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# GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

***Draft for public consultation***

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# Executive summary

Scientific progress in cellular and molecular biotechnology has led to the development of advanced therapy medicinal products, such as gene therapy, somatic cell therapy, and tissue engineering products. The European parliament and the Council have issued Regulation No 1394/2007 (hereafter referred as the Regulation) that set up specific rules for advanced therapy medicinal products (ATMPs).

Article 14 (4) of the Regulation requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. To meet this requirement, this guideline has been prepared by the EMEA and its scientific committees and working parties. It should be read and understood in conjunction with existing relevant guidelines, and provides a basis for the development of future detailed guidelines in the field.

The scientific rationale for specific rules for pharmacovigilance of advanced therapies is described as a list of main points that should be considered when preparing a risk management plan for advanced therapy medicinal products (ATMP.)

Safety and efficacy follow-up systems form part of the Risk management system and should be planned in the EU-Risk management plan (EU-RMP). Both follow up systems are defined as any systematic collection and collation of data that is designed in a way that enables learning about safety and/or efficacy of an ATMP. It may include passive or active surveillance, observational studies, or clinical trials. It is stressed that both the efficacy and the safety follow-up systems are not a substitute for the need for adequate data to be available at the time of authorisation to enable proper benefit-risk evaluation.

Two documents that are part of a marketing authorisation application are directly affected by this guideline – the EU Risk Management Plan (EU-RMP) and the Detailed Description of the Pharmacovigilance System (DDPS). It may be necessary to introduce additional elements to the description of the pharmacovigilance system to take account of the particular issues with ATMPs. In the Additional EU requirements of the safety specifications, a new chapter for ATMPs is introduced. Groups of risks that are more targeted to ATMPs should be discussed there in an order that follows the procurement in living donors, the product manufacturing, administration, and follow-up of patients. Part II of the RMP shall contain a new discussion on the need of efficacy follow-up. If the need is identified, details of an efficacy follow-up plan should be submitted as Annex 9 of the RMP.

The guideline also lists some points to be considered for efficacy post-authorisation studies, in particular sample size, use of data, reporting, choice of endpoints and examples of events of particular interest.

It is also acknowledged that support of electronic exchange of pharmacovigilance information will need some adjustments. It will be addressed with EudraVigilance stakeholders separately.

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# 1. INTRODUCTION

Scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to guarantee a high level of health protection, as well as to harmonise and facilitate market access, foster competitiveness and provide legal certainty.

The European parliament and the Council have issued Regulation No 1394/2007 (hereafter referred as the Regulation) that sets up specific rules for advanced therapy medicinal products (ATMPs). It regulates those ATMPs which are intended to be placed on the market in the European Economic Area, and that are within the scope of Directive 2001/83/EC as amended, i.e. products that are either prepared industrially or manufactured by a method involving an industrial process.

In its Chapter 5 the Regulation details post-authorisation requirements. Article 14 (4) specifically requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. In order to meet this request, the EMEA is issuing this guideline to complement the existing relevant guidelines. It should also provide a basis for the development of future detailed guidelines in the field.

This guideline concerns an area where knowledge is fast evolving and there is limited experience. Marketing authorisation applicants and holders are encouraged to apply for scientific advice from the EMEA as early as possible to prevent unnecessary mistakes in development and delays in the regulatory process.

In the foreseeable future, it is expected that with growing experience and establishment of the Committee on Advanced Therapies (CAT), there will often be a need to update the guidelines concerning ATMPs. Therefore, users of this guideline should always check whether a newer guideline has been published which further specifies the issues discussed below.

It needs to be highlighted that the concept for generation of long-term data is not a substitute for the need for efficacy and safety data at the time of marketing authorisation application. Quality, safety and efficacy data are required as the basis for approval and should be sufficient to enable a proper benefit-risk evaluation. Any lack of such data and the intention to generate post-authorisation data should be fully justified at the time of marketing authorisation application. Due to the novelty of these products, applicants are encouraged to seek scientific advice from the EMEA also in respect of risk management plans.

To ensure optimal assessment processes, regulatory authorities are encouraged to use multidisciplinary teams for assessment of risk management plans, particularly when the plan contains efficacy follow-up activities.

# 2. SCOPE OF THE GUIDELINE

The Regulation defines ATMPs as gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products.

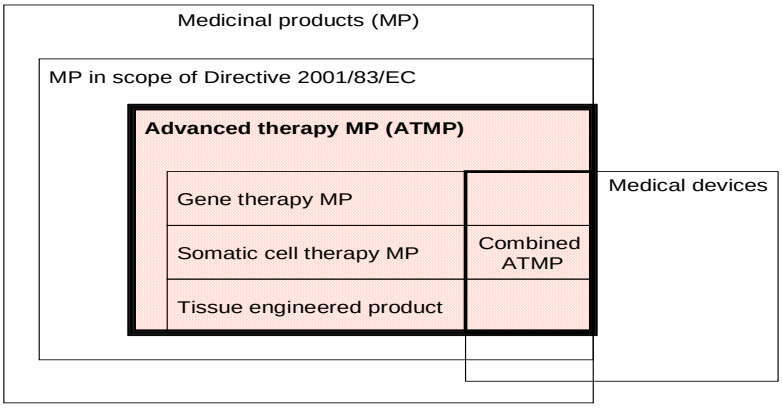
This guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs, as well as some aspects of clinical follow-up of patients treated with such products. The target audience includes in particular marketing authorisation holders, competent authorities for medicinal products, and health care providers.

