Innovative Medicines Initiative

5th Call for proposals 2012

Innovative Medicines Initiative

Version 1.1

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GENERAL PRINCIPLES

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership aiming to foster collaboration between all relevant stakeholders including large and small biopharmaceutical and healthcare companies, regulators, academia, and patients.

The aim of IMI is to support pre-competitive[1] pharmaceutical research and development (R&D) to foster the development of safe and more effective medicines for patients through removing identified bottlenecks in the drug development process, and to enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector.

The revised IMI Scientific Research Agenda http://www.imi.europa.eu/content/research-agenda describes the research bottlenecks in the drug development process and identifies new and established research priorities correlated to at least one of the seven IMI Areas of Research Interest.

The IMI 5th Call for proposals 2012 consists of one Theme: the European Lead Factory, which comprises two topics:

- European Screening Centre
- Joint European Compound Collection

This Theme falls under one of the new key research priorities: 'Beyond High Throughput Screening - pharmacological interactions at the molecular level', which is correlated to the following Areas of Interest: Strategies in R&D, and Tools and Techniques.

Submitted Expressions of Interest should address one of these two topics. At the second stage, the successful Applicant Consortium for each topic will merge with the EFPIA[2] consortium to prepare the Full Project Proposal for the Call Theme. The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

Before submitting an Expression of Interest, the various Call documents, such as the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest*; the *Rules for Participation*; the *IMI Intellectual Property Policy*, etc., shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the launch of the 5th Call 2012.

Synergies and complementarities with other EU funded projects should be explored in order to avoid overlaps and duplications and to maximise European added value in health research.

[1] In the present context, 'pre-competitive pharmaceutical research and development' should be understood as research on the tools and methodologies used in the drug development process.
[2] European Federation of Pharmaceutical Industries and Associations – www.efpia.eu

DURATION OF THE PROJECTS

The indicative duration of project is 5 years.

FUNDING OF THE PROJECTS

Usually, the total available financial contribution from the IMI JU to participants eligible for funding will be up to the amount that the research-based companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA – www.efpia.org) will contribute as 'in kind'[3] contribution.

For this Call, the indicative EFPIA in kind contribution will be EUR 89 million or above. In order to balance the EFPIA deficit arising from preceding Calls for proposals, the total indicative financial contribution from the IMI JU will account for up to EUR 80 million, representing 90 per cent (90%) of the indicative EFPIA contribution to this Call.

The indicative IMI JU contribution will be divided between the topics as follows:

Topic 1: European Screening Centre: EUR 40 million
Topic 2: The Joint European Compound Collection: EUR 40 million

The Applicant Consortia shall keep in mind that the budget of each Expression of Interest should be adapted to the scientific goals and the expected key deliverables of the project.

SYNOPSIS OF THE CALL AND EVALUATION PROCESS

The IMI JU supports research activities following open and competitive Calls for proposals, independent evaluation procedures, and the conclusion of Project and Grant Agreements.

The Theme included in the 5th Call for proposals is associated with a group of pharmaceutical companies that are members of EFPIA (hereafter called the 'EFPIA Consortia'), and which are committed to collaborating with public and private organisations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions to support their activities within the research projects.

The IMI JU applies a two-stage Call process. In the first stage, 'Applicant Consortia' (i.e. formed by academia, small and medium-sized enterprises (SMEs), patient organisations, non-EFPIA companies, etc.) are invited to submit, to the IMI JU, an Expression of Interest (EoI) in response to a Call topic.

In preparing their EoIs, the Applicant Consortia should carefully consider the research contribution that an EFPIA Consortium will make to a given project as well as the expectations from the Applicant Consortia, as outlined in topic texts below.

Each EoI submitted addressing one of the two topics will be reviewed by independent experts according to predefined evaluation criteria. The Applicant Consortium with the highest ranked EoI for each topic will be invited to jointly develop a Full Project Proposal

[3] In kind contribution is e.g. personnel, clinical research, equipment, consumables.

together with the EFPIA Consortium. The Full Project Proposal will then be subject to a final review by independent experts according to predefined evaluation criteria.

Only a Full Project Proposal that has been favourably reviewed in the evaluation process can be selected for funding. This project will then be invited by the IMI JU to conclude a Grant Agreement governing the relationship between the selected project consortium and the IMI JU.

For full details, applicants should refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest* published on the IMI JU website www.imi.europa.eu at the launch of the 5th Call 2012.

ELIGIBILITY TO PARTICIPATE IN PROJECTS AND TO RECEIVE FUNDING FROM THE IMI JU

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from the IMI JU are specified under the *Rules for participation* published on the IMI JU website www.imi.europa.eu.

The IMI JU financial contribution will be based on the reimbursement of the eligible costs. The following funding rates apply to the legal entities eligible for funding: For research and technological development activities, up to 75% of the eligible costs are eligible for funding. For other activities (including management and training activities), up to 100% of the eligible costs charged to the project are eligible for funding. For indirect costs (overheads), the legal entities eligible for funding may opt for one of the following indirect costs methods: the actual indirect costs; or the simplified method which is a modality of the actual indirect costs for organisations which do not aggregate their indirect costs at a detailed level, but can aggregate them at the level of the legal entity; or a flat rate of 20% of total eligible direct costs (excluding subcontracting costs and the costs of resources made available by third parties which are not used on the premises of the beneficiary).

For full details, Applicant Consortia are invited to refer to the *Rules for Participation* (www.imi.europa.eu).

The research-based companies that are members of EFPIA shall not be eligible to receive financial contributions from the IMI JU.

IMI INTELLECTUAL PROPERTY POLICY

The IMI Intellectual Property Policy (IMI IP Policy, www.imi.europa.eu/content/intellectual-property-policy) has been developed to be aligned with the objectives of the IMI JU to ensure knowledge creation, together with the swift dissemination and exploitation of knowledge, and fair reward for innovation.

The IMI IP Policy sets out *inter alia* basic principles regarding ownership of Background and Foreground, access rights depending on the entity and the purpose, and dissemination.

In submitting an EoI, the Applicant Consortia fully understand the principles laid out in the IMI IP Policy that will apply to all research projects conducted under the IMI JU.

The IP Policy does not foresee all details and does not aim to address all possible practical situations participants may be faced with. Flexibility is provided for participants to establish the most appropriate agreements (e.g. the Project Agreement) serving each individual project's objectives, and considering the wider IMI objectives.

Applicant Consortia are invited to read carefully the Guidance Note on the IMI IP Policy, whose purpose is to explore ways to handle related issues and pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

The Project Agreement is a private agreement which the participants of an IMI project conclude amongst themselves to implement the provisions of the Grant Agreement and to regulate internal issues related to work organisation and objectives for each participant, consortium governance, IP, financial and other matters.

All participants of a selected IMI project are requested to start negotiation on the Project Agreement between them in parallel to the preparation of the Full Project Proposal.

The Full Consortium shall ensure that the negotiation of the Project Agreement is completed no later than the finalisation of the full project Description of Work.

EUROPEAN LEAD FACTORY

This Call theme consists of two Topics:

- European Screening Centre
- Joint European Compound Collection

Submitted EoIs should address one of these two topics. At the second stage the successful Applicant Consortium for each topic will merge with the EFPIA consortium to prepare the Full Project Proposal for the Call Theme.

BACKGROUND

Discovery of novel small molecule lead structures is a major driver of the early drug discovery process. Among a diverse set of discovery strategies, experimental high-throughput screening (HTS) of comprehensive compound collections has provided a major avenue towards lead structure identification. The size, design, and quality of the compound libraries are of utmost importance for the output of HTS.

Despite continuous efforts and numerous success stories, a large number of disease-relevant drug targets still lack suitable lead structures. Reasons for this intractability are typically manifold, including a low druggability, e.g. protein-protein interactions, and/or difficulties combining target activity with the required pharmacokinetic and metabolic properties in one small molecule. Moreover, pharma discovery portfolios are increasingly dominated by such challenging targets, further jeopardising the productivity of early drug discovery, and consequently pharma's output of innovative medicines in general. The still limited understanding of many areas of disease biology is yet another challenge to early drug research, and this is reflected in a sparse flow of novel druggable targets with a sufficiently validated disease link.

HTS has gained relevance also in this field based on the notion that identified small molecule modulators of a specific molecular target or a cellular pathway might provide suitable tools to unravel target or pathway function in health or disease. In fact, marketed drugs and many candidates from discontinued pharma projects have served as powerful tool compounds in basic research activities.

Beyond pharma's lead discovery activities, the build-up of chemical libraries and HTS has gained increasing relevance also in the academic arena. Triggered by the National Institutes of Health (NIH) roadmap in 2004 in the United States[4], this area has recently seen active growth also in Europe, e.g. in the EU OPENSCREEN initiative. Academic HTS activities are quite scattered and of limited scale. Compound libraries, screening approaches, processes and culture typically reflect the basic science proposition of generating biology-related knowledge. The main goal is the identification of chemical probes for the targeted manipulation of cellular or biochemical function. In line with this notion, the definitions of 'chemical probe'[5] (or 'tool compound') generally cut back on major criteria required from tractable hits in industrial drug discovery programmes. It is

[4] Austin, C.P. *et al*. (2004) *Science* **306**, 1138-1139
[5] See, for example: http://mli.nih.gov/mli/

therefore not unexpected that the identification of probes that are also suited for drug development is a rare event in academia's chemical biology activities[6]. Moreover, in many academic programmes the general shortage of medicinal chemistry support in HTS follow-up prevents a further qualification of hits[7]. Thus while academic screening activities are by design not intended to copy industrial hit and lead discovery, they provide a rich source of novel ideas on molecular targets, disease-relevant pathways, and assay approaches. In contrast, industry screening activities aim to deliver hits ideally combining chemical novelty with medicinal utility.

The European Lead Factory is intended to bridge this gap between academic and applied research by providing an 'industry-like' small molecule discovery platform to public investigators with innovative ideas for discovery programmes targeting both lead structures for drug development or high quality probes for target research.

PROBLEM STATEMENT

As described above, pharma's capability to generate a sufficient number of innovative drug candidates is under increasing pressure. Pharma's discovery organisations are increasingly dependent on external ideas for novel treatment concepts, molecular targets or unprecedented assay approaches. Thus, in-sourcing of innovative ideas originating in the academic sector is considered vital to maintaining productivity in early drug discovery.

In addition to molecular targets and treatment hypotheses, the current thinking about chemical collections employed for HTS might also need some revisions. Corporate compound collections are still heavily safe-guarded by pharma companies and consequently tested against only a fraction of disease relevant targets determined by the company's therapeutic areas of interest. Also, individual collections provide insufficient coverage of the 'drug-like' chemical space and a comprehensive comparison of the underlying library design strategies is hampered by company boundaries.

Both private and public discovery programmes lack a sufficient number of quality lead structures to fuel early drug or target research. Suitable small molecule tool compounds for target validation by pharmacological means are equally rare. This gap cannot be closed in the foreseeable future by public HTS and chemical library activities.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Within the existing competitive framework of safeguarded pharma compound collections, their corresponding value remains incompletely realised. Sharing these collections between companies as well as with external partners holds the potential to result in valuable lead structures for thus far unexplored targets, ideally leading to innovative treatment options for patients. To this end, establishing a private-public initiative under the trusted framework of IMI will

[6] Oprea, T.I. *et al.* (2009) *Nature Chemical Biology* **5**, 441-447
[7] Kodadek (2010), ibid., 162-165

facilitate open innovation around compound collections from pharmaceutical companies, and allow drug discovery programmes from public originators and private consortium partners to benefit from these otherwise protected assets.

