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Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

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7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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Executive Summary

This guideline defines scientific principles and provides guidance for the development and evaluation of medicinal products containing genetically modified cells intended for use in humans. Its focus is on the quality, safety and efficacy requirements of genetically modified cells developed as medicinal products.

1. Background

Genetically modified cells may be developed either for therapeutic use (gene therapy medicinal products) or to use the genetic modification in the manufacturing process of a cell therapy / tissue engineering product.

The following are some examples of medicinal products containing genetically modified cells (GMC) that have been used in clinical trials:

- genetically modified cells for treatment of monogeneic inherited disease;
- genetically modified dendritic cells and cytotoxic lymphocytes for cancer immunotherapy;
- genetically modified autologous chondrocytes for cartilage repair; genetically modified progenitor cells for cardio-vascular disease treatment or for *in vivo* marking studies, particularly for *in vivo* biodistribution or *in vivo* differentiation analysis;
- genetically modified osteogenic cells for bone fractures repair; genetically modified cells for infectious disease treatment.

This guideline defines scientific principles and provides guidance to applicants developing medicinal products containing genetically modified cells. It is recognised that this is an area under constant development and guidance should be applied to any novel procedures as appropriate.

2. Scope

The focus of this document is on quality, non-clinical and clinical aspects of genetically modified cells. All cases of genetically modified cells intended for use in humans are included, no matter whether the genetic modification has been carried out for clinical indication or not (e.g. for enhanced manufacturing purposes). The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. In a medicinal product, the GM cells can be presented alone or combined with medical devices.

The requirements described in this document are those relating to market authorisation application, but principles may apply to development stages.

3. Legal basis

This guideline has to be read in conjunction with the introduction, general principles and part IV of the Annex I to Directive 2001/83/EC and with the Regulation on Advanced Therapy Medicinal Products (EC) No 1394/2007.

In addition, the procurement and testing of cells from human origin must comply with overarching Directive 2004/23/EC and technical directives drawn from it, Directives 2006/17/EC and 2006/86/EC.

4. Introduction

For the purpose of this guideline, human and xenogeneic cells and tissues are referred to as "cells". The terms "vector" and "genes" are used in the meaning of "nucleic acids" as defined in Annex I to Directive 2001/83/EC.

The following steps are usually carried out to transfer genes into cells *ex vivo*: (1) cells are selected or isolated from a suitable donor (either human or animal) or sourced from a bank of primary cells or tissues (2) cells are prepared for gene transfer, e.g. by expansion in culture; (3) the target gene in a suitable vector is transferred into the cells; (4) the genetically modified cells are further processed, formulated and stored.

In all issues related to the cellular part of the genetically modified cells, the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) should be followed. The Guideline on xenogeneic cell therapy medicinal products (EMEA/CHMP/CPWP/83508/2009) should be taken into account when a xenogeneic cell product is concerned as well as the draft Reflection Paper on stem cell-based medicinal products (EMA/CAT/571134/2009), when relevant.

In addition, the Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) should be followed. If applicable, vector specific guidelines and European Pharmacopoeia (E.P.) monographs or chapters should also be taken into account.

A risk analysis which may cover the entire development should be carried out according to part IV of the Annex I to Directive 2001/83/EC. The risk posed by the administration of genetically modified cells is highly dependent on the origin of the cells, the type of vector and the method of gene transfer used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use. The variety of the final products can lead to very different levels of risks for the patients, the medical personnel or the general population. This variety means that the development plans and evaluation requirements need to be adjusted on a case by case basis according to a multifactorial risk based approach.

Risk factors include but are not limited to the origin of the cells, the ability to proliferate, to differentiate and/or to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the integration of nucleic acids sequences or genes into the genome, their long time persistence or oncogenicity and the mode of use.

5. Quality Aspects

5.1. Materials

5.1.1. Starting materials

The starting materials for the production of genetically modified cells are:

1) the cells to be genetically modified,

2) the nucleic acid(s) to be transferred into the cells (transgene(s) with or without a vector).

The amount of data to be provided for each starting material is the same as required for, respectively, the drug substance of a somatic cell therapy medicinal product and the drug substance of a gene therapy medicinal product. Detailed information should be provided on manufacturing process, materials, characterization, process development, control of critical steps, validation process and stability. Vector characterisation and control data should be included in the Common Technical Document (CTD), either when the vector is internally produced or is supplied by another manufacturer.