Follow-up of subjects in interventional clinical trials with ATMPs is not directly in the scope of this guideline. Nevertheless, it is appreciated that many subjects of such clinical trials will require very long or even life-long follow-up. Therefore, when designing a post-authorisation patients' follow-up system, it is always necessary to take into account any existing requirements and guidelines for follow-up of subjects in clinical trials, as well as the follow-up system that was, or still is, in place for subjects of clinical trials with the particular ATMP.

The text of this document is based on existing pharmacovigilance and efficacy guidelines collected in The Rules Governing Medicinal Products in the European Union which set up common rules. Those rules are hereafter not repeated, or only a summary is provided when necessary. Readers are encouraged to follow the particular reference to get the full information.

For specific rules, this guideline considered in particular existing concepts and guidelines published, or drafted, by the EMEA, CHMP and its working parties in areas of gene therapy, cell therapy and tissue engineering, as well as pharmacovigilance and risk management.

**Figure 1 Scope of the guideline**




# 3. LEGAL BASIS

Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products introduces additional provisions to those laid down in Directive 2001/83/EC and Regulation (EC) 726/2004. Article 14 (4) of Regulation (EC) No 1394/2007 specifically requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. The EMEA issues this guideline to meet this request and to complement existing guidelines in the area.

## *3.1. Related legislation*

- Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 for Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- Annex I of the Directive 2001/83/EC, particularly Part IV – Advanced Therapy Medicinal Products.
- Directive 2004/23/EC and daughter Directive 2006/86/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and daughter directives 2005/61/EC as regards traceability requirements and notification of serious adverse reactions and events and 2005/62/EC as regards Community standards and specifications relating to a quality system for blood establishments
- Directive 2001/20/EC 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 2007/47/EC amending Directive 90/385/EC on the approximation of the laws of the Member States relating to active implantable medical devices and 93/42/EEC concerning medical devices

### *3.2. Relevant guidelines*

- The Rules governing medicinal products in the European Union, in particular
    - Clinical efficacy and safety guidelines in Volume 3
    - Pharmacovigilance guidelines in Volume 9A
    - Guidelines on Clinical trials in Volume 10
- Guidelines with additional provisions for advanced therapy medicinal products:
    - CPMP/BWP/3088/99: Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products
    - EMEA/CHMP/GTWP/125491/2006: Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products
    - CPMP/BWP/41450/98 Points to consider on human somatic cell therapy
    - CPMP/1199/02 Points to consider on xenogeneic cell therapy medicinal products
    - EMEA/CHMP/GTWP/405681/2006: Concept paper on the development of a guideline on the quality, preclinical and clinical aspects of medicinal products containing genetically modified cells.
    - EMEA/CHMP/GTWP/367513/2006: Concept paper on the development of a Guideline on clinical monitoring and follow-up of patients exposed to gene therapy/gene transfer medicinal products.
    - ICH Considerations – General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006)
    - Draft under CHMP/CPWP discussion: Guideline on Human Cell-Based Medicinal Products
    - Draft under CHMP/GTWP discussion: Guideline on clinical monitoring of subjects treated with gene therapy medicinal products
    - Draft under CHMP/CPWP discussion: Guidance on the post-marketing surveillance for cell-based medicinal products
    - Draft under CHMP/CPWP discussion: Guideline on xenogeneic cell therapy medicinal products.
    - Expected European Commission Guideline on traceability of advanced therapy medicinal products
    - Draft under development – Good Clinical Practice on clinical trials with advanced therapy medicinal products
- For combination medicinal products, also consider guidelines for medical devices MedDEV, in particular MedDEV 2.12/1 rev.5 on medical devices vigilance system

# 4. DEFINITIONS

This guideline works with definitions used in related legislation and guidelines, and ads some new ones. For ease of reference, the following definitions are used in this document:

***Pharmacovigilance***

Pharmacovigilance is defined by the World Health Organisation as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

***Risk Management System***

Defined in the Regulation EC/1901/2006 and in the Volume 9A as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions.

