

# Nonclinical Considerations for Cell-Based Products

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# Cell-based products regulated by CDE

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- Stem cell-derived cells
  - Adult (hematopoietic, mesenchymal, cardiac, neuronal, adipose)
  - Perinatal (placental, umbilical cord blood)
  - Fetal, (amniotic fluid, neuronal)
  - Embryonic
  - Induced Pluripotent Stem Cells (iPSCs)
- Functionally mature / differentiated human cells (i.e. chondrocytes, islet cells, hepatocytes, neuronal cells, various immune cells, etc.)
- Cell-based Vaccines: DC vaccines, neoantigen vaccines
- Genetically modified cells: CAR-T/NK、TCR-T、iPSC、Cell-based products derived from genome editing

- Ex vivo manipulation (i.e. expansion, genetic modification)
- Potential inflammatory / immune response to the administered CT (i.e. allogeneic)
- Inappropriate cell proliferation (i.e. tumor formation)
- Inappropriate cell differentiation (i.e. ectopic tissue formation)
- Cell migration to non-target sites / tissues
- Gene modification
  - Vector insertion/integration/transformation
  - Unintended immune responses to vector or transgene
  - Transgene effects

# Strategy for nonclinical Evaluation

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- Case by case, product by product
  - No “one-size-fits-all”
- Guidelines
  - Guideline on quality, non-clinical and clinical aspects of Cellular Therapy Products , 2017.12
  - Guideline on non-clinical aspect of medicinal products containing genetically modified cells (draft) ,2021.3
- Genetically modified cell products regulated as cellular therapy products
- Review on benefit : risk profile



# Nonclinical Testing Program

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- **Proof-of-concept (POC)**  
in vitro and in vivo
  
- **Cell fate**
  
- **Safety**
  - System toxicity
  - Tumorigenicity
  - Special considerations for genetically modified cells



# Data Supporting IND submission

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- **GLP-compliant toxicology studies**
- **Proof-of-concept studies**
- **Pharmacokinetics studies**
- **Published data in peer-reviewed journal**
- **Detailed clinical study reports from clinical trials**



# Communication With CDE

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## ➤ Pre-pre IND

- Non-binding
- early communication, discussion of specific issues

## ➤ Pre-IND

- Non-binding, formal, scientific discussion
- Preclinical data package (all completed preclinical studies), to support the use of specific product in a specific patient population



# Challenges for nonclinical Evaluation

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- Tumorigenicity assessment of cell-based products and timing
- The selection of animal species and disease/Injury model, and the predictability of the non-clinical data
- The evaluation of potential off-target editing in cell-based products derived from genome editing
- The evaluation of potential off-target toxicities of TCR modified immune cells and CAR-T cells



# Thank You