PURE BIOTECH MILESTONES FRAMEWORK

Innovation Maturity Level	Name	Overall Description	Innovation Maturity Level Milestones			
			Clinical Validation	**Market/Business**	**Technology**	**Regulatory**
1	**Need**	**Insights into unmet medical needs and available solutions**	❑ Unmet needs defined ❑ Disease state characterized ❑ Biological Mechanism of action identified ❑ Cellular disease pathway identified and described	❑ Deficiency in existing solutions identified ❑ Competitive landscape identified (academic, in pre-clinical/clinical development/commercial) ❑ Market Assessment/ Initial description of target population and its biological characteristics	❑ Molecular target/s identified ❑ Approaches for pharmacological targeting searched and identified ❑ Proposed technological modality explored (small molecule, antisense oligo, antibody, gene therapy, cell therapy, repurposed/repositioned product, etc) ❑ Initial patent landscape reviewed and patentability assessment done ❑ Initial institutional "Idea" (IP) disclosed to employer	❑ Clinical trials in the indication identified for reference trial design and timelines (ie. clinicaltrials.gov landscape)
2	**Idea**	**Potential solution to unmet need described, evaluated and selected**	❑ Biological pathway studied and intervention/perturbation approaches developed ❑ Biotechnological platform characterized and potential use cases developed ❑ Proposed patient population (SOP) defined including genetic or other bio markers (biochemical, cellular, imaging/digital/electrophysiological) if possible	❑ Envisioned Value Proposition ❑ Target Product Profile – (TPP) first iteration ready ❑ Identified complementary IP ❑ Initial dialogue with potential stakeholders (Pharma, VC, Corporate VC, Incubators) with positive feedback ❑ Investor ready business plan (milestone-based development plan R&D)	❑ Technological modality selected ❑ Mechanism of action of target group elucidated in vitro ❑ Compound starting point, screening and selection scheme planning done ❑ Compound selection assay development initiated ❑ Biological hypothesis and pharmacological hypothesis formulation identified ❑ For repurposed molecules not in the market (ie, shelved big pharma products) explore availability of clinical dossier from originator ❑ In licensing discussions with owners of IP have started (host institute, exclude originators of repurposed products until method of use patent is filed) ❑ Statement of employer issued ❑ Prior art has been assessed (Freedom to Operate analysis) and patentability of the innovation is confirmed by a patent attorney ❑ Translational models (patient sample based or in-vivo) identified	❑ Regulatory Familiarization started ❑ For rare disease, paediatric or cell & gene therapy: Consulted the regulatory roadmap pathways if applicable and familiarized with alternative pathways
3	**Proof of Concept (PoC)**	**Key component concepts validated in models and value proposition tested**	❑ Mechanistic and therapeutic hypothesis validated in genetic/metabolic models and/or patient derived cells – go/no-go decision ❑ For repurposed products: Proof of concept in relevant in vivo model obtained with repurposed candidate with favourable HED (prospective dose in humans below doses already tested or within safety margins)	❑ Business model defined - Value inflection points identified and preliminary value creation plan defined ❑ **Seed investment secured** ❑ Stakeholder map defined ❑ Scientific Advisory Board recruited ❑ Communication & public dissemination plan established (ie: thesis, papers & communications in relevant scientific forums) ❑ Killer experiment identified	❑ Initial hits/compound candidates synthesized and evaluated ❑ Initial pharmacology analysis – efficacy, safety, PK and bioavailability in rodent/relevant animal model (if applicable) ❑ **IP strategy defined and first IP filing initiated** ❑ For non-generic repurposed products: started negotiations with originators to access IP & clinical development - enabling data (updated IPMD, only if robust IP is filed) ❑ For biological or gene-therapy products: manufacturing roadmap and costing estimates defined ❑ If platform – initial creation and testing of platform modules and building blocks	❑ Preliminary regulatory pathway defined ❑ For advanced therapies or paediatric diseases: scientific advice / pre-IND meeting or equivalent feedback required
4	**Proof of Feasibility (PoF)**	**Feasibility of whole solution demonstrated in models and in feedback from stakeholders**	❑ **Hit/lead compounds efficacy and potency in animal model or patient derived model validated**	❑ Deal and market benchmark cases identified ❑ Collection of economic data compared to SoC initiated (e.g. validating beach-head market)	❑ Feasibility proven in essential experiment – safety, bioavailability, PK-PD. **For gene therapy product: biodistribution data in big animal (monkey, pig) provided** ❑ **Composition of matter IP filed** - IP search report is promising	❑ Drafted essential requirements checklist ❑ Retrospective study performed if data available