***EU -Risk Management Plan***

A document that describes a Risk Management System, which is specific to a particular product abbreviated as EU-RMP. (Volume 9A)

***Risk Minimisation***

Defined as a set of activities used to reduce the probability of an adverse reaction occurring or its severity should it occur. (Volume 9A)

***Report follow-up***

A part of routine pharmacovigilance that is aimed at obtaining further relevant information about an adverse drug reaction case from the reporting health care professional. If a targeted report follow-up is put in place for a specific product (i.e. using pre-defined product specific questionnaires), then it is considered to be an additional pharmacovigilance activity. (CIOMS V, Volume 9A)

***Traceability***

The ability to trace each individual unit of an ATMP from the donor and /or source material to the patient and vice versa. (For more details see the separate Guideline)

In addition, for the purpose of this guideline, the following definitions apply:

***Clinical follow-up***

A follow-up of individual patients conducted by healthcare professionals. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors.

***Safety follow-up***

Any systematic collection and collation of data that is designed in a way that enables learning about the safety of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials.

***Efficacy follow-up***

Any systematic collection and collation of data that is designed in a way that enables learning about the efficacy or effectiveness of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials.

***Living donors***

Donors alive at the time of donation.

# 5. COMMON RULES FOR POST-AUTHORISATION SURVEILLANCE OF MEDICINAL PRODUCTS

The rules for post-authorisation surveillance (pharmacovigilance) of medicinal products for human use apply to all advanced therapy medicinal products. These rules are set up in the legislation, and detailed guidelines are collected in Volume 9A of the Rules governing medicinal products in the European Union.

The Community system of Pharmacovigilance directly concerns health care professionals, marketing authorisation holders, national competent authorities for medicinal products, the European Medicines Agency and the European Commission. Some additional pharmacovigilance obligations are imposed by national law, and may concern healthcare providers, distributors, pharmacies, sponsors of clinical trials, non-commercial investigators, and ethics committees. The main stakeholder groups are patients, healthcare professionals, academia, the pharmaceutical industry and governments.

Any specific rules described in this guideline are set up in addition to the common rules. It is of utmost importance that the users of this guideline read it in conjunction with the legislation and guidelines detailing common rules for post-authorisation surveillance of medicinal products.

# 6. SCIENTIFIC RATIONALE FOR SPECIFIC RULES FOR POST-AUTHORISATION SURVEILLANCE OF ADVANCED THERAPY MEDICINAL PRODUCTS

### *6.1. Safety concerns*

Advanced therapy medicinal products provide new possibilities for restoring, correcting or modifying physiological functions, or making a diagnosis. At the same time, because of their novelty, complexity and technical specificity, they may bring along new, unexplored risks to public health and to individual patients. The specific rules described in this guideline should facilitate early detection of such risks and provide a framework for effective mitigation of their consequences to public health or to individual patients.

When preparing a risk management plan for a particular advanced therapy medicinal product, comprehensive scientific consideration should be given to the important identified or potential risks, and to the important missing information. The following features should always be part of such considerations:

- Risks to living donors, for instance:
    - Risks to living donors related to their conditioning prior to procurement (immunosuppression, cytotoxic agents, growth factors etc.)
    - Risks to living donors related to surgical/medical procedures used during or following procurement
- Risks to patients related to quality characteristics of the product, in particular:
    - Origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing
    - Characteristics of vectors for gene therapy medicinal products
    - Biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics)
    - Quality assurance and characteristics of the finished product in terms of defined composition, stability and biological activity
    - Risk related to transmissible diseases (viral, bacterial, parasitical infections and infestations, but also malignant disease and others)

- Risks to patients related to the storage and distribution of the product, for instance:
    - Risks related to preservation, freezing and thawing
    - Risks of breaking the cold chain or other type of controlled temperature conditions
    - Risks related to stability of the product
- Risks to patients related to administration procedures, for instance:
    - Biologically active substances used in preparation of the product prior to administration (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics)
    - Risks related to conditioning of the patient
    - Risks of related medical or surgical procedures such as infusion, transfusion, implantation, transplantation, anaesthesia...
    - Risks related to clinical follow-up (immunosuppression as co-medication or as necessary for treatment of complications, diagnostic procedures, hospitalisation…)
    - Risks related to mistakes or violations of the standard procedures for administration of the product (e.g. different administration procedures used by different healthcare establishments/healthcare professionals resulting in differing results)
- Risks related to interaction of the product with the patient, for instance:
    - Unwanted immunogenicity and its consequences (including anaphylaxis, graft versus host disease, graft rejection, hypersensitivity reactions, immune deficiencies, …)
    - Risks related to genetic modification of the patient's cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy)
- Risks related to scaffolds, matrices and biomaterials (biodegradation, mechanical factors…)
- Risk related to behaviour of the product in the patient, for instance:
    - Early and late consequences of homing, grafting, differentiation
    - Risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene, altered expression of the host's genes)
- Risks related to persistence of the product in the patient, for instance:
    - Availability of rescue procedures or antidotes and their risks
    - Late complications, particularly malignancies and autoimmunity
- Risks related to re-administration, for instance:
    - Immune reactions - anaphylaxis, neutralising antibodies…
    - Risks related to repeated surgical or administration procedures
- Risks to close contacts, for instance:
    - Based on the environmental risk assessment, virus shedding and its consequences
- Specific parent-child risks, for instance:
    - Risk of germ line integration of transgene, or other genetic transformation of the germ line
    - Foetal transmission (of vectors, biologically active substances, cells, infectious agents…)
    - Transmammary exposure of children in lactating women (to vectors, biologically active substances, cells, infectious agents…)