HTS and chemical libraries are a topic of increasing relevance also in the academic field, with a number of publicly funded activities emerging recently. All these initiatives aim to identify either "tool compounds" for the subsequent characterisation of target protein function by pharmacological means or to generate suitable lead structures for drug discovery programmes from academia and/or NGOs (non-governmental organisations). However, the fragmentation of these activities across numerous institutions with little knowledge transfer from industry, the lack of elaborated strategies for stringent hit selection, limited access to medicinal chemistry resources and expertise, and an overall lower quality of available chemical collections have thus far limited efficient value generation from these activities.

Providing not only access to a "pharma-like" high-quality compound collection and state-of-the-art screening processes, but also rigorous value-oriented selection processes incorporating industry expertise, will further improve the quality of the resulting "Qualified Hits". Finally, ensuring a meaningful medicinal chemistry follow-up of HTS results will further contribute to value creation for public discovery programmes seeking lead structures for drug research or tool compounds for basic research. This public-private approach will increase the chance of discovering innovative medicines.

OVERALL OBJECTIVES

KEY OBJECTIVES TO BE ADDRESSED

The project "Joint European Compound Library and Screening Centre" aims to provide:

(1) "Qualified Hits" for discovery projects originating from private or public projects;
(2) a unique platform to foster collaboration and exchange between industry and academia;
(3) a broad knowledge base to delineate successful strategies for library design.

The term "Qualified Hit" defines the final product of the intended screening efforts, including also possible medicinal chemistry follow-up activities. The "Qualified Hit" ideally constitutes:

(1) a compound with proven chemical structure (e.g. by resynthesis);
(2) experimentally proven target (or pathway) activity and specificity;
(3) an emerging structure-activity relationship (SAR) based on active and inactive analogues;
(4) overall chemical properties favourable for further optimisation for experimental pharmacology (and beyond).

This understanding of "Qualified Hit" applies to both early candidates for drug development and tool compounds for pharmacological research.

In contrast to the open information policies of academic screening initiatives, in the framework of the European Lead Factory the rules for the dissemination of compound structural information will balance the needs for the generation of intellectual property on future project results with public knowledge sharing. Furthermore, the Lead Factory will differentiate from already existing public initiatives in:

(1) its goal to deliver "Qualified Hits" selected for and sufficiently characterised to ideally justify additional investments in subsequent hit-to-lead optimisation (and beyond);
(2) its setup aiming for operational efficiency to convert academic proposals into value generating discovery programmes within a finite budget and time frame.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Potential for synergies with already existing Consortia might result from novel bioassay technologies as they are currently investigated in the human IPS (induced pluripotent stem cells) project (IMI 4th Call Topic) and IMIDIA (Improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes). Further options include other publicly funded initiatives in the field of chemical biology, HTS, and compound libraries, e.g. EU OPENSCREEN (http://www.eu-openscreen.de/).

Additional synergies may possibly result from a joint use of major infrastructure (e.g. the compound repository). Moreover, a close link between the European Lead Factory and academic screening initiatives will greatly facilitate the scientific exchange between basic science and industrial application in this important field of research. For a possible further advancement along the drug research value chain of Qualified Hits generated by the European Lead Factory together with public partners, one potential platform might be provided by the EATRIS (European Advanced Translational Research Infrastructure in Medicine) initiative (http://www.eatris.eu/).

Generally, for the selection of the Applicant Consortia in this Call, potential synergies with existing consortia cannot compromise the project objectives of delivering industry-standard quality in terms of the compounds and screening activities or the applicant requirements laid out in this document.

EXPECTED KEY DELIVERABLES

Due to the size and the nature of this Call it has been split into two major subtopics:

(1) European Screening Centre
(2) The Joint European Compound Collection

(1) European Screening Centre

The establishment of a European Screening Centre responsible for:

(i) managing the logistic processes around the compound library;
(ii) managing the data transfer of confidential information according to the 'honest data broker concept';
(iii) development and/or adaptation of target or pathway-specific bioassays for HTS;
(iv) performing HTS campaigns for publicly-sponsored projects;
(v) generating a suite of generic tests for follow-up studies ensuring a stringent hit selection process;
(vi) supporting all projects, private and public, in all aspects of data analysis and project management;
(vii) providing directly, or through associated partners, initial medicinal chemistry support, i.e. analytics, re-synthesis, limited hit expansion.

Once fully operational, the Centre will need to accommodate resources sufficient to support compound logistic processes for up to 48 HTS projects per year (24 from public projects and 24 from pharma company projects). The Screening Centre is expected to provide full experimental support for the 24 public projects. The pharma companies will receive a copy of the library and perform the screening in-house in a blinded fashion. Each company will qualify for up to 4 screens/year, depending on their compound contribution.

(2) The Joint European Compound Collection

Within the framework of this project, it is intended to establish a unique, comprehensive, and high quality compound collection for HTS within the European Screening Centre comprising two parts, i.e. the Pharma Consortium Collection and the Public Compound Collection:

i. *The Pharma Consortium Collection*

Each pharma company will provide up to 50 000 different compounds in an agreed upon quantity and format to populate the Pharma Consortium Library. With an intended number of 6+ EFPIA Participants in such a Consortium, the Pharma Consortium Library is expected to comprise at least 300 000 compounds.

EFPIA Participants will therefore compile a mutually agreed upon catalogue of selection criteria ensuring the uniform and high quality of compounds included in this Pharma Consortium Collection. The full catalogue of selection criteria will be detailed in the Full Project Proposal and is expected to include typical cut-off parameters, like Lipinski's rules, polar surface areas, rotatable bonds *etc*. In addition, diversity rules will be applied to individual subcollections within the Pharma Consortium Collection to provide an optimal chemical diversity.

