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POINTS TO CONSIDER ON THE MANUFACTURE AND QUALITY CONTROL OF HUMAN SOMATIC CELL THERAPY MEDICINAL PRODUCTS

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MANUFACTURE AND QUALITY CONTROL OF HUMAN SOMATIC CELL THERAPY MEDICINAL PRODUCTS

TABLE OF CONTENTS

I. GENERAL PRINCIPLES

1. Introduction

The application of traditional drug-based remedies for the treatment of various acquired and inherited dysfunctions afflicting man has evolved to include novel concept-based approaches. These arise from a better understanding of the underlying patho-physiology of diseases at biochemical and molecular levels and progress in the development of bio-engineering techniques. These novel therapeutic techniques include administration of live somatic cell preparations suitably adapted for transfer to an individual.

Somatic cell therapy is the administration of viable somatic cell preparations suitably adapted for transfer to an individual.

Somatic cell therapy involves a defined procedure of administering modified autologous or allogeneic cells for achieving specific cellular functions in specific tissues or organs of the recipients. The administered material may constitute an expanded and/or purified population of self-renewing stem cells, or may comprise more committed or terminally differentiated cells exerting a specific defined physiological function. Cells can be manipulated, for example in combination with a non-cellular matrix. Modification may result from the culture, expansion, isolation or pharmacologic treatment of cells that alters their genotypic and phenotypic characteristics.

The principal objective is reconstitution of cell/tissue functions. Various cell populations can serve as candidates for cellular therapy for specific therapeutic purposes.

The general principles considered in this document may apply to a range of cell therapy products and relevant manipulation procedures, as the key objective is to ensure that the product to be administered is of acceptable quality and standard, and free from contamination.

Although this document does not cover somatic cell therapy products consisting of non-viable cells and products derived from cells, the underlying scientific principles hereafter may be applicable.

Cell therapy products often involve small cell samples mostly to be used in a patient-specific manner. This will raise specific issues pertaining to quality control testing designs for each cell therapy product under examination.

All necessary control measures should to be considered in order to ensure:

- appropriate sourcing and control of all materials used in the manufacture of the cell therapy product
- minimising the risks of damage and ensuring integrity, desirable characteristics and function of the therapeutic product
- compliance with high quality and safety standards of establishments and processes involved in the manipulation of cell products.

This document is intended to provide general principles to be taken into consideration for the development and assessment of human somatic cell therapy products without prejudice to medical practice or national legislation which may be applicable.

2. Definition of a cell therapy medicinal product

Medicinal products are substances or combinations of substances which

i) are presented for treatment or preventing disease in human subjects; or

ii) are administered to human subjects for making a medical diagnosis or restoring, correcting or modifying physiological functions in these subjects.

For a human somatic cell therapy product consisting of autologous or allogeneic cells to fall within the definition of medicinal product as set out in the current medicinal products legislation[1], it should:

a) be subject to a manufacturing process carried out in dedicated facilities complying with GMP. The process encompasses expansion or more than minimal manipulation which may be designed to alter the biological, physiological or functional characteristics of the resulting cells;
b) further to such manipulation, the resulting cell product is definable in terms of qualitative and quantitative composition which may include biological activity.

3. Scope of the document

This document provides guidance relating to the characterisation and quality control of human somatic cells, other than transfusable blood products (e.g. platelets, red blood cells), and the control of the cell culture procedures employed in product manufacture in order to ensure product and process consistency. A common characteristic of cell therapy products is that they entail the application of a defined manufacturing process to cell samples.

Before and after the manufacturing process, consideration should be given to the operations involved in the collection and storage of cells prior to manufacturing and administration of the final product to the patient.

This points-to-consider document relates to the scientific and technical issues concerning i) the materials and safety parameters employed in somatic cell product manufacture, including control of the starting materials, ii) cell culture procedures, iii) characterisation, iv) specifications of the final product, v) validation of handling procedures, vi) batch identification, vii) release testing and quality control of the somatic cell products prior to administration.

