

EPPIC Net Dossier Questionnaire for HEAL Program Applicant

Summary: Import brief summary/rationale from preliminary application

1. Clinical trial overview and scientific rationale in concert with HEAL initiative goals

- a. Name of disease/condition/population to be studied, including comparison groups/populations
- b. Clinical unmet pain need in the disease that the clinical trial will address
- c. Disease/condition/population specifics
 1. Incidence/prevalence, including that for rare diseases
 2. Morbidity, mortality, disability (QALYS, DALYS data, if available) and its associated pain.
 3. Currently available treatment/s for the disease and its associated pain. State explicitly if there are currently no effective pain treatment
 4. Epidemiological background, including known genetic and/or mechanistic pathways
 5. Diagnostic criteria and how the disease/pain phenotype will be reliably clinically characterized for the study
 6. Place the asset in the setting of currently available treatments/competitive landscape
- d. Recruitment plan and logistics

2. Asset biology, pharmacology, and physiology

- a. Name of asset
- b. If development has been stopped, explain why. State explicitly if development was stopped for safety.
- c. For drugs and devices: Proposed target of asset activity
 1. Target expression and distribution (e.g. molecular, tissue or organ target)
 2. Asset mode of action.
 3. Asset potency and selectivity for target
 4. Summarize data on the MOA in humans including target engagement assessment or assays and/or direct binding to target.
- d. For drugs: Pharmacokinetic/pharmacodynamic information
 1. half-life
 2. duration of effect
 3. elimination pathway
- e. For devices;
 1. Mode of use (including whether observational or interventional, implanted or external, transient or permanent)
 2. onset of effect
 3. duration of exposure
 4. duration of effect

3. Target product profile (TPP)

- a. Describe the asset in relation to the disease being studied
- b. State how, based on the presumed mode of action, the asset is anticipated to result in pain amelioration and impact the unmet need identified above. Cite data supporting modification of pain/disease by target modulation in a relevant *in vivo* model.
- c. Exemplar Target Product Profile table

Patient Population	
Indication	
MOA	
Efficacy	
Safety	
Dosing/ Administration	

4. Preclinical Data

- a. Product optimization information (*including that from non-GLP, pilot, and/or proof-of-concept studies*)
 - i. What was the therapeutic target evaluation and selection process?
 - ii. How was the proposed therapeutic/device optimized and selected?
 - iii. Summary of key relevant preclinical testing for drug/device efficacy and safety, including GMP and GLP animal studies, as applicable
 1. Summary of relevant preclinical efficacy testing
 2. Summary of safety preclinical testing (e.g. biocompatibility, tolerability, pharmacologic and physiologic): Identify any safety concerns (e.g. cardiovascular, CNS, or behavioral effects)
 3. Include information on whether efficacy and safety preclinical studies have been replicated
 4. For drugs: Therapeutic index and toxokinetic data
 - a. Ames test for bacterial mutagenicity, in vitro micronucleus assay for mammalian clastogenicity and/or aneugenicity
 - b. Broad ligand profiling using a standardized CEREP panel or the equivalent
 - c. The most sensitive preclinical toxicology species for preclinical development
 - d. Potential drug interactions, including CYP analyses

