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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

TABLE OF CONTENTS

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.

4.1.6. Efficacy of a GT medicinal product

With respect to declining GT medicinal product efficacy, plasmids, non-viral vectors, replication-incompetent viral vectors, replicating viruses and genetically modified cells may show a decline of transgene expression with time after administration. Also, the number of vector- or virus-harbouring cells may decline with time. These factors may lead to a reduced GT medicinal product efficacy and hereby reduced clinical treatment efficacy requiring special attention or a need for reconsidering the treatment for the treated patients.

4.2. SYSTEM FOR THE DECISION ON INTENSITY AND DURATION OF CLINICAL FOLLOW-UP AFTER TREATMENT WITH GENE THERAPY MEDICINAL PRODUCTS

Relevant non-clinical studies to evaluate the risk for delayed adverse reactions are described in the Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (CHMP/GTWP/12549/06). These non-clinical studies are aimed to identify parameters of great importance for delineation of the safety profile of GT medicinal products. The design of non-clinical studies shall as much as possible be adapted to reflect the clinical settings with respect to the pharmacological response (including tissue specificity), formulation of product, route- and method of administration and the intended disease to be treated.

Non-clinical development shall include studies on biodistribution and vector persistence. Persistence is indicated if a sustained signal from vector sequences is obtained after the final administration of the product. However, the level of virus detection and its relevance for a clinical implication should be taken into consideration.

Relevant studies and their design for evaluation of delayed adverse risks associated with genetically modified cells are described in the guideline on human cell based products (EMEA/410869/2006).

The design of toxicity studies should include an assessment for the detection of delayed toxicity. The duration of studies, if the treatment is transient, should at least reflect the persistence period of the vector/cell and the produced product.

When planning the risk assessment of GT medicinal products and the risk management plan for GT medicinal products, the risk stratification system described in Table 1 could be applied. It is recommended to consider each of the individual risk factor for the GT medicinal product in a clinical trial application or in a marketing authorisation application. Then it should be possible to design a risk stratification profile for the GT medicinal product.

Table 1 Risk factors of GT medicinal products to be considered and examples of potential clinical consequences

The documented risk factor (the below list being not exhaustive), and the likelihood of its clinical consequence and severity, will impact on the extent/duration/type of clinical follow-up, as follows:

1. Established or suspected risk known from non-clinical/clinical data – clinical long-term follow-up is needed

2. Scientific data do not indicate safety concern – clinical long-term follow-up is not needed

Risk factor	**Examples of potential clinical consequence of the risk factor**
Chromosomal integration of a vector / gene	Cancer due to vector integration
Capacity of a vector / gene for latency/ reactivation	Clinical effects of a chronic infection and unwanted therapeutic gene expression
Capacity of a vector for inadvertent replication after complementation by viruses causing escape from latency and reactivation and	Infection by a new virus entity and/or chronic infection and/or unwanted therapeutic gene expression and/or biodistribution to non-target tissues/ organs

eventually leading to mobilisation	
Persistence or characteristics of vector / gene	Clinical effect of chronic infection and/or long-term expression of the gene product
Persistence of a gene product	Clinical effect of long-term expression of the gene product
Un-intended biodistribution[a]	Clinical effect of expression of the product in an un-intended tissue or organ
Replication incompetence or competence of a vector	Clinical effect of chronic infection and/or long-term expression of the gene product
Potential for recombination or re-assortment	Cancer due to new gene combinations and/or infection by a new virus entity and/or chronic infection and/or unwanted therapeutic gene expression and/or biodistribution to non-target tissues/ organs
Altered expression of a host gene	Auto-immunogenicity or cancer

a. Take into consideration route and method of administration and target organ.

4.3. RECOMMENDATIONS FOR CLINICAL FOLLOW-UP AFTER TREATMENT WITH GENE THERAPY MEDICINAL PRODUCTS

The clinical follow-up period is dependent on considerations such as the characteristics of GT medicinal products, the anticipated time for the occurrence of delayed adverse reactions, the clinical indication and expected life expectancy of the treated patients. The duration of clinical follow-up observations should be sufficient to observe the subjects for risks that may be due to the characteristics of the product, the nature and extent of the exposure, and the anticipated time of occurrence of delayed adverse reactions.

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

Healthcare professionals conduct the clinical follow-up of individual patients in a clinical setting. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors. To collect the appropriate data for detection of delayed adverse reactions, the clinical follow-up protocol needs to have very clear objectives, be hypothesis driven, and be based on appropriate risk assessment (consistent with the risk management plans as these need to be in place at the point of licensing).

Careful consideration should be given to the feasibility of long-term monitoring, the value it adds, and imposition on patients and clinicians.