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			❑ For biologicals or gene-therapy products: efficacy data in animal model obtained with regulatory compliant final candidate. ❑ Updated need description with confirmation of target patient population ❑ Proposed treatment scheme developed (preventive/therapeutic acute/chronic etc.) ❑ Clinical KOLs consulted in adhoc preparatory meetings, positive engagement and commitment to participate in clinical trials ❑ Draft clinical development plan completed (Incl. target population and line of care and target regimen) ❑ CRO screening initiated ❑ Potential biomarkers identified	❑ Pricing estimates validated through third party independent primary research ❑ Target Product Profile – (TPP) refined	❑ In-licensing or round-A discussions are in progress to mutual satisfaction ❑ Manufacturing expertise initial conversations	❑ Submission pathway defined and validated by a regulatory body (scientific advice in EMA or official pre-IND meeting for FDA) ❑ Biomarker validation study approved, if needed
5	**Proof of Value (PoV)**	**The potential of the solution to work and create value for all stakeholders is demonstrated**	❑ **Clinical lead candidate validated in clinically relevant animal model** ❑ Clinical advisory board recruited ❑ **Clinical protocol completed** ❑ Clinical CRO selected ❑ Clinical endpoints defined and validated vs. competition – clinical target efficacy value defined	❑ Peer reviewed publication(s) accepted - preclinical (consider strategic perspective) ❑ Collection of economic data compared to SoC completed ❑ Series A/B financing completed ❑ Advanced stakeholder partnering discussions ongoing ❑	❑ Minimum viable product (MVP) ready – clinical lead optimized ❑ CMC development started in parallel to IND-enabling safety tox preclinical package. ❑ Pharmaceutical development started ❑ **Full IP application – freedom to operate positive opinion.** ❑ In-licensing of essential IP is completed (For Repurposed products: including third party IND-enabling clinical data)	❑ Application form to competent authority submitted ❑ Submission data package defined (essential Requirements checklist) ❑ IND/CTA meeting scheduled/performed ❑ **IND/CTA approved** ❑ Clinical Investigation approval(s) achieved (Ethical committees/IRBs)
6	**Initial Clinical Trials (ICT)**	**Regulated production of prototypes and collection of clinical and economic data**	❑ **Endpoints Successfully achieved in clinical safety/efficacy trials (Phase 1/2 clinical trials)**	❑ Pharmacoeconomics analysis performed ❑ Advanced discussions for next steps with investors and stakeholders (pharma) ❑	❑ Pre-clinical development of additional portfolio products ❑ Long term safety studies if appliable ❑ Potential formulation updates for lead product explored	❑ Additional data submitted ❑ Scientific advise / FDA consultation to validate phase II design
7	**Validation of Solution (VoS)**	**The solution is shown to be effective and its value to all stakeholders is validated**	❑ **Endpoints Successfully achieved in clinical efficacy trials (Phase 2a/2b)** ❑ Preparation of Phase 3 clinical studies ❑ Peer reviewed publication(s) accepted -clinical ❑ Additional indications explored ❑ Biomarker /companion diagnostic validated (if applicable)	❑ **Collaboration in place with Pharma / multiple pharma's** ❑ Gearing up partnerships and development of new pipeline products ❑ Financing efforts in place for next round (private or public)	❑ Pharmaceutical development (final commercial formulation) completed ❑ Carcinogenicity studies if applicable. ❑ For biological products: full specs validated with regulatory bodies ❑ For immunological products: potency test validated with regulatory bodies ❑ Manufacturing of clinical batch for later phase clinical studies ❑ **Development of new products on the pipeline – IP submitted**	❑ Additional data submitted ❑ Proactive scientific advise / FDA consultation to validate phase III strategy
8	**Approval & Launch (A&L)**	**Institutional and regulatory approval received and sales launch**	❑ Specialty medical groups review in place ❑ KOL's and clinical leads recruited and supportive ❑ **Endpoints Successfully achieved in Phase 3 clinical studies** ❑ Post marketing trial initiated	❑ **Initial sales achieved** ❑ Expanding sales activities	❑ Three manufacturing batches validated ❑ Alternative manufacturers identified ❑ Manufacturing capability expansion planned	❑ **Registration approval and listing** ❑ CMS/Public Coverage and CPT/DRG code determination obtained
9	**Clinical Use (Use)**	**The solution is used successfully in day-to-day clinical practice**	❑ Included in practice guidelines ❑ Additional data published in peer reviewed journals	❑ Profitable sales achieved ramp-up ❑ New markets launched	❑ Key patents issued. ❑ Competition monitored ❑ Alternative manufacturing sites validated (it may take over 2 years)	❑ Monitoring/ inspections
10	**Standard of Care (SoC)**	**The solution is recognised as the standard of care**	❑ Recommended practice by medical specialty	❑ Dominant market share status ❑ Operating margin profile achieved	❑ Patents issued - Patent Lifecycle Management	❑ Health economic studies carried

Patient Population (SOP)- Standard operating procedures

KOL- Key Opinion Leader

HED- Human Equivalent Dose

PK/PD Modeling- pharmacokinetic/pharmacodynamic modeling

CRO- Contract research organization

CMC- Chemistry, manufacturing, and control

PCT- Patent Cooperation Treaty

IRB- Institutional Review Board

CTA- Clinical Trial Application

IND- Investigational New Drug

CMS- Centers for Medicare & Medicaid Services

CPT- Current Procedural Terminology

DRG- Diagnosis-related group