5. Clinical data and trial plan

- a. Study hypotheses/aims, including efficacy and safety aims
- b. Trial design and phase
 - i. Overall design, methodology.
 1. For drugs: drug dose, route of administration, timing, and duration of exposure.
 2. For devices: Device use methodology, timing and duration of exposure for an interventional device. Device use parameters/settings.
 - ii. Rationale for selected design ("is the MAD design adequate to support the proposed phase II design.")
 - iii. Efficacy outcome measures (direct and/or surrogate)
 - iv. Safety outcome measures (direct and/or surrogate)
 - v. Preliminary power analysis and proposed sample size to support feasibility
- c. For drugs: Prior IND GLP studies and Human Experience
 - i. PK parameters (C_{max}, T_{max}, AUC, t_{1/2}) in humans and relevance to the indication.
 - ii. Major metabolites, especially active metabolites relevant to the indication and their C_{max}, T_{max}, AUC, t_{1/2} in humans.
 - iii. Summary of any proof-of-concept studies completed
 - iv. Summary of any other known clinical trials with supporting information for the proposed early phase study (especially in similar populations or for similar indications. Include NCT #, populations, number of subjects and similarity/differences to planned clinical trial
 - v. Efficacy
 1. Relevant efficacy data
 2. State how therapeutic effectiveness has been assessed
 - vi. Safety
 1. Known adverse effects/safety concerns, both on- and off-target
 2. MTD if previously determined
 3. Tolerability signals important for this indication, frequency and severity; state if in vivo tolerance has been assessed and whether there has been limiting toxicity and if a Safety Risk Management plan is needed. If so, state the plan.
 4. Any known or potential drug-drug interactions, drug-device interactions, or drug-human factors interactions.
 5. Addiction potential
- d. For Devices: Prior IDE and human experience
 - i. Summary of any proof-of-concept studies completed
 - ii. Summary of any other known clinical trials with supporting information for the proposed early phase study (especially in similar populations or for similar indications. Include NCT #, populations, number of subjects and similarity/differences to planned clinical trial

- iii. Efficacy
 - 1. Relevant efficacy data
 - 2. State how therapeutic effectiveness has been assessed
- iv. Safety
 - 1. Known adverse effects/safety concerns, both on- and off-target
 - 2. Dosing/exposure, if previously determined in humans
 - 3. Tolerability signals important for this indication, frequency and severity; state if *in vivo* tolerance has been assessed and whether there has been limiting toxicity and if a Safety Risk Management plan is needed. If so, state the plan.
 - 4. Any known or potential device-device interactions, drug-device interactions, or device-human factors interactions.
 - 5. Addiction potential
- e. Biomarkers (if applicable)
 - i. Biomarkers that will be used in the study
 - ii. What the biomarker is a safety/efficacy surrogate for
 - iii. Data on the validation of the biomarker

6. Asset preparation for clinical trial

- a. For drugs:
 - Scale-up, manufacture, and resources
 - Structure of proposed therapeutic and the analytical methods
 - Measures of purity and release criteria
 - 1. Stability storage, shipping, handling, and usage information.
 - 2. Manufacture and scale-up history – including how many lots have been produced and in what quantity. State the largest production to date.
 - 3. Estimated asset cost, including drug cost, shipping, storage, and use.
 - 4. Availability of comparator drug/matching placebo, if applicable
- b. For devices:
 - i. Device schematic
 - ii. Measures of manufacturing, controls, safety standards
 - iii. Shipping, storage, maintenance and use information
 - iv. Estimated cost of device, shipping, setup, use and maintenance
 - v. Availability of sham device, if applicable
- c. For drugs and devices:
 - i. Provide information on sterilization and Packaging Validations; relevant standards and safety testing (ISO, IEC, IEEE, etc.)
 - ii. Site of manufacture/labeling
 - iii. Regulatory history
 - 1. Any pre-existing IND/IDE for the asset and the indication. Identify stage of IND/IDE application, if any.
 - 2. Any pre-existing IND/IDE for the asset and other indications.
 - 3. Any additional preclinical or biomarker validation studies that will be required by the FDA to support the proposed clinical trial
 - 4. For devices: Identify if there is an existing NSR designation available for the proposed indication.
 - iv. Competitive analysis
 - 1. Identify other therapies in use or development for same indication
 - 2. Identify other therapies in use or development with the same mechanism of action
 - 3. Identify the advantages of your asset over, or differentiation from, the competition (regardless of whether novel or not)

7. Additional considerations

- a. State if this trial can or will be conducted without HEAL funding
- b. Provide the further development plan if the project is successful
- c. State if there are commercialization considerations
- d. Identify any conflicts of interest
- e. Non-scientific reason for why the asset was de-prioritized or abandoned