II. POINTS TO CONSIDER ON DEVELOPMENT AND ASSESSMENT OF CELL THERAPY MEDICINAL PRODUCTS

1. Source and characterisation of Somatic Cell Populations

1.1 Cell type

The origin of the cell population should be defined as autologous or allogeneic and its tissue type classified and confirmed by appropriate analyses such as histology, phenotypic characterisation and biological functions

1.2 Criteria for donor selection

1.2.1 Allogeneic donation

Donors should be subjected to the same rigorous and stringent evaluations as blood and organ transplant donors. This may include typing for polymorphisms such as blood group antigens and major histocompatibility (HLA classes I and II) and possibly minor antigens. Donor suitability should conform with the standards set out in the following documents:

- Council of the European Union Recommendation on the "suitability of blood and plasma donors and the screening of donated blood in the European Community"
- Council of Europe Guide to the preparation, use and quality assurance of blood components
- CPMP/BWP Note for Guidance for plasma derived medicinal products, the principles of which may be relevant for cell therapy products, e.g. donor screening

[1] Directive 65/65/EEC as amended, Directive 75/318/EEC as amended, Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03).

Potential donors should be excluded on the basis of exposure or risk of infection by viral agents such as HIV, hepatitis B and C viruses. In addition and depending on the nature of the source cells, other risk factors, e.g. previous radiation exposure, other therapeutic approaches, should be considered and appropriate testing should be performed.

Biological characteristics of the donor include age, sex, medical history, current health status as well as reference to family history of any hereditary diseases which may compromise the suitability of the cells harvested. Presence or likelihood of infection by immunodeficiency or hepatitis viruses and other transmissible agents such as mycobacteria and lentiviruses and those causing spongiform encephalopathies should be registered as exclusion criteria.

In principle, cells of the donors who have been exposed to an infectious agent or who present risk factors should not be collected, and if collected, should be destroyed.

Procedures and standards employed for the selection of appropriate donors and the exclusion of high-risk or otherwise unsuitable candidates should be clearly delineated and justified.

If it is necessary to pool cells from different donors, consideration should be given to the possibility that the pooling of allogeneic cell populations from different sources may facilitate induction of immune tolerance or elicit adverse cell interactions and undesired immunological responses in the recipient. This may functionally modify the cellular product and compromise its therapeutic activity. In addition, pooling may increase the risk of disease transmission.

1.2.2 Autologous sourcing

The identity of the donor (the patient himself or herself) should be clearly indicated by clerical and tracking procedures (see also sections 3 and 5 of this document). Products available solely to the patient should be labelled "For autologous use only". Such cells are viewed as immunologically privileged by their very nature and their use is not contingent on the resolution of basic safety factors i.e possible adverse immunological responses or transmission of infectious pathogens. They are particularly useful since they can be collected and amplified to achieve functional efficacy.

The quality criteria for the autologous sourcing are the same as for allogeneic donation (sourcing) with respect to the microbiological/virological safety of the source cells and the serological characteristics of the patients (see section 1.2.1). In case of positive markers for transmissible agents, the issue of potential cross-contamination in the processing equipment should be considered.

2. Source and characterisation of other materials and reagents used in the manufacturing process

2.1 General recommendations

Various materials are needed for genetic or phenotypic modification, such as enzymes, antibodies, cytokines, sera, antibiotics, other chemicals or solid structures. However**,** exposure to such materials can also compromise the quality, safety and efficacy of the final therapeutic product. As a consequence, each substance used in the procedure should be clearly specified and evaluated as to its suitability for the intended use. Materials and methods involved in the collection, selection and manipulation of cells should be described in detail. The sterility, absence of contaminating agents and low endotoxin level of ancillary products should be ensured. Materials functioning as support for the growth and adhesion of cells in the form of a neo-organ or immuno-isolator should be evaluated and/or validated as to their suitability for the intended use.

Quality of culture media and additives such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents. It is recommended to avoid use of reagents with sensitisation

potential.

The manufacturing process of cell therapy products does not include stringent purification steps or any virus removal or inactivation steps and, therefore, acceptance criteria for all materials derived from human or animal origin should be very stringent .

