4. Regenerative Medicine

Stage	Technology Readiness Level	Definition
Ideation	TRL-1	Scientific findings are reviewed and assessed as a foundation for conceptualizing new technologies.
Proof of Principle	TRL-2	**Development of Hypotheses and Experimental Protocol Designs** - Hypothesis (es) generated, research plans and/or protocols are developed.
Proof of Concept demonstrated	TRL-3	**Target/Candidate Identification and their Characterization** Mandatory registration of Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC), with National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and CDSCO respectively Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components. -Sample collection after informed consent from the voluntary donor and begin characterization of candidate(s). -Preliminary efficacy demonstrated *in vitro* and *in vivo*. • Identify target and/or candidate. • Demonstrate *in vitro* activity of candidate(s) • Generate preliminary *in vivo* as proof-of-concept efficacy data (non-GLP).
Proof of concept established	TRL-4	**Candidate Optimization and Non-GLP *In Vivo* Demonstration of Activity and Efficacy** **Animal Models:** Initiate development of appropriate and relevant animal model(s) for the desired indications and perform non-GLP *in vivo* toxicity and efficacy **Assays:** Initiate development of appropriate and relevant assays and associated reagents for the desired indications. **Manufacturing:** Manufacture laboratory-scale (i.e. non-GMP) quantities of bulk product and proposed formulated product. • Demonstrate non-GLP *in vivo* activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration, and route).

		• Conduct initial non-GLP toxicity studies and determine pharmacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable). • Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).
Early stage validation	TRL-5	**Advanced Characterization of Candidate and Initiation of GMP Process Development** **Animal Models:** Development of animal models for efficacy and dose-ranging studies. **Assays:** Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate. **Manufacturing:** Initiate process development for small-scale manufacturing amenable to GMP. **Target Product Profile:** Draft preliminary Target Product Profile including shelf life, storage conditions, packaging and transport should be considered to ensure that anticipated use of the product is consistent with the intended use • Demonstrate acceptable absorption, distribution, metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing (wherever required). • Continue establishing correlates of protection, endpoints, and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose Application submitted to Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) constituted by CDSCO for conduct of cell therapy based clinical trials.
	TRL-6	**GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s)** **Animal Models:** Continue animal model development via toxicology, pharmacology, and immunogenicity studies. **Assays:** Qualify assays for manufacturing quality control and immunogenicity, if applicable. **Target Product Profile:** Update Target Product Profile as appropriate. • Conduct GLP non-clinical studies for toxicology, pharmacology, and immunogenicity as appropriate. **Manufacturing:** Manufacture GMP-compliant pilot lots.

		Manufacture, release and conduct stability testing of GMP-compliant bulk and formulated product in support of the IND and clinical trial(s) and submit Investigational New Drug (IND) package to DCGI and conduct Phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article. • Complete Phase 1 clinical trial(s) that establish an initial safety, pharmacokinetics and immunogenicity assessment as appropriate.
Late stage Validation	TRL-7	**Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)** Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate for Conduct Phase 2 clinical trial(s). **Animal Models:** Refine animal model development in preparation for pivotal GLP animal efficacy studies. **Assays:** Validate assays for manufacturing quality control and immunogenicity if applicable. **Manufacturing:** Scale-up and validate GMP manufacturing process. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production. **Target Product Profile:** Update Target Product Profile as appropriate. Conduct GLP animal efficacy studies as appropriate for the product at this stage. Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2)

Pre-commercialization	TRL-8	**Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials3, and DCGI Approval or Licensure** Finalize GMP manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit NDA/BLA. **Manufacturing:** Complete validation and manufacturing of consistency lots at a scale compatible with DCGI requirements. Complete stability studies in support of label expiry dating. **Target Product Profile:** Finalize Target Product Profile in preparation for FDA approval. Complete pivotal GLP animal efficacy studies or pivotal clinical trials (e.g., Phase 3), and any additional expanded clinical safety trials as appropriate for the product. Prepare and submit New Drug Application (NDA) or Biologics Licensing Application (BLA) to the DCGI. Obtain FDA approval or licensure
Commercialization and post market studies	TRL-9	**Post-Licensure and Post-Approval Activities** • Commence post-licensure/post-approval and Phase 4 studies (post-marketing commitments), such as safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate.