EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 January 2012
EMA/CAT/CPWP/686637/2011
Committee for Advanced Therapies (CAT)

Draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products

Draft

Draft Agreed by CPWP & GTWP	7 October 2011
Draft Agreed by BWP, SWP and Guideline Consistency Group	October/November 2011
Adoption by CAT for public consultation	9 December 2011
Adoption by CHMP for public consultation	19 January 2012
End of consultation (deadline for comments)	30 June 2012
Agreed by <WORKING PARTY>	<Month year>
Adoption by <COMMITTEE>	<DD Month YYYY>
Date for coming into effect	<DD Month YYYY>

Comments should be provided using this template. The completed comments form should be sent to veronika.jekerle@ema.europa.eu

Keywords	*Advanced Therapy medicinal products, risk-based approach, risk, risk factors*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Draft Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC for ATMPs

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Executive summary

The clinical use of Advanced Therapy Medicinal Products (ATMPs) in humans may be associated with specific risks to the patient and to third parties. These risks are determined by various risk factors, which are related to the quality, biological activity and application of the ATMP. Since ATMPs are very diverse in nature (i.e. gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs) and tissue engineering products (TEPs)), a flexible approach to address and evaluate potential risks associated with the clinical use of ATMPs is described in the 'Risk-based approach'.

The concept of a 'Risk-based approach' has been introduced to the legislation with the revision of Annex 1, part IV of Directive 2001/83/EC as amended by Directive 2009/120 EC. The aim of the risk-based approach in the development of ATMPs is to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the requirements of this Annex.

The application of the risk-based approach in the preparation of a MAA dossier is optional. However, in cases where the risk-based approach is being applied, the applicant is advised to follow the methodology as laid down in the present guideline.

1. Introduction (background)

The risk-based approach is based on the identification of various risks associated with the clinical use of an ATMP and risk factors inherent to the ATMP with respect to quality, safety and efficacy.

The risk factors associated with a specific risk (e.g. tumorigenicity, treatment failure) are likely to be product specific and multifactorial (see definitions of risk and risk factor in 4.1 and 4.2). Risk factors are related to, for example, the biological characteristics of the product, the manufacturing process, and the specific therapeutic use of the ATMP. For each risk factor, its contribution to an identified risk associated with the product under development will need to be evaluated. It is anticipated that on completion of the profiling of the identified risks/risk factor combinations a specific profile for each risk can be concluded.

This guideline describes the intention of the risk-based approach and details its methodological application. The methodology is based on the identification of risks and associated risk factors of an ATMP and the establishment of a specific profile for each risk. With the use of the identified risk profile the applicant shall justify the extent of data presented in the various sections of the MAA dossier.

2. Scope

This guideline is applicable to all ATMPs, as defined in Directive 2001/83/EC, Part IV, Annex I (somatic cell therapy and gene therapy medicinal products) and in Regulation (EC) No. 1394/2007 (tissue engineered products and combination products). The guideline should be read in conjunction with relevant technical guidance for cell–based therapy (somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products, i.e. the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and the Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99).

3. Legal basis

The 'Risk-based approach' is an optional approach that has been introduced to the legislation with the revision of Annex 1, part IV of Directive 2001/83/EC as amended by Directive 2009/120 EC.

4. Methodology of the risk-based approach

The risk-based approach, is defined as a strategy aiming to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC. The risk-based approach should be distinguished from Risk Management Systems as defined in Volume 9A of Notice to Applicants[1], Environmental Risk Assessment according Article 8(3) of Directive 2001/83/EC and the Benefit / Risk Assessment in the context of a marketing authorisation evaluation. It should also be differentiated from risk analysis such as it is used for medical devices or as part of quality management of ATMP production as described in ICHQ9/Annex 20 GMP guideline[2]. The Risk-based approach should also not be used to address risk-based quality management and risk factors, which are subject to principles of GMP, GLP and GCP. It is important to appreciate that the risk-based approach profiles each risk inherent to the product and not the risk of a product as whole. Thus it does not provide a rigid system classifying different degrees of product risk such as high- or low-risk products.