For quality aspects, the Note for Guidance on the production and quality control of medicinal products derived by recombinant DNA technology and the Note for Guidance on the production and quality control of monoclonal antibodies should be taken into account when relevant.

2.2 Specific recommendations for materials and reagents of human origin (e.g. albumin, immunoglobulin etc.)

Reagents of human origin necessary to ensure optimal growth of the cells should be evaluated for their suitability in a manner identical to that employed for plasma-derived products as recommended in the CPMP Note for guidance on plasma-derived medicinal products (CPMP/BWP/269/95, rev.2). Measures should be taken to reduce the risk of transmissible spongiform encephalopathies according to the relevant European legislation and guidelines. Autologous serum isolated from the same individual who donated the cells would be a possible alternative to serum from an allogeneic source.

2.3 Specific recommendations for materials and reagents of animal origin used in the manufacturing process

Animal derived reagents may harbour infectious agents and may provoke undesirable immunological responses in the recipient. It is preferable to avoid such additives in favour of non-animal derived reagents of defined composition. A possible alternative would be autologous serum isolated from the same individual who donated the cells or human serum from an allogeneic source. The use of material of animal origin should conform to the CPMP and CVMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01, rev.1). The use of irradiated animal sera and /or alternative synthetic media should be considered.

3. Cell culture procedures

During *in vitro* cell culture, consideration should be given to ensuring optimal growth and manipulation of the isolated cells. The processing steps should be properly designed to preserve the integrity and function of the cells. The procedures for such manipulation should be documented in detail, closely monitored according to specific process controls. Microbiological control is a pivotal aspect of process control and quality evaluation. Possible transmission of a communicable disease is a risk attendant to all cellular products although the likelihood of risk and the most suitable way of limiting it vary according to the source and characteristics of the tissue. Any risk assessment should take into account these parameters as well as the intended clinical use of the product and possible adventitious contamination from workers and reagents.

Monitoring of *in vitro* cell culturing must include verification of absence of adventitious agents, such as bacteria, yeast, fungi or mycoplasma, at selected stages of the production. The culture should be examined for any microbial contamination in accordance with the culturing procedure and growth characteristics of the cells. A specific viral testing programme should be established. Consistency/repeatability of the cell culture process should be demonstrated. Adequate limits should be set for critical parameters such as viability, cell density/confluence, purity, total duration of culture time, max PDLs

Cellular products harbouring infectious agents present greater risks of horizontal transmission of disease. The following factors should be considered as to whether or not horizontal transmission of communicable disease is a relevant concern:

- is the product intended for autologous or allogeneic use;
- is cross contamination likely to occur through processing and handling cells from multiple donors in a facility;
- how are the cells manipulated and under what conditions.

In the context of autologous and allogeneic cell therapy products, the fact that diverse cellular products are collected, processed and stored in the same facility may also increase transmission risk as an infected product may cross-contaminate another during each step of the procedure, i.e. in processing equipment or in storage containers such as liquid nitrogen tanks. Therefore, adequate control measures should be put in place.

Individuals that collect, store, transport or process cells should operate in compliance with specific donor screening, donor or product evaluation and cell quarantine measures. Inappropriate handling and improper processing can impair or destroy the integrity or function of the cell product and thus resulting in therapeutic failure. Cross-contamination of the cellular products, increases the potential risk of disease transmission. Complete screening and testing before the final release of the product for administration would therefore be necessary. On the other hand, due to the nature of the cell therapeutic product, it is not possible or practical to perform such quality controls before release. It will thus be necessary to define equivalent quality assurance measures to ensure preservation of product validation, in particular validated packaging that would ensure tight package sealing (see section 7, Special Cases paragraph).

3.1 Determination of cellular identity and retention of integrity of heterogeneous cell populations

The phenotypic and genotypic profile of the cell population should be characterised in terms of appropriate surface or biochemical markers typical of the final cell population as well as their functional activities particularly in the allogeneic setting.

Consideration should be given to the transformation potential of cells in response to growth factors since transformed cells may gain growth advantage over the non-transformed under defined *in vitro* culturing conditions.

Cell populations genetically engineered should be assayed for appropriate and reproducible expression of the newly acquired characteristics. As far as applicable and practicable, this should be quantified and controlled. Reference is made to the CPMP Note for Guidance on quality and pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) which specifies details on the quality control, characterisation and pre-clinical testing of gene transfer vectors.

3.2 Duration of cell culture

The principal genotypic and phenotypic traits of the primary cell cultures, of the established cell lines and the derived clones should be defined and their stability with respect to culture longevity determined. The culture conditions including the duration should be optimised with respect to the function of the cells suitable for the intended clinical use.

3.3 Establishment of a Cell Storage and Banking System

An adequately controlled cell storage system should be established. In the context of this points-to-consider document, it can be defined as a set of procedures, which allow proper storage, retrieval and supply of cells without any alteration of their final characteristics.

Where applicable, Master Cell Banks (MCB) and Working Cell Banks (WCB) should be established. The established cell population should be characterised as accurately as possible in terms of its biological structure and functional activities and certified to be free of endogenous and exogenous contaminating agents (bacteria, fungi, yeasts, viruses,

mycoplasma). The cells should be stored under controlled and optimal conditions, to ensure cell viability, density, purity, sterility and function. Identity should be verified by relevant genotypic and phenotypic markers and the proportion of cells bearing these identity markers evaluated as an indicator of a homogeneous population.

4. Development pharmaceutics (Formulation of the cell therapy medicinal products)

The administration of the therapeutic cellular product may be accomplished in several ways: the cells may be infused intravenously, injected site-specifically or surgically implanted. Such cells can be encapsulated in a matrix of bio-compatible polymers in order to bypass the recipient's immune surveillance following implantation. The polymers used should be characterised with respect to their physico-chemical properties, defined and controlled by a satisfactory specification. Their suitability for use in a clinical setting in terms of bio-compatibility and durability should be properly evaluated. Other auxiliary components such as fibres or beads introduced along with the cells for structural, biological or immuno-isolation purposes should be viewed as part of the final product and evaluated accordingly.

Cellular products may be combined with mechanical or synthetic structures, with drugs or with non-cell biologics. At the forefront of these combination products are those containing synthetic or mechanical parts that present concerns relating to function, compatibility and durability. It is imperative that these materials function correctly, that they persist for a sufficient length of time and that no adverse reactions occur with surrounding tissue.

As regards the administration of non-autologous cells for the purpose of long-term delivery, immunoprotection or immunosequestration of the cells from the recipient's immune system is imperative to the preservation of their integrity and function.

5. Validation of handling procedures and equipment

All the cell manipulation steps, including the equipment employed should be validated for the following parameters:

- microbiological control of the process
- cell viability
- cell growth and/or cell differentiation, as applicable.
- cell identity
- cell activity or function
- purity of the cell population
- gene-transduction efficiency, if applicable
- containers and procedures used for shipment

Validation should be carried out periodically according to GMP rules. In any validation study, consideration should be given to the adequacy of the cleaning procedures to avoid cross-contamination during use or as a result of carry-over from a previous campaign.

6. Quality assurance system

This section should be read in conjunction with any relevant guidelines relating to good manufacturing practice issued at Community level or through the International Conference Harmonisation (ICH). A quality assurance system must be operative in the facilities where the cells are collected, stored, manipulated, quality controlled and packaged in the final container. Each establishment involved in the above activities of the cells for therapeutic use should establish written documentation and instructions, and procedures for an effective quality assurance system. The quality assurance system should include the identification of the Qualified Person (QP). The qualified person shall act as described in Article 21 of Council Directive 75/319/EEC (as amended).

The following aspects should be considered:

- appropriate facilities for performing the functions;
- certification or validation of the equipment employed for the intended use;
- preparation of standard operating procedures;
- establishing adequate records to facilitate tracing of donations e.g. date of collection, quality control tests undertaken, results, etc.;
- setting specifications for the source cells before being further processed;
- adequate control of labelling, storage and transportation of source cells and final cell product;
- establishing quality audits and review.

