IMI2

17th Call for proposals

Annex I to the Decision of the IMI2 JU Governing Board No. IMI2-GB-DEC-2018-32 adopted on 12 December 2018

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Contents

Introduction

The Innovative Medicines Initiative is a jointly funded partnership between the European Union, represented by the European Commission, and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[1] following the principles below:

Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of Small- and Medium-sized Enterprises (SMEs).

The scope of the initiative should be expanded to all areas of life science research and innovation.

The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[2].

The IMI2 JU objectives are usually implemented through research and innovation actions (RIAs), and coordination and support actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[3], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal for each of the topics that are relevant for them. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

Applicant consortia, during all stages of the evaluation process, must consider the nature and dimension of the IMI2 JU programme as a public-private collaboration.

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Applicants should ensure that gender dimensions are also considered. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaboration at a global level to maximise the European Union's added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU), OJ L 169, 7.6.2014, p. 54–76.
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[5] and Clinical Trial Regulation (EU) 536/2014[6] (and/or Directive 2001/20/EC[7)] and any relevant legislation[8].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award[9], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

[5] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) , OJ L 119, 4.5.2016, p. 1–88.

[6] Regulation (EU) No 536/2014 **of the European Parliament and of the Council of** 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1-76.

[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive), OJ L 121, 1.5.2001, p. 34.

8 Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws, OJ L 281, 23.11.1995, p. 31–50.

[9] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Topic 1: Optimising future obesity treatment

Topic details

Topic code	IMI2-2019-17-01
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The prevalence of obesity is increasing and affects more than 650 million people of all ages to become one of the foremost global health threats [1]. Obesity is complex. We only have a crude understanding of its underlying causes and biology, how to best describe and define it. Defining obesity as a disease has been debated over the past years and it is still not recognised as such in many countries. However, obesity is included in the WHO classification system ICD10 under 'Endocrine, nutritional and metabolic diseases' [2][3]. Obesity can be preventable, but once it has occurred it is considered a chronic disease for which treatments/interventions are often inadequate. Currently we have no way of predicting who will respond to or benefit from what kind of treatment or intervention [4][10].

Obesity can seriously impair health through a broad range of complications such as cardiovascular disease, type 1 and 2 diabetes (T1D and T2D), cancer, musculoskeletal disorders, psychosocial imbalances, and reduced quality of life, and impacts the treatment of other conditions [5][7][5]. Weight reduction has been shown to have a positive effect on these co-morbidities and may increase the effectiveness of treatments specific for other co-morbidities. Lifestyle modification is an integral part of the weight management journey, but is often insufficient on its own, and can be complimented by pharmacological and surgical add-on treatments to achieve greater and more sustainable weight loss, as appropriate. It is likely that there are subgroups of patients that are more suited to certain types of treatment and results risk dilution of perceived efficacy unless these groups are identified and treatment is personalised. People with T1D have traditionally been thought to have low body mass index (BMI), but current research has shown otherwise [6][6]. The obesity prevalence in T1D is increasing faster than in the general population [7].

This topic focuses on multifaceted profiling of patients with obesity in order to define clinically meaningful and relevant subgroups as a premise for optimising future prevention and treatment of obesity and its complications. Stakeholders are expected to pool pre-existing observational and/or clinical data to establish a database with enough phenotypic granularity for a data-driven stratification of obesity into subgroups based on a set of operational parameters including subject characteristics, biomarkers[11] and questionnaires. The outcome of this proposal should work towards a common understanding and an aligned vocabulary among stakeholders to facilitate scientific, medical, economic, and political acknowledgement of obesity as a disease and the importance of weight loss and weight maintenance.

Need and opportunity for public-private collaborative research

This initiative, based on a public-private partnership, provides a unique scientific opportunity to address the challenges of maximising the efficacy of preventing and treating obesity. The major advantages of using the IMI

[10] In the context of this topic, treatment refers in a broad sense to a variety of different interventions for patients with obesity including lifestyle advice on appropriate diet and exercise alone or in combination with drugs or obesity surgery.

