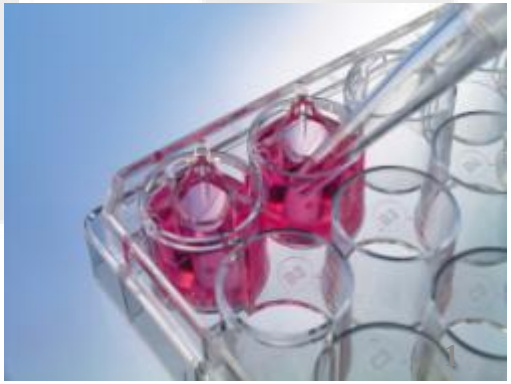
Approaches to the non-clinical development of advanced therapy medicinal products

Fernando Méndez-Hermida

SME workshop: Focus on non-clinical aspects

03rd of October 2016. European Medicines Agency, London, United Kingdom.



ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs)

- Medicinal products which includes
  - Cells
  - Genes
  - Tissues

REGULATION ON ATMPs (EC) No 1394/2007

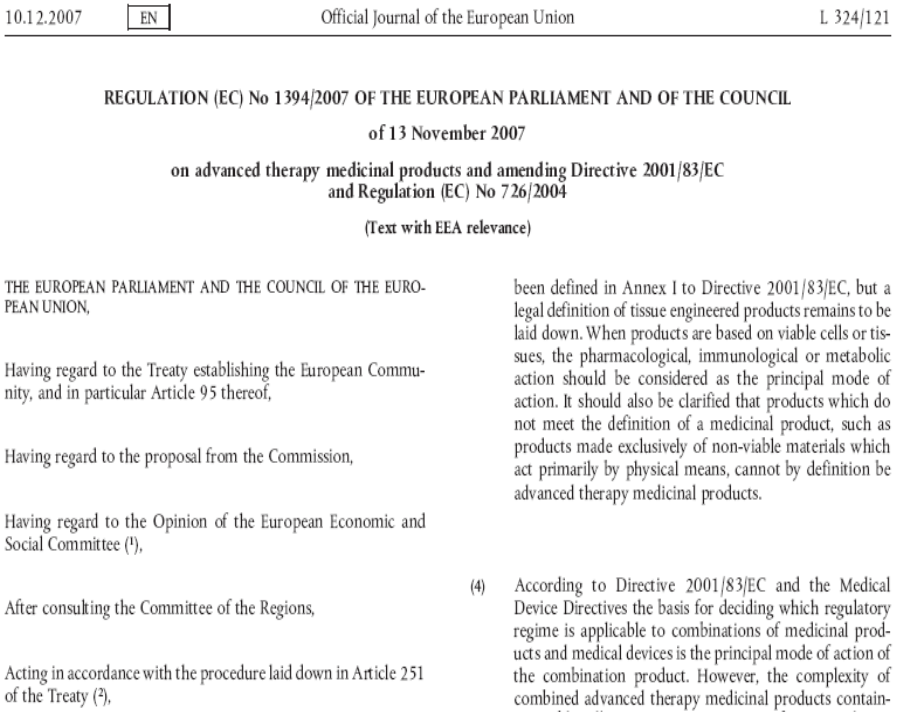
The main elements of the Regulation are:

•A **centralised marketing authorisation** procedure, to benefit from the pooling of expertise at European level and direct access to the EU market.

•A new and multidisciplinary expert Committee (**Committee for Advanced Therapies**), within the European Medicines Agency (EMA), to assess advanced therapy products and follow scientific developments in the field.

•**Technical requirements adapted** to the particular characteristics of these products.

•**Special incentives for small and medium-sized enterprises.**



10.12.2007 EN Official Journal of the European Union L 324/121

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products contain-

Reg No 1394/2007 Art. 2

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a tissue engineered product as defined in point (b).

(b) 'Tissue engineered product' means a product that:

- contains or consists of engineered cells or tissues, and
- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

You think you have an ATMP?

What should I do next?

- Refer to your NCA
  - First contact for clarification
  - Request a National Scientific Advice or Similar.
- Contact with the EMA
  - CAT
    - Classification
    - Certification
  - Scientific Advice request

CAT Classification

- Companies can consult the European Medicines Agency (EMA) to **determine whether a medicine they are developing is an advanced therapy medicinal product (ATMP).**
- The criteria for ATMPs are set out in Article 17 of Regulation (EC) No 1394/2007. The **classification procedure is optional.**
- **Responses in 60 days.**

Article 18
Certification of quality and non-clinical data

- Small and medium-sized enterprises developing an advanced therapy medicinal product may **submit to the Agency all relevant quality and, where available, non-clinical data** required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

Certification objectives

- The certification system aims at giving the SMEs an **incentive to develop ATMPs.**
- The certification procedure is a **stand-alone evaluation procedure**, which is independent from a future application for marketing authorisation. A certificate issued by the EMA **is not legally binding** with regard to any future regulatory procedure. Any relevant data, even if already certified, **should be submitted again** for the purpose of any future regulatory procedure. It could, nevertheless, facilitate the evaluation of any future application for clinical trial authorisation or a marketing authorisation application (MAA), provided that these applications are based on the same data.

CAT Certification procedures for micro-, small- and medium-sized enterprises (SMEs)

- Certification procedure for ATMPs under development by SMEs. This is an opportunity for SMEs to get an assessment of the data they have generated and **check that they are on the right track for successful development**.
- **Scientific evaluation** of quality data and, when available, non-clinical data
- Aim: **Identify any potential issues** early in the product development
- The evaluation and certification procedure takes **90 days**.
- CAT recommends issue certification that is issued by the EMA
- Certification: Confirms that available data **comply with the standards required for Marketing Authorization Application (MAA)**
- The certification procedure is defined in Article 18 of Regulation (EC) No 1394/2007 (the 'ATMP Regulation').