### *6.2. Efficacy concerns*

Given the nature of advanced therapy medicinal products and the characteristics of the diseases they are intended to treat, only limited efficacy data may be available at the end of pre-authorisation clinical trials (slow dynamics of the disease and effects of the treatment, rare disease…). Therefore, full efficacy assessment may need several years of follow-up. As a consequence, there might be situations that require the efficacy profile to be further studied in a "real-life" setting, i.e. in the post-authorisation phase. Relevant examples might include:

- Many of the ATMPs incorporate living organisms. Efficacy of these ATMPs is subject to their changing characteristics after their administration to patient over long periods of time (months, years, decades). This may result in an increase (e.g. overexpression of a gene of interest) or decrease of efficacy, and may not be fully documented during the course of pre-authorisation clinical trials; therefore post-authorisation follow-up might be necessary.
- The time needed for the new tissue to be fully functional may be counted in years. In such a situation proof of concept and a positive trend in clinical trials using acceptable surrogates (e.g. amount of newly formed cartilage tissue in a joint) might be sufficient for the unequivocal evidence of effect required for granting a marketing authorisation. Nevertheless, the efficacy profile, including clinical endpoints (e.g. prevention of osteoarthritis), might need to be confirmed in post-authorisation phase.
- In many cases, use of ATMPs is expected to be a once in a life-time treatment. Sustainability of efficacy over time is a question that can only be answered by long term efficacy follow-up.
- Efficacy of many ATMPs is notably highly dependent on the quality of the administration procedure, including conditioning of the patient, surgery and clinical follow-up. This may differ significantly between a controlled pre-authorisation clinical trial setting, and post-authorisation normal health-care, as well as between various health-care establishments. These issues may be captured and addressed only via good post-authorisation efficacy follow-up system.

### *6.3. Points to consider when designing the studies*

To consider all the points relevant for designing the clinical trials and observational studies is outside the scope of this guideline. In this chapter, only a selection of issues are highlighted, based on the experience so far with the kind of problems encountered by developers of advanced therapies as discussed by EMEA scientific committees and the innovation task force. A Marketing Authorisation Applicant/Holder should always consult existing clinical guidelines, particularly those published in Volume 3 of the Rules Governing Medicinal Products in the European Union.

For ATMPs in general, it is likely that at the time of marketing authorisation there will be continuing follow-up of subjects of pre-authorisation clinical trials. This should be always taken into account when designing further post-authorisation studies.

#### *6.3.1. Sample size for follow-up*

The legislation does not give clear guidance on whether the required safety and efficacy follow-up should be applicable to all recipients of an ATMP.

Based on the epidemiology of the target population (disease), anticipated frequency of risk and chosen endpoints for safety or efficacy follow-up, sample size may incorporate all exposed patients or a defined subset. When a subset of exposed patients is used, scientific justification should be provided. A subset will not be acceptable for orphan drugs.

Sample size calculations should take into account the high potential for drop-outs over the years of follow-up. It may be appropriate to request scientific advice for this purpose from the EMEA.

### *6.3.2. Dynamics of the disease and effects of the product*

Detection of early complications (infectious diseases, complications linked to the related surgical procedures) and late complications (malignant diseases, emerging diseases...) are likely to need different approaches. Moreover, they need to be considered in conjunction with the possible gradual increase or decrease of efficacy of the administered product over time. Design of the studies needs to take into account such dynamics, and may require specific timing of procedures, treatment adjustments, and laboratory investigations to be tailored for individual patients.

### *6.3.3. Comments on clinical follow-up*

Recommended clinical follow-up in the form of particular laboratory and clinical investigations for patients treated with the particular product must be described in the SPC and PIL. These recommendations should always take into account existing general guidelines for clinical follow-up of patients treated with ATMP in both the clinical trial setting and post-authorisation setting (see Chapter 3.2 “Relevant Guidelines”).

Studies used in safety and efficacy follow-up should use the “normal practice” of clinical follow-up procedures whenever possible to limit unnecessary interventions. This should enable wider use of observational designs for studies in post-authorisation where suitable for generating or testing a particular hypothesis.

### *6.3.4. Comments on safety follow-up of living donors*

A Marketing authorisation holder of an ATMP may be required to conduct safety follow-up of living donors (i.e. donors that are alive at the time of donation). The aim is to ensure that production of the product does not bring undue risk to living donors, and also to ensure that in the event that an infectious disease with a long latency emerges in the donor, the receivers may get appropriate screening and treatment (using a traceability system).