[11] Biomarkers should be understood in a wide sense, i.e. any measure that can be used for clinically meaningful and operational sub-classification of obesity, e.g. including the microbiome, should such data exist.

platform are the ability to address these challenges in an independent effort, to engage with multiple stakeholders that otherwise might not interact in this context such as academia, patient organisations, clinical researchers, pharmaceutical industry, food, diagnostic companies including small and medium-sized enterprises (SMEs) with knowledge and interest in obesity and its complications. Recognised academics in this field and a range of companies with expertise in obesity and its complications approaching this topic from each their own individual angle would be needed to optimally analyse and interpret the large pool of data and impact the obesity landscape. The industry partners contribute with the necessary expertise to ensure that the scope of the analysis is fit for the purpose of developing innovative treatment paradigms and medicines. The participation of patient organisations will ensure the relevance for patients and they should be actively consulted as a source of unique knowledge. Therefore, to ensure success of the action, it is important to engage with a broad range of stakeholders including patients, clinicians and decision makers.

Scope

The scope of the topic is to identify pathophysiologically and clinically meaningful subgroups of obesity that will allow for optimisation of prevention and treatment of obesity and its complications. Establishing (or revisiting) a robust sub-classification may include the current use of body mass index as the best anthropometric measure, or alternatively waist circumference or waist-to-hip ratio; it may include a direct or indirect measure for the duration of disease (e.g. acknowledging the difference between paediatric onset obesity and decades of metabolic insult); genetics, phenotypes, markers of fatty liver disease, characteristics of the gut microbiota, and epigenetics, to name a few.

More specifically the objectives of the topic are to:

- establish a federated database by pooling of the baseline data from pre-existing cohorts from observational or interventional studies to achieve as broad and detailed information on patients with obesity as possible, including sufficient clinical phenotyping and multi-omics data;
- perform data-driven analysis of the federated database to identify and characterise patient subgroups and potential biomarkers for diagnosis, prediction of the development of complications, and potentially inform on appropriate type of and response to treatment as well as identifying markers for effective weight management;
- fill the gaps of information regarding selected biomarkers by reanalysing pre-existing biobank samples. Such biomarkers should be affordable and operational in the context of real-world clinical practise and clinical development of innovative medicines and other treatments;
- address specifically type 1 diabetes (T1D) and type 2 diabetes (T2D) as examples of conditions in which both clinical phenotype and treatment is influenced by obesity in an intricate manner, including public education about obesity in T1D. While there is a lot of data available on obesity in relation to T2D, there is little on T1D and obesity, therefore one focus will be on generating new knowledge on T1D. As part of this, data sets from the T1D Exchange programme will be available;
- collect and integrate patient perspectives in relation to diagnosis and treatment of obesity to understand the need, perceived barriers and value of determining medical treatment for patients with obesity;
- conduct a shared value analysis among key stakeholders reflecting values and challenges within the obesity landscape for optimising treatment and prevention. Engagement of external stakeholders is encouraged to generate educational material to support a common understanding of obesity. The content could include determinants and consequences of obesity including weight management.
- Establish a Patient Advisory Board including representatives from patient organisations in order to ensure that patient-driven research and insights relevant for the project are identified and considered within and across the different work packages.

Expected key deliverables

The ambition is that the proposed topic should lead to:

- a federated database of pre-existing phenotypic characterisation that can be used for the funded action and sustained for future analysis (see below on estimate on size of database);

- a set of operational variables that can be used for stratification of obesity into clinically meaningful patient subgroups, i.e. subgroups that may require different or respond differently to treatment of obesity and its complications;
- a detailed description of the clinical characteristics and manifestations of the identified patients subgroups, and wherever possible any existing or expected differences in treatment preference, effect, size, and sustainability of the effect and safety;
- an algorithm based on the set of operational variables that can be used to identify subjects that require and respond differently to prevention and/or treatment of obesity in clinical practice;
- description of the impact of obesity on T1D and T2D in terms of patient characteristics, clinical manifestation, treatment and outcomes, whether similar or different from non-obese patients with T1D or T2D. Use of corresponding data from the federated database is expected to be very useful to contrast or balance these findings;
- documentation of patient preferences regarding diagnosis and treatment of obesity;
- a shared value analysis among key stakeholders and the establishment of a common understanding and vocabulary about obesity as a disease.