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SCIENCE MEDICINES HEALTH

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Multidisciplinary guidelines

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The European Medicines Agency's multidisciplinary guidelines on the development of human medicines help applicants prepare marketing authorisation applications. Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives.

The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. Before that, they should seek scientific advice, to discuss any proposed deviations during medicine development.

Multidisciplinary guidelines are provided for:

- Paediatrics
- Cell therapy and tissue engineering
- Vaccines
- Biosimilars
- Gene therapy
- Herbal medicinal products
- Nanomedicines
- Pharmacogenomics

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AMTPs EMA guidelines

CBMP & TE

Topic	Documents	Reference number	Publication date	Effective date
Clinical aspects related to tissue engineered products	Overview of comments Adopted reflection paper Draft reflection paper	EMA/CAT/573 420/2009	December 2014	December 2014
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	Adopted guideline Draft guideline Concept paper	CAT/CPWP/68 6637/2011	March 2013	February 2013
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products	Adopted guideline Overview of comments Draft guideline	CHMP/CAT/B WP/353632/ 2010	June 2011	June 2011
Reflection paper on stem cell-based medicinal products	Overview of comments Adopted reflection paper Draft reflection paper	CAT/571134/ 09	February 2011	January 2011
Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee	Overview of comments Draft reflection paper Adopted reflection paper	CAT/CPWP/56 8181/2009	May 2010	April 2010
Potency testing of cell based immunotherapy medicinal products for the treatment of cancer	Overview of comments Adopted guideline Draft guideline	CHMP/BWP/2 71475/06	December 2007	May 2008
Guideline on xenogeneic cell-based medicinal products	Adopted guideline Draft guideline Concept paper	CHMP/CPWP/ 83508/09	December 2009	January 2010
Human cell-based medicinal products	Overview of comments Adopted guideline Draft guideline	CHMP/41086 9/06	June 2008	September 2008

GTMP

Topic	Documents	Reference number	Publication date	Effective date
Management of clinical risks deriving from insertional mutagenesis	Reflection paper	CAT/190186/ 2012	Aug 2013	
Design modifications of gene therapy medicinal products during development	Reflection paper	CAT/GTWP/4 4236/2009	Feb 2012	
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products	Adopted guideline Overview of comments Draft guideline	CHMP/CAT/B WP/353632/ 2010	June 2011	June 2011
Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	Adopted guideline Overview of comments Draft guideline Concept paper	CHMP/GTWP/ 671639/200 8	May 2012	
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	Adopted guideline Draft guideline Concept paper	CAT/CPWP/6 86637/2011	Mar 2013	Feb 2013
Questions and answers on gene therapy	Adopted guideline	CHMP/GTWP/ 212377/08	Dec 2009	Dec 2009
Quality, non-clinical and clinical aspects of gene therapy medicinal products	Draft guideline Concept paper	EMA/CAT/80 183/2014	Release for consultation May 2015	
ICH Considerations General Principles to Address Virus and Vector Shedding	Concept paper	CHMP/ICH/4 49035/09	July 2009	July 2009
Quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral vectors	Overview of comments Adopted guideline Concept paper	CHMP/GTWP/ 587488/07	Release for consultation Mar 2009	
ICH Considerations - Oncolytic Viruses	Adopted guideline Draft guideline	CHMP/GTWP/ 607698/08	Oct 2009	
Non-clinical studies required before first clinical use of gene therapy medicinal products	Overview of comments Adopted guideline Draft guideline Concept paper	CHMP/GTWP/ 125459/06	May 2008	Nov 2008
Follow-up of patients administered with gene therapy medicinal products	Overview of comments Adopted guideline Draft guideline Concept paper	CHMP/GTWP/ 60436/07	Nov 2009	May 2010
Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products	Overview of comments Adopted guideline Draft guideline Concept paper	CHMP/GTWP/ 125491/06	May 2008	Nov 2008
Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors	Overview of comments Adopted guideline Draft guideline	EMEA/27397 4/05	Dec 2006	May 2007
Development and Manufacture of Lentiviral Vectors	Adopted guideline	CHMP/BWP/2 458/03	May 2005	Nov 2005
Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products	Adopted guideline	CPMP/BWP/3 088/99	Apr 2001	Oct 2001

Non clinical assessment-
Gene therapy vs. Cell Therapy and TE

Gene Therapy	Cell Therapy
Proof of concept.	Proof of concept
Biodistribution	Biodistribution
Vector expression	Cell differenciation
Immunogenicity	Integration of the product
	Functional integration
	Paracrine effects
	Immunogenicity
Toxicity Assessment	Toxicity Assessment
Carcinogenicity	Tumorigenicity
Insertional Mutagenesis	
Germline transmission	Gonads assessment
Environmental Risk Assessment GMOs	