The collection of data within the concept of the risk-based approach should be an on-going process prior to the submission of the MAA. It is important to note that this process starts at the beginning of product development and matures over time, as the knowledge of the product and its characteristics increases. Nonetheless, applicants, using the risk-based approach, are expected to present in the application dossier the picture of the risk profiles as it is at the time of MAA (see section 4.3).

4.1. Risks

For the purposes of this guideline 'risk' is defined as an "unfavourable effect that can be attributed to the ATMP and is of concern to the patient and/or to third parties"[3]. Risks include risks to the patient, other populations (e.g. caregivers) and off-springs.

Risk identification should start as early as product development.

Risks associated with ATMPs include for example: unwanted immunogenicity, tumour formation, treatment failure, unwanted tissue formation, and inadvertent germ line transduction, as well as toxicity due to degradation/leaching of toxic compounds from structural components, due to unintended alteration of cell homeostasis, due to unwanted targeting of cells/organs, and due to deregulated therapeutic gene expression.

4.2. Risk factors

For the purposes of this guideline, `risk factor´ is defined as a "qualitative or quantitative characteristics that contribute to a specific risk following administration of an ATMP".

[1] Volume 9 A of the Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance for Medicinal Products for Human Use)
[2] e.g. management of risks during production such as those associated with microbial contamination, equipment, disposable materials.
[3] adapted from benefit-risk methodology project (see EMA 549682/2010)

Aspects that should be taken into account when identifying risk factors include, but are not limited to the nature of the product, non-cellular components, biodistribution, manufacturing issues and clinical aspects.

Examples of risk factors that can be associated with cell-based medicinal products could include, but may not be limited to, the origin of cells (autologous vs. allogeneic), the ability of cells to proliferate and differentiate, the ability to initiate an immune response (as target or effector), the level of cell manipulation (in vitro/ex vivo expansion/activation, genetic manipulation), aspects of the manufacturing process, non-cellular components, the mode of administration (ex vivo perfusion, local, systemic) and the duration of exposure (short to permanent).

Risk factors that can be associated with GTMPs depend on the vector as well as on the transgene expression cassette used, and, in the case of a cell-based GTMP also on the cell population to be genetically modified. Typical risk factors include, but may not be limited to, the potential of the vector for and its extent of chromosomal integration, vector immunogenicity, the capacity of the vector for latency/reactivation and/or mobilization and its potential for recombination/re-assortment and biodistribution to non-target sites. Risk factors may also be attributable to expression of the therapeutic or any other transgene delivered and to the duration of expression. In the case of a cell-based GTMP, risk factors as described for cell-based medicinal products may also be applicable. The replication-incompetence or -competence of a vector and its capacity to inadvertently replicate after complementation by a respective wild-type or helper virus may also have to be taken into consideration as risk factors.

Furthermore, the clinical use of the ATMP should also be considered when identifying risk factors. Patient-, disease-, and medicinal procedure-related risk factors may be present and may contribute to a specific risk.

4.3. Risk profiling

The risk profiling is defined as a methodological approach to systematically integrate all available information on risks and risk factors in order to obtain a profile of each individual risk associated with a specific ATMP. The four steps towards risk profiling are detailed below.

The Methodology of Risk Profiling

1st step: To identify risks associated with the clinical use of the ATMP

The risk-based approach starts with the identification of risks associated with the clinical use of the ATMP. Take into consideration any relevant risks to the patient and/or third parties. Risk identification should start as early as product development and can be supported by reference to published data. In general the risks of an ATMP are not necessarily any different to those of other classes of medicinal product. Examples of risks are given in section 4.1.

2nd step: To identify product specific risk factors contributing to each identified risk

The applicant should identify any relevant risk factor that may contribute to the identified risk. These risk factors may be related for instance to the nature and composition of the product, manufacturing process, nonclinical and clinical aspects. Please note that these risk factors may contribute to several risks and may be interlinked in their impact on a specific risk. Risk factors associated with an ATMP under development and its medical application should be identified starting at the beginning of product development and continue during production and testing.