Expected impact

Paving the way for an optimised and more personalised future obesity treatment, the identified patient subgroups should, where data are available, be analysed for treatment results, including weight loss and weight maintenance, and prevention and/or development of complications. Importantly, novel ways of defining and diagnosing obesity may also develop and detail the classification of obesity, and contribute to improving prevention, personalising health and lifestyle interventions, and weight management as well as the precision of evidence-based medicine and development of novel treatments. Deciphering the heterogeneity of obesity and the potentially differential effect of weight loss and weight maintenance should lead to:

- novel ways of describing and defining the obesity disease;
- potential for novel and innovative diagnostics for classification and evaluation of the obesity disease;
- increased understanding and respect for obesity as a chronic disease entity;
- increased potential to contribute to the development of more targeted prevention and lifestyle interventions;
- increased potential to develop targeted delivery of safe and effective treatments to clinically meaningful subgroups of patients with obesity;
- reducing the barrier of entry for innovative translational research and medicines development;
- improved clinical trial design;
- increased precision of evidence-based obesity medicine;
- better understanding of how to design effective measures to prevent and treat obesity based on its stratification into patient subgroups;
- increased understanding of the effect or lack of effect of weight loss on a broad range of obesity related complications;
- increased understanding of how obesity impacts other diseases as exemplified by impact on incidence, characteristics, treatment, costs, and outcomes of e.g. T1D.

Applicants should also demonstrate how their proposal will impact the competitiveness and industrial leadership of the European Union by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, duplication of efforts and funding.

The action generated by this topic should consider initiatives such as previous IMI projects and other projects, consortia that have addressed the compilation of cohorts from legal/ethical and technical/analytical perspectives e.g:

EMIF (European Medical Information Framework) http://www.emif.eu/,

DIRECT (Diabetes Research on patient stratification) https://www.direct-diabetes.org/

RHAPSODY (for precision therapy and prevention of diabetes) https://imi-rhapsody.eu/

MetaCardis (the role of gut microbes in cardiometabolic diseases) http://www.metacardis.net/

Diogenes (Diet, Obesity and Genes)

http://www.diogenes-eu.org/; https://cordis.europa.eu/result/rcn/51783_en.html

Joint Programming Initiative Healthy Diet for Healthy Life (https://www.healthydietforhealthylife.eu/) with European Nutritional Phenotype Assessment and Data Sharing Initiative (http://www.enpadasi.eu/index.html and the two projects: Confronting Obesity: Co-creating policy with youth: https://cordis.europa.eu/project/rcn/216413_en.html and Science and Technology in childhood Obesity Policy: https://cordis.europa.eu/project/rcn/214762_en.html

Data from these projects within the obesity and diabetes areas could also be of importance for the current topic.

In order to have the same federated database platform, the applicants should also consider interacting with the project **EHDEN** resulting from the topic European Health Data Network IMI2 – Call 12[12], which will deliver an operational, federated network in order to have direct access to RWD for developing new or incremental services in healthcare area.

Likewise, IMI2 **PREFER** project should be considered regarding patient preference for preventive measures and treatment https://www.imi-prefer.eu/**.**

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Novo Nordisk A/S (lead)
- Boehringer Ingelheim
- Sanofi

In addition, the industry consortium includes the following IMI2 Associated Partners:

- Juvenile Diabetes Research Foundation (JDRF)
- Obesity Action Coalition (OAC)
- T1D Exchange

The industry partners will bring in-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity. The industry partners will also provide know-how

[12] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf

and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time.