Compounds included will in part originate from historic medicinal chemistry programmes and shall not be available from commercial sources, rendering this library a unique asset for lead finding. The value of this collection is related to the extended medicinal chemistry expertise reflected in the design of the compounds. Many of the underlying structural motifs are linked to or have

evolved from precursors with demonstrated (target) bioactivity. In addition, compounds from historic pharma projects have been intentionally optimised towards favourable metabolic and pharmacokinetic properties. Lessons learned regarding the structural and physico-chemical properties of successful candidates have subsequently guided pharma's library extension programmes. Combining compounds from a number of pharma companies with a diverse indication (and therefore target) background will provide a unique collection of unprecedented quality far outbalancing its limited scale.

The Screening Centre will perform an in-depth *in-silico* analysis and profiling of the compounds provided by the EFPIA partners to ensure the uniqueness of compounds included and provides a cross-company comparison of compound properties. This activity will be under the guidance of the Advisory Board (AdBoard –see below for the composition) ensuring compliance with the predefined selection criteria. The involvement of otherwise competing companies in this process - as members of the AdBoard - will ensure a true and critical 'peer review'. However, the AdBoard shall in no event have access to explicit chemical structure information.

Explicit chemical structural information will be made available to the Screening Centre to:

(i) perform the above-mentioned *in silico* analysis and profiling of compounds;
(ii) organise the (un)blinding of compound structural data;
(iii) facilitate HTS data analysis.

In addition, chemoinformatic descriptors based on agreed-upon two dimensional (2D) fingerprints will be shared on a need-to-know basis within the Consortium (and beyond) to support the overall project goals.

Due to the complexity of existing intellectual property rights associated with part of the compound collections to be shared, it is mandatory to perform all screening operations, including sub-contracted activities, in an EU Member State or country associated to the Seventh Framework Programme (FP7) where national patent law provides for an appropriate "research exemption", thus allowing the use of any such collections for research purposes, without running risk for infringement of existing third party IP. It is recognised that the scale of the planned transfer of compounds also precludes a complete analysis of all legal or contractual obligations potentially restricting the use of individual compounds. Therefore, a clearance process by the compound provider for selected hit compounds prior to inclusion into a "Qualified Hit List" (see below) and disclosure to the project owner will be necessary. This clearance process will:

(i) not require the disclosure of the identity of the project owner or any project details (target, assay etc.);
(ii) be based on criteria agreed upon in the consortium and predefined – to the extent possible - in the Full Project Proposal;
(iii) take no longer than two to four weeks.

It should be emphasised at this point that the removal of hit compounds from the process because of the above mentioned 3rd party IP rights will be the rare exception. It is generally acknowledged that for both the Pharma Consortium and Public Compound Collection, due to the complexity and continuous evolution of

patent rights pertaining to small molecule substances, the 3rd party intellectual property status cannot be determined for larger sets of compounds at any project stage, including an analysis of 'freedom-to-operate' at the stage of "Qualified Hit List", and that the resulting ambiguity has to be dealt with by the project owner.

ii. *The Public Compound Collection*

During the course of this initiative, the Pharma Consortium Collection will be supplemented by a Public Compound Collection aggregating multi-faceted design approaches. The aim is to generate up to 200 000 different compounds from the public sector, with about 100 000 being available within the first 3 years of the project. The focus of this collection will be a diversity-based coverage of novel chemical space, including compounds whose preparation is based on new methodology. Special emphasis should be given to the design of compound classes which address targets which are only barely addressed by current chemotypes and which truly expand the chemical space beyond the one already addressed by the pharma compound collection. It is envisioned that between several hundred and a thousand smaller libraries will be designed. Already available design principles and libraries that fit to the very stringent design and quality criteria above can be included.

The Pharma Consortium Collection and the Public Compound Collection will be brought together and housed in the Screening Centre where it will constitute the **Joint European Compound Collection**. The data in the "Qualified Hit List" compiled as the result of the HTS and subsequent hit characterisation process, which contains not more than 50 different compounds originating from the Joint European Compound Collection and their associated bioactivity data collected in the project, should constitute FOREGROUND of the project as defined in IMI's Intellectual Property Policy. The broad knowledge base generated in the course of the project shall be shared with the broad scientific community to elaborate novel insights into principles of library design. Rules and timing of dissemination of FOREGROUND will be specified in the Project Agreement.

CONSORTIUM

EFPIA PARTICIPANTS

Bayer HealthCare, Janssen Pharmaceutical, Merck-Serono, AstraZeneca, Sanofi, UCB, and Lundbeck (as of date)
The major contribution of the EFPIA member companies to the European Lead Factory project will be the 50 000 compounds donated by each to fill the Pharma Compound Collection. With an average replacement cost of EUR 200 per compound, this will constitute an in-kind contribution of EUR 60 million.

In addition, EFPIA Participants will contribute to a variety of project activities:

- design and implementation of a selection process for compounds to be included in the Joint European Compound Library;
- HTS project work for EFPIA projects (24 projects per year); these activities range from assay development to hit qualification and selection;
- continuous support of Screening Centre and Public Compound Collection activities, including scientific project/proposal review, expertise to review and comment on project and assay design, experimental strategies for hit

qualification and selection, medicinal and theoretical chemistry support for the Public Compound Library;
- management support for both Call Topics.

Overall, EFPIA Participants will contribute scientific, technical and legal expertise to ensure an effective realisation of the European Lead Factory proposal. All administrative and scientific activities described above involving EFPIA member company scientists constitute yet another source of 'in kind' contributions with an indicative volume of EUR 24 million over the duration of the project.

In addition to the above outlined in-kind contributions, EFPIA will carry also costs generated by the Screening Centre for the support of the private screening campaigns during the confidential unblinding process from hit to the Qualified Hit List.

