Cell and Gene Therapy Product Development Matrix – Preclinical Pharmacology/Toxicology

	Optimization (Research to Pre-IND)	Development (Pre-IND to IND)
Product Tested	• Initial description of investigational product	• Detailed description of investigational product
Initial Animal Studies References 1, 2, 3, 4	• Animal model(s) o Relevance of model, rationale for selection • Proof of Concept (POC) study plan and study conduct. Should include: o Hypothesis for biological activity/POC o Study rationale o Should use relevant animal model(s) of disease/injury • Dose determination study plan and study conduct. Should include: o Animal model o Dose ranges o Route of administration o Measures of biological activity • Toxicology study plan and study conduct. Should include: o Healthy animals o Dose ranges o Route of administration o Toxicity measures	• As for Optimization, with more detail and summary of completed studies including: o Description of POC studies, study data and interpretation o Description of dosing studies, study data and interpretation, should include: ▪ Proposed initial safe dose ▪ Dosing regimen ▪ Dose escalation scheme for clinical study, i.e., dose cohorts, timing ▪ Route of administration (ROA) o Toxicity study summary, should include: ▪ Toxicities observed in normal animals and disease model(s) ▪ Toxicity types, frequencies, and severity o Toxicity risk analysis, should include: ▪ Potential clinical toxicities, projected risks, organ(s) affected, and indicators
Cell Fate, Survival/Engraftment References 1, 2, 3	• Limited, targeted histological examination, with immunohistochemistry (IHC). Should address: o Cell engraftment/survival after administration. o Cell proliferation after administration	• Comprehensive histological examination, with IHC, should address: o Cell engraftment/survival after administration o Cell trafficking/migration after administration o Cell proliferation after administration o Cell differentiation after administration. This may include intended and unintended cell phenotypes, plasticity, transdifferentiation, fusion.

	Optimization (Research to Pre-IND)	Development (Pre-IND to IND)
Tumorigenicity References 1, 2, 3	• Tumorigenicity study plan. Should include: o Study design (*in vitro* testing) o Test conditions o Study duration	• Tumorigenicity study plan. Should include: o Study design (*in vitro* and basic *in vivo* testing) o Animal species/model o Testing with clinically relevant ROA o Study duration o Determination of source/origin of cells for any tumors detected
IND-Enabling GLP Animal Studies References 1, 2, 3, 4	• Summarize animal studies and prepare plan for IND-enabling GLP preclinical studies, to be reviewed in the Pre-IND meeting	• If Pre-IND meeting has not yet been held, list Preclinical Pharm/Tox questions for Pre-IND meeting. • If Pre-IND meeting has been held, list comments from Preclinical Pharm/Tox reviewer. o Brief explanation of how each issue has been or is being addressed. • Conduct IND-enabling GLP preclinical animal studies, include results and interpretation in IND
Gene Therapy Products References 1, 2, 3	• Description of animal model and rationale for selection. Model should be: o Vector permissive (or sensitive) o Biologically responsive to the transgene of interest • Description of study design(s). o Hybrid pharmacology-toxicology study designs are preferable, if possible ▪ Toxicology studies may be conducted in healthy animals or animal model of disease. ▪ Studies with activity endpoints conducted in animal model of disease/injury o Should include activity and toxicology endpoints ▪ Should use adequate numbers of animals/sex/dose group/time point	• As in Optimization, but with more detail
Gene Therapy Vector Class-Specific Issues References 1, 2, 3	• Preclinical study plan should address issues related to vector class, including: o Safety/activity via the intended clinical ROA o Aberrant localization to non-target cells/tissues	• As in Optimization, but with more detail

	Optimization (Research to Pre-IND)	Development (Pre-IND to IND)
	o Level and/or persistence of vector and transgene expression o Level of viral replication in non-target cells/tissues o Inappropriate immune activation o Immune response directed against the vector o Phenotype/activation state of target cell(s) o Potential for insertional mutagenesis and/or oncogenicity o Transgene-related concerns: ▪ Local expression vs. systemic secretion ▪ Level and duration of expression ▪ Acute/chronic effects ▪ Immunogenicity/neutralization directed against the transgene product ▪ Immunogenicity directed against self/endogenous proteins	
Vector Biodistribution References 1, 2, 3	N/A	• Vector biodistribution study plan o Applies to viral vectors with novel characteristics. o Should use DNA PCR readout o Should plan to complete prior to Phase I

References

Reference	Title	Description	File Name
1	Design of Preclinical Safety and Efficacy Studies: The Basics of Cell, Gene, and Oligonucleotide-Based Therapies	Slides from a teaching session on preclinical studies of cell therapy, gene therapy, and oligonucleotide products	Design of Preclinical Safety and Efficacy Studies, The Basics of Cell, Gene, and Oligonucleotide-Based Therapies – 2011.pdf
2	FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products - 2013	Regulatory considerations and requirements for preclinical studies of cell therapy and gene therapy.	FDA Guidance - Preclinical Assessment of Investigational Cellular and Gene Therapy Products – 2013.pdf
3	Pre-Pre-IND Process - Mercedes Serabian, FDA OCTGT	Purpose and description of Pre-Pre-IND meetings and information reviewed	Pre-Pre-IND Process - Mercedes Serabian, FDA OCTGT.pdf
4	FDA Guidance for Industry: ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals - 1997	Guidance document describing preclinical studies of biologic/biotech products	FDA Guidance – ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals – 1997.pdf