Limited supplementary funding could be made available for supporting further analysis of biobanked samples and development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis (to be discussed by the full consortium).

The industry consortium will provide access to the following observational cohorts:

Gutenberg Health Study (Univ. Med. Center Mainz, Germany)

The Gutenberg Health Study (http://www.gutenberg-gesundheitsstudie.de/ghs/willkommen.html) [8][8] is a population-based, prospective, single-center cohort study including more than 15 000 subjects with 5- (completed) and 10 year (planned) follow-up that started in 2007 at the University Medical Center Mainz and is supported by Boehringer Ingelheim. Approximately 3 500 subjects with a BMI >30 kg/m^2 at baseline have been included. The study focuses on cardiovascular diseases, cancer, eye diseases, metabolic diseases, diseases of the immune system and mental diseases. The study aims at improving the individual risk prediction for diseases, and includes a comprehensive data set comprising anthropomorphic characteristics, general health status, disease status, and clinical chemistry parameters. In addition, DNA, citrate/EDTA plasma samples, serum and urine samples have been banked and are available for -omics analyses. Access is granted to the Gutenberg Health data after review of specific research studies proposed by the selected consortium and release by the GH Steering Committee. Support for data analysis of the Gutenberg Health Study, as well as further biomarker research/validation by omics methods analysis of bio-banked samples, will be provided by Boehringer Ingelheim.

The T1D Exchange database

The T1D Exchange clinical registry comprises data from about 35 000 children and adults with T1D in the U.S.; about 2/3 of adults and close to half of youth being overweight or obese. There is prospective 5-year-follow-up data and biosamples are available for a subset of the subjects [9][10]. The registry's aim is to characterise the population of adults and children with T1D in the U.S. with respect to diabetes history and medical history. The registry includes a comprehensive data set of anthropomorphic characteristics, general health status, disease and treatment status, and clinical chemistry parameters.

Anonymised data from clinical trial cohorts from industry partners can be made available supplementing the academic cohorts, e.g. for validation of findings or addressing specific research questions.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 8 301 139.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 7 100 000 and an indicative IMI2 JU Associated Partners in-kind contribution of EUR 1 201 139. The latter includes EUR 1 000 000 financial contribution provided by JDRF whose allocation will be decided by the full consortium at stage 2 when preparing the full proposal.

The financial contribution from IMI2 JU is a maximum of EUR 8 301 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following:

- existing research activities either within public health or clinical services in the field of obesity treatment with interests in better defining phenotypes of obesity and their responses to treatment, and;
- expertise in e.g. anthropology, epidemiology, public health, health economics, data management and harmonisation, bioinformatics, systems medicine or multi-omics analysis, lifestyle treatment, public relations; healthcare professionals skilled in obesity care and/or research;
- access to general databases of obesity including both obese with or without T1D and T2D. In addition, since T1D is often juvenile onset and T2D is now becoming more frequent in adolescents, special attention should be paid to including childhood obesity cohorts;
- access to pre-existing clinical cohorts (expected total number from public and private data sets n=50 000) with as broad and detailed relevant phenotyping as possible and access to biobanked specimens for selected biomarker analysis wherever available (including documented informed consent), ideally including both childhood and adult cohorts across different ranges of obesity and when relevant different treatment approaches

The involvement of patient organisations is imperative to making findings relevant. They should be involved at least as advisors to the analysis and interpretation, and as advocates for the community outreach. In addition, the results from the project should be discussed in a dialogue with regulators.

Relevant SMEs with proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of the European Union. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs could be considered in providing expertise and activities such as data and knowledge management; project management with expertise and experience relevant to IMI2 JU/H2020 projects.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal. However, there are already from the participating partners some cohorts and data available that the applicants may want to consider how to include and analyse. A plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

In addition to being an active contributor to the key deliverables of the relevant work packages, the participating patient organisations will support communication internally and help disseminate information externally. The Patient Advisory Board is expected to meet with work package leads four times a year, either in person or via a

teleconference. Both industry and academic partners are expected to contribute to Patient Advisory Board activities, and thus funds should be reserved for this purpose.