The type of delivery vector or vehicle used for *ex vivo* genetic modification should be justified based on the target cells, the clinical indication and other considerations. The molecular design of the transfer vector should be driven to achieve safety and efficacy criteria. For integrating vectors, an appropriate design to reduce the risk of insertional mutagenesis and increase vector safety (e.g. SIN vectors) is recommended. For transient production of lentivirus (LV), retrovirus (RV) and associated adenovirus (AAV) vectors from packaging cell lines, the sequence of plasmids used to provide vector function(s) should be verified before their use in the transient production. The use of known oncogenes should be avoided unless properly justified, e.g. when the genetic modification is intended to be transient and foreign genetic material is removed from the final cell product.

Prior to its use, the transfer vector should be shown to be free from any unwanted viral contamination, including helper or hybrid viruses such as in AAV production systems, adventitious contamination or replication-competent vectors for vectors intended to be replication-incompetent. Use of unpurified transfer vectors in the transduction process should be justified and avoided where possible; otherwise a robust justification for the use of such transfer vectors will be required.

5.1.2. Other materials, reagents and excipients

Materials and reagents used for the transduction process and subsequent steps should be of appropriate quality, including testing for sterility, absence of adventitious agents and endotoxin among other controls, in order not to compromise the quality, safety and efficacy of the final product. Viral safety as well as measures taken to minimise the risk of transmitting agents causing TSE of any reagent or material of animal origin should be demonstrated. Recombinant proteins such as enzymes, antibodies, cytokines, growth or adhesion factors should be characterised and controlled, where appropriate and relevant, in accordance with the principles described in the Agency guidelines on "Production and quality control of medicinal products derived by recombinant DNA technology" and "Production and quality control of Monoclonal Antibodies".

Use of sensitising agents such as β-lactam antibiotics should be avoided, unless justified, e.g. as in special cases of target cell sourcing procedure for autologous use.

When structural components (matrixes, scaffolds, devices) are used in manufacture of a medicinal product containing genetically modified cells, the requirements defined in the Guideline on cell-Based medicinal products (EMEA/CHMP/410869/2006) should be followed.

5.2. Manufacturing Process

A detailed description of the manufacturing process of the drug substance and of the drug product should be provided. The acceptance criteria and process ranges should be carefully designed and justified.

5.2.1. Cell preparation and culture

Variability in culture conditions during production should be minimised, as it may lead to changes which cause alteration of the cells. Procedures to ensure consistency of production conditions as well as of the resulting cells are imperative.

5.2.2. Gene transfer

Gene transduction into recipient cells is a biologically dynamic process; nevertheless its control is a critical step. Gene transfer can be achieved by a number of approaches. When using viral vectors, direct exposure to the cells may suffice whereas naked DNA usually requires chemical (e.g. liposomes, polycations, and peptides) or physical (e.g. electroporation, microinjection, particle bombardment) facilitation. Efficiency of gene transduction depends on many factors including the nature of the cells (primary or cell lines, adherent or in suspension, dividing or quiescent), the phase of the cell culture, cell viability, the type and amount of vector and cells (and transfection reagent if used), concentration, and culture media components. A detailed description of methods used for gene transfer should be provided. Primary cell transduction should be carried out in the conditions optimised during process validation. When using integrating vectors (e.g. LV and RV), multiplicity of infection should be kept at the minimum shown to be effective by transduction efficiency studies and clinical studies.

5.2.3. Further manufacturing steps

After the gene transfer procedure, cells are generally subject to one or more additional steps (e.g. selection, culture), before being formulated and filled into the final containers (drug product). For bankable genetically modified cells, a clear cell bank system should be established and appropriately controlled.

A complete description of methods used for purification and/or cell selection should be provided where applicable together with full details of in-process controls. The consistency of the purification process should be demonstrated including its capacity to remove specific impurities.

In some cases, only transient genetic modification is sought. This can be achieved by removing the integrated material or by episomal expression. If the genetic material used to modify the cells is to be removed in order to obtain the final product, a complete description of the methods employed should be provided. Appropriate controls should be introduced to demonstrate elimination of the foreign nucleic acids sequences.

