TRL Levels and Milestones	TRL 1		TRL 2		TRL 3		TRL 4		TRL 5		TRL 6		TRL 7		TRL 8		TRL 9	
	Basic Research				*Preclinical Research/Proof of Concept*				*Mfg. Valid./Late Preclinical*		*Clinical Phase*				*Regulatory Clearance & Market Preperation*			
	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL	Milestones & Submilestones	DL
ATMP	1 Review of Scientific Knowledge Base		2 Development of Product Hypothesis		3 Identification and Characterization of Product Candidate		4 Optimization and Initial Demonstration of Safety and Efficacy		5 Advanced Characterization of Product and Initiation of Manufacturing		6 Regulated Production, Regulatory Submission, and Clinical Data		7 Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)		8 Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and Approval or Licensure		9 Launch & Operational Activities for Commercial Deployment	
	1.1 Medical Need & Scientific Knowledge Analysis		2.1 Hypothesis / Product Idea		3.1 Initial Proof of Concept (preliminary data) in vitro/in silico/in vivo preclinical models		4.1 Non-GMP Manufacturing Optimisation		5.1 Transfer to GMP		6.1 GMP Manufacturing Authorization		7.1 Scale-up manufacturing		8.1 Manufacturing		9.1 Post-approval Activities – Marketing, Phase 4 Trials	
	1.1.1 Analysis conducted to identify therapeutic and societal needs		2.1.1 Disease epidemiology characterized		3.1.1 Primary and secondary outcome measurements (safety and efficacy) defined		4.1.1 Material/equipment/antibodies etc. for GMP process identified		5.1.1 Process transfer: process (as is) test runs: - materials/machines/equipment adapted to GMP needs.		6.1.1 Quality management extension: - quality management handbook (description of the "company")		7.1.1 Manufacturing process optimized: - feasibility of scale-up/ improvements etc.		8.1.1 Extended product stability validated			
	1.1.2 Explanation for the scientific application of the defined problem(s).		2.1.3 Experimental Designs developed		3.1.2 In vivo Tox analysis/biodistribution		4.2 Optimization and Proof of Concept in Validated Preclinical Models		5.1.2 Quality management ("foundation stone") initated: - risk analysis, SOPs, specifications, IPC strategy etc.		6.1.2 Responsibility delimitation contracts (RDC); (Verantwortungsabgrenzungs-verträge (VAV) with external/ internal partners/ contractors)		7.1.2 Process transfered to industrial partners		8.1.2 International shipping validated			
	1.1.3 Patient and specialist organizations (patient interest groups/ organizations) interviewed		2.1.4 Research plan has been developed		3.2 Development Candidate/Strategy (Target Identification) selected		4.3 Safety Profile, Hints of Mode-of-Action		5.1.3 Qualification of machines/ equipment: - planning, realization & report (e.g. centrifuge, laminar flow, FACS machine etc.)		6.1.3 Contractors audited: - planning, realization & report (e.g. analysis laboratories for HLA-typing etc.)		7.1.3 GMP implementation: - notice of change and validation (if necessary) (if improvement, new manufacturing authorization might be necessary)		8.2 Pivotal Phase 3 Trial			
			2.1 Opportunity Check		3.2.1 Realisability of different candidates/strategies (advantages/disadvantages) analyzed		4.3.1 Regulatory strategy developed		5.1.4 Validation of methods: - planning, realization & report (e.g. cell counting, flow cytometry etc.)		6.1.4 Procurement authorization (if not covered by RDC)		7.1.4 Quality management extension: - revision of ALL existing documents (latest every 3 years or for specific documents after each change)		8.2.1 Clinical trial application submitted to European Medicine Agency for Scientific Advice			
			2.1.1 Feasibility of technology, patient access, preclinical models, etc.checked		3.2.2 Candidate/strategy selected		4.3.2 Preliminary risk/-benefit analysis based on: - adverse events and efficacy outcomes in animals - product and material tests		5.2 External Activities		6.1.5 Manufacturing documents submitted		7.2 Documents submitted and Approval Updated IND Application (See TRL 6; possibility to skip a few steps)		8.2.2 Clinical trial application submitted to member state authorities			
			2.1.2 Product-related Risk Assessment and mitigation plan conducted						5.2.1 Contractors identified, offers obtained and compared		6.1.6 Acceptance inspection of Regulatory Authorities (LAGeSo & PEI) conducted		7.3 Clinical Phase 2 Trial/Preliminary Efficacy and Confirmed Safety (See TRL 6; possibility to skip a few steps)		8.3 Approval phase			
			2.1.3 Initial intellectual property search for patentability						5.2.2 Validation of external/outsourced (analytical) methods: - planning, realization & report (e.g. sterility, serology etc.)		6.1.7 Authorization Approval				8.3.1 National: Clinical trial dossier submitted to Paul Ehrlich Institut (PEI)			