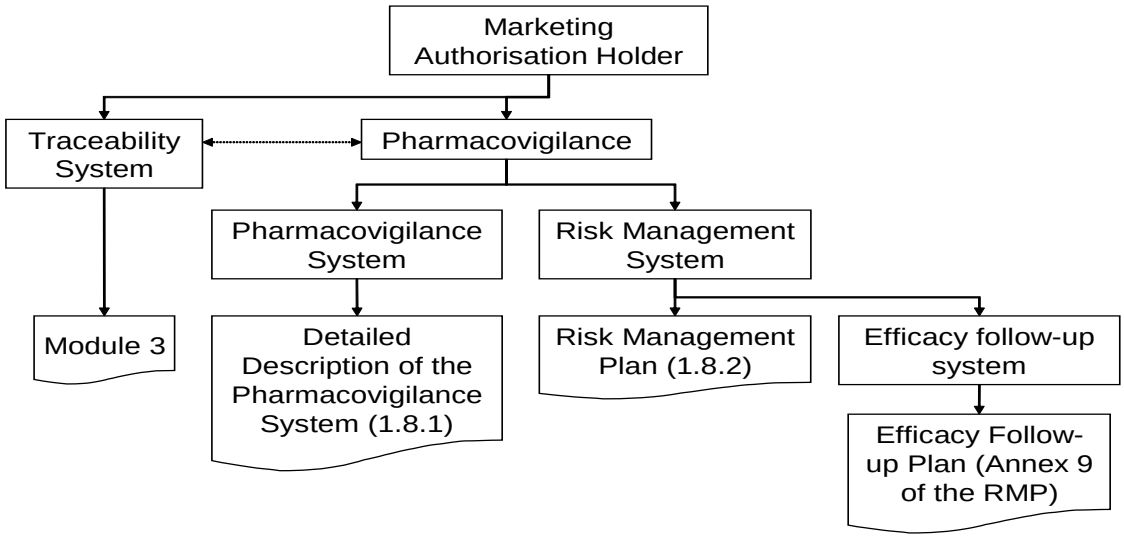
The particular design and length of such follow-up should be decided on a case by case basis, and needs to be proportionate to the nature of the procurement procedure, identified and potential risks to donors and health characteristics of donors.

As with the majority of pharmacovigilance obligations, this activity may be outsourced to another legal entity based on a written agreement. As a minimum, the agreement shall specify the data to be collected and procedures for data exchange, quality assurance of the system, length of the follow-up of donors, and responsible persons on both sides. It is expected that traceability data may be used for facilitation of such follow-up.

### *6.3.5. Safety follow-up of close contacts and offspring*

When a need for safety follow-up of close contacts and offspring is identified, feasibility is an important feature in the design such a study. Scientific advice from the EMEA is strongly recommended.

**Figure 2 MAH's systems of post-authorisation surveillance of ATMPs and their description in the marketing authorisation application dossier**




# 7. ADDITIONAL REQUIREMENTS FOR THE PHARMACOVIGILANCE SYSTEM OF MARKETING AUTHORISATION HOLDERS

As a part of the application for marketing authorisation of a medicinal product, the applicant is requested to provide a detailed description of its pharmacovigilance system. This is further detailed in the Guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections in Volume 9A.

Article 14(1) of the Regulation requests the applicant to detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto. This obligation shall be fulfilled by:

1. Description of additional pharmacovigilance activities and the efficacy follow-up system in the Risk management plan that is submitted in Module 1.8.2 of the CTD.

2. Description of the elements of the pharmacovigilance system necessary to support such additional pharmacovigilance and efficacy follow-up activities. This should be included in the Detailed Description of the Pharmacovigilance System that is submitted in Module 1.8.1 of the CTD.

In addition, the pharmacovigilance system of ATMP marketing authorisation holders should include, where applicable:

- Procedures for data exchange with other vigilance systems as applicable based on the nature of the products of the marketing authorisation holder/applicant (for example tissues and cells vigilance, haemovigilance, and vigilance of medical devices – see the legislation references above).
- Databases or other record systems capable of record linkage with traceability data (for instance via the batch number).

**Table 1 Examples of additional elements to be described in the DDPS**

| **Additional pharmacovigilance activity** (in the Module 1.8.2 – Risk Management Plan) | **Elements of the pharmacovigilance system** (in the Module 1.8.1 – Detailed Description of the Pharmacovigilance System) |
|---|---|
| Safety follow-up - registry study with use of traceability data | Infrastructure to support the registry study<br><br>Record linkage between pharmacovigilance and traceability databases and/or other record systems (e.g. medical records) |
| Active surveillance - Sentinel sites for both safety and efficacy follow-up | Infrastructure to support fulfilment of the active surveillance protocol<br><br>Support to the relevant disease registries where suitable<br><br>Availability and qualification of staff involved in a review of medical records or interviews with patients and/or physicians<br><br>Procedures for ongoing risk-benefit evaluation |
| Efficacy follow-up based on observational study/studies | Support of observational studies with efficacy endpoints<br><br>Procedures for ongoing risk-benefit assessment, including co-operation between parts of the company involved in clinical research, pharmacovigilance, and regulatory and medical affairs |

The marketing authorisation holders/applicants may outsource some of the pharmacovigilance activities to other legal entities. More information may be found in Volume 9A.