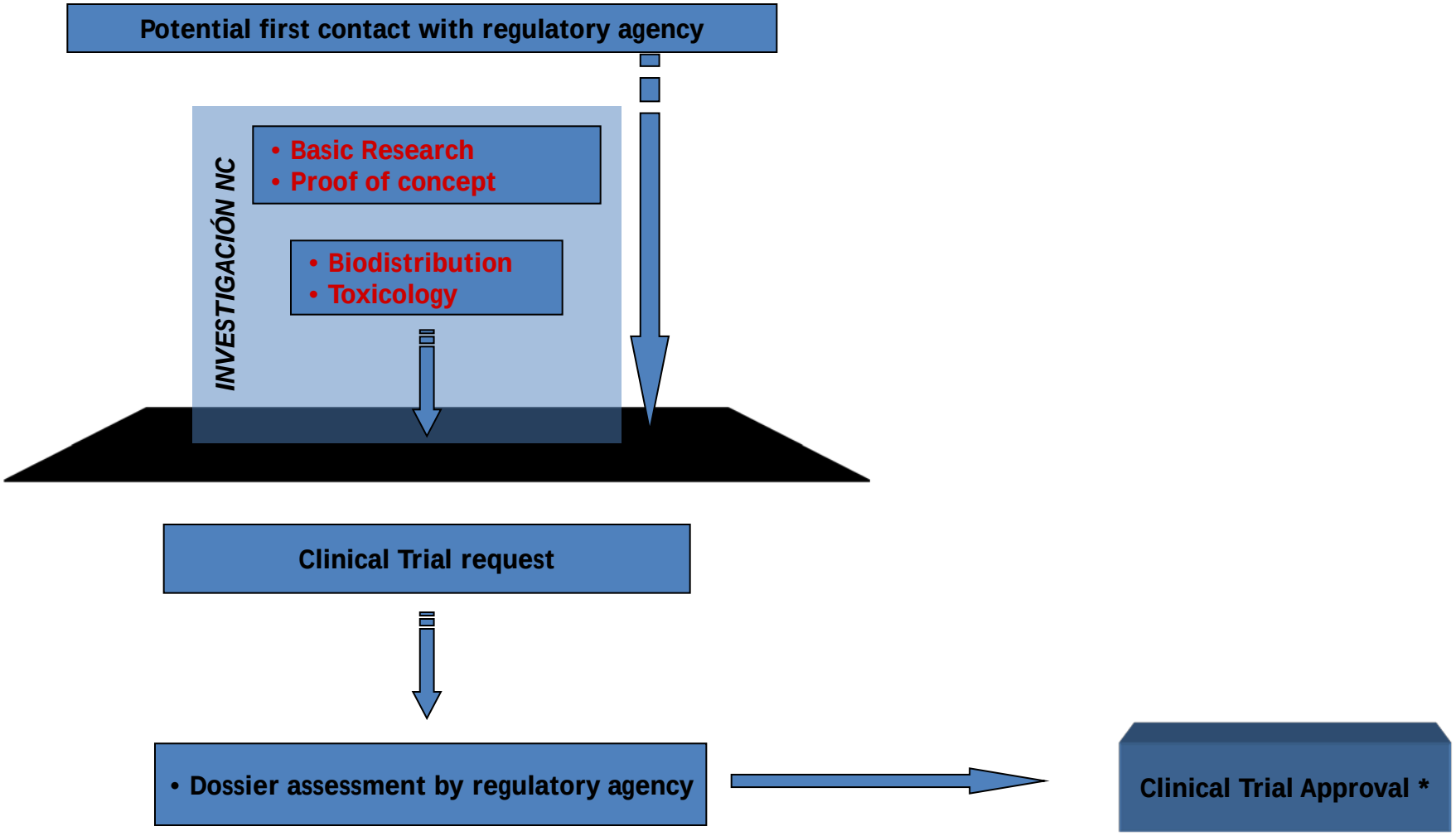
Studies to be included in a Non-Clinical dossier

. Pharmacology studies
. Toxicokinetic and pharmacokinetic studies
. Single dose toxicity studies
. Repeated dose toxicity studies*
. Marketing authorisation
. Estimation of the first dose in human
. Local tolerance studies
. Genotoxicity studies
. Carcinogenicity studies
. Reproduction toxicity studies

