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

485 therapy investigational products, and in Volume 9a for marketed gene therapy medicinal products. In
486 addition to the information required to be included in the Annual Safety Reports for gene therapy
487 investigational products or in the Periodic Safety Update Reports for marketed gene therapy medicinal,
488 the traceability in the donor-product-recipient axis, or of the product-recipient for autologous products,
489 is required in all circumstances (including for cell-lines based products) as described in the Directive
490 2004/23/EC and in the Regulation No (EC) 1394/2007.

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

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

498

499 9. Environmental Risk Assessment

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

502

503 10. References

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

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

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

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

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

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

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

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

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

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

520 Guideline on non clinical studies required before first clinical use of gene therapy medicinal products
521 (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)

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

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GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

This guideline is describing recommendations for clinical monitoring and follow-up after treatment with Gene Therapy (GT) medicinal products in order to detect early or delayed signals of adverse reactions, to prevent clinical consequences of such reactions and to ensure timely treatment and to gain information on the long-term safety and efficacy of the intervention. The principles laid down in this guideline are applicable for patients enrolled in clinical trials using GT medicinal products and for patients administered with authorised GT medicinal products. The clinical follow-up recommendations take into consideration the risk profile of the gene therapy, the disease, co-morbidity and the patient target population and characteristics.

1. INTRODUCTION

The initial clinical monitoring and follow-up after treatment with Gene Therapy (GT) medicinal products is described in the CPMP Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99). As for all medicinal products with new active substances, a risk management plan should detail the measures envisaged to ensure such follow up, with additional specificities for advanced therapy medicinal products described in the guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008). The scientific principles of follow-up of the patients included in or after GT medicinal product trials, respectively, are also described hereafter. The authorization of gene therapy clinical trials is within the responsibilities of each EU member state (Directive 2001/20/EC).

This guideline takes into consideration that the nature of the follow-up recommendations might vary depending on the risk profile of the gene therapy approach including the specificities of the GT medicinal product and of the transfer vector, the disease, co-morbidity and the patient target population and characteristics. With regard to the risk assessment of GT medicinal products, the data from non-clinical studies and early clinical studies as well as the data available in the public domain with similar products should be taken into consideration.

The guideline should be read in conjunction with all relevant current and future guidelines on GT medicinal products, pharmacovigilance/risk management or specific product-related guidelines (e.g. vaccines, or guidelines addressing specific conditions / diseases). The upcoming guidelines related to advanced therapy medicinal products on traceability and Good Clinical Practice will be important to consider when available.

2. SCOPE

This guideline addresses specific aspects of the active clinical follow-up of patients administered with GT medicinal products in order to detect signals of early or delayed adverse reactions, to prevent clinical consequences of such reactions, to ensure timely treatment and to gain information on the long-term safety and efficacy of the intervention. As such, this guideline aims at complementing the "overarching provisions" of the Guideline on Safety and Efficacy Follow-up – Risk Management of advanced Therapy Medicinal Products, which describes the measures envisaged to ensure the follow-up of efficacy and adverse reactions of advanced therapy medicinal products and of adverse reactions specific aspects, as per article 14 of Regulation (EC) No 1394/2007.

The principles laid down in this guideline are applicable for patients enrolled in clinical trials using GT medicinal products and for patients administered with authorised GT medicinal products. The guideline is relevant to GT medicinal products, including genetically modified cells or tissues that have been transduced ex vivo by any route of administration. The principles outlined in this document also apply to all oncolytic viruses and to microbes intended to transfer plasmid DNA into human cells in vivo.

3. LEGAL BASIS

This guideline addresses specific aspects of the measures envisaged to ensure follow-up of efficacy and of adverse reactions for gene therapy medicinal products, as required in article 14 of Regulation (EC) No 1394/2007 and in the Annex I to Directive 2001/83/EC ("specific requirements regarding Module 5" for advanced therapy medicinal product). As such, it aims at complementing the

"overarching provisions" of the Guideline on Safety and Efficacy Follow-up – Risk Management of advanced therapy medicinal products.

The principles laid down in this guideline are also applicable for patients enrolled in clinical trials using GT medicinal products.

This guideline should be read in conjunction with the introduction and general principles and Part IV of Annex I to Directive 2001/83/EC, as well as with the Regulation of the European Parliament and of the Council on advanced therapy medicinal products (Regulation (EC) No 1394/2007) and with the Regulation (EC) No 726/2004.

4. FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

Healthcare professionals conduct clinical follow-up of individual patients. It includes prevention, screening, monitoring, diagnosis and treatment of diseases to detect injuries, complications, adverse reactions, medical errors, and indicators of declining medicinal product efficacy in humans after administration of a GT medicinal product. Clinical follow-up activities may be needed within days, weeks or years after completion of a clinical trial or a compassionate use regimen or after administration of an authorised medicinal product. Routine pharmacovigilance apply for all authorised medicinal products. Besides, requirements for additional pharmacovigilance activities should be proportionate to the identified balance risk / benefit of the product. If later, new data become available indicating a substantial or potential risk, follow-up measures may have to be taken.

The clinical follow-up of subjects receiving GT products as investigational medicinal product (IMP) in trials or compassionate use before marketing authorisation should be carefully justified in each clinical protocol / IMP dossier. The clinical follow-up of clinical trial subjects administered with a product failing to be authorised or the development of which is discontinued should be justified on the basis of the accumulated evidence and submitted as substantial protocol amendment to the relevant competent authorities and, if applicable, to the concerned ethics committees.

The post-authorization clinical follow-up should be in agreement with the rules for post-authorization surveillance set up in the legislation and guidelines (as collected in Volume 9A of the Rules governing medicinal products in the European Union), should take into account the recommendations from the Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (ATMP), and additional recommendations presented hereafter. Any specific recommendations described in this guideline are set-up in addition to the common rules.

The marketing authorisation holder or sponsor of a clinical trial with a GT products shall ensure that traceability data on the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used, are in accordance with Regulation (EC) No 1394/2007 (art. 15), and upcoming guidelines related to ATMP Traceability and Good Clinical Practice. In case of bankruptcy or liquidation of a marketing authorization holder without a legal entity taking over the marketing authorization, the traceability data will be transferred to EMEA. The case of bankruptcy of a sponsor of a clinical trial is addressed in the upcoming guideline on GCP specific to advanced therapies.

The definitions of terms used in this guidance can be found in section 4 of the Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products.

4.1. RISKS ASSOCIATED WITH GENE THERAPY MEDICINAL PRODUCTS OF IMPORTANCE FOR FOLLOW-UP

The assessment of risks of early or delayed adverse reactions, the risk of efficacy concerns caused by decreasing medicinal product efficacy, or additional unexplored risks with GT medicinal products, should take into consideration existing non-clinical and clinical information obtained with the medicinal product under investigation , the experience with other similar GT medicinal products and the importance of missing information. Furthermore, the list of possible risks described in section 6 of the Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products should also be considered.

For the risk assessment and the decision about the extent/duration of clinical follow-up, the following aspects should be taken into consideration, among others:

- Potential for and extent of chromosomal integration of a vector/ gene
- Capacity of a vector/ gene for latency/ reactivation
- Capacity of a vector for inadvertent replication after complementation by viruses causing escape from latency and reactivation and eventually leading to mobilisation
- Persistence of expression of the gene/vector/gene product
- Replication incompetence or competence of a vector
- Potential for recombination or re-assortment
- Altered expression of (a) host gene(s)
- Biodistribution to target / non-target organ(s) / tissue(s) /cell(s)
- Known interactions with concomitant treatments or known interactions associated with previous exposure to potent agents (chemotherapy, radiotherapy etc.).

The decision on the extent/duration/type of clinical follow-up depends on the criteria listed below which should be known or investigated and taken into account.

4.1.1. Viral vectors

Vectors with the capacity for integration or latency require long-term clinical follow-up considerations because they persist for the life-span of target cells or tissues. However, the life-span of the cells in vivo, which is in general different for stem vs. differentiated cells, and the viability of the cells (e.g., viable live cells with proliferative capacity vs irradiated cells) should also be taken into account because in vivo cell persistence for a short period of time is expected to pose less risk for malignant transformation.

Chromosomal integration of vectors is considered to present a risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation or alteration of host cell genes. Viral vectors with integration machinery such as gammaretroviral and lentiviral vectors, or vectors modified to induce integration, are used and this integration will last for the life-span of the modified cell in vivo. In addition, all viral vectors capable of mediating transfer into the nucleus are considered to have the potential for integration. The extent of integration, meaning the % of cells harbouring integrated vector and the copy number of integrated vector per cell should be taken into account. The lack of capacity of the vector to integrate or undergo latency and/or reactivation should be documented. Measures implemented to reduce the risk of insertional mutagenesis should be verified, if less or no follow-up is to be proposed. For vectors that show a persistent signal without being integrated into the genome, propensity of the vector to undergo latency and reactivation will determine if a long-term clinical follow-up is required.