As the European Lead Factory is envisioned as a platform to nurture collaborations, it is expected that 1 out of 6 public projects will be partnered by an EFPIA Participant. In the realisation of such public projects for which the project owner has entered into a collaboration agreement with a selected EFPIA Participant, such member will carry part of the costs occurred at the Screening Centre to jointly develop the project results.

Direct cash contributions of EFPIA Participants are expected to be in the range of EUR 5 million.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is five (5) years. However an expected outcome of this topic is to develop an infrastructure and a European capability that is sustainable beyond the duration of this project.

INDICATIVE BUDGET

The indicative 'in-kind contribution' from EFPIA Participants is expected to amount to EUR 89 million or above. The IMI JU financial contribution, which is up to EUR 80 million, will match by 90 per cent (90%) the indicative in kind contribution of EFPIA Participants. The indicative IMI JU contribution will be divided between the topics as follows:

Topic 1: European Screening Centre: EUR 40 million
Topic 2: The Joint European Compound Collection: EUR 40 million

APPLICANT CONSORTIUM

(to be selected on the basis of the submitted Expressions of Interest)
An Applicant Consortium applying for one of the topics of the Call will not be obliged to apply for the other topic. However due to the integrated nature of the topics the successful consortia (one for each topic) are expected to work together

to come up with one Full Project Proposal. Indicative expectations from the applicants, by topic:

Topic 1: European Screening Centre

Applicant consortia should:

- demonstrate extensive experience in the execution of HTS to industry standards, providing solutions also for complex experimental protocols, e.g. with multiple liquid handling and signal detection steps, kinetic readouts, etc.;
- have experience of assay development, both employing platform techniques and introducing novel experimental approaches;
- provide appropriate infrastructure, including laboratory automation and robotics, to support both compound logistics and HTS;
- provide the necessary expertise in molecular and cellular pharmacology and medicinal chemistry to drive a rigorous hit characterisation process;
- have extensive experience in applying information technology (IT) solutions to the management of compound collections and HTS data management from quality control to chemoinformatic analysis of HTS activity data;
- supporting IT landscape and computational chemistry expertise to perform the indicated library analysis and to support the evaluation and possible progression of hits in medicinal chemistry follow-up activities;
- provide solutions to firewall its IT infrastructure handling data related to the Joint European Compound Collection.

The knowledge base, i.e. target-specific bioactivities of "Qualified Hits", to be generated within this project greatly depends on a high degree of coherence and comparability of the data across all projects. To ensure this quality, the standardisation of processes and a limited diversification of technical approaches will be key. The experimental HTS activities should consequently be aggregated in only a single or two units covering broadly standard assay read-out technologies. Realisation of specialised assay formats can be achieved – where necessary – also by out-sourcing/subcontracting of selected project activities. The minimal fragmentation of activities should ultimately contribute to the Centre's operational efficiency needed to generate tangible results within a limited budget frame and thus finite resources and ambitious project cycle times.

Therefore, in order to comply with IP requirements related to the nature of the project, and mitigate the risks related to housing an EFPIA Pharma Consortium Collection which is confidential and proprietary, the proposed European Screening Centre should organise itself so as to include:

- one single, centralised entity for the collection, storage, distribution and management of the Joint European Compound Collection;
- one or two centralised units for carrying out the HTS screening operations on the targets originating from the non-EFPIA Partners. A clear preference will be given to applicant consortia that can offer the HTS operations through one single centralised unit;
- one single, centralised unit with dedicated staff bound by confidentiality and non-use obligations, responsible for compound data management and HTS data analysis, operating under the 'honest broker concept' principles, with confidential structural information associated with the Joint European Compound Collection.

Topic 2: The Joint European Compound Collection

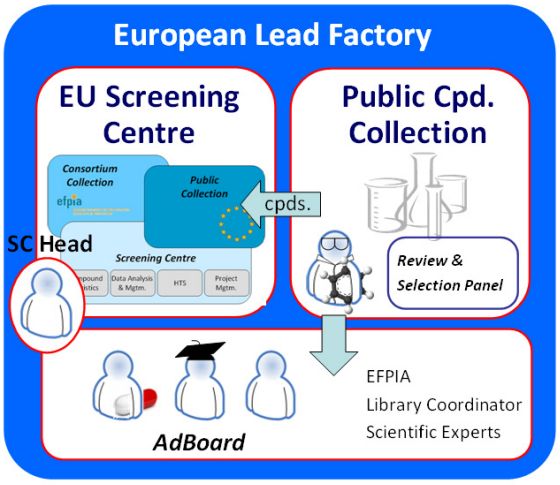
Applicant consortia should:

- provide necessary know-how to actively participate in generating innovative design proposals;
- provide extensive expertise in the field of high-throughput chemistry and compound library generation for HTS;
- demonstrate a suitable IT infrastructure to support:
  - capture and exchange of relevant chemical information;
  - chemoinformatic analysis;
  - and overall data management.
- In addition, applicants must provide a technical solution for the collection of proposals from a broad public audience together with its efficient review and selection process by a decentralised mechanism involving EFPIA scientists and selected external experts forming a 'Review and Selection Panel'. The design of this process must also ensure confidentiality of information and disclosure of such only on a need to know basis.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

Each Applicant Consortium is expected to address the research objectives for the chosen topic and make key contributions to the defined deliverables in synergy with the EFPIA consortium.

GOVERNANCE OF THE JOINT EUROPEAN COMPOUND LIBRARY AND SCREENING CENTRE



The diagram illustrates the integration of the Joint European Compound Collection Topic and European Screening Centre Topic into the European Lead Factory Consortium. For both topics, Applicant Consortia will provide a model describing the management structure, firewalling confidential information, and division of activities and corresponding responsibilities underlying their operational routines. Governance of both projects will be provided by an Advisory Board (AdBoard) made up of EFPIA company representatives (6+), selected external experts (4-5), the coordinator of the Public Library Topic, and the selected head of the Screening Centre.