* Depending on the clinical dosing those studies may not be necessary

Safety is the primary factor

Research phase/ Safety assessment of ATPMs

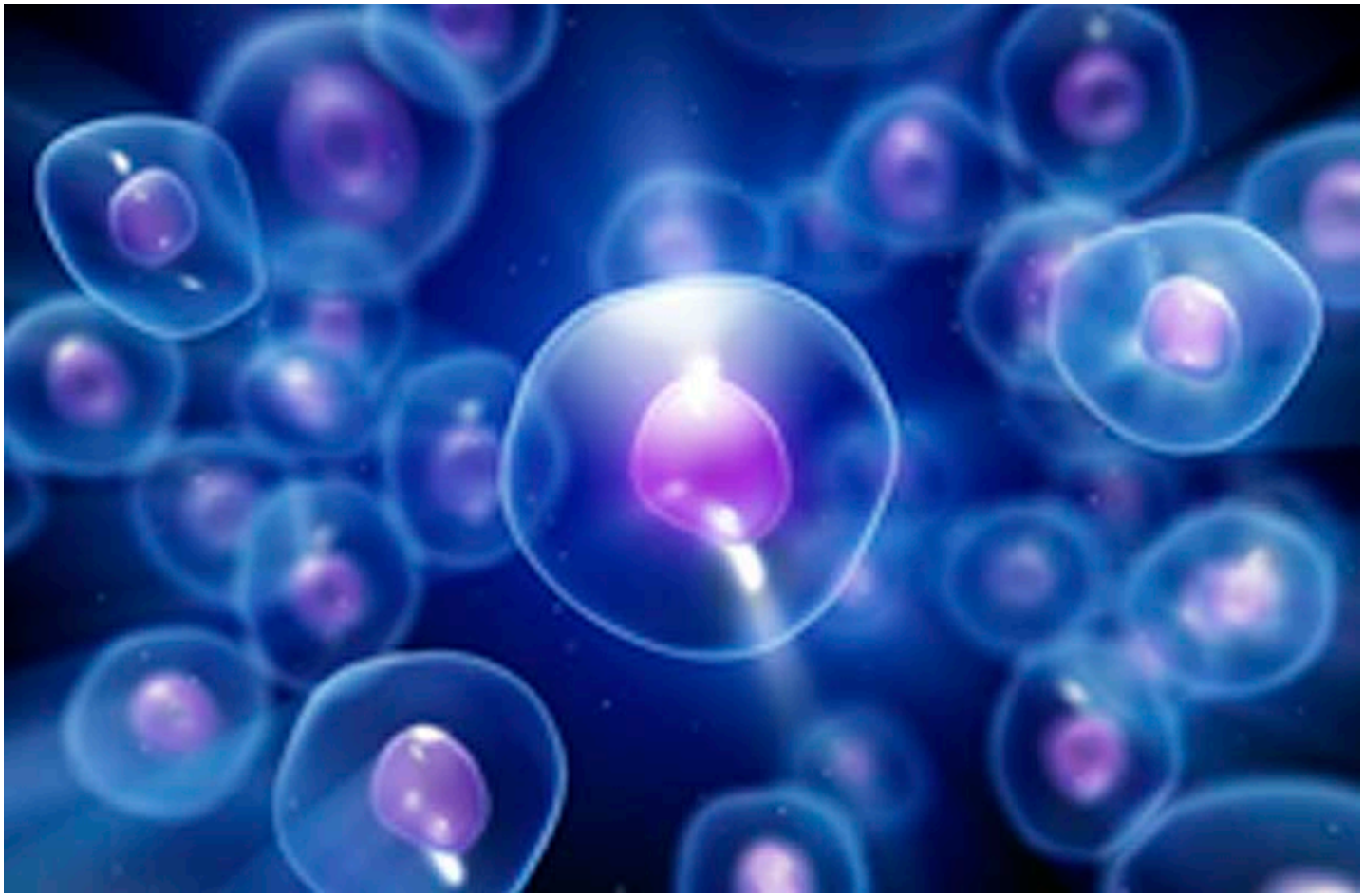


Important issues to take into account for the NC development of a product

- Previous experience available in animal models and maybe in humans with the same product.
- Previous experience available in humans with a similar product
- Availability of:
  - Relevant animal models
  - Relevant scientific literature

“Non clinical requirements for Cell based Medicinal products (CBMP)”

General Aspects

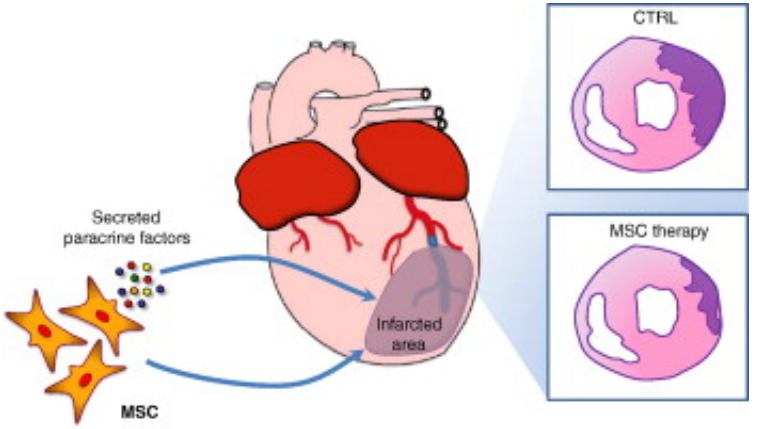


CBMP- ***Pharmacology***

- Demonstrate the **proof of concept** of the CBMP in a model of disease (*in vitro*/*in vivo*)
  - Similar characteristics between the animal model and humans
  - Identify limitations of the models chosen and justify the relevance
- Animal models (immunosuppressed/knockout, transgenic, homologous models)
- Identify and employ markers of biological activity when available.

CBMP- ***Pharmacology***

- Identify a potential efficacious dose
- Frequency of administration
- Evaluate the manufacturing procedure

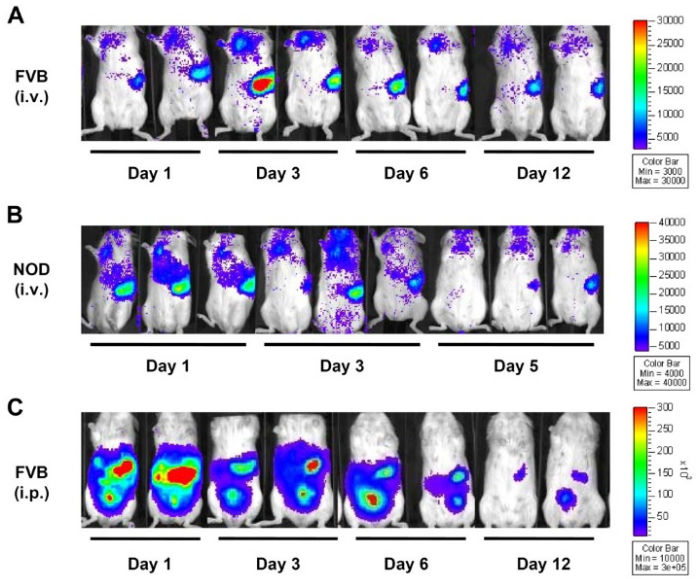


- Secondary pharmacology
- Safety pharmacology

Gnecchi et al. 2012. Mesenchymal stem cell therapy for heart disease. Vascul Pharmacol. 2012 Aug 19;57(1):48-55.