3rd step: To map the relevant data for each identified risk factors against each of the identified risks

In order to evaluate the contribution of each risk factor to an identified risk, the relevant source of data regarding each risk factor should be mapped with the help of a 2 dimensional table (see examples shown in the Annex to this guideline). With the help of this matrix the association between risk factors and risks could be systematically scanned for risk factor – risk relationships. For those risk factor-risk combinations, where a relationship has been identified, the following information should be included to the field: 1. scientific description on the relationship; 2. studies performed to address this relationship, or justification for omission of own studies, 3. locations of these studies in the Common Technical Document (CTD) of the application dossier.

4thstep: To conclude on the risk factor – risk relationships

The risk-based approach is presented in form of a matrix table as outlined in the example tables and as narrative text addressing risks and risk factors identified to be of relevance for the use of the respective ATMP.

Risk factor-risk combinations for which, based on current scientific knowledge, a reasonable relationship has been identified shall be further detailed in respect to

(i) their causative scientific relationship;

(ii) an overview of studies that have been performed to determine the impact of the identified risk factors on the particular risk. In case such studies have been omitted, a scientifically sound justification shall be provided why experimental and clinical data are not needed to be presented in the dossier;

(iii) a conclusion whether the provided scientific data (quality, non-clinical and clinical) and published information addressing the individual risk factor-risk combinations are considered adequate and sufficient to support an MAA.

4.4. Fictitious examples to illustrate the risk-based approach

Examples of different matrix tables regarding a GTMP (see Annex 1), a CTMP (Annex 2) and a TEP (Annex 3) are provided in the Annex to this guideline to illustrate the methodology of the risk-based approach. It should be noted that these are fictitious, non-exhaustive examples. They are given for illustration purposes and to serve as a guide to use the methodology, but not as technical guidance. In the matrix table, examples of risk factors and risk are also given for illustrative purposes and are not exhaustive. The applicant should identify relevant risk factors and risks specific to his product.

For technical guidance on cell-based and gene therapy medicinal products, the reader is referred to relevant technical guidance for cell–based therapy (somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products (i.e. Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99), Directive 2009/120/EC and other more specific guidelines and reflection papers).

In the matrix tables, blank boxes indicate that based on the current knowledge no reasonable risk factor/risk relationship is existing.

5. Consequences for the MAA dossier

It will be important for the applicant to present the risk-based approach to the development of their product in a logical and meaningful way, in order to contribute to the justification of the data package at the time of MAA assessment. This information should be included to Module 2 of the CTD.

There are no prescribed templates for the presentation of this information as such the applicant can develop a format of their choosing. However it is recommended to follow the methodology delineated in this guideline and to include a well written and concise overview of the strategy and a discussion of the conclusions and justifications in relation to the extent of data included in the MAA dossier.

The result of the risk-based approach, when applied and as described in Module 2, can be used as one starting point for the safety specifications as part of the Risk Management Plan (see also Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

6. Glossary

Risk-based approach: a strategy to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application dossier.

Risk: an unfavourable effect that can be attributed to the ATMP and is of concern to the patient and/or to third parties.

Risk factor: a qualitative or quantitative characteristic that contributes to a specific risk following administration of an ATMP.

Risk profiling: a methodological approach to systematically integrate all available information on risks and risk factors in order to obtain a profile of each individual risk associated with a specific ATMP.

