MANUAL TO WRITE AN INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER FOR A (SOMATIC) CELL THERAPY MEDICINAL PRODUCT

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER
<(SOMATIC) CELL THERAPY MEDICINAL PRODUCT>, VERSION <XX.YY>,
<DATE>

AUTHORS

THE USE OF THIS MANUAL

This manual can be used for the development of an Investigational Medicinal Product Dossier (IMPD) for a Cell Therapy Medicinal Product. It should be used as a guidance to write an IMPD according to the template published on the website of the CCMO.

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CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DATA

1. INTRODUCTION

Provide a short introduction to the cell therapy medicinal product, types of manipulation and the phase of clinical development. This description should be clear for persons not working in the field.

2.1.S DRUG SUBSTANCE

In most Cell Therapy Medicinal Product there is no intermediate or half product in the manufacturing process. Therefore, a difference between the chapters 'drug substance' and 'medicinal product' is difficult to define. In those cases it can be considered to limit the IMPD to a description of the 'Drug Product' and state that a description of the 'Drug Substance' is not applicable.

In case the final Cell Therapy Medicinal Product does contain an intermediate product, both chapters 'Drug Substance' and 'Medicinal Product' are relevant and should be described. The general outline of this chapter is described in the template published on the website of the CCMO.

2.1.P MEDICINAL DRUG PRODUCT

2.1.P.1 Description and Composition of the Cell Therapy Medicinal Product

Nomenclature
Name of the cell therapy medicinal product.

Specific Examples:
- *CMV-specific T-cells*
- *GP100-loaded DC*

General properties
Provide a brief description of the cell therapy medicinal product, biological and/or immunological characteristics of this product and proposed mechanism of action.

2.1.P.2 Pharmaceutical Development

2.1.P.2.1 Components used in the generation of the Medicinal Product

Control of Starting Material
Screening of the (donor of) cellular starting material should be described in this section. When the starting material is released by another department/manufacturer and screening of the (donor of) cellular starting material is part of the release process, this can be stated here. Indicate the specification for the starting material (preferably tabulated).

Control of ancillary materials*,
**Ancillary materials are materials and reagents used in the manufacturing process of the cell therapy medicinal product, such as media, cytokines, etc. that are not intended to be present in the cellular end-product.*

A list of ancillary materials used during production of the cell therapy medicinal product should be provided. Describe who is responsible for release of the materials and indicate the grounds, on which the materials are released (Certificate of Analysis, Certificate of Origin, additional "in house" testing, etc) in the column qualification. Provide certificates in the Appendices. It is recommended to discuss potential risks of ancillary materials used during production in chapter 2.4. 'Risk Assessment'.

Table : Ancillary materials

Material	*Manufacturer*	*Source*	*Qualification*	*Remarks*	*(theoretically) Dilution factor in end product*

Example:

Table 1. Ancillary materials

Product name	*Manufacturer*	*Source*	*Qualification*[1]	*Remarks*	*(theoretically) Dilution factor in end product*
Ficoll amidotrizoaat *Foetal Calf Serum* *Etc*	*Manufacturer A* *Manufacturer B*	*Bovine*	*CoA* *CoA, CoO, VS, CoI*		

[1]*Qualification: CoA=Certificate of Analysis, CoO=Certificate of Origin, VS=Viral Screening, CoI=Certificate of Irradiation*
Certificates are provided in Appendix

In case of using a feeder cell line different from the starting material or when using cells from a cell bank (Master Cell Bank, Working Cell Bank) details should be provided here, including genotypic characterization, origin (donor (human/animal), tissue, cell type), viral screening and history.

In case of using an expression vector, which is (commercially) manufactured elsewhere and released for the production process of the cell therapy medicinal product on its qualifications, details should be provided on the expression vector, cloning steps and packaging cell line. The expression vector will be considered as half product. This information must also be described in Aanvraagformulier Beoordeling van Klinisch Onderzoek met Gentherapeutica

In case of using expression vectors, which are generated by the department or researchers of the cell therapy medicinal product itself, this IMPD is not sufficient for all details, please be referred to chapter 2.6. Additional Information.

Control of excipients for administration*

** Excipients for administration are reagents added to the cellular end-product for stabilization, antiadherence, etc, and will be infused into the patients with the cellular end-product.*

A list of excipients used for resuspension and/or administration of the cellular end-product should be provided. Describe who is responsible for release of the materials and indicate the grounds, on which the materials are released (Certificate of Analysis, Certificate of Origin, additional "in house" testing, etc) in the column qualification. Provide certificates in the Appendices.

Example:

Table 2. Excipients for administration

Product name	*Manufacturer*	*Source*	*Qualification*[1]	*Remarks*
NaCL 0.9% *Etc*	*Manufacturer C*		*CoA*	

[1]*Qualification: CoA=Certificate of Analysis, CoO=Certificate of Origin, VS=Viral Screening, CoI=Certificate of Irradiation*
Certificates are provided in Appendix

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

Name and address of the facility/facilities where the cell therapy medicinal product is manufactured.
Provide information on the facility where the cell therapy medicinal product will be generated. Provide a copy of the appropriate license(s) (i.e. Manufacturing license)
Provide name of the Qualified Person (QP).

2.1.P.3.3 Description of Manufacturing Process and Process Controls

Starting material

In the majority of cases the starting material will be of cellular origin. Describe briefly the collection and transfer of the starting material.

> *Example:*
> *Leukopheresis: At the Hemapheresis Department of the Institute protocols have been implemented for the collection of blood products. The material will be collected at the Hemapheresis and will be released by the Medical Officer of the Hemapheresis and transported to the manufacturing facility.*

Procedure

Describe the manufacturing procedure. In order to define the specific production steps it is advised to divide the description of the complete procedure in small sections and refer to Standard Operating Procedures. It is recommended to include a figure describing the production process in a flow diagram.

> Example:
> T cells will be isolated from PBMC ex vivo as described in a Decision Tree flow (Figure 1). The reagents are listed in Table 1.
>
> Isolation of PBMC
> Blood will be diluted in PBS and PBMC will be purified using Ficoll gradient centrifugation. Following further washing procedures, the centrifuged cell pellet will be counted and resuspended in culture medium (…).
>
> Isolation of T cells
> Stimulation and Expansion of T cells
> Cryopreservation of T cells
> Thawing of T cells

Administration of cell therapy medicinal product

Describe how the cell therapy medicinal product will be administered to the patient. If the product undergoes a final dilution/concentration step at a location other than the location mentioned under 2.1.P.3.1, describe this location concisely and describe how long before administration this procedure will take place.

> Example:
> T cells for clinical use, when they meet release criteria (Table 3), will be suspended in a solution of NaCl 0.9% supplemented with 2% human albumin. The final individual preparation will be performed in a Laminar Airflow Cabinet (class A) in a cleanroom (Class B/C) environment.

Batch Size

Describe for how many patients and/or for how many administration per patients this cell therapy medicinal products will be prepared. Since the majority of cell therapy medicinal products are prepared for an individual patient the batch size will in general be n=1.

2.1.P.3.4 Controls of Critical Steps and Intermediates

Describe the control of critical steps (each step in the production process that may affect the quality of the end product) and intermediates in the production process that are pertinent to the safety and/or quality assessment. Also include the criteria of these steps (or range) of these critical steps/in process testing and provide information on the tests. It is recommended to include a figure to identify the critical steps.

Example:
At several critical points in the production process for the T cell product in process controls will be undertaken (see Appendix, Figure 2).
In process (IP) testing:
The number of PBMC after PBMC isolation is more than $0.5x10^9$ PBMC
% of the T cells that needs to be antigen specific
…

2.1.P.3.5 Manufacturing Process Development, Batch analysis, Justification of Release Criteria and Process Validation

The aim of this paragraph is to provide information on the stability and robustness of the manufacturing process.

When the manufacturing procedure has changed compared to a previous described manufacturing process (previous IMPD) the changes and the potential impact of these changes should be stated here. Compare old and new data if applicable.

