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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

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

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INTERESTED PARTIES

EMEA: Gene Therapy Working Party (GTWP), Pharmacovigilance Working Party (PhVWP), Safety Working Party (SWP), Cell-based Product Working Party (CPWP), Paediatric Committee (PDCO), Biologics Working Party (BWP) and Vaccine Working Party (VWP).

EXTERNAL CONSULTATION:

Pharmaceutical industry, academic networks and learned societies within the EU.

[1] Last day of relevant CxMP meeting
[2] Last day of the month concerned

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EXECUTIVE SUMMARY

The guideline is describing recommendations for clinical monitoring and follow-up after treatment with Gene Therapy (GT) medicinal products in order to detect early signals of delayed 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 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. The scientific principles of follow-up of the patients included in or after GT medicinal product trials, respectively, are also described here. Authorization of gene therapy clinical trials is within the responsibilities of each EU member state (Directive 2001/20/EC).

This guideline will take into consideration that the nature of the follow-up recommendations might vary depending on the risk profile of the gene therapy approach including the specifics 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 of 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 medical 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, Good Clinical Practice and post-authorisation follow-up of safety and efficacy, and risk management will be important to note when available. There might be national legislation, which will require a longer follow-up than recommended in the guideline.

2. SCOPE

This guideline addresses the principles for follow-up of patients administered with GT medicinal products in order to detect early signals of delayed 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 guideline is relevant to GT medical 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 should be read in conjunction with the introduction and general principles and Part IV of Annex I to Directive 2001/83 as amended, as well as with the Regulation of the European Parliament and of the Council on advanced therapy medicinal products (No 1394/2007), with the Directive 2001/83/EC and with the Regulation (EC) No 726/2004.

4. MAIN GUIDELINE TEXT

Clinical follow-up of patients is defined as any measures intended to detect, analyse and investigate suspected adverse reactions or indicators of declining medicinal product efficacy in humans after administration of a GT medicinal product. Follow-up measures should be taken within days, weeks or years after completion of a clinical trial or a compassionate use regimen or after administration of an authorised medicinal product. The active follow-up period may also end with the completion of a trial or compassionate use or treatment regimen with an authorised medicinal product, if no risk is assumed. If later new data become available which indicate a substantial risk, follow-up measures may have to be re-installed.

The 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. In the event that a product is not authorised or development discontinued the further follow-up of clinical trial subjects needs to be reviewed with the competent authority at that point. The follow-up should be justified on the basis of the accumulated evidence and submitted as substantial protocol amendment to the competent authorities and, if applicable, to the ethics committees concerned.

The follow-up post-marketing authorisation should be in agreement with the legislation and the follow-up for GT medicinal product recommendations here. In addition, the holder of a marketing authorisation shall for the follow-up include a plan to keep traceability data on the sourcing, manufacturing, packaging, storing, transport and delivery to the hospital, institution or private practice where the product is used for at least 30 years.

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

The assessment of risks for delayed adverse reactions and for decreasing medicinal product efficacy and the risk management plan for GT medicinal products should take into consideration existing non-clinical and clinical information obtained with the medicinal product under investigation and experience with other similar GT medicinal products.

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

- 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
    a. Route and method of administration
    b. Target organ/ tissue / cell
- Concomitant treatments or 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. Viruses

Vectors with the capacity for integration or latency require long-term 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 in many cases poses less risks 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 are used with the intention to integrate 100% into the chromosome of cells and this integration will last for the life-span of the modified cell in vivo. All viral vectors, mediating transfer of vector into 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. 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 follow-up is required. The lack of capacity of the vector to integrate or undergo latency and/or reactivation should be documented. For example, by modifying the vectors to increase their utility as a GT medical product, some previously non-integrational vectors can now induce integration of their gene material, i.e. modified adenovirus. Measures to reduce the risk of insertional mutagenesis should be tested for their ability to reduce these risks, if less or no follow-up is considered.

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).

Allogenic cells are, due to immunologic incompatibility, mostly expected to have a limited life-span and hence constitute a low risk for delayed adverse reactions. However, in particular cases (e.g. immune suppressed patients or when used allogenic mesenchymal stromal cells) the life-span of allogenic 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 biodistribution route and the method of administration could influence 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. This risk could also be increased by changing the route of administration resulting 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. The 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 will cure some patients and in other patients only reduce the extent/progression of the disease.

Therefore, the patient target 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 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 medical 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 often limits the possibility to conduct extensive clinical follow-up investigations. In addition, patients cured for a disease may not want to participate in extensive long-term follow-up schedule if the scope of the follow-up is not clear. 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, 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 requiring special attention for the treated patients.

4.2. SYSTEM FOR THE DECISION OF LONG-TERM FOLLOW-UP OR NOT AFTER TREATMENT WITH GENE THERAPY MEDICINAL PRODUCTS

Relevant pre-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 be focused on 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 intended to be applied for a clinical trial or for marketing authorisation application. Then it should be possible to design a risk stratification profile for the GT medicinal product.

Table 1. Risk stratification of GT medicinal products and follow-up
Documented risk factor, and likelihood of its clinical consequence and severity, and the impact on the extent/duration/type of follow-up:
1. Established or suspected risk known from non-clinical/clinical data - long-term follow-up is needed
2. Scientific data do not indicate safety concern - 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 eventually leading to mobilisation	Infection by a new virus entity and/or chronic infection and/or unwanted therapeutic gene expression and/or biodistribution to non-target tissues/ organs
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 LONG-TERM FOLLOW-UP AFTER GENE THERAPY MEDICINAL PRODUCTS

The follow-up period is dependent on a summary of considerations such as the characteristic 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 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 follow-up for an approved follow-up plan 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 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, the level of active monitoring, and imposition on patients and clinicians.

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

As a minimum requirement information on the following reactions shall be collected on an annual basis:

- Mortality, including primary cause of death and date

  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 medical 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 or clinical evaluation indicate a treatment induced side-effect/adverse event, then a more regular and extensive 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 samples during the first year are negative, 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 a full clinical evaluation has to be performed.

Dependent on the vector used and the known risk of delayed adverse reactions, the 1-year follow-up could be arranged as a visit with a healthcare professional or as a questionnaire forwarded to the patients.

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

4.3.3 Plasmids

Clinical gene therapy trials using plasmids are considered to have a low risk for delayed adverse reactions. 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 indicate a treatment induced adverse reaction, then a more regular and extensive follow-up should be undertaken.

Dependent on the plasmid used and the known risk of delayed adverse reactions, the years 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 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 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 with 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. However, some patients will be cured but many of the patients will have diseases with a continuous progression of the disease with time, which can make it 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 in accordance with the current EU legislation and pharmacovigilance guidelines has to be submitted. This plan shall take into account the risks identified during the development procedure of the GT medicinal product and the potential risks associated to the nature of the product. In principle this plan will follow the principles and recommendations detailed in this guideline. Based on scientific and clinical risk knowledge, the studies included into the risk management plan do not have to include all treated patients, but can be based on a sample of the patients. If post-marketing additional information of importance for an approved risk management plan is accumulated, then the applicant should implement this in a revised risk management plan.

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. 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 by the European Commission.

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 *(Official Journal L 311, 28/11/2001 p. 67 - 128)*. Consolidated 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. In particular Part IV of Annex I, as amended.

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 (*Official Journal L 121, 1/5/2001 p. 34 - 44*).

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.

The 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 the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified cells (under development; based on the concept paper CHMP/GTWP/405681/06)