Cell and Gene Therapy Product Development Matrix – General

	Optimization (Research up to Pre-IND)	Development (Pre-IND to IND)
General References 1, 2	• Optimization plan should include/address: o Testable hypothesis for product mechanism of action (MOA)/biological function(s), and how MOA/function(s) affect delivery and route of administration, dosing, and other clinical considerations o Direct or indirect nature of the hypothesized biological function *Direct: primary action of the cell therapy product.* *Indirect: product elicits action from the local microenvironment.* o Potential for MOA/biological function(s) to be mediated by cell release of humoral factor(s) o Cell fate -- long-term engraftment *vs*. transient *in situ* residence o Need for scaffold or other device to maintain cells at target location *in situ*? ▪ If location-stabilizing scaffold or similar device is needed, Optimization should include testing scaffolds compatible with cells and intended use. Select scaffold by end of Optimization stage. o Route of administration (ROA), local *vs*. systemic delivery o Establish ROA by end of Optimization stage.	• As in Optimization, but with more detail. For example: o If cells are expected to release humoral factor(s), these should be identified, with further testing in place to define details of specific factors, concentrations, kinetics. o If a scaffold will be used, scaffold device testing should be completed by end of Development stage.
Target Product Profile (TPP) Reference 3	• Draft TPP addressing main TPP elements: o Indication: Disease targeted for the product o Biological activity: Hypothesized biological function(s) o Efficacy: Proposed efficacy endpoints o Safety: Potential safety risks associated with the product o Dosage Form, Dosing: Proposed dosage form and dosing o Route of Administration (ROA): Proposed route of delivery for the product. *TPP should capture key goals regarding clinical indication and target product quality characteristics. Not all TPP elements are applicable to cell therapy products, but a draft version of the intended application and key*	Revised version of TPP, incorporating information from preclinical and CMC development. *The TPP should be revised periodically in the course of preclinical and clinical development, reflecting growing understanding of the product.*

	Optimization (Research up to Pre-IND)	Development (Pre-IND to IND)
	product characteristics, as above, provide fundamental goals for product development.	
Product Development Risk Analysis References 4, 5	• Optimization plan should include a basic risk analysis and risk mitigation plan for overall product development. This should include: o Identification and assessment of risks for development delay or failure. o Brief discussion of strategies that could be deployed to mitigate major risks (e.g., Go/No-go decision points and criteria for Go/No-go decisions). • Failure Mode Effects Analysis (FMEA) is a useful risk analysis framework but is not required.	
Regulatory References 6-11	• Request for Designation o If developing a combination product (ex., cells on a scaffold is a cell/device combination product), a Request for Designation should be submitted to FDA to establish the Centers responsible for primary and secondary review. • Pre-Pre-IND meeting (optional) o Identify questions to address, prepare Pre-Pre-IND briefing document o Schedule and conduct meeting • Modify development plan based on Pre-Pre-IND comments • Pre-IND meeting o Identify questions to address, prepare Pre-IND briefing document o Schedule and conduct meeting	• Modify development plan based on Pre-IND comments • Response to FDA Pre-IND comments – Modify development plan, follow-up with individual reviewer(s) as needed • Task list for IND preparation • Draft and revise IND application, submit

References

Reference	Title	Description	File Name
1	Stages of Product Development	Slide illustrating the product development pathway, indicating development activities at different stages of development.	Stages of Product Development.pdf
2	PAS 83: Developing human cells for clinical	Overview of cell therapy product development, including practical aspects	PAS 83 - Developing human cells for clinical applications in the EU and USA – 2012.pdf

	applications in the EU and USA - 2012	and US FDA regulatory considerations.	
3	FDA Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool – 2007	Describes content, preparation, and uses of Target Product Profile.	FDA Guidance - Target Product Profile.pdf
4	FDA Guidance for Industry: ICH Q9 Quality Risk Management – 2006.	Describes considerations for risk management/mitigation in development of biologic products	FDA Guidance – ICH Q9 Quality Risk Management – 2006.pdf
5	Risk Analysis and Management	Slides outlining FMEA risk analysis in cell and gene therapy development.	Risk analysis and risk management slides.pdf
6	US Regulation of Cell and Gene Therapy Products	Slides outlining the FDA regulatory pathway and requirements for cell and gene therapy products.	US Regulation of Cell and Gene Therapy Products.pdf
7	Development Pathway for Cell and Gene Therapy Products - Interactions With FDA	Slide illustrating the product development pathway, indicating where meetings with FDA and regulatory submissions take place.	Development Pathway for Cell and Gene Therapy Products - Interactions With FDA.pdf
8	Determining applicable regulatory pathway	Slide illustrating decision pathway for determining whether a cell therapy or tissue-engineered product is regulated as a 351 or 361 product.	Determining applicable regulatory pathway.pdf
9	Regulatory Considerations for Initiating Clinical Trials	Slides outlining key regulatory considerations and questions to address to enable a successful IND application.	Regulatory Considerations for Initiating Clinical Trials.pdf
10	Questions to address for successful IND	Slide summarizing questions that should be addressed in development studies and discussed in the IND application.	Questions to address for successful IND.pdf
11	Wonnacott, *et al*., Investigational new drugs submitted to the Food and Drug Administration that are placed on clinical hold: the experience of the Office of Cellular, Tissue and Gene Therapy	Paper discussing the most common causes of clinical holds on cell and gene therapy INDs. All or nearly all are preventable by careful development work.	Wonnacott, et al., 2008 - INDs Placed on Clinical Hold.pdf