7. Batch identification, finished product, lot release testing

A clear batch identification system should be adopted to facilitate complete traceability to the cell donor(s). A clear definition of cell preparation batch from cell sourcing to labelling of final container should be provided. Each stage of the process should be clearly documented. In the autologous setting, the manufactured product should be viewed as a batch whose unique nature should be taken into account so that there is greater flexibility in conforming to specifications and requirements. In general, the final cell therapy product is the cell preparation that has been subjected to all the necessary manipulation steps. These may include selection of cell types for further cell expansion, growth and/or differentiation, pharmacological or physical treatment, gene transduction, purification and further selection of phenotype for the intended clinical intervention. In the context of this points-to-consider document, the cells are usually stored or banked under appropriate cryo-preservation conditions.

The final cell therapy product should be subjected to quality control and lot release testing as well as to any tests / measurements conducted to evaluate shelf-life of the product, such as an assay for bioactivity. Specifications and limits should be established based on production experience and process validation. It is recommended that an inventory of retained samples be kept for future analysis.

A properly validated potency assay measuring bioactivity should be established and product stability examined to assure its integrity. The cell product should be labelled clearly and accurately. Cell identity, method of processing, as well as product screening and the results should also be documented. The cell therapy product should be assigned a valid in-use shelf life. This should be supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity.

Product specifications should include *mutatis mutandis* criteria for acceptance of the product, namely size, storage conditions and temperature range, absence of microbial contaminants and limits set for other product and process related contaminants, viable cell count and function. Methods for freezing and thawing materials and performing contamination and viability testing should be documented. If at any time it is deemed necessary to determine the integrity and quality of the cell therapy product and its batch consistency, a cell viability analysis should be performed. This measurement will allow an estimate of the viable cell count prior to administration to the recipients for the intended clinical intervention.

Two special cases may occur in the cell product preparation:

a) cell products prepared on an individual patient's basis, by means of a process that results in significant changes in the biological characteristics of the cells, as previously described in this document, and re-administered to the patient immediately after completion of manipulation steps;

b) cell products for which, due to i) very limited cell numbers at source, and/or ii) the cells are deliberately manipulated to limit their proliferation potential in order to avoid unwanted transformation, hence the final product is limited to the clinically necessary cell doses.

In these cases, samples and/or time are often insufficient for complete control testing and lot release.

The entire cell manipulation process should be validated in all instances. It is recommended that such validation - using a cell preparation process fully comparable to those intended for clinical use - be performed on a regular basis, e.g. 6 monthly interval, for sterility, absence of mycoplasma and adventitious viruses, cell identity, cell activity, cell viability, cell proliferation, purity, gene transduction efficiency if applicable. Immediately prior to clinical use, a set of essential tests (e.g. viability, bacterial contamination, phenotype, cell number per dose), in compliance with the pre-determined specification limits must be performed before the cell product is released for clinical use. Whenever feasible, retention samples should be stored for future analysis.

For cell products that require further manipulation, albeit limited, immediately prior to administration to the patient, such procedures should be included in the relevant section of the Summary of Product Characteristics (SPC), and specific written information about the necessary manipulation should be given to the user(s) of the product. These steps should be included in the process validation programme and results provided in the relevant documentation.

Appendix

Examples of somatic cell therapy include:

(1). Administration of autologous or HLA-compatible allogeneic hematopoietic stem cells, primarily to counteract myelodepletion and reconstitute hematopoiesis.

(2). Introduction of immunogenic cell populations such as lymphocyte or dendritic cells activated for the purpose of adoptive immunotherapy *in vivo* following *ex vivo* purification, expansion and activation or priming.

(3). Implantation of modified tissue-specific cell populations designed to perform complex biological functions and serving as potential sources of damaged or otherwise defective tissue.

(4). Autologous tumour cells extracted, processed and subjected to biological manipulation and/or genetic modification *ex vivo*.

(5). Stem Cell Therapy: The versatility of the hematopoietic stem cell (HSC), the primordial populating cell of the entire blood and immune system, renders it a particularly attractive candidate for application to cell-based gene therapies in the treatment of cancer, autoimmune and genetic diseases.