EBF Training Day

Regulatory Requirements for Preclinical Development of Gene and Cell Therapy Products

September 15, 2020

Dr. Manuela Braun / Version 1.0

The views and opinions expressed in this presentation are those of the author and do not necessarily represent the views, policy, or position of Bayer.

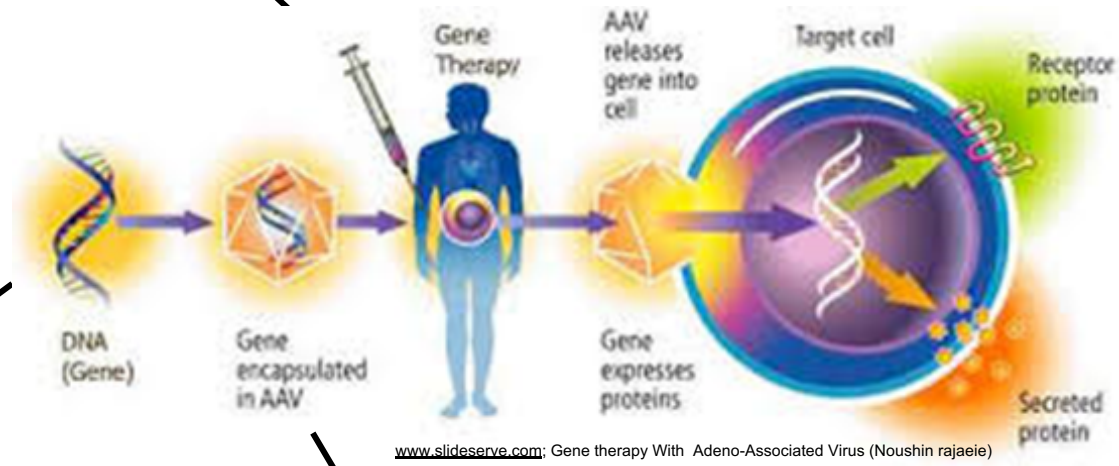
Gene Therapy Products

(GTPs)

Components of a Gene Therapy Product (GTP)

Each component of a GTP has its specific properties which contribute to the overall efficacy and safety profile of the GTP!

Delivery procedure
- *ex vivo, in vivo* GT
- device
- RoA
- formulation



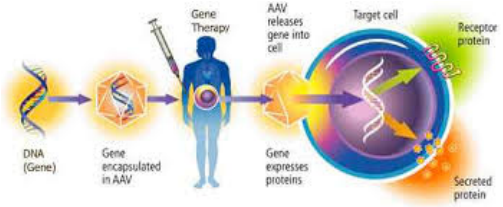
www.slideserve.com: Gene therapy With Adeno-Associated Virus (Noushin rajaeie)

Transgene Product
- mRNA
- protein

Genetic construct
- transgene
- promoter (e.g. inducible, tissue specific)
- vector specific structures (e.g. ITR sequence of an AAV)
- regulatory elements (e.g. miRNA)

Vector
- plasmid
- viral vector, virus (e.g. integrating, replication conditional)
- cell (e.g. CAR T, CAR NK, iPSCs secreting antitumor agents)

Component-Specific Contribution to the Safety & Efficacy Profile



Genetic construct

- biodistribution (e.g. tissue-specific promoter)
- persistence (e.g. inducible promoter)

Vector

- biodistribution (e.g. tropism)
- persistence (e.g. replicating, persisting virus)
- immune response (e.g. cytokine storm, efficacy loss)
- genome integration (e.g. retrovirus vs. AAV)
- germline integration (e.g. retrovirus vs. AAV)
- shedding (e.g. replicating vs. non-replicating)
- infectivity (e.g. replicating infective virus)
- teratoma/tumor formation (e.g. iPSC vectors)
- graft vs. host disease (e.g. CAR cells)