References

- Regulation (EC) No. 1394/2007 on advanced therapy medicinal products
- Directive 2001/83/EC on the community code relating to medicinal products for human use
- Directive 2009/120/EC amending Directive 2001/83/EC relating to medicinal products for human use as regards advanced therapy medicinal products
- Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Note for guidance on gene transfer medicinal products (CPMP/BWP/3088/99)
- ICHQ9 Quality Risk Management
- EUDRALEX Volume 4. EU Guidelines on Good Manufacturing Practice Annex 20 GMP guideline
- Volume 9 A of the Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance for Medicinal Products for Human Use)

Annex 1: Example: AAV vector expressing the human fictionase enzyme (FE) administered i.m. for the treatment of FE deficiency disease

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting from unintended alteration of therapeutic gene expression
Recombination/mobilisation	Recombination may lead to replicating AAV. Tumor formation depends on level of AAV genome integration into host genome. Addressed in CTD 3.2.P.5 - Control of DP and CTD 4.2.3 –Toxicology (toxicology/integration studies).	Recombination / Mobilisation may lead to increased immunogenicity due to higher number of vector / RCV particles. Addressed in CTD 3.2.P.5 - Control of DP and CTD 4.2.3 -Toxicology.	Recombination during manufacture might lead to loss of the transgene and consequently loss of function. Addressed in CTD 3.2.P.5 - Control of DP.	Mobilisation (with wt and helper coinfection) might result in higher levels of therapeutic gene expression. Toxic effects other than immunogenicity due to overexpression is considered to be low. Addressed in CTD 4.2.1 - Pharmacology and CTD 4.2.3 - Toxicology studies, and justified by literature information.
Integration	AAV vectors are able to integrate into the genome albeit at low levels. Integration studies are performed (CTD 4.2.3- Toxicology). See also risk factor 'biodistribution' (CTD 4.2.2 -Pharmacokinetics)			
Type of transgene and transgene expression levels		The therapeutic gene is of human origin and respective endogenous gene product in patients is present but defective. This might cause unwanted immunogenicity. Expression of therapeutic protein addressed and justified in CTD 5.3.5 -Reports of efficacy and safety studies.	Impaired transgene expression might lead to treatment failure. Transgene expression and potency studies and in vivo proof-of-concept studies. Addressed in CTD 3.2.P.5 - Control of DP and 4.2.1. - Pharmacology.	Over-expression of transgene in target cells is not considered to be of concern. Toxic effects other than immunogenicity due to over-expression is considered to be low. CTD 4.2.1 - Pharmacology, CTD 4.2.3 - Toxicity and justified by literature data.
Vector type	AAV is not known to be tumorigenic *per se*. A low potential of AAV for insertional mutagenesis exists (see RF 'integration'). Addressed in integration studies (CTD 4.2.3 - Toxicology). Justification of lack of tumorigenicity studies based on respective integration data.	AAV is known to be immunogenic. Addressed in immunogenicity and Toxicity studies (CTD 4.2.3), and Clinical safety studies (CTD 5.3.5 - Reports of efficacy and safety studies,).	Pre-existing immunity to the vector might impair efficiency of treatment. Furthermore repeated administration may increase immunologic responses against the vector that might also impair efficiency of treatment. Addressed in CTD 4.2.1 - Pharmacology and 5.3.5 - Reports of efficacy and safety studies.	
Impurities	Impurities might contribute to tumour formation. Full information and documentation on starting	AAV can be difficult to purify. Amount and type of impurities may lead to immunogenic reactions.	Impurities can negatively influence the efficacy of treatment. Addressed in drug	