CBMP- ***Pharmacokinetics***

- Conventional ADME studies are normally not relevant for this type of products.
- Kinetics, migration and persistence
  - Viability
  - Distribution
  - Growth
  - Differentiation
  - Persistence



Lymphoid tissue–specific homing of bone marrow–derived dendritic cells
Rémi J. Creusot et al, Blood 2009 113:6638-6647;

CBMP- ***Toxicology***

- Finished product
- Toxicity may evolve, for example, due to unknown cellular alterations
  - Manufacturing process related issues
  - Allogeneic use of the product
  - Proliferation in an unwanted quantity
  - or in an unwanted location.

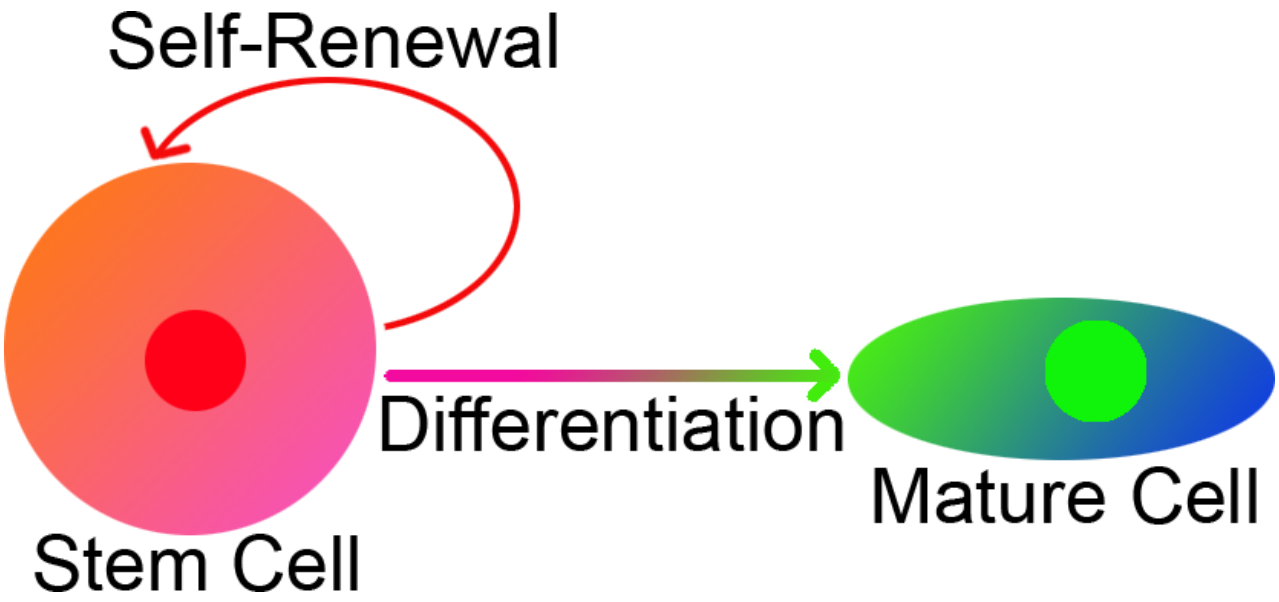
Note: The combination in one study of Proof of concept

Biodistribution and/or Toxicology may be acceptable

CBMP- ***TOXICOLOGY***

- Single and repeated dose studies
  - The route of administration, frequency should reflect the one projected in humans. The duration of the studies may be longer than the anticipated in other non clinical guidance and will be often hinted by previous data of Pharmacology/Biodistribution/ Toxicity and/or from published data from similar products.
    - (NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS FOR PHARMACEUTICALS ICH Topic M 3 (R2) CPMP/ICH/286/95 **DOES NOT APPLY**
- Other toxicity studies
  - Conventional carcinogenicity studies are not warranted for this type of therapy, although the potential tumorigenicity should be assessed *in vitro/in vivo*.

Stem cells



Guidance

European Medicines Agency

London, 21 May 2008
Doc. Ref. EMEA/CHMP/410869/2006

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS	
DRAFT AGREED BY CPWP AND BWP	November-December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2007
AGREED BY CPWP and BWP	April 2008
ADOPTION BY CHMP	30 May 2008
DATE FOR COMING INTO EFFECT	1 September 2008

14 January 2011
EMA/CAT/571134/2009
Committee for Advanced Therapies (CAT)

Reflection paper on stem cell-based medicinal products

Draft Agreed by Biologics Working Party (BWP) and Safety Working Party (SWP)	March 2010
Draft Agreed by Cell Products Working Party (CPWP)	March 2010
Adoption by Committee For Advanced Therapies (CAT) for release for consultation	12 March 2010
End of consultation (deadline for comments)	30 June 2010
Revision agreed by CPWP, BWP and SWP	03 December 2010
Adoption by CAT	14 January 2011

Cell therapy products which have received MAA

ATMP	ChondroCelect®	MACI®	Provenge®	Holoclar®	Zalmoxis®
Indications	Repair of cartilage defects of the femoral condyle of the knee in adults.	Repair of cartilage defects of the knee in adults.	Treatment of metastatic castrate resistant prostate cancer in male adults.	Treatment of limbal stem cell deficiency due to ocular burns in adults.	Add-on treatment in adults who have received a haematopoietic stem cell transplant from a partially matched donor
Type of product	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Matrix-applied characterised autologous cultured chondrocytes	Autologous peripheral-blood mononuclear cells including a minimum of 50 million autologous CD54+ cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Allogeneic T cells **genetically modified** with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)
Approval date authorization	2009	2013	2013	2015	2016
Current status	The marketing authorisation has been withdrawn at the request of the MAH.	The marketing authorisation for Maci has been suspended at the recommendation of the Agency's Committee for Medicinal Products for Human Use (CHMP).	The marketing authorisation has been withdrawn at the request of the MAH.	Conditional Approval	Conditional Approval