Transgene product

- biodistribution (e.g. secreted vs. locally expressed protein)
- persistence (e.g. half-life)
- immune response (e.g. efficacy loss)
- transgene specific risks (e.g. growth factor vs. FVIII)

Delivery procedure

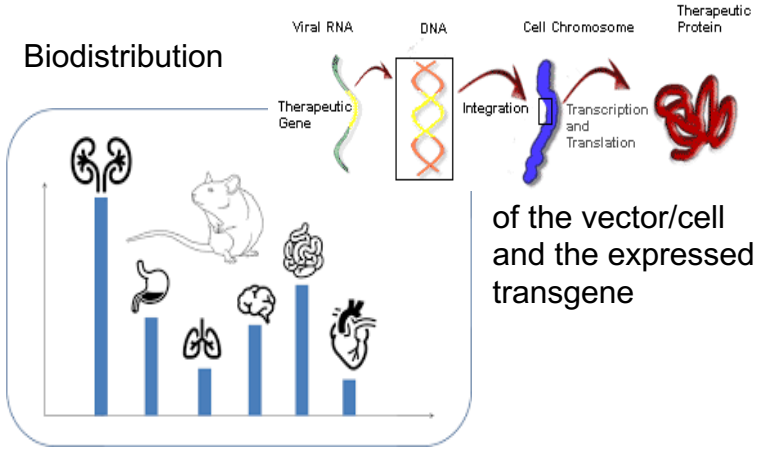
- cell survival (e.g. *ex vivo* GT; shear stress in/adsorption to the device)
- biodistribution (e.g. intracranial vs. iv administration)
- immunogenicity (e.g. intracranial vs. iv administration)
- genome integration (e.g. *ex vivo* or *in vivo* gene therapy)

Preclinical PK, PD & Immunogenicity Assessment of a GTP

Show **Pharmacodynamic** “proof of concept” in non-clinical model(s) *in vitro* and *in vivo*

Evaluate **distribution, persistence, mobilization** and **clearance** of

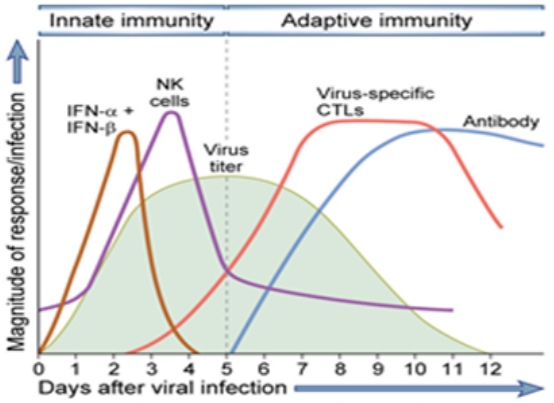
- the **vector** in target & non-target tissues
- the **expressed transgene** (mRNA and/or protein) in target tissue and any transduced tissue
- Consider conduction of **long-term preclinical studies**



of the vector/cell and the expressed transgene

Asses the **immune response**

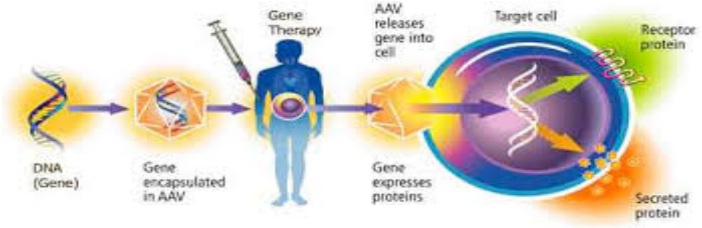
- against the **vector** (before and after treatment)
- against the **transgene product** (protein)
- innate & adaptive (humoral & cell-based)



Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology, 8th ed. Philadelphia: Elseviers Saunders; 2015

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Preclinical Toxicity Assessment of a GTP