Therefore, the clinical follow-up period should only be extended as long as feasible and clinically relevant.

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 GT investigational products and in Volume 9a for marketed GT products. In addition to the information required to be included in the Annual Safety Reports for GT investigational products or in the Periodic Safety Update Reports for marketed GT products, the following complementary information shall also be collected:

- Mortality

If patients die during the observation period, attempts should be made to obtain biopsy material to perform assay for replication competent retrovirus or other relevant part of the GT medical product and to ascertain the cause of death, if appropriate.

- Development of any new/recurrent cancer

The incidence and nature of malignancies reported from all sources should be monitored. Efforts should be made to perform investigation on samples. The investigation plan shall take the type of

vector and the properties of the gene expression product into consideration i.e. integration of genetic material from the vector in the host genome and expression of the gene product and it's receptors in the tissue sample.

- Development of infection

The nature and incidence of opportunistic and serious infections in patients receiving gene therapy treatment should be monitored. Effort should be made to obtain complete information including concomitant medication(s), laboratory results, and the identification of infecting agents.

- Immunogenicity related reactions

Unwanted immunogenicity could be observed, for example, due to the persistent gene expression. The consequences of such immune reactions range from transient appearance of antibodies or cell mediated immunity without any clinical significance to severe life threatening conditions.

If it is clinically relevant antibody and cell mediated immunity testing shall be a part of the clinical trial and the observation period should be sufficient to detect a signal. If the antibody is a non-neutralising antibody, not targeting epitopes linked to the activity of the protein, and therefore without any impact on the efficacy of the GT medicinal product, then screening tests are not needed.

Immediate hypersensitivity reactions would be noticed in the clinical trial, however delayed reaction such as antibodies to the gene expression protein might occur.

Antibodies interfering with the activity of the gene vector or expression protein might lead to a lack of efficacy (in case it is desired to have continuous gene expression) and they can cross-react with the endogenous protein in cases where endogenous protein is still produced. In this case the consequence would be autoimmunity.

- Participation in other clinical studies
- Further safety endpoints e.g. neurological or cardiovascular could be of relevance determined by the nature of the disease to be treated and the target organ for the vector.
- Subsequent exposure to highly potent treatment e.g., radiotherapy, cytotoxic agents.

4.3.1 Viral vectors which can integrate or have the potential for latency followed by reactivation

It is recommended that patients enrolled in clinical GT medicinal product trials, where non-clinical tests or evidence from other clinical trials using identical vectors or modifications of vectors indicate a potential for integration or late re-activation have a monitoring plan with a brief clinical history and sample testing at the following time points: pre-treatment, 3, 6 and 12 months after treatment for at least 5 years, and then yearly until data indicate that there is no longer any risk to be followed. If any post-treatment samples are positive, indicating integration or re-activation, or clinical evaluation indicate a treatment induced side-effect/adverse event, then a more regular and extensive clinical follow-up should be undertaken.

The safety monitoring plan should include methods and analyses aimed at vector tracking and the evaluation of eventual consequences connected with the presence of the vector. The studies should be designed to cover aspects of the specific risk profile connected with the type of vector and hetereologous gene.

In case all the samples are negative during the first year, the remaining samples can be archived. Retention samples from each time point have to be stored for five years, in order to allow further testing if a relevant adverse event appears during the follow-up period.

The method used to monitor persistence should be directed towards the detection of vector sequences (e.g. PCR). In special cases (if sampling does not allow for the detection of vector sequences) monitoring could be performed by detection of expressed product. It is recommended to use validated methods to analyse the sample.

If any post-treatment samples are positive, indicating integration or re-activation, or clinical evaluation indicate a treatment induced side effect/adverse event, then a more regular and extensive clinical follow-up should be undertaken.

4.3.2. Viral vectors without integration, latency or reactivation potential

Viral vectors without integration, latency and re-activation potential present a low risk for gene therapy-related delayed adverse reactions. However, if non-clinical or clinical data indicate persistence of the vector, or the vector product for a prolonged period, or they raise concerns about a risk of delayed adverse reactions, then follow-up observations should be extended to long-term risks monitoring.

If vectors with known potential for delayed adverse reactions are modified to reduce this risk and the effect is supported by data, then the need for performing long-term follow-up observations can be reassessed.

It is recommended that patients enrolled in clinical GT medical product trials with viral vectors without integration, latency and re-activation potential have a monitoring plan with a brief clinical history and sample testing at the following time points: pre-treatment, 3, 6 and 12 months after treatment, and then yearly thereafter for a minimum of 5 years.