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting from unintended alteration of therapeutic gene expression
	materials is given. Control of cellular and viral impurities are addressed in release testing (CTD 3.2.S.4 – Control of critical steps and intermediates, and 3.2.P.5 – Control of DP).	Addressed in CTD 3.2.S.2 (Manufacture), 3.2.S.4 (Control of DS), 4.2.3 (Toxicology), and 5.3.5 - Reports of efficacy and safety studies.	substance control CTD 3.2.S.4 - Control of DS.	
Biodistribution	Biodistribution of the vector contributes to the risk of tumour formation via vector persistence and integration events (see risk factor on integration). Inclusion of transduced non-target organs in studies on episomal/ integrated vector status. Addressed in CTD 4.2.2- Pharmacokinetics (biodistribution), CTD 4.2.3 – Toxicology (integration studies).	Biodistribution of the vector to non-target, immunogenic sites. Addressed in biodistribution / immunogenicity studies -CTD 4.2.2 - Pharmacokinetics (biodistribution), CTD 4.2.3 - Toxicology (immunogenicity), CTD 5.3.5 -Reports of efficacy and safety studies, (clinical safety).	Treatment failure might be induced by unwanted immunogenicity due to biodistribution to non-target, immunogenic sites. Addressed in biodistribution and long-term transgene expression studies. CTD 4.2.1 - Pharmacology and CTD 4.2.2 – Pharmacokinetics.	Toxicity as a result of transgene-overexpression in non-target cells considered to be low. Evaluation of toxicity and transgene expression levels in non-target tissues and cells. CTD 4.2.2 - Pharmacokinetics (biodistribution) and 4.2.3 - Toxicology (toxicity)
Relevance of animal model		Animal model is not predictive for immunogenicity in patients due to differences in immune responses. An additional animal model to address immunogenicity was used. Addressed in CTD 4.2.3 - Toxicology (immunogenicity) and in clinical studies CTD 5.3.5 - Reports of efficacy and safety studies.	Animal model may not be predictive for treatment failure due to differences in the immune status of animal and patients. Immune status of the animal model has been matched to the patient's situation (e.g. pre-treatment with the vector to induce seroconversion in animals). See CTD 4.2.1 - Pharmacology and 4.2.3 - Toxicology.	
Patient-related		Immune reaction might be triggered dependent on immune status of the patient. Addressed in non-clinical studies using vector-pretreated animals (CTD 4.2.3 - Toxicology) and in CTD 5.3.5 - Reports of efficacy and safety studies (clinical safety)	Immune status e.g. pre-existing immunity to the vector of patient might influence efficiency of therapy. Addressed in non-clinical (CTD 4.2.1 - Pharmacology) and clinical studies (CTD 5.3.5 - Reports of efficacy and safety studies)	
Disease-related	The underlying disease might be linked to a higher incidence of cancer. This might bias the safety data. Addressed in CTD 5.3.5 - Reports of efficacy and safety	Variable levels of dysfunctional protein may be expressed in the patients resulting in immune reactions to the therapeutic protein. Addressed in CTD 5.3.5 -Reports of	Immune response against the transgene might compromise treatment efficacy. Addressed in the non-clinical pharmacology (CTD 4.2.1) and toxicology	

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting from unintended alteration of therapeutic gene expression
	studies.	efficacy and safety studies.	studies (CTD 4.2.3), and in Reports of efficacy and safety studies (CTD 5.3.5).	
Medical procedure-related	Concomitantly administered immune suppressants might lead to tumour formation. Addressed in CTD 5.3.5 - Reports of efficacy and safety studies.	A high local dose administered i.m. might cause local inflammatory response due to immunreaction to a vector component or the expressed therapeutic protein. Addressed in CTD 4.2.3 - Toxicology and 5.3.5 - Reports of efficacy and safety studies.	Difficult administration of multiple injections i.m. might result in incomplete dosing. Addressed in CTD 5.3.5 - Reports of efficacy and safety studies and SmPC	

Blank box means that based on the current knowledge no reasonable risk factor/risk relationship is existing.

Annex 2: Example: human embryonic stem cell-derived cells secreting bioactive substances injected into the CNS

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell starting material	hESC have inherent capability for teratoma formation. Risk addressed in other sections of this table and in CTD 3.2.S.2.3 - Control of Materials	Possible HLA mismatching. Controlled by donor screening and selection. CTD 3.2.R – Regional information.		Information on cell origin not complete. Lack of information on donor and derivation addressed through viral testing. CTD - 3.2.S.2.3 - Control of Materials (control of HSA used in IVF medium), CTD 3.2.A.2 - Adventitious Agents Safety Evaluation		
Culture / feeder cells and growth factors	Culture with GFs or hormones to enhance proliferation/trigger differentiation may induce tumour formation. Process related impurities controlled - CTD 3.2.S.2.3 - Control of Materials; 3.2.S.2.5 - Process validation and/or evaluation;	Possible immune reaction to animal derived materials, feeder cells - impurities controlled in CTD 3.2.S.2.3 - Control of materials; 3.2.S.3.2 - Impurities.		Potential for disease transmission from cell source, animal derived materials / feeder cells. Viral safety testing of relevant starting and raw materials. CTD 3.2.S.2.3 - Control of materials; 3.2.S.3.2 - Impurities.		