5.2.4. In process controls

Appropriate in-process controls should be performed at key intermediate stages, using molecular (e.g. transgene) and biological (e.g. mycoplasma, cell morphology) parameters. Test methods and acceptance criteria should be described. If storage of intermediates occurs, it is necessary to validate the storage conditions (e.g. time, temperature).

5.2.5. Process validation

An acceptable number of consecutive production runs should be performed in order to validate the production process and to ensure consistency of the product. The studies should include a range of appropriate and validated methods such as molecular, biological, and immunological methods to characterise and control the product as well as methods to detect and identify impurities.

Given the complexity of the process, it is essential that all variables are optimized and taken into account. The whole production process should be fully validated.

In addition to the requirements described for process validation in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006), the following aspects should be addressed: absence of adventitious viruses, replication-competent vector, release of vector from transduced cells, transduction efficiency, vector copy number, sequence of transgene (and of other regions as needed), level of transgene expression, quality of the expressed molecule(s), removal or elimination of the desired nucleic acid sequences when appropriate for transient genetic modification. Process validation will be critical if the nature of the product and/or the indication does not allow a complete program of control testing for release purposes.

In special cases, if appropriately justified, it is possible that process validation be carried out on donated cells obtained from a healthy volunteer and of the same type as those to be used in the product, instead of using the product itself.

The variability of the cell product as a whole should be monitored and taken into account, particularly where the cells may be derived from different sources/donors) and long term expression or manifestation of the transduced genetic material is being followed.

5.3. Characterisation

Rigorous characterisation of the genetically modified cell medicinal product (either alone or in combination with medical device) is essential. If genetically modified cells are combined with a medical device, characterisation should take into account the medical device itself and its contribution to the structure and function of the final product.

The use of a range of appropriately validated molecular, biological, and immunological methods for the following characteristics should be addressed:

- identity,
- sequence and integrity of transgene,
- identity and integrity of vector,
- gene copy number per cell,
- vector integration profile,
- transduction efficiency (e.g. percentage of transduced cells),
- vector/transgenes removal or elimination (when applicable),
- identity and activity of the expressed gene product,
- cell phenotype / morphology,
- homogeneity of the cell population (e.g. percentage of sub-populations),
- proliferation and/or differentiation capacity of the genetically modified cells,
- vector release from cells,
- vector replication competence and possibility of reactivation,
- genetic stability upon in vitro proliferation and/or differentiation.

Vector release and /or vector replication competence data should be discussed in relation to the risk for vector shedding/mobilisation. The possibility of virus reactivation should be studied, if justified by a risk analysis.

The gene copy number per cell should be justified in relation to the safety data and the intended use of the product. Transduction and transgene expression efficiency should be justified in relation to clinical efficacy data. To address the risk of insertional mutagenesis, the integration profile of integrating vectors or plasmids should be studied in relation to known oncogenes/tumour suppressor genes, where applicable. If the genetically modified cells have proliferative potential and are intended to sustain an *in vivo* repopulating activity, clonality and chromosomal integrity of the cell population derived from the genetically modified cells should also be studied.

Homogeneity and genetic stability of transduced cells should be thoroughly characterised. Any observable unintended changes in cell morphology, functions and behaviour, e.g. migration characteristics, of the genetically modified cells when compared with the original unmodified cells should be well documented. Any unexpected modification of phenotype, proliferation/differentiation properties, and activity should be investigated and discussed in relation to the intended use. Transduction-induced increase of target cell immunogenicity (e.g. in cancer immunotherapy), should also be addressed.

5.3.1. Identity

Identity testing should include an assay to detect the presence of the intended genetic modification, and an assay specific for the cell population. The test methods should be specific for those components.

5.3.2. Purity

Purity is generally related to transduction efficiency, i.e. percentage of transduced cells. The degree of purity should be defined taking into account the nature and intended use of the product, the method of its production and also the degree of consistency of the production process.

The purity criteria should be established and be within specified limits. Tests should be applied to determine levels of contaminants of cellular origin, e.g. cell fragments, as well as materials which may have been added during the production processes. In the case of replication deficient retro/lentiviral vectors, tests to show the absence of replication-competent viruses are essential.

When the foreign nucleic acid sequences have been removed in the final cell population as for transient genetic modification, tests to show the absence of cells carrying the foreign nucleic acid sequences are essential.

