plants can be profitable, especially in prefabricated or modular construction. Consortia or start-ups can quickly get to their own production and might generate reimbursement faster. However, for this a well-defined project management plan is necessary.

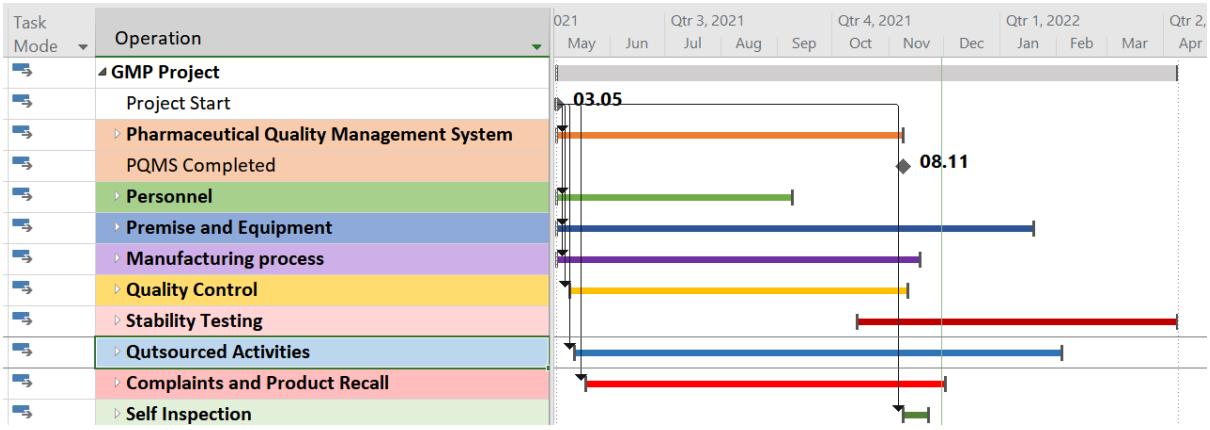


**Figure 2. Different tasks are addressed in a project management plan. It enables to identify which processes can be performed in parallel, and others, which are dependent on predecessors.**

**Benefits of a project plan**

Many activities need to be considered to establish a manufacturing facility from up the concept to achieve a manufacturing authorization. A project plan helps to structure the sequence, defines which activities can be done in parallel and estimates the effort (see Fig. 2).

The ATMP GMP guideline specifies conditions and requirements that must be met. Pharmaceutical Quality Management is key in order to meet all requirements. It helps to ensure appropriate process performance for pharmaceutical development. Different management tools are used to address and guarantee all issues of quality, efficacy, and safety.

A GMP-compliant facility has qualified premises and equipment. Adequate experienced personnel must be trained and developed in GMP tasks. Processes for manufacturing and quality control must be developed, implemented, and validated to achieve stable and reproducibly products as specified. For medicinal products, shelf life must be established and guaranteed. This needs a concept and a structured testing program.

If work is outsourced, responsibilities must be delineated and quality guaranteed. Responsibilities of the sponsor can also be defined if necessary; for investigational medicinal products, the requirement for complains, recalls and returns is narrowly defined in accordance with Annex 13 of the EU GMP Guideline.

***Advantages of a generic plan***

Valicare has such a comprehensive project plan available based on the experience in a lot of successfully completed projects. In new projects, this generic plan is adapted to the customer's needs.

A plan like this allows coordinating all design tasks, construction, and the qualification of the plant. More important, the implementation of the processes can start very early.

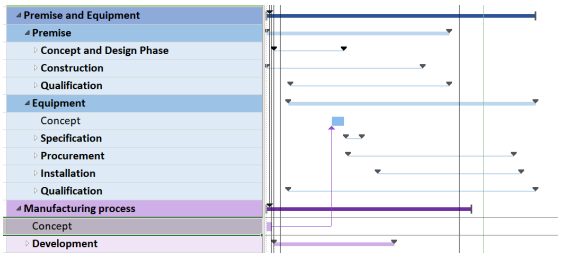


**Figure 3. Each task is precisely defined by a break-down of the requirements and process sections.**

The generic design helps to define different work packages, explores processes that need to run in parallel, integrate different work groups and adjust the necessary work capacity. Nesting parallel processes saves a lot of time.

More strikingly, however, is that the engineering activities run in parallel with the support of the GMP activities. A transfer from the development can be brought directly to the site of later production, thus saving time and effort. In fact, not only a production building is completed, but production can start up almost simultaneously.

The time that is required until the start of production depends primarily on the production time of the ATMP itself, since the manufacturing process and the aseptic processing have to be validated in a qualified environment.

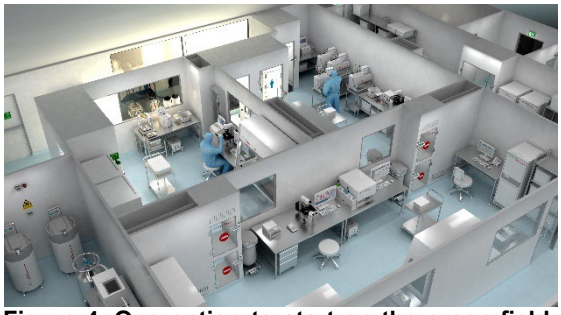

**Figure 4. One option to start on the green field: the cult.tainer®, customized design from Valicare and Syntegon Technology GmbH**