For viral vectors designed to be replication-incompetent, inadvertent replication and reactivation after complementation by wild-type viruses may cause escape from latency. Replicating (oncolytic) viruses may always undergo latency after initial in vivo replication. It is encouraged to develop methods for detecting if such reactivation has occurred in patients administered with respective vectors or viruses.

In summary, viral vectors mediating transfer of their genetic material into the cell nucleus and replicating (oncolytic) viruses are considered to have a high risk for delayed adverse reactions. Vectors or viruses remaining cytoplasmic or undergoing abortive replication present a low risk for malignant transformation.

4.1.2. Plasmids and non-viral vectors

Plasmids and non-viral vectors are generally considered as having a low integrating capacity, especially after intra-muscular administration of naked DNA in the absence of additional mediators or transfer procedures such as electroporation, and, if the low integration capacity of the specific medicinal product has been substantiated in a suitable model, may therefore be considered to have a low risk for delayed adverse reactions. On the other side, they allow for long-term persistence of the

gene and its expression, which may indicate a high risk for delayed adverse reactions, e.g., with regard to immunopathology. Improved methods of in vivo delivery could substantially modify their integration capacity. It is therefore important, in order to obtain a relevant risk evaluation that the same method of delivery is used in non-clinical safety studies as in the clinical protocol.

4.1.3. Genetically modified human cells

The risk for delayed adverse reactions and decreasing efficacy for genetically modified cells is correlated 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. Related to a possible life-long persistence of genetically modified autologous 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).

Allogeneic cells are, due to immunologic incompatibility, mostly expected to have a limited life-span. Allogeneic cells with shorter life-span may constitute a lower risk for delayed adverse reactions than cells with longer life-span. However, in particular cases (e.g. immune suppressed patients or when allogeneic mesenchymal stromal cells are used) the life-span of allogeneic cells could be prolonged and thus the risk for delayed adverse reactions increases. If mesenchymal stem cells are used for the delivery of the gene, allogeneic mesenchymal stem cells might be immunologically compatible. In addition, for allogeneic cells of haematological origin, the risk for graft versus host disease needs to be considered as a potential cause of serious adverse event. However, this graft versus host reaction is normally not considered a delayed reaction and not related to the genetic modification of the cell.

4.1.4. Route and method of administration

Changes to the route or method of administration could influence the biodistribution and the potential for serious delayed reactions. An improved method of gene transfer could increase the risk for integration and thereby increase the risk for delayed effects. Changing the route of administration could result in an increased local dose to tissues not represented in safety studies. Furthermore, latency and / or reactivation of viral vectors are often a tissue-specific phenomenon and the evaluation of such risk could be compromised if different tissues than those in the safety studies are exposed to the product.

4.1.5. Clinical patient population

The patient populations enrolled in GT trials are very heterogeneous. Some patients have a chronic disease with long life expectancy while other diseases have a short life expectancy. The treatment may cure some patients and in other patients may only reduce the extent/progression of the disease.

Therefore, the target patient population and characteristics, general health status and expected survival rate of the patients with the disease treated with GT medicinal products can have significant impact on the relevance of recommending long-term clinical follow-up independent of the vector used. The patients intrinsic risk profile for inadvertent long-term complications should be considered in the follow-up planning.

The majority of GT medicinal product trials (approx. 70 %) are presently conducted in patients with cancer. However, this may change in the future. The cancer patients enrolled are often terminally ill and with a short life expectancy. The previous exposure to potent agents (chemotherapy, radiotherapy, GT medicinal products etc.) can potentially interfere with the interpretation of data collected in the follow-up period. Moreover, their poor clinical situation and degree of exhaustion may limit the possibility to conduct extensive invasive clinical follow-up investigations. In addition, patients cured for a disease may not want to participate in extensive long-term follow-up schedule. Inclusion of a parallel control group in many of the GT medicinal product trials has to be considered when planning follow-up and risk management plans.

Therefore patients with multiple morbidities, widespread disease and/or exposure to agents with potential for delayed adverse reactions, may not be candidates for long-term follow-up of adverse reactions caused by GT medicinal products. However, the clinical follow-up should be as long as possible and necessary.