Gene Therapy

Types GT products

TABLE 1

TYPES OF GENE TRANSFER MEDICINAL PRODUCTS	EXAMPLES
(a) naked nucleic acid	natural or synthesised nucleic acid, generally ligated into appropriate plasmids or cassettes (see section 1.3; excluding antisense oligonucleotides) with or without adjuvant.
(b) complexed nucleic acid or non viral vectors	(i) as above, but complexed with polycations (e.g. oligodendomer), proteins (e.g. transferrin) or other polymers (e.g. DEAE-Dextran, polylysine) (ii) as above (i) but encapsulated or associated (for example in liposomes (iii) as above, but coated on colloidal particles
(c) viral vectors	Usually replication-deficient viruses, including adenoviruses, retroviruses, adeno-associated virus, herpes simplex virus; in some cases replication-competent viruses e.g. vaccinia virus.
(d) genetically modified cells	Allogeneic, xenogeneic, or cells of microbiological origin carrying a newly introduced nucleic acid segment.

EMEA/273974/2005

Gene Therapy

GT- PRIMARY PHARMACOLOGY

- FIRST STEPS
- Determine the capability of the GTMP to induce the pharmacological/biological effect needed. *(in vitro/in vivo)*
- From *in vivo* studies, important data may be drawn. Such data will help to design appropriate biodistribution/toxicology studies.
- Dose response
- Evaluation of animal models adequacy.

GT-Biodistribution

- Assessment of the biodistribution of the vector in organs/tissues where it is expected the presence of the vector (where the therapeutic action is bound to occur) and in those locations where it is less likely to be found.

  - Assessment of the presence of the vector
    - Presence in germline related organs.
    - Presence in locations not specific for the vector.
    - Viral shedding.
    - Insertional mutagenesis.

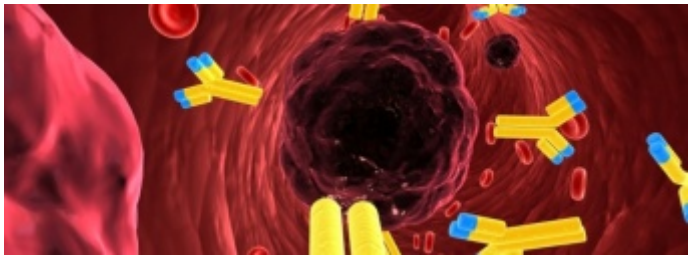
GT-TOXICOLOGY

- **Assessment of the vector exposure**
- **Assessment of the transduced gene expression**
  - Persistence and levels of expression. Over expression may lead to Adverse Effects (Aes).
  - Identify target organs of toxicity.
  - Assessment of reversibility of Aes reported
- **Evaluate the full construct vector and gene**
  - Toxicity assessment of the construct
  - Identify NOAEL-MTD. Safety margins
- **The animal dosing should reflect the dosing in humans-> Repeated dosing in humans should be assessed by preclinical repeated dosing**

GT-TOXICOLOGY

- **Integration studies**
  - Integration should be assessed and the extent of the data required is dependent on the nature of the product under assessment.
  - When a positive result is reported additional testing should be considered before first in humans administration (FIH)
  - When paediatric populations are to be included in the CTs or when dealing with not severe or not deadly diseases, integration studies will need a more careful approach before FIH

GT-TOXICOLOGY



- **<u>Inmunogenicity and inmunotoxicity</u>**
  - GTMPs administration may result in immune responses (innate and adaptive)
  - Immunity against potential preexistent exposure to the vector or the transgene (including also repeated administration) should be assessed.
  - Complement activation should be also considered and its possible consequences.

GT-TOXICOLOGY

- **Germline Transmission**
  - Definitions:
    - Integrating vectors: Those vectors wich have the necessary machinery for integration in the host genome
    - Non integrating vectors: Those vectors that lack of the previously defined characteristics.

GT-TOXICOLOGY

- **Germline transmission**

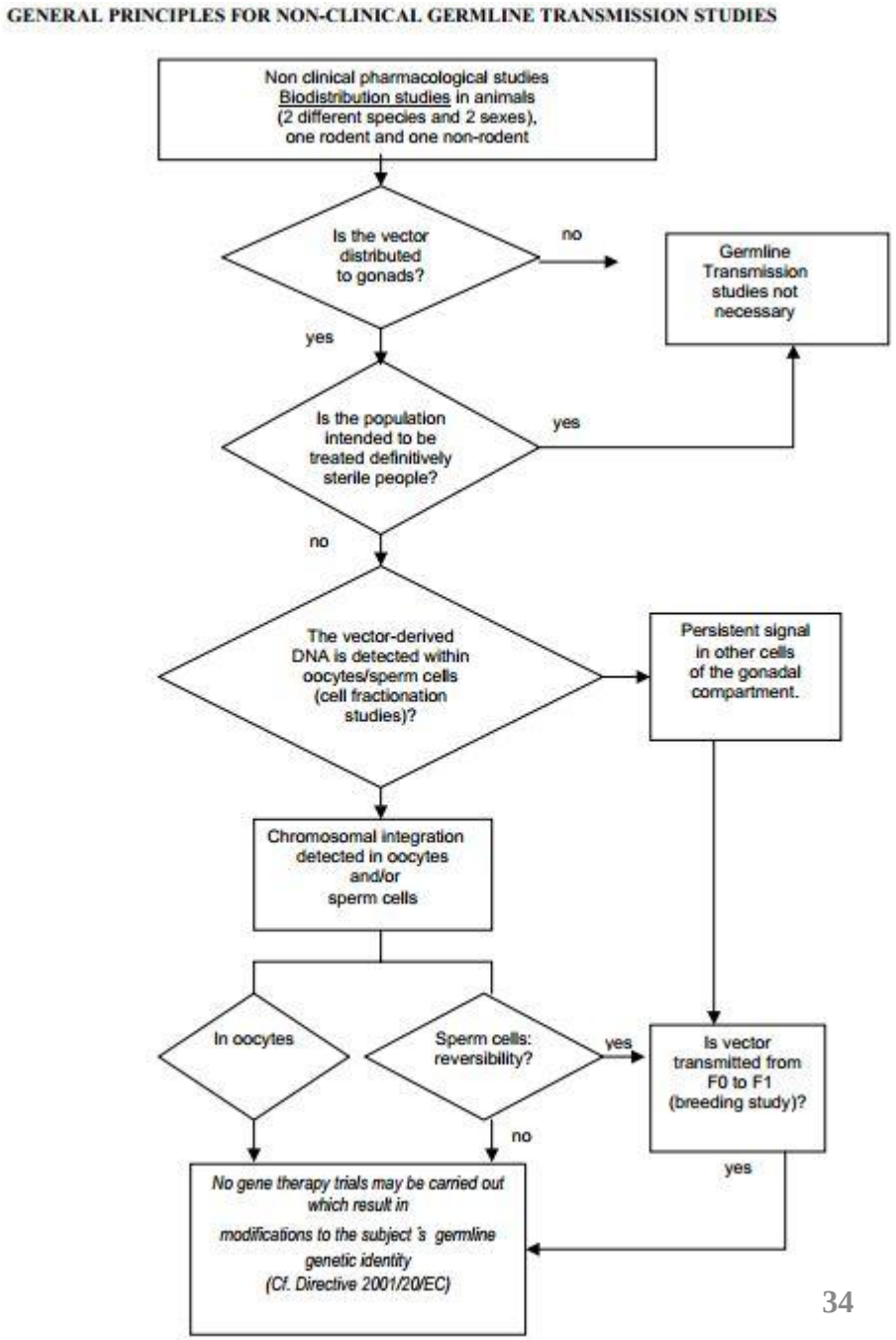
Table 1: Classification of integrating and non-integrating vectors based on the parental virus/plasmid characteristics

Integrating vectors	Non-integrating vectors
• gamma-retroviral vectors • lentiviral vectors	• adenoviral vectors/viruses • adeno-associated viral (AAV) vectors* • Herpes simplex-1 viral (HSV-1) vectors/viruses • pox viral vectors/viruses (non-nuclear) • naked DNA • non-viral vectors • paramyxoviral vectors (non-nuclear)

*Currently used AAV vectors are devoid of the integration machinery of wild type AAV and are therefore considered non-integrating vectors according to the above-mentioned definition, although it is possible that future AAV vectors may contain integration machinery

Germline transmission

Decision tree



GT-TOXICOLOGY

- **Tumorigenicity**
  - Standard classic rodent life time studies are not generally required
  - The nature of the assessment should take into account:
    - The type of vector and insertional mutagenesis data
    - Type of transgene
    - Data from toxicology studies. Tumorigenic signals.
    - Signs of immune suppresion or hormone imbalance.

GT-TOXICOLOGY

- **<u>Environmental Risk Assessment (ERA).</u>**
  - Although such studies are not needed for other medicinal products until MAA, when dealing with GTMPs an adequate ERA should be performed from FIH
    - **"This guideline describes the ERA for marketing authorisations. However, the conclusions from a preliminary ERA e.g. for a clinical trial adequate for the development stage of the GMO-containing medicinal product must be taken into account"**

– Guideline on scientific requirements for environmental risk assessments of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 April 2012
EMA/CAT/GTWP/671639/2008
Committee for Advanced Therapies (CAT)

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Draft Agreed by GTWP, CPWP, BWP	**January-March 2010**
Consultation of CAT, SWP, EWP	April 2010
Draft Agreed by CAT	May 2010
Adoption by CHMP for release for consultation	20 May 2010
End of consultation (deadline for comments)	30 November 2010
Agreed by CAT Gene Therapy Working Party	07 October 2011
Adoption by CAT	13 April 2012
Date for coming into effect	1 November 2012

Keywords	***Genetically modified cell, advanced therapy, gene therapy, cell therapy, somatic cell, quality, non-clinical, clinical***

Gene therapy products which have received MAA

ATMP	Glybera®	Imlygic®	Strimvelis®
Indications	Treatment of familial lipoprotein lipase deficiency with severe or multiple pancreatitis attacks in adults.	Treatment of unresectable melanoma (Stage IIIB, IIIC and IVM1a) in adults.	Treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).
Type of product	Alipogene tiparvovec (adeno-associated virus serotype 1 (AAV1) viral vector delivers an intact copy of the human lipoprotein lipase (LPL) gene to muscle cells)	Talimogene laherparepvec ((oncolytic) virus engineered from herpes simplex virus 1 (HSV-1))	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells
Approval date authorization date	2012	2015	2016
Current status	Approved (additional monitoring, exceptional circumstances)	Approved (additional monitoring)	Approved (additional monitoring)