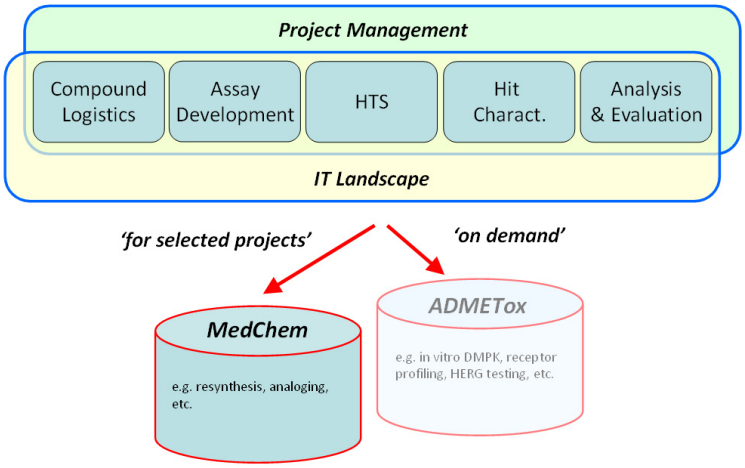
The head of the Screening Centre will assume overall operational responsibility for steering the European Lead Factory in conjunction with the EFPIA consortium. This head shall also represent the European Lead Factory to the outside academic world to establish an active network with existing screening initiatives, e.g. EU OPENSCREEN, to foster the exchange of best-practices in scientific and process-

related questions. The Library topic will receive additional support from a "Review and Selection Panel" as described later in this document.

The AdBoard will provide not only oversight of the activities of both project topics but will also be tasked with the review and selection of public proposals for HTS within the Screening Centre. As such, the AdBoard will be the ultimate decision body for project selection from public proposals. Proposals will be evaluated based on their innovation potential regarding target, patho-mechanism, and assay approach in relation to past and current pharma project portfolios. In addition, proposals related to rare and neglected diseases will be considered, especially if the project also allows the generation of knowledge transferable to major pharma target classes. However, the AdBoard will not be involved in the Qualified Hit List evaluation process. This will be managed by the Screening Centre.

TOPIC 1: EUROPEAN SCREENING CENTRE

As outlined above, the Screening Consortium, i.e. the European Screening Centre will take responsibility for a number of interlinked activities – as illustrated in the figure shown. All activities should ideally be embedded in a unifying IT infrastructure (i.e. IT landscape), supporting the quality control and standardisation of microtiterplate-based assay data, chemoinformatic data analysis and overall data management.



The Screening Centre will be the only party within the project with full access to both, bioactivity and chemical structural information. The dedicated Screening Centre scientists operating with confidential information, most prominently chemical structure data associated with the Joint European Compound Collection, will be bound by confidentiality and non-use obligations. No explicit structural information shall be disseminated either alone or in combination with bioactivity data beyond the 'Qualified Hit List' disclosed to the project-owning party only. In contrast, no restrictions apply to the scientific background on target or assay biology. Projects shall be jointly driven by the project-owning party in collaboration with a Screening Centre Scientist based on an agreed upon project plan. The work packages Assay Development and HTS may be supported through supplementary subcontracting based on project specific aspects, efficient resource utilisation, and/or budget consideration.

Additional 'on demand' activities to be performed in selected projects with external partners include medicinal chemistry follow-up (if no internal resources available) and *in vitro* ADMETox profiling.

In the submitted EoI by Applicant Consortia, the technical aspects requested below should be detailed. In addition, EoIs should also reveal (i) requested human resources and expertise, (ii) a transparent initial calculation of anticipated running costs and its cross-relation to the quantitative goals set forth in this proposal. Applicants are also invited to suggest (iii) proposals for the future development and sustainability of the Screening Centre (beyond the 5 years of the project).

Work Package 1 - Compound Logistics

- The storage, distribution, HTS logistics (i.e., hit picking, support of follow-up studies), and tracking of the Joint European Compound Collection (comprising a Pharma Consortium Collection with about 300 000 compounds and a yet to be generated Public Compound Collection comprising up to 200 000 compounds) should be detailed. The Pharma Consortium Collection will be assembled from individual subsets of 50 000 compounds provided in DMSO solution on microtiterplates in a concentration and format yet to be determined. However it is expected that the storage and handling proposed will be compatible with current industry standards regarding preservation of compound integrity.
- Applicants are requested to provide detailed information on the logistic processes needed to match the planned HTS activities. It is expected that the Screening Centre will handle 48 HTS screens per year:
  (i) 24 projects per year to be performed with pharma participants; primary and confirmatory HTS tests will be executed by the EFPIA participants using copy plates in a blinded fashion (i.e. no structural information to be provided); additional copies for further specificity or selectivity tests;
  (ii) 24 projects for public partners to be executed by the Screening Centre (primary HTS and re-testing).
- During the funding period, the growing Public Compound Collection needs to be rapidly available for screening; compounds will be provided as solid material or in DMSO solution. Therefore applicants are requested to propose an appropriate concept for plating and, possibly, storage of the bulk material.
- Options for up-scaling the compound logistics aspects in this concept (e.g. by integration of additional library initiatives) are welcome.

Work Package 2 – Assay Development

Projects introduced from the public sector into the EU Lead Factory will come with different degrees of groundwork. This will be particularly evident in the aspect of bioassay concepts and provision of assay materials. In their submitted EoI applicants are requested to demonstrate:

- the required expertise to successfully tackle the many technical challenges in the design of appropriate bioassays for high-throughput screening coming from these different sources;

- how the Screening Centre will translate or adopt - in collaboration with the investigator(s) - project proposals to become scientifically and technically sound HTS assays;
- how the effective discrimination of assay artefacts and compounds with unwanted mode-of-action will be achieved in the primary assay and a limited set of secondary tests performed in the subsequent hit characterisation process.