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
	3.2.S.4 - Control of DS.					
Cell population, heterogeneity & differentiation potential	Undifferentiated and undesirable lineage commitment cells resulting from non synchronised differentiation. Product related impurities controlled CTD 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS.	Undesirable lineage commitment cells resulting from non synchronised differentiation; immune reaction CTD 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS.	Presence of cells with inappropriate characteristics resulting from non-synchronised differentiation / Undifferentiated and undesirable lineage committed cells CTD 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS (potency assay for DS) CTD - 3.2.S.3 - Characterisation and for DP CTD 3.2.P.5 - Control of DP and CTD 3.2.P.8 - Stability			
Ancilliary substancesdevices			Potential lack of compatibility of cells with administration device. CTD 3.2.P.2. - Pharmaceutical Development			
Genetic stability	Genetic instability is associated with tumorigenicity. Genetic stability tested. CTD - 4.2.2.3 - Pharmacokinetics - Distribution (in vivo tumorigenicity study)		Genetic instability may result in potential loss of secreted bioactive substances. Stability of cells in the final formulation - CTD 3.2.P.8 – Stability			
Biodistribution	Tumour formation in different organs - Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution	Distribution of cells may increase risk of immunogenicity. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution	Potential loss of activity due to loss of cells by migration. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution		Tissue formation in different organs. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution	Secretion of bioactive substances in unintended microenvironments may lead to toxic effects. Biodistribution

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
						study. CTD 4.2.2.3 - Pharmacokinetics - Distribution
Relevance of the animal model	Age, dosing, Immunocompetence and duration of the available animal study may not be appropriate for detection of tumor formation - In vivo tumorigenicity study CTD 4.2.3.4 - Toxicology - Carcinogenicity		Limitations of used animal model may reduce predictive value of efficacy, POC study - CTD 4.2.1 -Pharmacology		animal study may not be appropriate for detection of unwanted tissue formation PoC CTD 4.2.1 - Pharmacology and biodistribution CTD 4.2.2.3 - Pharmacokinetics - Distribution	
Patient-related	Malignancy in patients may result from the patient's medical/treatment history including age and immunosuppressive status. Reports of efficacy and safety studies and Post-marketing studies. CTD 5.3. - Clinical Study Reports;	Unwanted immunogenicity may be caused by HLA mismatching, release of bioactive substances or mode of delivery. Reports of efficacy and safety studies including immunomonitoring and Post-marketing studies. CTD 5.3. - Clinical Study Reports;	Possibilities for treatment failure may be due to patient's age, disease phase, false stratification for treatment. Set inclusion/exclusion criteria based on preclinical testing. Reports of efficacy and safety studies and Post-marketing studies. CTD 5.3. - Clinical Study Reports;		CNS microenvironment may support unwanted tissue formation due to patient history, prior therapies. CTD 5.3. - Clinical Study Reports; CTD 5.4. Literature References	Patient's medical/treatment history may determine the potential for hypersensitivity to bioactive substances. Pre-treatment testing and stratification. CTD 5.3. - Clinical Study Reports;