			2.2. Product Definition						5.2.3 Pre-scientific Advice / Scientific Advice		6.2 Biomarker Portfolio				8.3.2 National: non-routinely manufactured Advanced Therapy Medicinal Products (ATMP) according to 4b (3) Arzneimittelgesetz (AMG)			
			2.2.1. Report planed Product						5.2.4 Quality management extension		6.2.1 Disease and product specific biomarkers identified				8.3.3 National: preparations in accordance with §21a (1) Arzneimittelgesetz (AMG)			
			2.2.2. Advice Patients organisations/representatives						5.3 GMP-pilot		6.2.2 Biomarker validated: - planning, realization & report				8.3.4 European: Clinical trial dossier submitted to European Medicine Agency			
									5.3.1 Aseptic processing (Mediafill) validated: - planning, realization & report		6.2.3 Cross check conducted (if biomarker enable new/extended ATMP): - specification(s)/ release criteria				8.3.5 European: Assessment report from Committee for Advanced Therapies			
									5.3.2 Clean room test runs and subsequent test with patient material conducted		6.3 Clinical trial application submitted and Approved (Ethical & Authority)				8.3.6 European: Adoption by Committee for Medicinal Products for Human Use and approval by European Commission			
									5.3.3 Transport validated: - planning, realization & report (NB sometimes 2-ways!)		6.3.1 Scientific Advice							
									5.3.4 Manufacturing process validated: - planning, realization & report		6.3.2 Sponsoring							
									5.3.5 Quality management extension		6.3.3 Quality management extension: - Pharmacovigilance system							
									5.4 Advanced Characterization		6.3.4 Investigational Medicinal Product Dossier							

									5.4.1 Stability tested: - “expiration date” of the ATMP		6.3.5 Investigators brochure							
									5.4.2 Genetic stability: - Karyotype analyzed		6.3.6 Clinical Trial Protocol							
									5.4.3 Cryo-preservability tested		6.3.7 Institutional Review Board							
											6.3.8 EU Clinical Trial Register (EudraCT)							
											6.3.9 Finalization of Clinical Trial Application (CTA) package Ethics							
											6.3.10 Finalization of CTA package PEI							
											6.3.11 Transport approval Phase III							
											6.3.12 Approval							
											6.4 Phase I/II Trial							
											6.4.1 Electronic Case Report Form (eCRF)							
											6.4.2 Registry for clinical data on ATMPs and PV							
											6.4.3 Study initiated							
											6.4.4 1st patient in							
											6.4.5 Monitoring reports (mostly outside-by externals)							
											6.4.6 Clinical data							
											6.4.7 Re-validation of critical steps (if necessary)							
MedTech	1 Review of Scientific Knowledge Base		2 Development of Product Hypothesis		3 Identification and Characterization of Product Candidate		4 Optimization and Initial Demonstration of Safety and Efficacy		5 Advanced Characterization of Product and Initiation of Manufacturing		6 Regulated Production, Regulatory Submission, and Clinical data		7 Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)		8 Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and Approval or Licensure		9 Launch & Operational Activities for Commercial Deployment	
	1.1 Medical Need & Scientific Knowledge Analysis		2.1 Hypothesis / Project Idea		3.1 Initial Proof of Concept (preliminary data) in vitro/in silico/in vivo preclinical models		4.1 Non-GMP Manufacturing Optimisation		5.1 Transfer to GMP		6.1 GMP Manufacturing Authorization		7.1 Scale-up manufacturing		8.1 Pivotal Phase 3 Trial		9.1 Post-approval Activities – Marketing, Phase 4 Trials	
	1.1 .1 Initial analysis/survey on the benefits of current technologies. Existing academic concepts vs. Existing medical products?		2.1 .1 Literature research and protocol planning have been reviewed and approved		3.1 .1 In vitro/in silico/in vivo tox on chosen materials.		4.1 .1 Prototype (pre-clinical): Laboratory-scale experiment and testing to evaluate and review the level of safety, side effects, and efficacy (identificatopn of complications)		5.1 .1 Product-layout defined and fixed. GMP-conform production verified (possibility verified or already established?).		6.1 .1 Industrial-scale limited validation testing of the prototype on its efficacy and side effects, and its disruption to/by other devices. (for medical device classes 1-2);		7.1 .1 Scale-up to mini-series for clinical evaluation or respectively first clinical data (on humans)		8.1 .1 Phase 3 clinical trial			