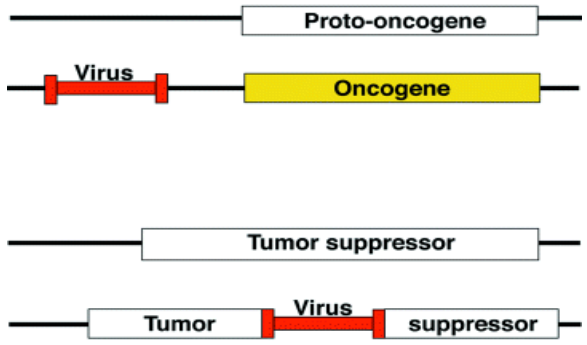


Address **vector & transgene product toxicities.**

Perform **single** and if required **multiple dose toxicity studies.**

Investigate **horizontal transmission** of vectors from treated individuals to other individuals.

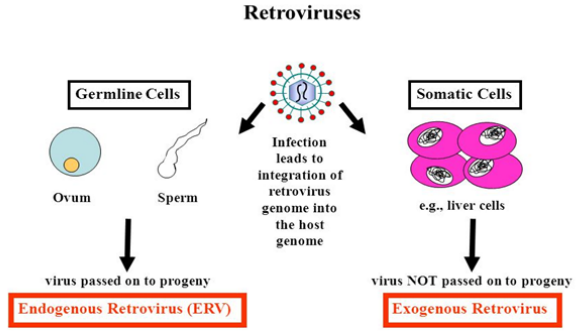
Perform **shedding analysis** and evaluate **infectivity** if required**.**



Cancer Sci (2005) 96: 7–12

Address the potential for **oncogenicity formation or insertional mutagenesis.**

Perform **tumorigenicity, genotoxicity and reproductive & developmental toxicity studies** if necessary**.**



www.slideserve.com; Genomic Repetitive Elements (Human Focus) – PowerPoint PPT Presentation

Address the risk of **germline transmission.**

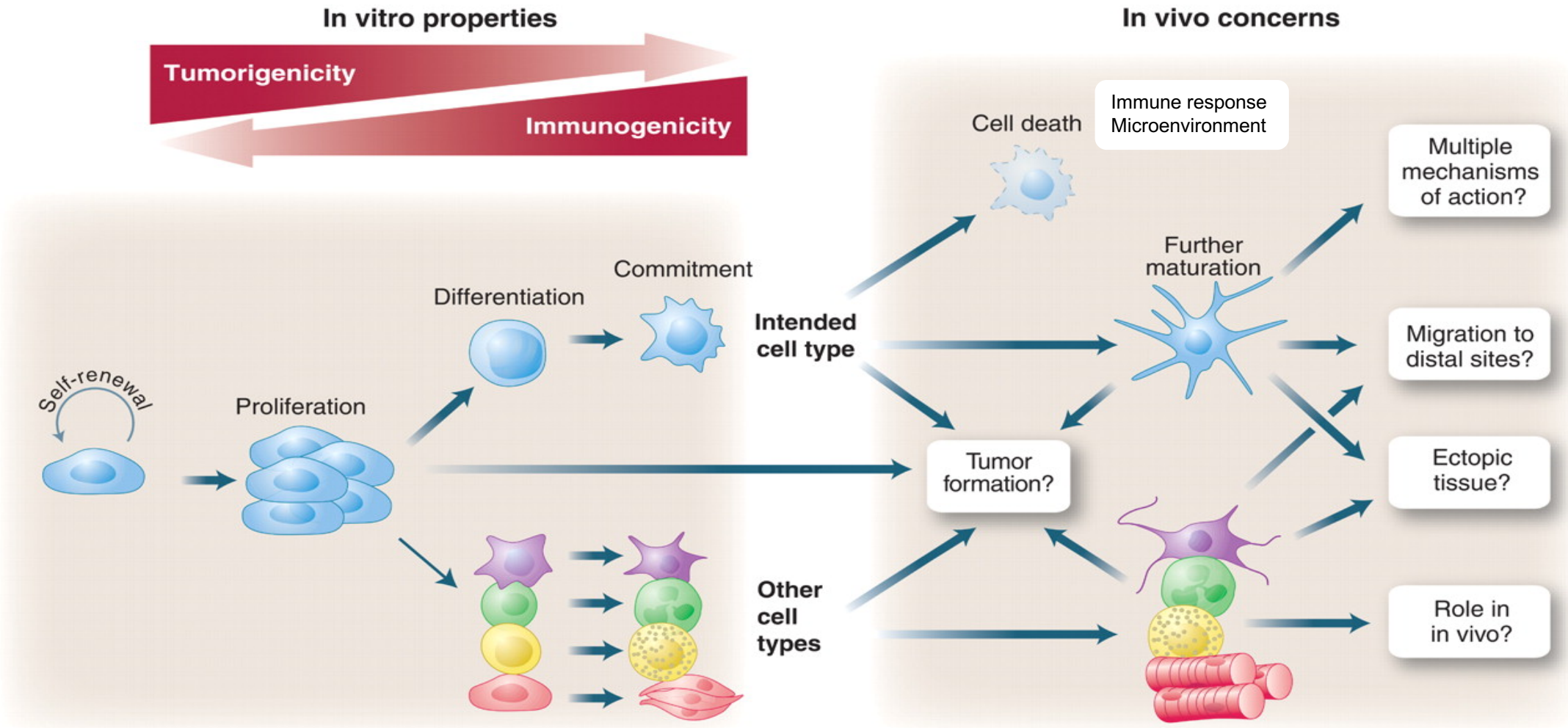
Perform **integration studies** if necessary**.**

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Cell Therapy Products

(CTPs)

Properties and Risks of Stem Cell-Derived CTPs



Fink. FDA Regulatiom of SC-Based Products. Science (2009) 324: 1662-63

Preclinical Assessment of a CTP

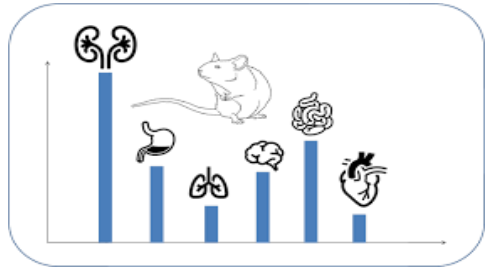
Show **Pharmacodynamic** “proof of concept” in non-clinical model(s) *in vitro* and *in vivo*

- Consider that **cell survival/engraftment** is influenced by
  - **biocompatibility** of cell delivery device (e.g. shear stress, adsorption)
  - **ROA** (e.g. intravenous vs intracranial administration)
  - **genetic relationship** of the cells to the host animal (e.g. autologous, allogenic, xenogenic)
  - **immune response** of the host (-> immune status of the host animal)
  - **inflammatory response** in target/non-target tissues
  - **timing of cell administration** relative to the onset of the disease/injury (e.g. microenvironment in target tissue)

(FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Preclinical Assessment of a CTP

Evaluate **distribution and migration** to target and non-target organs/tissues



// **various methods** like imaging methods, PCR (gold standard), IHC can be used; ***in vivo* imaging** can be used to reduce the number of animals

// use **whole organ homogenates** for bioanalytical analysis (-> cells might be distributed irregularly)

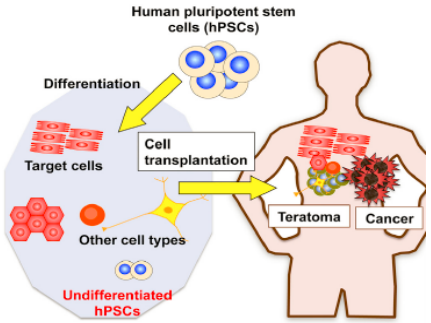
Evaluate **differentiation and integration into organs/tissues**

// assess cell morphology, phenotype, level of differentiation in target and non-target tissues

Perform **tumorigenicity studies**

// use the **intended clinical product**, not analogous animal cells

// show ***in vivo* survival** for a **sufficient length of time** to allow for **potential tumor formation**



