

TRL level	Description	DRUG OR BIOLOGICAL	THERAPEUTIC DEVICE	DIAGNOSTIC (ASSAY/TEST)
1	Review of Scientific Knowledge Base	Scientific findings are reviewed and assessed as a foundation for characterizing new technologies	Scientific findings are reviewed and assessed as a foundation for characterizing new technologies	Active monitoring of scientific knowledge base. Identify links between disease in humans and animals
2	Development of Product Hypothesis	<p>Activities: Scientific studies to identify and validate disease target. Screen potential compounds (HTS, antibody, etc) to develop preliminary hits. Develop assays to test activities of candidate compounds <i>in vitro</i>. Initial intellectual property search for patentability. Characterize disease epidemiology.</p> <p>Milestone: Identify compound series</p>	<p>Activities: Scientific "paper studies" to generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues. Characterize disease epidemiology. Use of computer simulation or other virtual platforms to test hypotheses where possible. Initial intellectual property search for patentability and to refine prototype configuration options</p>	<p>Activities: Scientific "paper studies" to generate research ideas, hypotheses, and experimental designs for addressing the related scientific issues. Characterize disease epidemiology. Initial intellectual property search for patentability.</p>
3	Identification and Characterization of Product Candidate	<p>Activities: Decision on which compounds to advance in development. Synthesize novel series of compounds; test efficacy and toxicities <i>in vitro</i>. Test PK/tox of selected compounds in relevant <i>in vivo</i> models on a non-GLP level. Survey relevant patent literature to identify white space and assess patentability of compound series. Survey clinical literature to characterize current care patterns and unmet need(s). File a provisional patent on the pharmacophore. Synthesize and assess several potential lead compounds.</p> <p>Milestones: Demonstrate <i>in vitro</i> efficacy. Preliminary efficacy demonstrated <i>in vivo</i> in appropriate small animal model. Identify lead series. File patent.</p>	<p>Activities: Explore prototypes, identify and evaluate critical technologies, critical design features needed, and components. Survey clinical literature to characterize current care patterns and unmet need(s). Initiate user feedback on prototypes.</p> <p>Milestones: Demonstrate <i>in vitro</i> efficacy. Preliminary efficacy and safety demonstrated <i>ex vivo</i> or <i>in vivo</i>. Identification of reimbursement and regulatory classification (pathway identification). File a provisional patent.</p>	<p>Activities: Explore assay components via prototypes and screening; identify and evaluate critical technologies and components, and begin characterization of lead design. Survey clinical literature to characterize current care patterns and unmet need(s). Initiate user feedback</p> <p>Milestones: Demonstrate preliminary assay with simplified sample/artificial matrices. Demonstrate sensitivity and specificity with spike/recovery studies in the appropriate matrices.</p>
4	Optimization and Initial Demonstration of Safety and Efficacy	<p>Activities: Initiate experiments to identify markers, assays, and endpoints for further non-clinical and clinical studies. Assess endpoints for relevant impact in clinical practice. Conduct <i>in vivo</i> distribution and elimination studies. Non-GLP <i>in vivo</i> toxicity and efficacy of lead compound; pharmacokinetic studies.</p> <p>Milestones: Finalize formulation appropriate for route of administration. Draft Product Profile. Determine Regulatory strategy. Characterize current reimbursement mechanisms, economic burden of illness and treatment costs. Identified preclinical candidate compound and animal models for GLP tox studies.</p>	<p>Activities: Collection of user feedback on prototypes utilized to refine design inputs and identify new ones as needed. Iteration and elimination of prototype designs based user feedback, bench testing, <i>ex vivo</i> and non-GLP <i>in vivo</i> testing. Integration of critical technologies. Initiation of animal model development for desired indication (if necessary). Initiation of experiments to identify endpoints for further non-clinical and clinical studies.</p> <p>Milestones: Initiate Design Control activities, establish Design and Development Plan, capture Design Inputs. Determine IFU, Regulatory & clinical strategy. Characterize current reimbursement mechanisms, economic burden of illness and treatment costs. Preliminary FDA meeting. Non-GLP <i>in vivo</i> efficacy demonstration in accordance with the product's intended use.</p>	<p>Activities: Integration of critical technologies and components (including hardware and software). Select appropriate candidate reference and QC (quality control) reagents.</p> <p>Milestones: Assay/ test method validation in accordance with the product's intended use (Sample type, volume, assay components). Establish Draft Product Profile. Characterize current reimbursement mechanisms, economic burden of illness and treatment costs. Formulate initial regulatory and reimbursement strategies.</p>

5	Advanced Characterization of Product and Initiation of Manufacturing	<p>Activities: Develop a scalable and reproducible manufacturing process amenable to GMP. Develop assays/analytical methods for product characterization and release (potency, purity, ID, sterility, etc). Perform IND-enabling toxicology studies. Identify KOL's that can help design a clinical trial strategy/sequence, including collection of health economic and longer-term patient outcomes measures. Identify clinical sites and begin contract negotiations. Begin stability testing on drug substance (i.e., API).</p> <p>Milestones: Identify candidate. Demonstrate acceptable ADME characteristics and/or immune responses in GLP animal studies as necessary for regulatory filing. Identify manufacturing partners. Pre-IND meeting with FDA. First draft of a target product profile/package insert.</p>	<p>Activities: Develop test methods for device characterization, performance testing, and product release if relevant. Explore potential manufacturing options as well as manufacturability and sustainability of device design, including third-party partners. Develop a scalable and reproducible manufacturing process amenable to GMP. Milestones: Demonstrate intended device design addresses. Design inputs to support regulatory filing (Design freeze). Preliminary FDA meeting (depending on device type and classification). First draft of a target product profile/product label and reimbursement strategy.</p>	<p>Activities: Design freeze. Develop a scalable and reproducible manufacturing process aligned with regulatory guidelines (as needed). Finalize QC criteria.</p> <p>Milestones: Identify supply chain and/or manufacturing partners. Demonstrate acceptable performance as necessary for regulatory filing and for impact on clinical care. Preliminary FDA meeting.</p>
6	Regulated Production, Regulatory Submission, and Clinical data	<p>Activities: Prepare and submit IND. Initiate Phase I study.</p> <p>Milestones: Manufacture GMP-compliant pilot lots. Prepare and submit regulatory package to FDA and conduct Phase 0 and/or 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article.</p>	<p>Activities: Initiate manufacturing using scalable and reproducible process. Integrate Quality. Complete testing, bench, in vitro and in vivo GLP study, if necessary, intended to verify and validate the product design (per Design Controls) to support Regulatory submission at design freeze. Initiate Shelf Life/Product Stability studies. Finalize packaging of the device and sterilization validation. Milestones: Manufacture GMP-compliant devices. Complete Design Verification and Validation testing. Prepare and submit regulatory package to FDA (510k, IDE, as needed).</p>	<p>Milestones: Manufacture product compliant with quality protocols. Based on regulatory classification (e.g. CLIA vs IVD route), submit regulatory package</p>
7	Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)	<p>Activities: Post Phase 2 meeting with FDA. Determine dosing and treatment population for Phase 3 study.</p> <p>Milestones: Scale-up and validate GMP manufacturing process at a scale compatible with USG requirements. Complete stability studies of the GMP drug product in a formulation, dosage form, and container consistent with Target Product Profile. Complete Phase 2 clinical trials.</p>	<p>Activities: Validate manufacturing processes at scale intended to support production. Implement CAPA and other Quality requirements. Support activities needed to complete clinical trials (for de novo or PMA pathway , if needed).</p> <p>Milestones: Design Transfer activities such as scale-up and validate GMP manufacturing process. Complete clinical trials (as needed for IDE or EFS). Regulatory submission of results.</p>	<p>Milestones: Assays used to assess product quality are validated. Assays used to assess critical outcomes in clinical trials and in animal efficacy studies are validated.</p>
8	Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and FDA Approval or Licensure	<p>Milestones: Finalize GMP manufacturing process. Complete clinical efficacy trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit New Drug Application or Biologics Licensing Application NDA/BLA.</p>	<p>Milestones: Complete Design Transfer into finalized GMP manufacturing process. Prepare and submit for market approval: Premarket Approval (PMA), Premarket Notification (510(k)), HUD or Humanitarian Device Exemption (HDE). Prepare postmarket clinical strategy/surveillance plan.</p>	N/A

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