# 8. ADDITIONAL REQUIREMENTS FOR THE RISK MANAGEMENT SYSTEM OF ADVANCED THERAPY MEDICINAL PRODUCTS

According to Article 14 (2), the European Commission, on the advice of the EMEA shall require as part of the marketing authorisation that a risk management system is set up and specific post-marketing studies are carried out. Both of these requirements should be met by a submission of the EU-Risk Management Plan as per the Guideline on Risk Management Systems for Medicinal Products for Human Use (incorporated in Volume 9A).

Currently, all medicinal products with new active substances submitted via centralised authorisation procedure must provide a description of the risk management system, unless otherwise justified. It is expected that for majority of ATMPs a risk management system including specific post-authorisation studies will be requested. Because of the wide range of products covered by this guideline, the novelty and high speed of development in this area, applicants are encouraged to seek scientific advice for Risk Management Planning from the EMEA.

Assessment of the effectiveness of the risk management system, as well as the results of any newly finished studies should be regularly included in the Periodic Safety Update Reports (PSUR) and regular updates of the EU-RMP as per Volume 9A.

It is recognised that some of the parts of the Guideline on Risk Management System for Medicinal Products for Human Use (in Volume 9A) might not be suitable for a particular ATMP. In such a case, that part of the EU RMP template may be omitted subject to scientific justification. Nevertheless, where an analogy exists between the terminologies of chemical drugs, biologics and advanced therapy medicinal products, this should be used. For example “pharmacological class effects” may be presented as effects known to be common for certain types of vectors, cells, tissues, scaffolds or matrices.

The content and extent of the EU-Risk Management Plan must be proportionate to the risks of the particular product. It should not simply copy other parts of the dossier submitted for the marketing authorisation application. Information provided in the EU-RMP, and particularly in its Safety

Specification should be presented in a summary fashion (if necessary, with appropriate cross referencing to other parts of the dossier) with the aim of providing sufficient information within the EU-RMP to enable a decision on whether additional risk minimisation activities are needed, and whether the routine ones are appropriate. It is a plan for the identification and management of safety concerns and needs to be drafted in a way that allows for quick orientation to the important safety issues and their management.

For practical reasons, efficacy follow-up should also use the same reporting systems to competent authorities, i.e. expedited and periodic reports. Management of the efficacy follow-up should use existing tools, i.e. the EU-Risk Management Plan.

The EU-Risk Management Plan should detail both the safety and efficacy follow-up activities. To ensure that safety and efficacy data are comparable in their quality and scientific robustness, efficacy follow-up systems should use the same infrastructure that exists for safety follow-up whenever feasible.

Study protocols and detailed description of other activities for efficacy follow-up should be submitted as Annex 9 of the RMP. This is to ensure consistency with the safety surveillance, and at the same time enable proper assessment by efficacy, safety and pharmacovigilance assessors.

Periodic Safety Update Reports (PSURs) and their assessment reports should discuss ongoing cumulative efficacy and safety data. A specific new chapter in the PSUR assessment report might be introduced for this purpose. This chapter should also discuss safety data relating to donors and close contacts.

In addition to the requirements for risk management systems detailed in Volume 9A, the points below shall be included in the RMP of an ATMP.

### *8.1. Safety specifications*

#### *8.1.1. Additional EU requirements*

**Specific risks of advanced therapy medicinal product**

A new section under "Additional EU Requirements" should consider specific risks of ATMPs, taking into account the points mentioned above in Chapter 6 "Scientific rationale for specific rules for post-authorisation surveillance of ATMPs". This section should provide an opportunity to discuss risks that would not fit into other parts of the safety specifications in the EU-RMP. Specific risks shall be included in the following order:

a. Flow-Chart of the logistics of the therapy (for instance harvesting, transport, controls, manipulation, conditioning, administration, clinical follow-up…)
b. Risks to living donors (where applicable)
c. Risks to patients in relation to quality characteristics, storage and distribution of the product
d. Risks to patients related to administration procedures
e. Risks related to interaction of the product with the patients
f. Risks related to scaffolds, matrices and biomaterials
g. Risk related to behaviour of the product in patients
h. Risks related to persistence of the product in the patient
i. Risks to healthcare professionals, care givers, off-spring and other close contacts with the product or its components, or with patients, presented in a summary fashion and based on the environmental risk assessment

### *8.2. Summary of safety specifications*

For many ATMPs, the following examples are likely to represent potential or identified risks:

- Transmission of infectious agens to the patient and to close contacts
- Graft dysfunction and/or rejection
- Induction of autoimmunity or immunogenic reactions
- Induction of malignancies
- Impossibility of discontinuing the product
- Potential of the vector for latency and reactivation, integration of genetic material into host genome, prolonged expression of the transgene, altered expression of the host's genes, potential for germline integration