	1.1 .2 Basic concept review (robustness, relevance) of scientific theories underlying the related medical device technology.		2.1 .2 Through literature review and scientific discussions, a research and study plan is prepared to identify the potential and opportunity for therapeutic targets. Documented in the form of protocol or research plan to be reviewed and approved.		3.1 .2 Design verification, component specification determination and various alternatives evaluated		4.2 Optimization and Proof of Concept in Preclinical (Animal) Models		5.2 External Activities		6.1 .2 Industrial-scale limited phase 1 clinical testing of the prototype to find out its safety level and efficacy (for medical device class 3)		7.2 Clinical Phase 2 Trial/Preliminary Efficacy and Confirmed Safety					
	1.1 .3 Formulation of basic concept and theoretical substantiation		2.2 Opportunity Check		3.1 .3 Identify materials and existing material combinations, fabrication methods and expected hurdles for translation of the chosen approach for medical device approval		4.2.1 Preparation and standardization of procedures and methods to be applied in non- clinical and clinical studies;		5.2.1 Lab-scale approval of prototype’s safety level and efficacy.		6.1 .3 Industrial-scale limited substantiation of the prototype’s safety level and efficacy		7.2.1 Phase 2 clinical trial – larger test group of target users/patients					
	1.1 .4 Scientific literature review in relation to the technology’s basic principles and potential applications.		2.2.1 Initial intellectual property search for patentability		3.1 .4 Verification of suitability of chosen fabrication method. (Is scale-up possible?)		4.3 Safety Profile, Hints of Mode-of-Action		5.2.2 Documentation requirements fufilled		6.2 Submission of clinical trial application and approval (Ethical & Authority)							
	1.1. 5 Summary: Description (quatitative & qualitative) of medical need		2.2.2 IP Analyse		3.1 .5 Documentation of results of laboratory-scale experiments providing initial proof of concept of the capabilities of a medical device’s technology		4.3.1 Proof of concept of the technology, risk analysis to determine correspondent safety level in small product series. (patent application?)		5.2.3 Proposal on advisory board & external funding		6.2.1 Submit and acquire Medical Device Regulation (MDR) authorization (local: LAGeSo, relevant German/European/International agencies)							
					3.1 .6 Decision of Classification of Medical Device/Technology (acoording to EU-rules) - (NB: This decides the following milestones/phases)		4.3.2 Publication (peer-reviewed) of data about proof of concept of the technology and safety level.		5.3 GMP-pilot		6.2.2 Pathway for combinatory products (see then ATMP path)							

					3.1 .7 IP-strategy		4.3.3 Optimization of product design and user comfort based on feedback from laboratory experiments		5.3.1 Final definition of the designation of classification (class 1, 2, or 3) of the medical device based on (a) its equivalence with existing medical devices and (b) eventual first clinical data (definition of regulatory pathway, definition of product risk level and component testing required)									
							4.3.4 Safety Profile and eventually intended "Mode-of-Action" of the MedTech device		5.3.2 Lab-scale or preclinical testing of prototype's safety level against the applicable standard (for example: iec60601); 5.3.3 Lab-scale validation testing on prototype's efficacy and side effects, and its disruption to/ by other devices. (for medical device classes 1-2)									
Repurposed Use	1 Review of Scientific Knowledge Base		2 Development of Product Hypothesis		3 Identification and Characterization of Product Candidate		4 Optimization and Initial Demonstration of Safety and Efficacy		5 Advanced Characterization of Product and Initiation of Manufacturing		6 Regulated Production, Regulatory Submission, and Clinical data		7 Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)		8 Completion of GMP Validation and Consistency Lot Manufacturing, Clinical Trials Ph3, and Approval or Licensure		9 Launch & Operational Activities for Commercial Deployment	
	1.1 Freedom to operate confirmation		2.1 Novelty confirmation (from an IP standpoint)		3.1 Creation of a Target Product Profile										8.1 Pivotal Phase 3 Trial		9.1 Post-approval Activities – Marketing, Phase 4 Trials	
	1.2 Gap analysis for safety aspects for the proposed indication and administration route		2.2 Submitted IP		3.2 Pre-clinical data support (cell culture / animal research) - for animal research also the animal ethics application can be a milestone													
			2.2.1 Positive First Search Report on the submitted IP		3.3. Testing of Material (feasibility & durability)													
					3.4. Testing Devices (Bio-compatibility)													