Work package 1 – Project management

The goal of this work package is the overall project coordination including:

- financial management and monitoring of deliverables and milestones;
- legal and contractual management;
- ethics management.

Work package 2 – Data federation and database management

The goals of this work package are as follows:

- provision of pre-existing observational and/or clinical data from obese and obesity-risk cohorts;
- provision of multi-omics data, where possible;
- converting data from different cohorts into a standard format;
- perform a quality control of biobanked cohort samples, before these are analysed for additional biomarkers (i.e. ensure standardised quality and fitness-for-purpose of the samples);
- harmonisation of anonymised and converted data into a common structure to be able to be pooled;
- making data accessible to database for analysis;
- construction of a federated database and establishment of suitable database analysis tools;
- database management and administration of users, permissions and security;
- ensure legal issues including data sharing agreements;
- develop plan for sustainability of database and ways to ensure creation of value from the project results beyond the project period.

Work package 3 – Systems biology and data analysis

The goals of this work package are as follows:

- setup of a web portal and tools enabling analysis and visualisation of data, including an Application Programming Interface (API) for programmatic access for data analysis;
- perform integrative analysis across data sets and cohorts to identify the patient sub-groups;
- comparison of patient cohorts and identifying relevant gaps and biosamples for analysis;
- perform additional biomarker analysis in bio-banked samples for relevant gaps identified;
- identify and/or establish assays for analysis of biosamples.

Work package 4 – Analysis of T1D, T2D and obesity

The goals of this work package are as follows:

- epidemiology: determine prevalence of overweight/obesity among people with T1D, T2D and obesity in general population, by demographic group (age, income, ethnicity), by lifestyle (diet, exercise frequency, etc.);
- characterisation of the obese phenotype in T1D, T2D and obesity;
- determine how obesity and its converse, weight loss, affect T1D, T2D and obesity disease characteristics, treatment effectiveness, clinical outcomes;

- identify mechanisms underlying the effect of obesity on T1D, T2D and obesity metabolism and outcomes toward the goal of developing improved treatments in the future;
- assess the effects of long-term obesity in people with T1D, T2D and obesity, and 'metabolic memory' phenotypes conferred by obesity that may persist even after weight loss;
- assess whether any of the above is distinct for T1D due to the autoimmune milieu and whether specific therapeutic strategies should be targeted or not;
- weight management in T1D, T2D and obesity: determination of effective therapeutic and lifestyle interventions for obesity prevention and weight loss in people with T1D, T2D and obesity;
- communication of findings to the public to educate all customers about T1D, T2D and obesity and to increase citizen and patient involvement in identifying relevant approaches and optimising study design.

Work package 5 – Patient preferences

The goals of this work package are as follows:

- collection and generation of information on patient preferences in relation to the need, value and assessment of obesity treatment, taking the social, cultural and other environment of the patient into account;
- apply an analytic mindset and tools to synthesise a patient perspective to ensure the relevance and value to patients across the project. Liaise and collaborate with patients and key stakeholders to facilitate outcomes and learnings including educational material with relevant patient organisations.

Work package 6 – Shared value analysis and communication

The goals of this work package are as follows:

- establish a network consisting of key internal and external stakeholders to engage in collaboration around obesity from public health and payers' perspective;
- conduct a shared value analysis to extract common values and challenges. Based on this analysis, generate a shared value package/communication to reflect current thinking among stakeholders;
- engage across work packages to shape communication and deliverables as relevant to address public health perspectives and support knowledge about obesity, prevention and treatment opportunities.

Industry contribution

In summary, the industry consortium will provide the following to the project:

- access and support for analysis of the Gutenberg Health Study;
- access to the T1D Exchange data;
- anonymised data from clinical trial cohorts from industry partners supplementing the academic cohorts;
- in-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity;
- know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time;
- limited supplementary funding for supporting further analysis of biobanked samples;
- limited supplementary funding of development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis;
- management of the consortium including the Patient Advocacy Board.

Expected Applicant consortium contribution:

In summary, the applicant consortium is expected to provide the following:

- pre-existing cohort data from patients with obesity and data from comparative non-obese patients;
- biobanked samples for analysis;
- data-driven analysis tools and expertise;
- follow-up analysis of data and definition of further biomarker analysis needs;
- generation of a subgrouping tool, e.g. an application based on a diagnosis algorithm including a measure of the confidence level of the suggested subgroup;
- bioinformatic expertise;
- public-health and public relations skills;
- capability of omics analysis;
- access to validated platforms for analysis of bio-samples;
- assay development;
- data reformatting and harmonisation.

References

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[10] Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, Maahs DM, Tamborlane WV. Current state of type 1 diabetes treatment in the US: Updated data from the T1D Exchange Clinic Registry. Diabetes Care. 2015;38:968-70.

Topic 2: Open access chemogenomics library and chemical probes for the druggable genome

Topic details

Topic code	IMI2-2019-17-02
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Background and specific challenges to be addressed

In biomedicine, discoveries arising from novel enabling technologies and reagents have garnered a quarter of the Nobel Prizes for chemistry and medicine in this century. Among the myriad of these transformative techniques and reagents, bibliometric evidence shows that pharmacological modulators (chemical and biological probes) have both the greatest scientific citation impact, the greatest sway on exploratory biomedical research, and provide the best mechanism to understand the relevance of a protein as a potential drug target [1][1]. Indeed, the field of drug discovery and the development of new molecular entities are predicated on the availability of sound mechanistic principles. Unfortunately, our understanding of human disease remains inadequate, and as a result clinical success rates for novel mechanisms remain low. Currently only one out of ten clinical drug candidates reaches the Open Access Chemogenomics Library and Chemical Probes for the Druggable Genome market after an average of 10 years and at a cost of at least EUR 2 billion in R&D expenses per drug.

Ultimately, the most effective method of dramatically improving the efficiency of R&D is to initiate studies on the 'right' target, and this is possible only if we dramatically increase our understanding of disease mechanisms. Experts agree that genetics and big data are promising approaches to select the right target, the appropriate biomarkers and the patients that are most likely to respond to any given treatment. However, this promise is a long way from reality in most cases; experience has shown there still remains a difficult path from prioritising a candidate gene with human genetics through to a successful R&D project [1][2].

We urgently need to close the gap between establishing a genetic link and the underlying disease mechanism for potential drug targets, and, to this end, we believe that there is an immediate need to design a set of open access (*i.e.* unencumbered and free of intellectual property restrictions) chemical compounds for the entire druggable genome. The set, which would comprise an openly accessible chemogenomics library and selected high-quality chemical probes will provide scientists across the world with the tools to interrogate and validate independently new candidate genes identified by modern genetic studies and bioinformatics in a variety of informative biological systems [1][3][1][4][1][5][1][6][1][7] among which advanced, patient-derived assays will be the most relevant.

Need and opportunity for public-private collaborative research

The creation of an open access set of tools with which to interrogate the entire druggable genome is a challenge of scale and breadth that cannot be solved by a single institution. Moreover, a partnership between EFPIA members, mid-sized companies, Associated Partner organisations, academia and SMEs will be essential to achieve this goal, as these institutions have complementary resources and expertise necessary for success. For example, industry has extensive medicinal chemistry and screening facilities, but these capabilities must be used in the context of biological validation, most commonly performed in academia. Access to patient samples that are genotyped and accompanied by their clinical histories must be accessed by involving physician scientists in academic institutions. New technological and experimental approaches will also be needed to speed up the process of creating new tool compounds. We also believe that impact is dependent on open science because a pre-competitive, shared risk investment model will allow the partnership to provide the wider community access to the generated reagents quickly and with no strings attached, thus amplifying its impact. Moreover, open science also better assures adherence to high standards of quality and the reproducibility of results (a major issue in biological research), with

concomitant increases in productivity and innovation. Finally, through a public-private partnership, both funding and expertise will be highly leveraged.

Scope

Currently, the druggable human genome is estimated to consist of at least 3 000 genes. This topic aims to generate potent, well-characterised, functional, small-molecule modulators for a significant number of these and, at the same time, lay the foundation for identifying a set of openly accessible (i.e. unencumbered from restrictions on use) tool compounds for the entire druggable human genome. With this set of chemical tools available, scientists will be poised to interrogate the latest findings emerging from big data approaches and human genetic studies, thus compressing time from gene discovery to target prioritisation, and ultimately to patient benefits. Importantly, although we imagine the consortium can make great progress by assembling and characterising pre-existing compounds into an initial chemogenomics set, this is not enough. It is imperative to fill the significant gaps by discovering and developing novel chemical tools/probes against under-studied proteins (or protein families) that may be involved in the initiation and progression of disease.

The overall aim of this topic will be as follows:

- establish a framework to assemble an open-access chemogenomics library for the druggable genome – namely a physical library supported by compound meta-data;
- further enrich the open access library by inventing new, deeply characterised chemical probes to selected specific protein families;
- develop open-access assays from well characterised human disease tissue with a special emphasis on immunology, oncology (including immune-oncology) and neuroscience to profile the chemical tools and chemical probes;
- establish sustainable infrastructure, with high priority on accessible platforms and appropriate governance, for prolonged discovery and dissemination of tool compounds, assays, and associated data, beyond the lifetime of this project;
- develop a communication plan to facilitate the dissemination of the compound sets and to ensure their appropriate use.

N.B. A chemogenomics library describes the use of target family-directed chemical libraries in target or cell-based assays as a means of accessing new areas of biology and accelerating drug discovery research based on the assumption that similar receptors bind similar ligands. Such sets, although containing compounds that individually do not fulfill the stringent criteria of a chemical probe, can still be used to interrogate multiple members of protein families to help prioritise the most therapeutically relevant ones that could then form the basis of a chemical probe project. In contrast, a chemical probe is a small molecule that modulates the function of a protein in a specific and selective way. The compound must exhibit a defined *in vitro* potency for a single target and possess a minimum 30-fold selectivity relative to other sequence-related proteins of the same family. Furthermore, the probe must be profiled against a standard selection of other unrelated, pharmacologically relevant targets and large protein families of relevance to drug discovery (specificity), and, finally, have demonstrated on-target effects in cells (cellular activity).

Expected key deliverables

The consortium will generate an open access chemogenomics library consisting of about 5 000 compounds that cover roughly 1 000 protein targets (i.e. one third of the current druggable genome). Here, the term open access includes not only the right to publish findings using these tools, but also includes the unencumbered and pre-publication dissemination of the results, the tools themselves, the assay protocols, and all the associated data packages. This open access chemogenomics set will serve as a substantial head start on generating a library covering the entire druggable genome. In addition, the consortium will develop chemical probes for two to three jointly agreed target families with an initial focus on E3 ligases and solute carriers (SLCs), which may be carried out in partnership with existing IMI consortia, such as ReSolute. For this component, up to 100 novel, well

characterised, high-quality chemical probes, as defined by leaders in chemical biology [1][5][1][6][1][7][1][8] are intended to be generated. To achieve this goal, the consortium will generate recombinant proteins, solve crystal structures, and establish all biochemical and cellular assays needed to ensure that the probes meet the established stringent quality criteria, including target engagement in cells [1][9]. Finally, the consortium will develop scientific and sociological mechanisms to extract biological and disease information from the chemogenomics libraries and chemical probes – and their targets. Given the technical issues that plague interpretation of data from established cell lines, we strongly believe that this will depend on accessing more relevant assays through which to profile the compounds. These assays must be shown to be reproducible, to be derived from genotyped and deeply phenotyped patient-derived tissue and the results to be made available broadly, so that biological data from all the assays can be combined and mined [1][10]. The partnership is expected to develop around 20 novel human tissue-derived assays in three major therapeutic areas of immunology, oncology (including immune-oncology) and neuroscience and test tool molecules and chemical probes in these assays.