Molecular Therapy: Methods & Clinical Development (2017) 5: 51-58

// include one dose level that constitutes the **maximum absolute amount of cells** that can be administered

// target the planned **clinical anatomic site** using the planned **clinical device**

(FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Preclinical

Biodistribution and Persistence Assessment

For GTPs/CTPs

Biodistribution and Persistence Assessment for a GTP/CTP

- Perform **biodistribution study** in animals, if possible **integrated into a pharmacodynamic or toxicology study**
  - cover **maximum level/cell number** of administered GTP/CTP in **target and non-target sites**
  - **mimic the clinical dose/cell number** with appropriate safety margins, e.g. 10-fold adjusted to the animal model
  - cover the **GTPs/CTPs clearance** over time (until there is **no detection** or **a long-term plateau phase** is reached)
- Use **route of administration, device and treatment regimen** (frequency, duration) intended for clinical use
- Determine **distribution and persistence** of the cell or the vector & its expressed transgene **in target & non-target tissues / biological fluids, incl. germline**
- Harvest all **relevant organs and tissues**
- Use **whole organ homogenates** for biodistribution analysis in CTP studies
- **PCR methods** regarded as **'gold standard'** for biodistribution assessment in IND-enabling studies

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Animal Species / Model Selection for GTP/CTP Assessment

- **Safety and effectiveness** *in vitro* and *in vivo* can be evaluated in **one animal species**

- **“Non-standard” test species** like genetically modified rodents (transgenics, knockouts etc.) or large animals (sheep, pigs, goats, horses etc.) acceptable

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Animal Species / Model Selection – GTP Specific Considerations

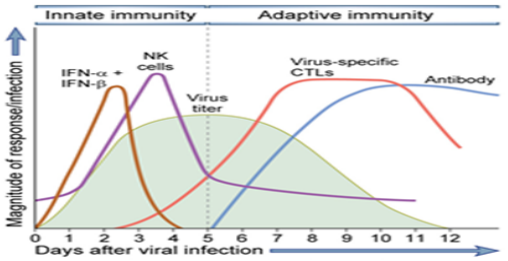
- Selected animal species should be comparable to humans with regard to:
  - **infectivity/transduction and replication ability** of the vector
  - **cellular and tissue sequestration** of the vector and/or transgene product
  - **distribution** of the vector & its transgene product within the organism
  - **activity and control** of **regulatory elements** (promoter, enhancer) driving tissue-specific expression
  - **transgene expression level**
  - **biological response** to the transgene product

- Consider the **immune status** of the animal and **potential pre-existing immunity** against the vector or the transgene product

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Animal Species / Model Selection – CTP Specific Considerations

- Ability to **access the anatomic site** for product administration as intended in clinical studies
- Ability to deliver a **specific absolute cell dose** to the target site
- Consider possibilities to **overcome immunogenicity** against the CTP that allow **long-term assessment**
  - **immunodeficient animals**
  - **immunosuppressive agents** in immune-competent animals
  - administration into **immune privileged site** (e.g. brain)



Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology, 8th ed. Philadelphia: Elseviers Saunders; 2015

- Administration of **analogous cellular products** in the preclinical PoC studies might be an option
  - but not for tumorigenicity studies

(EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products; FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products)

Summary – Preclinical Studies and Evaluations to Consider

- Show **pharmacodynamic proof of concept** in non-clinical model(s) *in vitro* and *in vivo*
- Perform **toxicity studies** (depending on the product properties)
  - **Single & multiple dose** to assess **cell or vector & transgene product toxicities**
  - **Tumorigenicity, genotoxicity, reproductive & developmental toxicity**
  - **Integration**
- Evaluate **biodistribution** in pharmacodynamic and/or toxicity studies
- Assess **shedding and infectivity** in pharmacodynamic and/or toxicity studies (depending on the product properties)
- Evaluate **immunogenicity**

Overview on Guidelines

on Cell and Gene Therapy

in the Back-Up

(no guarantee for completeness)

Thank you for your attention!

Overview on Guidelines / Whitepapers on Cell and Gene Therapy

General Guidelines

- Regulatory Considerations for **Human Cells, Tissues, and Cellular and Tissue-Based Products**: Minimal Manipulation and Homologous Use (FDA 12/2017)
- Recommendations for **Microbial Vectors** Used for **Gene Therapy**; Guidance for Industry (FDA 09/2016)
- **Cellular Therapy** for **Cardiac Disease** (FDA 10/2010)
- Guidance for Human **Somatic Cell Therapy and Gene Therapy** (FDA 3/1998)

Overview on Guidelines / Whitepapers on Cell and Gene Therapy

Guidelines for Pre-Clinical and Clinical Assessment

- Guideline on the quality, **non-clinical and clinical** aspects of **gene therapy medicinal products** (EMA/CAT/80183/2014)
- Guideline on the quality, **non-clinical and clinical** aspects of **medicinal products containing genetically modified cells** (EMA/CAT/GTWP/671639/2008)
- Reflection paper on quality, **non-clinical and clinical** issues related to the development of **recombinant adeno-associated viral vectors** (EMEA/CHMP/GTWP/587488/2007 Rev1)

- **Preclinical Assessment** of Investigational **Cellular and Gene Therapy Products** (FDA 11/2013)
- Guideline on the **Non-clinical Studies** Required Before First Clinical Use of **Gene Therapy Medicinal Products** (EMEA/CHMP/GTWP/125459/2006)

- Considerations for the Design of **Early-Phase Clinical Trials** of **Cellular and Gene Therapy Products** (FDA 6/2015)
- **Clinical Considerations** for Therapeutic **Cancer Vaccines** (FDA 10/2011)
- **Gene Therapy Clinical Trials** - Observing Subjects for **Delayed Adverse Events** (FDA 11/2006)
- Supplemental Guidance on Testing for **Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products** and During **Follow-up of Patients** in **Clinical Trials** Using **Retroviral Vectors** (FDA 11/2006)
- Guideline on **follow-up of patients** administered with **gene therapy medicinal products** (Doc. Ref. EMEA/CHMP/GTWP/60436/2007)

Overview on Guidelines / Whitepapers on Cell and Gene Therapy

Guidelines on Risk Assessment

- Guideline on the **risk-based approach** according to Annex I, part IV of Directive 2001/83/EC applied to **Advanced Therapy Medicinal Products** (EMA/CAT/CPWP/686637/2011)

Genome Integration Risk Assessment:

- Reflection Paper on Management of **Clinical Risks** deriving from **Insertional Mutagenesis** (EMA/CAT/190186/2012)
- General Principles to Address the Risk of **Inadvertent Germline Integration** of **Gene Therapy Vectors** (CHMP/ICH/469991/2006)
- **Non-clinical** testing for **inadvertent germline transmission** of **gene transfer vectors** (EMEA/273974/2005)

Shedding Evaluation:

- Design and Analysis of **Shedding Studies** for **Virus or Bacteria-Based Gene Therapy and Oncolytic Products** (FDA 8/2015)
- General principles to address **virus and vector shedding** (Concept Paper EMEA/CHMP/ICH/449035/2009)

Environmental Risk Assessment:

- Determining the Need for and Content of **Environmental Assessments** for **Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products** (FDA 3/2015)
- Guideline on scientific requirements for the **environmental risk assessment** of **gene therapy medicinal products** (EMEA/CHMP/GTWP/125491/2006)

Overview on Guidelines / Whitepapers on Cell and Gene Therapy

Guidelines on Special Topics

- **Assay Development** for **Immunogenicity Testing** of **Therapeutic Proteins** (FDA 12/2009 Draft)
- **Eligibility Determination** for Donors of **Human Cells, Tissues, and Cellular and Tissue-Based Products** (FDA 8/2007)