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Disease-related			Nonresponsiveness to expected released substance, due to patient's medical/treatment history, may result in treatment failure. Exclusion criteria, stratification and preventive measures. Reports of efficacy and safety studies and Post-marketing studies. CTD 5.3. - Clinical Study Reports;		CNS microenvironment may support unwanted tissue formation due to patient history, prior therapies. CTD 5.3 - Clinical Study Reports; CTD 5.4. Literature References	
Medical procedure-related - dose	Risk for tumour formation due lacking of dose definition from non-clinical studies. Dose finding studies. CTD 5.3. - Clinical Study Reports;		Risk for treatment failure resulting from inefficacious dose. Set limits for determination of dose optimum by dose finding studies. CTD 5.3. - Clinical Study Reports;		CNS microenvironment w/wo supratherapeutic dose may support unwanted tissue formation CTD 5.3. - Clinical Study Reports and 5.4. Literature References	Potential risk for toxicity due to supratherapeutic dose and/or ectopic administration and excessive production of active substances. CTD 5.3. - Clinical Study Reports; CTD 5.4 Literature References.
Medical procedure-related - concomitant treatment	Risk for tumour formation due to previous use of immune suppressants. In vivo tumorigenicity study. Safety AEs reported in CTD 2.5 - Clinical overview, CTD 2.7 - Clinical Summary, CTD 5.3 - Clinical Study reports.		Risk for treatment failure due to effect of concomitant treatment on engraftment and biological activity. Safety AEs reported in CTD 2.5 - Clinical overview, CTD 2.7 - Clinical Summary, CTD 5.3 - Clinical Study reports	Risk of infection or reactivation of latent infection due to use of immune suppressants. CTD 4.4.Safety AEs reporting. CTD 2.5 clinical overview, CTD 2.7 Clinical Summary, CTD 5.3 Clinical Study reports.	Risk for unwanted tissue formation due to effect of concomitant treatment on engraftment, differentiation state and biological activity of cells. Safety AEs reported in CTD 2.5 - Clinical overview, CTD 2.7 - Clinical Summary, Nonclinical biodistribution CTD 4.2.2.3 - Pharmacokinetics - Distribution; CTD 5.3. - Clinical Study Reports;	Additive effect of concomitant treatment on toxicity at a given cell dose (e.g. effect of immuno-suppressive therapy (e.g. potential reactivation or latent virus). Safety AEs reported in CTD 2.5 -Clinical overview, CTD 2.7 -Clinical Summary, CTD 5.3 - Clinical Study reports.

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Medical procedure-related -mode of administration (injection into the brain)	Potential tumor formation at local and/or distant sites resulting from administration procedure. In vivo tumorigenicity study CTD 4.2.3.4 - Toxicology - Carcinogenicity, CTD 5.3 - Clinical Study Reports and CTD 5.4 - Literature Reference		Treatment failure may result from inadequate administration. Validation of surgical procedures. CTD 5.3 -Clinical Study Reports		Risk from unwanted tissue formation (e.g. scar and/or ectopic tissue formation). Validation of surgical procedure and proof of concept nonclinical studies. Biodistribution studies CTD 4.2.2.3 - Pharmacokinetics - Distribution, CTD 4.2.3 - Toxicity, CTD 5.3 - Clinical Study Reports, CTD 5.4. Literature References	

Blank box means that based on the current knowledge no reasonable risk factor/risk relationship is existing.

Annex 3: Example: autologous chondrocytes in suspension for the treatment of articular defects due to trauma

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell starting material						
Culture conditions	Risk for cell transformation due to culture conditions. Limit to population doubling, CTD 3.2.S.2.4. & 5, literature data for similar products and cell senescence studies. CTD 3.2.S.2.5 -Process validation and/or evaluation & 3.2.S.4.2. -Analytical procedures.	Potential for immune reaction in patient. Removal of animal-derived materials and antibiotics. CTD - 3.2.S.2.3 - Control of materials, 3.2.S.3.2 - Impurities.	Influence of cell culture (i.e. time, population doublings) on chondrocyte senescence / dedifferentiation may result in treatment failure. Control of population doublings. CTD 3.2.S.2.3 - Control of materials, 3.2.S.3 - Characterisation, cartilage formation model in vivo. CTD 4.2.2.3 - Pharmacokinetics - Distribution	Potential for mycoplasma contamination. Microbiological control. - CTD 3.2.A.2 - Adventitious Agents Safety Evaluation		