5.3.3. Potency

While characterising the biological activity of genetically modified cells and in order to establish the potency, the minimal or optimal effective amount of genetically modified cells shown in clinical studies to achieve the desired effect should be linked to the minimal or optimal expression level of the transgene (s), and in turn to gene copy number and/or to product activity level.

To estimate the potency of the transduced cells, biological tests should be applied to determine the functional properties achieved by the genetic modification. The potency test(s) should provide quantitative information on the newly acquired characteristics (expression of the transgene, phenotypic/genotypic changes of the cells etc.). Wherever possible, a reference batch of cells with assigned potency should be established and used to calibrate tests.

5.4. Quality Controls

Release criteria

In addition to general pharmaceutical tests (e.g. sterility, endotoxin, appearance etc.), release testings should include identity, purity, potency, impurities, cell viability, cell number/dose, percentage of transduced cells (in case of *ex vivo* approaches).

For cells transduced with a replication defective integrating vector, the absence of replication competent vector (RCV) should be demonstrated. Vector/plasmid copy number per cell should be tested on each batch of final product. The result of RCV testing should be known before clinical use. The limit of detection of the test method should allow the detection of one RCV particle per clinical dose of genetically modified cells. If RCV is detected, the batch should be rejected. These requirements should be applied also during the clinical development of the product (e.g. from the "first in man" clinical trial).

When foreign genetic material has been removed from the final product, this should be demonstrated at release by an appropriate sensitive test.

When the shelf-life of the product does not allow a complete program of control testing for release purpose, a reduced release testing program may be carried out. In such cases, the missing information at release level should be compensated by an appropriate in process testing and a more extensive process validation, as outlined above. Such a reduced release testing program should be clearly described and justified. The absence of identity and potency testing is unlikely to be considered justifiable.

5.5. Stability Studies

Stability studies should be conducted according to the principles described in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006). Critical quality parameters to be followed during stability studies should be defined on the basis of characterisation studies and should be able to detect clinically meaningful changes in the product.

6. Non-Clinical Aspects

In the non-clinical development of a medicinal product containing genetically modified cells, the Guideline on human cell based medicinal products (EMEA/CHMP/410869/2006), the Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) and the Guideline on non clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006) should be taken into account.

A rationale for the product design (vector and cell construction) should be given in light of the proposed clinical indication and pharmacological characteristics of the product.

While the objective of non-clinical studies is similar to other medicinal products, e.g. to demonstrate the proof-of-principle and to define the pharmacological and toxicological effects predictive of the human response and safety, non clinical studies should be designed to maximise the information obtained on dose selection for the clinical trials, to support the route of administration and the

application schedule. They should also allow determining whether the observed effect is attributable to transduced gene, to transduced cells or to both, e.g. toxic effect due to over/under-expression of transgene by a correct number of cells as compared to normal expression by an abnormal number of cells.

The non clinical studies should be carried out with batches of transduced cells produced and quality controlled according to the validated production process and should use state-of-the art and adequately validated techniques.

The non clinical studies should be performed in relevant animal models in light of the target cell population and clinical indication. When feasible, several issues can be addressed in one study. It is acknowledged that studies in animal models may be impaired by xenoreactions and/or by transgene product species-specificity. In such cases, homologous models or immune-deficient animals might be advantageous. Any modification of vector construction and /or of target cells carried out to obtain a homologous animal model should be detailed and justified in comparison with the medicinal product.

6.1. Pharmacodynamics and Pharmacokinetics

Pharmacodynamic studies should address and demonstrate:

- the expected effects of genetic modification, such as cell differentiation and/or proliferation induced by gene product or recovery of the intended physiological function,
- the quality of expression, regulation, localisation, duration of expression and structural integrity of the gene product,
- the vector integrity in the cells (either episomal or integrated),
- the intended therapeutic effect, its localisation and its limitations to the intended organ/tissue (efficacy and safety),
- any interaction with an effect on surrounding tissue (e.g. suicide of bystander cells in addition to those carrying suicide transgene),
- any unexpected loss of expression.

Pharmacokinetic studies should be designed in order to address the expression, distribution and persistence of the transgene product.

The *in vivo* fate (biodistribution, homing, life span) of genetically modified cells should be investigated and compared to non genetically modified counterparts.

Germline transmission aspects should be investigated according to the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005).

For cells that are encapsulated in biocompatible material and designed to secrete a gene product, data should be provided to support appropriate secretion activity; beneficial as well as potential toxic effect of gene product should be studied.