Work package 3 – HTS

Applicants are requested to describe in detail how they will execute and manage the major part of experimental HTS activities. Applicants are requested to demonstrate that they have access to a sufficiently broad coverage of the most relevant bioassay read-out technologies. Laboratory automation and robotics need to balance the anticipated throughput requirements with the flexibility to also realise complex protocols. Plate formats and laboratory automation proposed should generally be compatible with the required sample throughput and project cycle times.

It is expected that the Applicant Consortium will address these issues in their EoI. Restricted by the available budget (total of ca. EUR 40 million) over the 5-year funding period to cover all Screening Centre activities), it is intended to support up to 24 projects from the public sector per year (up to 500 000 compounds per screen) by the Applicant Consortium (including also subcontracted activities). Screening of only pre-selected subsets of the collection, i.e. focused libraries, is not foreseen.

Work package 4 - Hit Characterisation

Applicants are expected to demonstrate clearly how, following confirmation of primary activity and discrimination of unwanted activities identified from cross-assay analysis, the remaining hits will be subjected to a rigorous testing scheme designed to ensure target (or pathway) specificity. To this end, the Screening Centre, in conjunction with the project owner directly or via subcontracting, is expected to generate a defined set of 'orthogonal tests' to probe for specificity, counter assays to exclude unwanted activities, and selectivity assays to generate a dataset to discriminate the few meaningful potential "Qualified Hits" from the vast number of potential artefacts. These assays can be supplemented by a suite of generic assays provided by the Screening Centre to identify the most relevant sources of unspecific interference.

It is expected that a description of how this process will be rationally planned to ensure the efficient selection of the compounds to be documented in the "Qualified Hit List" is included in the EoI. It is also expected that this "Qualified Hit List" which will include not more than 50 different compounds will constitute Foreground of the project as defined in IMI's Intellectual Property Policy.

Work Package 5 - Medicinal Chemistry

Applicants must provide details of how the Centre will follow-up on (i) the analytical validation of hit compounds and (ii) post-HTS activities involving chemical laboratory work.

- Analytical validation of hit compounds is a necessary step in hit characterisation and should be covered by Screening Centre resources. Moreover, in-depth medicinal chemistry expertise will be essential to the Centre, in its task to objectively and independently steer the selection process jointly with an expert nominated by the project-owning party. The selection process is concluded with the compilation of a "Qualified Hit List" containing only a limited number (max. 50) of candidate compounds. Notably, this data-driven, value-oriented triage process might also end with no tractable hits identified.
- Post-HTS activities involving chemical laboratory work starting from re-synthesis of active samples to analoging to elaborate initial structure-activity relationships can be realised either through an associated consortium member or subcontracted partner.

In both cases, proposals for this chemistry work will have to be (i.) realised in a budget framework of not more than EUR 2 million per year, thus requiring a suitable gatekeeping or selection process; and (ii) be jointly steered by the Screening Centre and project owner to ensure selection of goal-oriented projects and their timely progression.

Work Package 6 - Information Technology (IT)

Applicants are requested to provide details of the IT infrastructure in place to co-ordinate all of the activities of the Screening Centre, particularly the management of HTS and follow-up. A functional HTS IT landscape should include:

- tools to capture and manage microtiterplate-based bioactivity data for quality control;
- data standardisation and analysis;
- chemoinformatic tools to guide the interpretation and visualisation of data;
- supporting IT landscape and computational chemistry expertise to perform the indicated library analysis and to support the evaluation and possible progression of hits in medicinal chemistry follow-up activities for compounds from the Joint European Compound Library;
- suitable processes and IT instruments to safeguard the confidentiality of information related to the Joint European Compound Library.

In addition, applicants are requested to provide a concept needed for broadly sharing the wealth of pharmacological activity data generated in the course of the project, i.e. "Qualified Hits" and their associated bioactivity data.

Work Package 7 – Project Application, Review & Selection

EFPIA Participants and academic investigators will contribute project proposals to the European Lead Factory. Generally, individual projects - defined by a molecular target (or pathway) and the desired mode-of-action of hit compounds – will be screened only once. The nomination and selection process for projects originating from EFPIA Participants will be regulated in the Project Agreement.

For projects originating from the public sector, applicants should lay out a scheme for how to generate a continuous flow of project proposals and introduce these proposals to a brief review process supporting a final approval decision by the Lead Factory AdBoard (see above).

Beyond a sound scientific and technical evaluation, successful proposals need to provide innovative aspects in either molecular target or pathomechanism, thus differentiating clearly from past and current pharma projects.

Additional positive selection criteria include:

- targeting areas of medical need, rendering the project an attractive candidate for early public-private partnerships;
- targeting rare or neglected diseases, especially if the anticipated project results might have relevance also for prominent pharma target classes.

This list makes no claim to be complete and should serve only to provide some examples of the desired project qualities sought in this initiative. To this end, one overarching theme is value generation which also will be key for project selection.

EFPIA Contribution

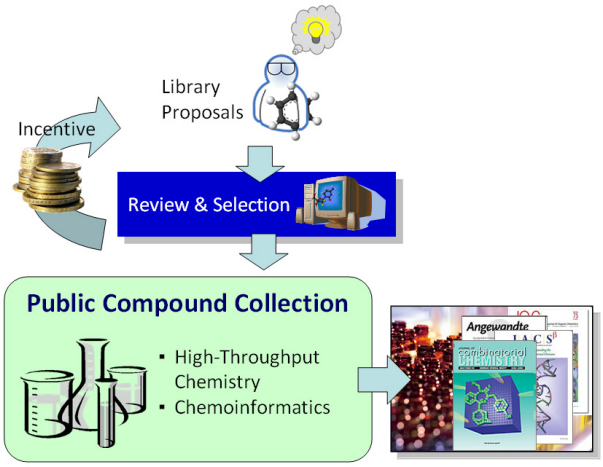
The Screening Centre will benefit from the support of EFPIA company representatives on the AdBoard.