European Medicines Agency

London, 17 December 2009
Doc. Ref. EMA/CHMP/CPWP/708420/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE RISK-BASED APPROACH ACCORDING TO ANNEX I, PART IV OF DIR. 2001/83/EC APPLIED TO ADVANCED THERAPY MEDICINAL PRODUCTS

AGREED BY Cell Products Working Party, Gene Therapy Working Party and Biologics Working Party	November 2009
ADOPTION BY CAT/CHMP FOR RELEASE FOR CONSULTATION	17 December 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2010

RISK-BASED APPROACH

- This guideline application is not compulsory.
- Applicable to all ATMPs
- One of the usefulness of this guideline is that allows to provide an risk assessment with sufficient information that permits the evaluation of a particular risk when any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC is identified and precludes the Applicant from obtaining experimental data.

RISK-BASED APPROACH

- RISK PROFILING
- 1st step: To identify **risks associated with the clinical use** of the ATMP
- 2nd step: To identify **product specific risk** factors contributing to each identified risk
- 3rd step: To **map the relevant data for each** identified risk factors against each of the identified risks
- 4thstep: To **conclude on the risk factor** – risk relationship

RISK-BASED APPROACH
Examples

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 FP 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 FP 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 FP.	Mobilisation (with wt virus 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 have been performed (CTD 4.2.3- Toxicology) and demonstrate absence of integration. 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 FP 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.	

RISK-BASED APPROACH
Examples

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		
Structural / functional integrity			Sub-optimal extracellular matrix formation and function. Potency assay for FP CTD 3.2.P.5 - Control of FP 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.	

Animal models

- RELEVANT ANIMAL MODEL.
  - Classic animal models
    - Traditional animal models (rodents and non rodents)
  - Non Traditional animal models
    - Models that spontaneously develop the disease
    - Non spontaneous models (the disease is induced)
    - Genetically modified animals
      - Animals with gene modifications
      - “humanized” animal models
  - Important to understand the limitations of the animal model selected.

  - **The three Rs Principles:**
    - The welfare of animals used in research is of most importance for the regulators and cornerstone for future research
    - Agencies with Scientist and animal carers are making continued efforts in order to Replace, Reduce and Refine the way experiments are carried out.

Animal models

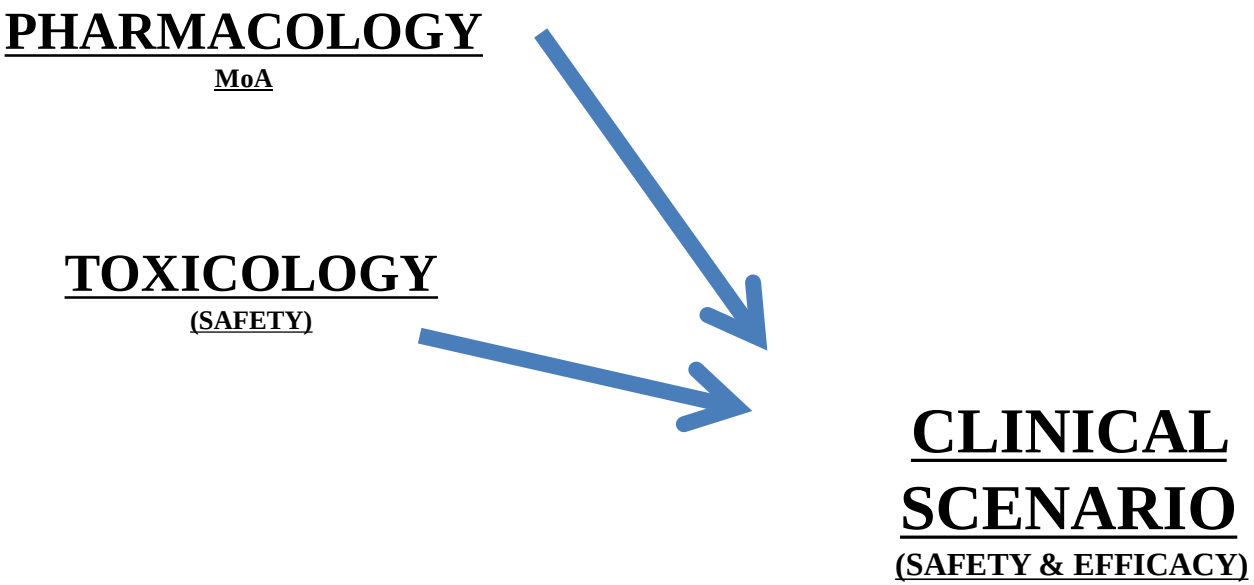
SELECTION OF AN APPROPRIATE MODEL

- IS IT A RELEVANT ANIMAL MODEL?

Animal models

- Is it a predictive model?

Relevant Animal Species



Wrap up…

- ATMPs have **special considerations for SMEs** in the EU. Take advantage of them.
- Please get in touch with any EMA (CAT-Scientific Advice) and/or any NCA within EU from early stages of development in order to **avoid unnecessary delays and time waste** by performing needless studies or lacking of necessary ones.
- **Bear in mind the available EMA guidance** is there to be followed unless justified.
- In the end the aim of all NC development is to find the necessary **balance between risk and benefit** for the patients.
- The use of **non relevant animal models** for the product develoment is **discouraged**.

I would like to thank all my colleagues at my Agency and all other European Agencies for creating a wonderful working environment where knowledge and good atmosphere is shared all year through.