### *8.3. Pharmacovigilance plan (incorporating safety follow-up)*

In addition to routine pharmacovigilance, additional pharmacovigilance activities may be introduced to characterise further identified risks, detect early potential risks and complement missing information. For ATMPs the Pharmacovigilance plan should consider:

- Any specific aspects of routine pharmacovigilance if applicable, e.g. any adjustment of spontaneous reporting, targeted reports follow-up/investigation, use of reports from patients/caregivers, specific methodology for signal detection, additional chapters of PSURs etc.
- Active surveillance should often be put in place, particularly when the ATMP is expected to be used in a few "centres of excellence" that could serve as sentinel sites.
- It is expected that for ATMPs specific clinical follow-up including laboratory investigations will become a part of normal practice described in the Summary of Product Characteristics (SPC). Non-interventional post-authorisation safety studies should be designed in a way that maximises the use of data from these normal practice laboratory investigations.
- Any ongoing compassionate use and follow-up of patients exposed to the product in clinical trials needs to be described and should serve as a basis for the development of long-term surveillance/post-authorisation safety studies. The length and form of safety follow-up should be set up according to existing guidelines, and on a case by case basis.
- Use of traceability data for surveillance purposes (e.g. an established registry of batches of products distributed to a particular centre and its record linkage to the pharmacovigilance database of reports received from that centre.)

### *8.4. Evaluation of the need for efficacy follow-up*

This new chapter should be incorporated in PART II of the EU Risk Management Plan. It should discuss the scientific need for efficacy follow-up. Some examples of the rationale for such a need are listed in chapter 6.2 above.

For efficacy follow-up, the existing systems for safety follow-up should be used as much as possible to save resources and increase the motivation of healthcare professionals that is the key to success of any such system.

It should be highlighted that 'loss of efficacy' or 'less than expected efficacy' of a medicinal product used in life-threatening diseases is considered to be a safety issue (see Volume 9A). Therefore, for this kind of concern, safety follow-up alone might be appropriate. The efficacy follow-up should only be considered in situations which require further study of the product's efficacy profile in the post-authorisation phase, and when it is inappropriate to use safety follow-up alone for this purpose.

When a need for efficacy follow-up is identified, the Annex 9 described in the chapter 8.6 below should be produced and attached to the EU-RMP.

### *8.5. Risk minimisation plan*

Based on the existing tools and feasible approaches to risk minimisation, the following should be considered to reduce particular risks:

- Limitation of the use of the product to adequately trained and experienced clinicians only, possibly including a controlled distribution system to specialised (accredited) centres only. Selection and accreditation of centres by marketing authorisation holder and/or member states authorities might also be part of the risk minimisation plan.
- Specific risk communication (patient alert cards; patient ID cards; risk communication components of the educational programs; informed consent forms; protocols and mechanisms ensuring that any recipients who have received treatment prior to the age of consent or in need of information at a later stage will receive risk communication; guidance for recipients on how to communicate risks to close contacts and offspring where they could be at risk...)
- Introduction of barriers to errors (design of the product, cross checks, double patient identification, second opinions, dedicated teams…)
- Training of healthcare professionals in respect of procurement, storage, handling, administration, clinical follow-up, and their protection based on the environmental risk assessment
- Education of support personnel, family and caregivers – for instance indicative symptoms of important identified or potential adverse reactions, clinical follow-up procedures, protection based on the environmental risk assessment etc.

#### *8.5.1. Effectiveness of the risk minimisation measures*

Specific tools to measure effectiveness of risk minimisation via objective metrics (systems of measurement and assessment of such measurement) should always accompany any risk minimisation activity. Examples of such metrics for particular risk minimisation activity may include:

- If an educational plan is in place, test of the knowledge and skills of the target audience that should have been improved by the particular educational plan should be conducted and evaluated on regular basis
- If barriers to errors are introduced (e.g. product design), active surveillance of such errors may serve as metrics of a barrier's effectiveness
- If a controlled distribution is implemented, traceability data may be used to evaluate real pathways of the product to patients.

### *8.6. Efficacy follow-up plan (Annex 9 of the RMP)*

This Annex should describe details of the efficacy follow-up when a need for it is identified in Part II of the RMP. The following structure is recommended for this document:

#### *8.6.1. Scientific rationale for the efficacy follow-up*

Based on the evaluation of the need for efficacy follow-up, the rationale for the chosen design of the system should be discussed in this chapter.

Any ongoing compassionate use and follow-up of patients exposed to the product in clinical trials needs to be described and should serve as a basis for the development of long term efficacy studies. The length and form of efficacy follow-up should be set according to existing guidelines, and on a case by case basis.

### *8.6.2. Overview of the study protocols for efficacy follow-up*

It is recommended to use the table below to keep consistency with the format of the tables used for safety follow-up in the Pharmacovigilance plan.

| Study | Protocol version | Protocol status | Planned date for submission of interim data | Planned date for submission of final data |
|---|---|---|---|---|
| | | | | |

### *8.6.3. Detailed protocols of the efficacy follow-up studies*

All the protocols listed in the overview table above should be included. When protocols are not ready at the time of submission, at least their drafts (outlines) should be incorporated.