All EFPIA HTS projects will be subject to similar processes performed through EFPIA internal resources. All activities will be based on an agreed upon project plan. Screening data generated by the EFPIA Participants will be transferred for further analysis to the Screening Centre. The EFPIA project owner and dedicated Screening Centre scientists will jointly drive the subsequent hit characterisation process to compile the "Qualified Hit List". The EFPIA project owner will compensate the Screening Centre for additional experimental work in this effort. This parallel HTS activity employing the Joint European Compound Library will add to the generation of a common knowledge base, i.e. a database containing structural information on qualified hits with their associated bioactivities, to guide future library design activities.

In addition, for all work packages, EFPIA will provide scientific expertise to support the Screening Centre in setting up quality and goal-oriented processes for public projects.

TOPIC 2: THE PUBLIC COMPOUND COLLECTION

Compounds provided by EFPIA Participants will be placed directly into the European Screening Centre. Therefore this topic covers only the Public Compound Collection to be contributed to the Joint European Compound Library. The European Lead Factory seeks to generate a comprehensive Public Library of up to 200 000 novel compounds. The focus of the library should be on compounds which are designed to address difficult and so far intractable targets in particular.



Therefore, the majority of the library should consist of compounds which have been designed and synthesised specifically for this purpose. It is of special importance that the compounds of this collection go beyond the chemical space that is addressed by the majority of the compounds in the pharma compound collections. Already available compound collections, e.g. from public or other sources, can be added to the Public Compound Collection only if they fulfil very stringent design and analytical criteria - *vide infra*.

GOVERNANCE OF THE PUBLIC COMPOUND COLLECTION

Within the governance structure of the European Lead Factory Topic, it is expected that the 'Public Compound Collection' project will have also have an advisory panel, i.e. a Review & Selection Panel, to give oversight on project activities. Importantly, this panel will also be responsible for the review of public proposals and the selection of new chemistries for inclusion in the Public Compound Collection. This panel will be composed of consortium members, EFPIA Participant representatives and independent experts with a total size of not more than 12-15 members.

This panel will also have an important role in ensuring fairness in administering reimbursement for selected ideas, the fair application of IPR, and the resolution of any issues that may arise.

To ensure a maximal impact of this novel collection on the parallel HTS efforts, a minimum of ca. 100 000 compounds should be available for screening within the first 3 years of the project. Therefore applicants are invited to describe in detail

proposed methodologies to address the deliverables outlined in the work packages below:

Work Package 1 - The collection of design proposals

Successful applicants should provide the know-how and documented expertise to generate innovative design proposals to be translated into compound libraries for lead discovery. In addition, Applicants are requested to propose a scheme by which a 'Call' is organised to identify novel chemistries from public bodies and how these proposals are captured for review.

EFPIA Contribution:
EFPIA will contribute theoretical and medicinal chemistry expertise for the evaluation of design proposals.

Work package 2 - The review and selection of qualifying proposals

While EFPIA experts and Library Consortium scientists will catalogue exclusion criteria, a precise definition of the 'innovative and differentiated chemistry' targeted for the Public Compound Collection is not available yet. This programme depends on the initially unbiased collection of ideas from the public sector and its subsequent review and selection process to capture novel ideas and define a more specified and targeted strategy for the second (and onward) wave of proposals. Such a "crowd-sourcing" derived strategy will be a second key deliverable within the Public Compound Collection subtopic. It is expected that the Applicant Consortia will provide details of how this process will operate and how novelty, innovation and quality are ensured in the selection of public compounds. However, the following principles should be included in the approach:

Public proposals should be incentivised by two mechanisms.

(i) Experimental results provided by the Public Compound Collection Consortium demonstrating the technical realisation of the proposal are free for publication by the public investigator. Publications will be restricted to selected example structures illustrating the proof-of-principle.
(ii) Externally generated proposals selected for experimental validation by the Consortium will be rewarded an investigator price by the Public Compound Collection Consortium.

Acceptance of a proposal to make a new chemical entity will not affect the ownership of the compounds included in the proposal; this will remain with the person or group who submit the proposal. However, the owner of this new molecule will grant full access rights to the project consortium and the Screening Centre for inclusion in the 'Joint European Compound Collection' and its use in all Screening Centre activities. It is envisaged that should a compound from the Public Compound Collection be identified in a screen and be clinically developed, at a certain point in its development, e.g. Investigational New Drug (IND) filing, then the owner of the compound will be eligible for an additional milestone payment.

EFPIA Contribution
EFPIA Participants will support this process by providing resources and know-how in the field of theoretical chemistry and designing and evaluating compound libraries.

Work Package 3 - The experimental validation of such proposals

Applicants are requested to propose an approach in which the selected chemistries may be synthesised at small scale, and the synthetic route validated in preparation for subsequent manufacture to industry standard. Applicants should provide the necessary know-how and request appropriate resources to put their proposal into practice.

EFPIA Contribution
EFPIA will support the work package by providing expertise and theoretical background in high-throughput and medicinal chemistry.

Work Package 4 - The successful delivery of compound samples according to agreed upon quality and quantity criteria

Applicants are requested to describe in detail how they will ensure the delivery of at least 100 000 compounds to the Joint European Compound Library within 3 years, and a total of 200 000 compounds over the duration of the project. Ensuring that the compounds produced meet strict technical quality criteria, e.g. purity (>85%, LCMS), that must not differ from industry standards.