The choice and the relevance of *in vitro* and/or *in vivo* models for pharmacodynamic and pharmacokinetic studies should be justified.

6.2. Toxicology

Toxicological endpoints could be addressed in *in vitro* and/or *in vivo* studies which should be designed to investigate any adverse effects induced by the genetic modification.

The following endpoints and considerations should be addressed:

- Any unintended and unexpected change of cellular morphology, phenotype, function and behaviour, such as unwanted proliferation, differentiation, immortalisation or induction of a transformed phenotype, which could occur in genetically modified cells as compared with the unmodified cell population, as well as any pathological changes in the sites where transgene expression occurs.
- Any toxicological consequences of the vector/transgene expression, product activity and persistence or any unexpected property of the genetic modification, e.g. unwanted immune response.

Uses of allogeneic or xenogeneic cells may lead to an unwanted immune response to the administered cells and *in vivo* animal studies may give some useful information regarding the toxicological consequences of such an immune response.

When cells are transduced with integrating vectors (e.g. retroviral or lentiviral), the number of integration sites and their characterisation, if feasible, as far as adjacent gene identity and function, should be discussed in relation to clinical application. Special attention should be paid to activation of oncogenes and/or inactivation of tumour suppressing genes and risk of insertional mutagenesis. If genetically modified primary cells are shown to have a clonal integration profile, and /or integration is found within oncogenes or tumour suppressor genes, oncogenesis studies are required.

The possibility that genetically modified cells release transfer vector *in vivo* should be investigated, including the potential for interactions with other infectious agents or disease-related drugs, when applicable. The extent of these studies will depend on the transfer vector used to transduced cells, its replication capacity and its integration status in the cells. Dissemination of transfer vector to various tissues and organs, particularly to gonads, and to the environment should be investigated. Identity, infectivity, persistence and activity of disseminated agent should be determined. In addition, the possibility that latent viruses (such as herpes zoster, Epstein-Barr virus and cytomegalovirus) have been reactivated leading to the production of infectious virus should be investigated, when applicable based on the type of vector and/or of recipient cells used.

7. Clinical Aspects

7.1. General Considerations

This section considers pre-authorisation studies aiming at evaluating safety and efficacy of the genetically modified cells. Requirements for clinical follow up of patients treated with a medicinal product containing genetically modified cells are laid down in the Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/405681/06).

The requirements are complementing the clinical requirements for cell based medicinal products (EMEA/CHMP/410869/2006) and for gene therapy medicinal products (CPMP/BWP/3088/99)), the Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008) and provide specific requirements for genetically modified cells.

The clinical trials should be designed with the aim of determining as far as possible whether the observed clinical effect is attributable to transduced gene, to transduced cells or to both.

The delivery of the genetically modified cells to the target organ and tissue will require administration through specific surgical procedures or percutaneous or intravascular delivery to obtain the intended therapeutic effect. The biological effects of genetically modified cells are highly dependent on the *in vivo* environment and route of administration, and may be influenced by the replacement process or the immune reaction either from the patient or from the cell based product or from the gene product. The therapeutic procedure as a whole, including the method of administration and eventually the required concomitant medication such as immunosuppressive regimens, needs to be investigated considering benefit versus risk.

In general, for genetically modified cells considered as medicinal product, the same principles as for any other medicinal products apply for the clinical development, especially current guidelines relating to specific therapeutic areas.

Any deviation from the legal requirements (Annex I to Directive 2001/83/EC) and existing guidelines needs to be justified.

7.2. Pharmacodynamics

When genetically modified cells are used and the intended treatment effect is related to the gene introduced into the cell, the level the gene expression should be assessed and a correlate with appropriate functional or pharmacodynamic parameters should be established. The duration of the observed changes of these parameters should be monitored. The studies should be extended to non-target tissues, when feasible.

7.3. Pharmacokinetics

As described in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006), although conventional absorption/distribution/metabolism/elimination studies are usually not relevant for cells, they might be relevant for the transgene product. The principles described in the guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins should be considered for drug-drug interactions studies with the transgene products.

Attention should be paid to the monitoring of the viability, proliferation / differentiation, body distribution / migration and functionality of the genetically modified cells. The methodology used and its limitations should be discussed.