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell population, heterogeneity & differentiation potential		Potential for immune reaction against activated autologous cells CTD 3.2.S.2.3 - Control of materials, 3.2.S.3.2 - Impurities.	Presence of non-target cells. Limit cell population doubling - CTD 3.2.S.2.4 - Controls of critical steps and intermediates and 3.2.S.2.5 - Process validation and/or evaluation, specification for fibroblasts CTD 3.2.S.4.1 -Specification, potency assay addressing hyaline cartilage formation CTD 3.2.S.3 - Characterisation and 3.2.P.5 - Control of DP. Apoptosis assay 3.2.P.5 - Control of DP.		Presence of cells with inappropriate characteristics. Set specification limits for fibroblasts. CTD 3.2.S.2.4 - Controls of critical steps and intermediates and 3.2.S.2.5 - Process validation and/or evaluation.	
Genetic stability	Potential for genetic instability due to long cell culture. Limit to population doubling literature data & cell senescence studies CTD 3.2.S.2.5., Process validation and/or evaluation, 4.2.3 - Toxicology.					
Structural / functional integrity			Sub-optimal extracellular matrix formation and function. Potency assay for DP CTD 3.2.P.5 - Control of DP and CTD 3.2.P.8 - Stability			
Ancilliary substances, devices & formulation			Potential impact of administration device on biological activity; biocompatibility with device studied - CTD 3.2.P.2 - Pharmaceutical Development			Potential toxicity of device. Device CE marked for intended purpose. CTD 3.2.R - Regional information
Biodistribution			Failure of containment of cells in situ. Biodistribution study. CTD-4.2.2. - Pharmacokinetics or: Justification based on biodistribution studies with similar products.		Potential migration of cells out of implantation site. Biodistribution study. CTD 4.2.2. – Pharmacokinetics.	

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Relevance of the animal model	Age, dosing, immuno-competence and duration of animal study not appropriate for detection of tumour formation. Tumourigenicity Study CTD 4.2.3.4 - Toxicology - Carcinogenicity		Available animal model is not reflecting human disease. See proof of concept. - CTD 4.2.1 - Pharmacology and discussion in CTD 2.4 - Non -clinical overview			
Patient-related		Risk for unwanted immunogenicity due to patient history (Allergy to components of product). Patient selection criteria (Contraindication), pre-treatment testing for allergies. CTD 5.3 - Clinical study reports	Risk for treatment failure due to patient history (age, suboptimal microenvironment) and insufficient dose finding data. Determination of age optimum and dose limits based on in vivo and/or in vitro testing CTD 5.3 - Clinical study reports		Risk for unwanted tissue formation due to microenvironment (lack of maturation in situ, scar tissue formation) CTD 2.5.- Clinical overview	
Disease-related			Risk for cell failure to differentiate due to chronic inflammation and other factors. Stratification based on patient history and pre-treatment testing. Reports of efficacy and safety studies and Post-marketing studies. CTD 5.3.5 - Reports of efficacy and safety studies, 5.3.6 - Reports of post-marketing experience and 5.3.7 - Case report forms and individual patient listings			

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Medical procedure-related		Unwanted immune reaction & allergy to concomitant substances at site of application (Joint). Contraindication in patient history, pre-treatment testing for allergies. Safety AEs reported in CTD 2.5- Clinical Overview, 2.7 - Clinical Summary & 5.3 - Clinical Study reports	Accidental ectopic dissemination. Validation of method for surgical procedures CTD 5.3. – Clinical study reports	Risk for joint infection. CTD 2.5. - Clinical Overview; 2.7. - Clinical Summary; 5.3. - Clinical Study reports	Hypertrophic growth due to surgical procedure; Safety AEs reported in CTD - 2.5 -Clinical Overview; 2.7 - Clinical Summary; 5.3 - Clinical Study reports	

Blank box means that based on the current knowledge no reasonable risk factor/risk relationship is existing.