If applicable, a safety-monitoring plan should be developed to cover the risk profile of this product as identified in non-clinical safety evaluations or from clinical experience with similar products types. If any post-treatment samples are positive or clinical evaluation indicate a treatment induced side-effect/adverse event, then a more regular and extensive clinical follow-up should be undertaken.

Dependent on the vector used and the known risk of delayed adverse reactions, the yearly clinical follow-up could be arranged as a visit with a healthcare professional or as a questionnaire forwarded to the patients.

4.3.3 Plasmids and non-viral vectors

Clinical gene therapy trials using plasmids are considered to present a lower risk. However, if they have a prolonged expression of the gene or have been modified and non-clinical tests indicate an increased integration capacity, then a prolonged follow-up observation period for adverse reactions should be performed.

It is recommended that patients enrolled in clinical GT medical product trials with plasmid have a monitoring plan with a brief clinical history and sample testing at the following time points: pre-treatment, 3, 6 and 12 months after treatment, and then yearly thereafter for a total of 5 years.

If any post-treatment samples are positive or clinical evaluation indicates a treatment induced adverse reaction, then a more regular and extensive clinical follow-up should be undertaken.

Dependent on the plasmid used and the known risk of delayed adverse reactions, the yearly clinical follow-up could be arranged as a visit with a healthcare professional or as a questionnaire forwarded to the patients.

4.3.4 Genetically modified human cells

The risk for adverse reactions after treatment with genetically modified cells is dependent on the used gene vector, cell type and persistence of the cells and genes after delivery to the patient. In addition to these parameters, the risk of inducing an immunologic reaction host vs graft or graft vs host shall be considered. However, these immunologic reactions are normally seen within a short period after initiation of the treatment.

It is recommended, that the clinical follow-up after treatment with genetically modified cells follow the recommendations for the gene vector used unless non-clinical or clinical data indicate a need for a different follow-up regimen.

If applicable, a safety monitoring plan should be developed to cover the risk profile of this product type as identified in non-clinical safety evaluations or from clinical experience with similar products types.

4.4. FOLLOW-UP OF EFFICACY OF GENE THERAPY MEDICINAL PRODUCTS IN POSTMARKETING APPROVAL SETTINGS

In the marketing authorisation application, the applicant shall outline a plan for follow-up of efficacy of GT medicinal products and of adverse reactions thereto. The principles of presentation of such data are described in the Guideline on Safety and Efficacy Follow-up Risk Management of Advanced Therapy Medicinal Products.

The GT medicinal products will be used in a broad range of clinical indications, targeting a heterogeneous patient population with regard to factors such as underlying disease, co-morbidity, and concomitant therapy.

The methods and parameters to evaluate the long-term efficacy, in addition to patient related factors such as patients' characteristics, natural history and progression of underlying disease, life expectancy and co-morbidity should be taken into consideration when planning studies and follow-up of efficacy of a GT medicinal product. The clinical efficacy endpoint is determined by the disease / condition to be treated. Some patients will be cured, however many of the patients will have diseases with a continuous progression with time, which can make difficult to perform long-term efficacy monitoring of a GT medicinal product treatment. The efficacy follow-up plan does not have to include all patients, but can be based on a sample of the treated patients.

The importance of including a relevant control group should be considered. The choice of the control group for GT medicinal products depends on the underlying condition and available treatment for the disease.

It can be expected that patients receiving GT medicinal products will receive other medicinal products either for the underlying disease or for treatment of concomitant diseases. Thus it is of importance to monitor also the type and dosage of these medications as well as further medical interventions during the follow-up phase.

4.5. PHARMACOVIGILANCE, RISK MANAGEMENT AND TRACEABILITY IN POSTMARKETING APPROVAL SETTING

With the marketing authorisation application, a risk management plan has to be submitted in accordance with the current EU legislation and pharmacovigilance guidelines (see Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products). The holder of a marketing authorisation for a GT medicinal product shall establish and maintain a system ensuring that the individual product can be traced through the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used. The marketing authorisation holder shall keep these data for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation. (Regulation (EC) No 1394/2007 – Art. 15).

In addition, the hospital, institution or private practice where the GT medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it. A guideline on traceability of advanced therapy medicinal products is under preparation.

5. REFERENCES

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to

the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

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

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

EMEA/CHMP Guideline on non-clinical studies required before first clinical use of gene therapy medicinal products (CHMP/GTWP/125459/06)

EMEA/CHMP Guideline on risk management systems for medicinal product for human use (EMEA/CHMP/96268/2005)

EMEA/CHMP Guideline on non-Clinical testing for inadvertent germ line transmission of gene transfer vectors (EMEA/273974/05)

EMEA/CHMP 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: Guidelines on Pharmacovigilance for Medicinal Products for Human Use
- Volume 10: Clinical Trials