

EU Lead Factory – Guidance for applicants

Introduction

The aim of the EU Lead Factory is to deliver drug candidates to benefit patients. To help achieve this we need to establish a risk-balanced portfolio of programmes. The EU Lead Factory will assess all applications in a rigorous peer-review and selection process. Submitted proposals will be checked for eligibility for IMI funding, (technical) compatibility with the available screening infrastructure and potential ethical issues. In the next step, a review committee consisting of drug discovery experts from within and outside the consortium will evaluate the proposals for scientific quality, defined by several aspects further described below. In parallel, experts from the consortium will assess the quality, technical aspects and costs of the proposed assays and screening cascade. Final selection will be based on patient benefit, scientific impact, risk diversity and economic potential of the total EU Lead Factory portfolio. All proposals will be kept confidential throughout the submission, review and selection process. The EU Lead Factory aims to send applicants feedback on their proposal within 3 months after submission.

Review criteria

The review committee of the EU Lead Factory will evaluate the proposals for scientific quality by assessing the following aspects:

- Target/phenotype validation
- Chemical and screening tractability
- Level of innovation
- Differentiation
- Clinical and market exploitation potential

Below you will find a more detailed description of these topics, and the related questions reviewers may consider while reading your proposal. You can use these as guidance to include all relevant information on these topics in your proposal. Please add literature references with PubMed hyperlinks and details of unpublished results to support statements made.

Target/phenotype validation

Validation of the target or phenotypic response and screening approach in the disease area of interest. The applicant can refer to a disease hypothesis in the literature or propose a novel disease hypothesis. Note that for infectious diseases not all questions may be applicable. Some additional questions have been listed for those.

Questions to consider:

- Does the target have a particular cell and tissue expression pattern that links it to a function that might be amenable to the intended therapeutic pharmacological intervention? If so, have those data been generated in human and/or rodent and how robust are those data?
- Has human genetic association of the target been demonstrated? Has this been done by a single group or by multiple independent groups?
- Are there any gain of function mutations or loss of function mutations that are necessary and sufficient to initiate and/or progress a disease?
- Which target/mechanism related side effects can be expected with what level of evidence?

- Do mouse transgenic/KO or other model organisms have the disease-like phenotype and does pharmacological intervention at the target demonstrate preclinical efficacy?
- Has efficacy of compounds/tool reagents been demonstrated in preclinical in vivo models that are relevant to the disease phenotype or target mechanism? Are those tools selective and does the PK/PD (pharmacokinetic/pharmacodynamic) relationship behave as expected? Has the predictive value of these models to man been proven?
- Are the target characteristics and relevant biochemical/physiological/neurophysiological pathway(s) conserved between the model organism and humans?
- Is this an existing validated target for a different therapeutic indication where marketed products have been shown to be safe and effective?

Additional questions for infectious diseases proposals:

- Is the relationship between the target and viability of the pathogen known?
- Is the relationship between viability of the pathogen and disease state of the patients known?
- Is there any evidence that targeting the pathogen is sufficient to reduce or stop (the symptoms of) the infection?
- Is there a close human homologue to the pathogen target?
- What is the intended spectrum of pathogens to be addressed?
- What is the intended patient population that can be addressed with this spectrum?

Chemical and screening tractability

Likelihood of finding useful hits in the compound library based on previous experiences, existing chemical matter and competition in the field.

Questions to consider:

- Why do you believe HTS is a useful paradigm for your programme?
- Has the proposed assay format proven to be successful in HTS before? And if so, what chemistry was identified?
- Is there any other screening modality(ies) that could be considered in addition to the one proposed?
- Are there any existing hits with proven activity for the target of interest or for the target class?
- Was the ligand efficiency good and were there any major alerts in the standard profiling panel?
- What is the external medchem knowledge around the target class?
- Have small compounds from competitors appeared in patent applications for the target of interest? When? What was the proposed indication?
- Are endogenous & exogenous ligands for the target known which could be used as programme starting points or tool compounds? Are they drug-like?
- Is structural information about the target available to the applicant, enabling fragment-based design techniques or rational design of ligands? Does it show the presence of possible binding pockets for small molecules (orthosteric or allosteric)?
- Does the target belong to a proven druggable family or has it a history of being 'un-druggable'?

- What is the rationale to achieve selectivity for the target family?
- How will the flow-chart of experiments to optimize molecules look like?
- Is there a hit-to-lead strategy available?
- Are there any predictable feasibility issues?

Level of innovation

Novelty of target and/or mode of target engagement (depending which of both has the strongest case).

Questions to consider for a novel target with first-in-class potential:

- Is the data validating the drug target potential published?
- Is there any unpublished knowledge or unique expertise regarding the target that the applicant will bring?
- Are there any tool compounds available?
- What are the nearest on-target or on-pathway competitors and at which stage in the discovery or development process are these?

Questions to consider for a novel mode of engagement for a known target:

- Is the data validating the new mode of target engagement published?
- Is there any unpublished knowledge or unique expertise regarding the target or mode of engagement that the applicant will bring?
- Are there marketed products or tool compounds available?
- Are there any clinical candidates for the target? In which indication? How many? What is their development state?
- Is the applicant's science on the target or pathway competitive with external science?
- How old is the key target/pathway information?
- Does the applicant have freedom to operate in this area?
- How old are the earliest indications of the drug target potential? Are these published?

Differentiation

Difference compared to existing treatments (e.g. unmet medical need, potential economic or societal impact).

Questions to consider:

- Is this a first in class therapy (no therapy exists for the disease)?
- What is the current standard of care for the proposed indication(s)?
- What is the competitive advantage/patient benefit of this proposal relative to existing treatments and alternative approaches in the pre-clinical pipeline?
- Are predictive preclinical models available to guide clinical differentiation of the therapy?



- Can the therapy be differentiated in terms of either better efficacy (either on the primary indication or by treating additional secondary indications), or fewer non-responders, or a better dosing regimen (e.g. oral vs parenteral) that can be confirmed in a clinical study?
- Can the target be linked to a stratification approach (e.g. biomarker driven) in clinical trials?

Clinical and market exploitation potential

Likelihood that this idea will reach patients.

Questions to consider:

- Is the proposal aiming for a therapy or a diagnostic that can be marketed, or is the proposal aiming for a tool compound to validate the target?
- What is the intended disease area?
- How well is the drug development pathway in this disease area understood?
- What is the intended patient population?
- Does the intended treatment improve efficacy, safety, tolerability or patient comfort?
- Is there a biomarker approach that can help defining the right patient population, to prove target engagement or to monitor progression of the disease?
- Is there a target engagement marker available to be used in phase I trials?
- What is your strategy for attracting investors or pharma companies to your programme?