The possibility that transduced cells, intentionally designed for this purpose or not, release any vector or plasmid *in vivo* should be investigated. The design and extent of such investigations will depend on the properties of the construct and the outcome of the non-clinical studies.

Persistence and if applicable pharmacokinetic properties of the transgene expression protein need to be evaluated.

If multiple treatments are considered, the schedule should be discussed also under the light of the pharmacokinetic properties of the transgene product.

The dose and treatment schedule should be based on appropriate pharmacodynamic response, and the pharmacokinetic properties of the transgene product.

7.4. Clinical Efficacy

The study design and duration should be based on the existing guidelines for the specific therapeutic area. Any major deviation(s) from these guidelines should be explained and discussed.

The efficacy studies should also be designed in order to detect clinically meaningful parameters (endpoints) linked to the transduced cell number and /or gene product expression level and /or gene products activity level, to support the recommended posology, and to evaluate the duration of the therapeutic effect of the product.

If the intended outcome of the therapy is the long-term persistence and functionality of the genetically modified cells/transgene expression product, this should be reflected with an adequate duration of follow-up. The design and duration of follow-up has to be specified in the protocol and might be completed post- marketing.

7.5. Clinical Safety

The risk for delayed adverse reactions and decreasing efficacy for genetically modified cells is related to the actual risk profile of the vector used for the genetic modification of the cell, the nature of the gene product, the life-span (persistence) of the modified cells, and the biodistribution. In relation to a possible life-long persistence of genetically modified stem or progenitor cells, special risk for delayed effects associated with the integrated vector and its expressed products should be considered (e.g. oncogenesis, immunogenicity or vector reactivation).

The safety database should be large enough to detect common short- and long-term adverse events that may be associated with the use and/or application procedure of the genetically modified cells.

If additional information of importance for the risk evaluation is becoming available during a clinical trial or post-marketing, then the applicant should change the risk stratification and implement this in a revised clinical follow-up plan.

7.6. Clinical Follow-up

The clinical follow-up of patients enrolled in clinical trials with genetically modified cells should be ensured according to the principles laid down in the Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/405681/06) to detect early or delayed adverse reactions, a change in the efficacy profile, or additional unexplored risks with genetically modified cell products. The clinical follow-up should take into consideration existing non-clinical and clinical information obtained with the gene therapy medicinal product or cell type under investigation, the experience with other similar genetically modified cell products and the information unknown at the current stage.

8. Pharmacovigilance

The rules for routine pharmacovigilance (including immediate or periodic reporting) are described respectively in Volume 10 of the Rules governing medicinal products in the European Union for gene

therapy investigational products, and in Volume 9a for marketed gene therapy medicinal products. In addition to the information required to be included in the Annual Safety Reports for gene therapy investigational products or in the Periodic Safety Update Reports for marketed gene therapy medicinal, the traceability in the donor-product-recipient axis, or of the product-recipient for autologous products, is required in all circumstances (including for cell-lines based products) as described in the Directive 2004/23/EC and in the Regulation No (EC) 1394/2007.

Genetically modified cells may need specific long-term studies to monitor safety issues including lack of efficacy and risk of vector dissemination or reactivation.

The long-term safety issues, such as infections, immunogenicity/immunosuppression and malignant transformation as well as the durability of the associated medical device/biomaterial component should be addressed in the Risk Management Plan. Specific pharmaco-epidemiological studies may be needed. Those requirements are related to the vector type and to the biological characteristics of transduced cells.

9. Environmental Risk Assessment

Reference is made to the Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/2006).

10. References

Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products.

Directive 2001/83/EC on the Community code relating to medicinal products for human use

Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Directive 2006/17/EC implementing Directive 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

Directive 2006/86/EC implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)

Guideline on xenogeneic cell therapy medicinal products (EMEA/CHMP/CPWP/83508/2009)

Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)

EMEA guideline on the production and quality control of medicinal products derived by recombinant DNA technology (3AB1A)

EMEA guideline on the production and quality control of Monoclonal Antibodies (3AB4A)

Guideline on non clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)

Guideline on follow up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/405681/06)

Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)

Rules governing medicinal products in the European Union, Volume 9a and Volume 10

Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/2006)

Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (EMEA/CHMP/GTWP/587488/2007)

Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)

Draft Reflection Paper on Stem Cell-based Medicinal Products (EMA/CAT/571134/2009)

Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)