In addition to the points listed in 6.2 and 6.3 above, the following should be taken into account when drafting the protocol of post-authorisation efficacy studies:

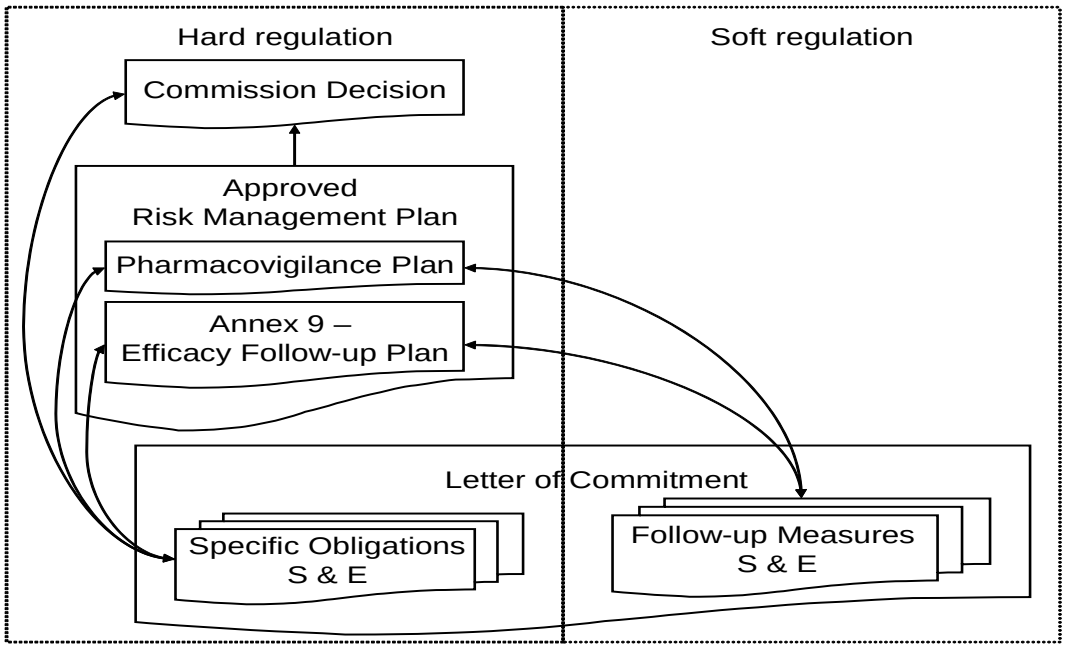
- Existing guidelines on efficacy studies should be followed when applicable.
- Design of any post-authorisation observational study should build on existing or recommended clinical follow-up of patients.
- Wider spectrum of endpoint(s) should be considered reflecting real life effectiveness (clinical monitoring, laboratory monitoring, and biomarkers). Surrogates should not be used unless necessary.
- Reasons for drop outs, and cases of re-administration or re-initiation of therapy should be of particular interest for efficacy follow-up.
- Long-term efficacy (observational) studies should normally be of comparative design. The choice of comparator or lack thereof should be justified. It is acknowledged that changes in the standard of care over time may influence the conduct of such studies. This should be discussed with regulators on regular basis as part of relevant reports (e.g. in PSUR, Annual Safety Reports, updates of the EU-RMP).

# 9. USE OF REGULATORY TOOLS IN POST-AUTHORISASTION SURVEILLANCE OF THE ADVANCED THERAPY MEDICINAL PRODUCTS

There are number of tools available for management of various post-authorisation commitments for products authorised via centralised procedure. These include letters of commitments; follow-up measures; conditional approvals or approvals under exceptional circumstances with specific obligations and their annual re-assessments; and there are number of reporting obligations too (expedited and periodic reports, EU-RMP updates, various special reports requested by regulators, sunset clause reporting etc.)

Use of these tools is covered by common rules for medicinal products. All of these tools have their appropriate use and their effective combination should ensure high quality post-authorisation benefit-risk management of the product. Both regulators and marketing authorisation holders should ensure consistency in use of these various tools. This consistency between soft and hard (legally enforceable) regulation in the area of post-authorisation surveillance may be illustrated by the following figure:

630 **Figure 3 Illustration of the need for consistency in (parallel) use of various tools in the post-authorisation**
631 **surveillance of ATMPs.**

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633 # 10. ELECTRONIC EXCHANGE OF PHARMACOVIGILANCE
634 # INFORMATION

635 It is recognised that the length of some data fields set up by the ICH E2B (M) for Individual Case
636 Safety Report, and consequently length of some fields in the EudraVigilance Medicinal Product
637 Dictionary (EVMPD) might not be sufficient for the needs of Advanced Therapy Medicinal Products.
638 At the same time, a need for additional fields needs to be considered. The EMEA will address this
639 issue with EudraVigilance system stakeholders and keep the users informed via the EudraVigilance
640 website.