The following information can be provided; the amount of test-batches in the cleanroom and pre-clinical batches at the research laboratory that have been manufactured and their results (preferably tabulated) regarding release criteria and characterization. It is possible to include a "list of Process changes" to describe the development of the production process. From these results it should also be justified how the in process testing and release criteria have been determined. Additional results that illustrate the decision criteria chosen for release of the cell therapy medicinal product can also be stated here. A reference can be made to chapter 2.2. Non-Clinical Data.
Furthermore, information may be provided on the validation status of the process itself and the aseptical process.

2.1.P.4 Control of Excipients

A reference can be made to paragraph 2.1.P.2.1 Components used in the generation of the Medicinal Product were the excipients have been described.

2.1.P.5 Control of Cell Therapy Medicinal Product

2.1.P.5.1 Specifications (s)

Provide a list with techniques used to elucidate the cellular end-product and the specification of the cellular end-product, preferably tabulated. Also include the criteria on which basis the product is released. These tests can be performed on the end-product, but these can also include in process controls or intermediates. Analytic procedures used for characterization of the cellular end-product should not be fully described but should be available on request. The validation status of the analytical procedures can be described in 2.1.P.5.3
Describe the procedure and responsibilities for quality control and release of the cellular end-product.
Furthermore, retrospective analysis can also be described here. Potential risk of retrospective analysis can be discussed in chapter 2.4. 'Risk Assessment'.

Table : Release Criteria for cell therapy medicinal product

Description	*Release criteria*	*Method*	*WI/SOP*

Example:
Before administration the T cell product will be released only when they meet the following release criteria (Table 2).

Table 3. Release criteria of T cells for administration

Description	*Release criteria*	*Method*	*WI/SOP*
Identity	*% of the cells specific (cell markers)*	*FACS analysis*	
Microbiological contamination (starting material and 24 hours for administration)	*Negative*	*BacTec blood culture system*	
Etc			

Results of the release criteria-testing will be reported in the certificate of analysis (Analysis report). The product can be released by the QP when the T cell product meets the release criteria.

2.1.P.5.3 Validation of Analytical Procedures

Provide description that analytical procedures (for in process controls and release testing) are adequate to detect significant deviations from the release criteria.

2.1.P.5.5 Characterization of Impurities

In this paragraph potential impurities can be described. The presence of potential impurities in the cellular end-product can be justified by 1) calculation of the concentration of impurities originating from the ancillary materials used during production after dilution, 2) determination of potential impurities during the process validation, or 3) direct measurement of impurities in the cellular end-product before release.

2.1.P.7 Container Closure System

Describe the packaging of the cell therapy medicinal product and discuss the appropriateness of the packaging system.

2.1.P.8 Stability, Storage Conditions, Transport and Logging

If stability tests have been performed on test-batches generated in the cleanroom or pre-clinical batches from the research laboratory, information and conclusions should be provided including a proposed shelf life (after cryoporeservation). If stability test are still ongoing, this information can be stated here.

If the cell therapy medicinal product is stored/cryopreserved prior to administration, discuss the storage condition for the cryopreservation of the cell therapy medicinal product and how the stability is controlled (for instance by determination of viability, cell characteristics and potency before and after freezing). This information could also be achieved from pre-clinical development as part of the process validation.

Provide information on the storage conditions, including temperature logging. In case the product is transported provide information on the transport conditions and temperature logging during transport.

2.2 NON-CLINICAL DATA AND TOXICOLOGY

When available provide information on toxicity studies (in vivo or in vitro) performed with respect to the cellular end-product. Furthermore, other relevant results obtained with (pre-) clinical batches, other than the release criteria already described in this document, could be stated her.

Dependent on the clinical experience obtained with the specific product, it can be considered to describe this information in a separate Investigator Brochure. In that case a reference will be sufficient.

2.3 CLINICAL DATA

Dependent on the clinical experience obtained with the specific product, it can be considered to describe this information (clinical data and human exposure) in a separate Investigator Brochure. In that case a reference will be sufficient.

In case the specific cell therapy medicinal product as described in this IMPD will be administered to humans for the first time a clinical rational can be stated here

2.3.1 Clinical rationale

Describe here the grounds on which it is justified to use this product for clinical application in patients.

2.3.2 Human exposure

Describe the clinical experience obtained with the specific product in previous human exposure.

2.4 OVERALL RISK AND BENEFIT ASSESSMENT

When this product will be infused for the first time in humans, this section should give a concise justification of the proposed study and discuss why the data provided do allow this study to be performed. It is recommended to illustrate this justification with a risk analysis, in which the level of knowledge about mechanism of action, previous exposure of human beings to similar biological mechanism, selectivity of the mechanism to target tissue (in animals), analysis of potential (adverse) effects, predictability and management of (adverse) effects is being discussed.

Furthermore, potential risks related to ancillary materials, retrospective analysis, or other subjects can be discussed in this section.

In case the clinical trial protocol and the IMPD is accompanied by an Investigators Brochure (IB), it is recommended to make this section a part of the IB and to provide a reference.

2.5 ADDITIONAL INFORMATION

Additional information can be found at:

Guidance for a risk-based approach for qualification of ancillary materials: US Pharmocopeia 31-NF26S2, <1043> Ancillary materials for cell, gene and tissue-engineered products.

Systematic approach of a risk analysis of a (cellular) product: M.J.Kenter and A.F.Cohen Establishing risk of human experimentation with drugs: lessons from TGN1412, Lancet 2006: 368:1387.

Expression vectors and gene transfer: http://bggo.rivm.nl/paginas/loket.htm

2.6 REFERENCES

2.7 APPENDICES

Example:

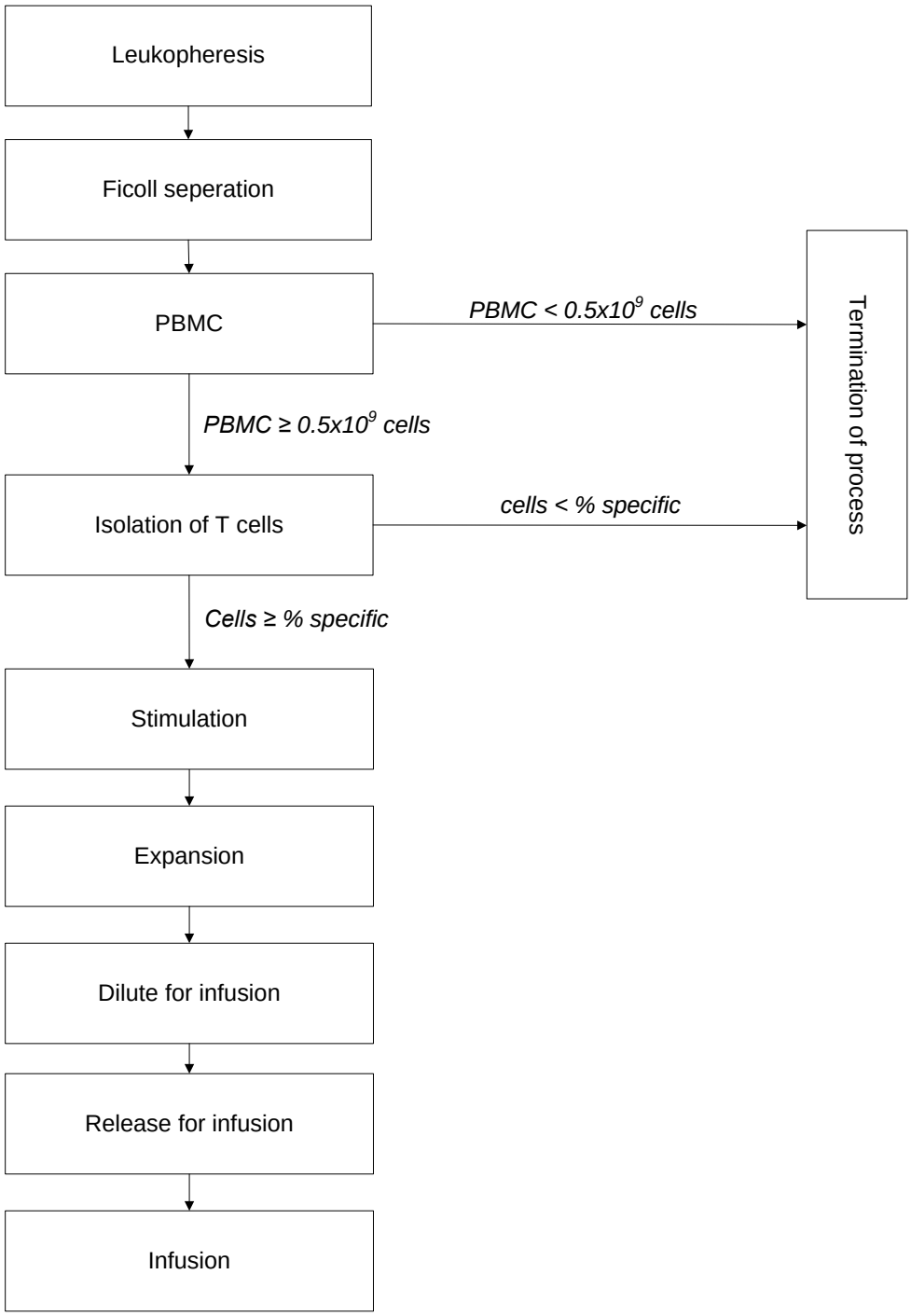

Figure 1: Decision tree/production flow diagram for the manufacturing of T cells

Example:

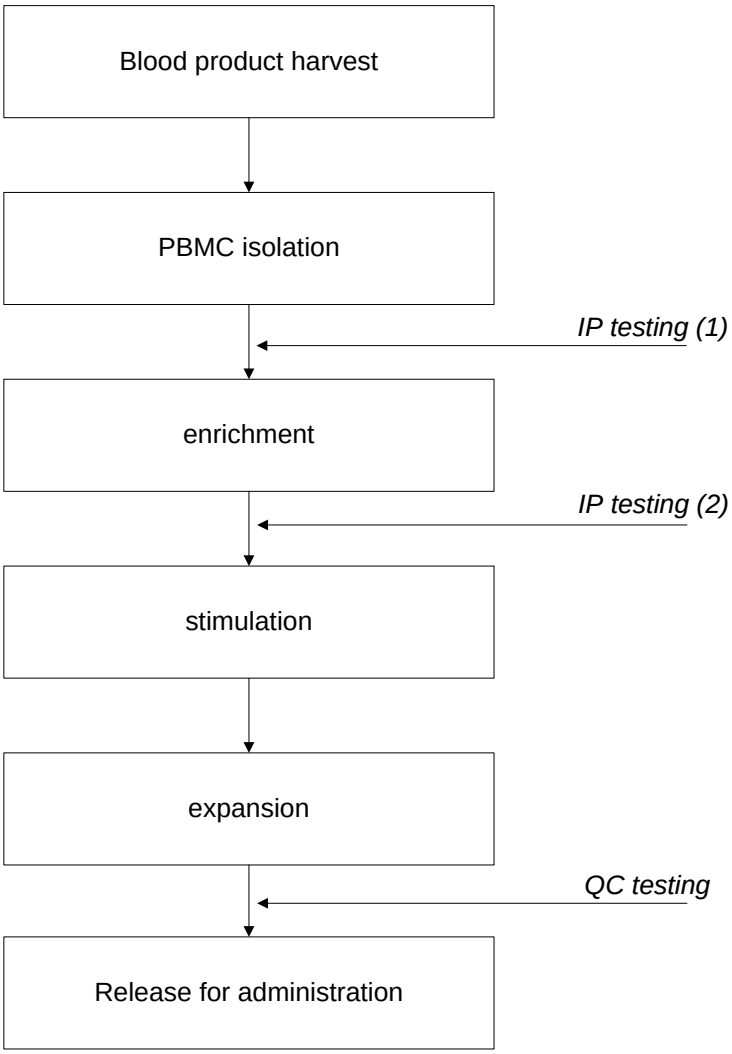

Figure 2: Controls of Critical Steps and Intermediates
Numbers of IP-testing refer to 2.2.4 controls of critical steps and intermediates