Project success will require the partnership to establish enabling infrastructure to generate the probes. This includes cell and biochemical assay panels for characterisation of the compounds, including off-target analysis, a complementary database and a modern, scalable compound store and compound logistics. In addition, the partnership must explore new technologies in the field of fragment-based screening and high-throughput proteomics to accelerate the process of tool compound generation and characterisation. Finally, the consortium will set up platforms that permit broader access to these technologies both from within and outside the consortium – so the community can participate and help achieve, or exceed, the projects goals.

With this proposal, it is planned to lay the foundation on which to build and organise a worldwide network of laboratories to generate chemical tools for the entire druggable genome. Outstanding scientific leadership will be required in order to achieve this vision. It is also envisaged that this endeavor will help identify new scientific opportunities, identify and build strategic partnerships with other projects (e.g. patient groups, international consortia, other IMI projects), and promote truly openly accessible science.

The chemogenomics library, the chemical probes, and the accompanying metadata (potency, selectivity, activity in cell-based assays) are intended to be open access, i.e. use of the compounds will be made available unencumbered, in a pre-publication state and free from restrictions on use. After quality control, assays and data generated by the consortium will also be made publicly available without restrictions. In addition, technologies developed throughout the project must be likewise non-exclusive, platform-oriented, ready for application, openly and freely available for use, dissemination, and commercialisation during and following the completion of the project. Finally, as part of a sustainability concept, the partnership will provide non-exclusive access to the synthetic routes of these compounds to large and/or mid-size vendors that are willing to distribute the chemogenomics library and/or chemical probes and their controls worldwide.

Expected impact

This project will provide the wider academic community with unencumbered access to the highest quality tool compounds for a large number of novel targets, and the expected impact should therefore be transformative. Presently, many companies and organisations are already in the process of setting up their own chemogenomics libraries. Although these have the potential to be phenomenal resources for the companies, their utility is also limited: they are not widely available to academia, they are likely to overlap, and each compound set is not as deeply characterised as could be managed within a larger, more focused, more resourced and more transparent project. By making a high-quality, broader compound set available, the consortium will seed a massive community target prioritisation and target deconvolution effort [1][2]. Moreover, in providing chemical tools without restriction, the consortium will also make available tools to invent new assays and unencumbered starting points for probe development or drug discovery. The consortium's centralised, cell-based and biochemical assay panels will serve as a resource for the entire chemical biology community. The ability to access these capabilities will provide significant incentives for external scientists to contribute innovative compounds to the network, thus expanding the impact with donated resources. The cell and tissue platform with the high-quality, patient-derived cell assays will provide the opportunity for clinical scientists to undertake translational medical research and biomarker discovery, and will provide the roadmap for other clinical centers to access the libraries and make important translatable discoveries.

The availability of chemical probes to unprecedented targets will also open up exciting new research avenues. As an example, open access, novel E3 ligase binders will provide much needed starting points for the development of new protein-targeting chimeras (PROTAC). In addition, the research strategies undertaken in this topic may serve as a template for the technology development to expand the project to include tool generation for areas of the genome currently not considered as druggable.

The management and data infrastructure and the assembled global collaborative network will lay the foundation for unparalleled progress in providing high-quality, open-access tool compounds as a basis for reproducible research. Indeed, this topic has the potential to cause a fundamental shift towards a more open and pre-competitive approach to the costly field of target prioritisation and discovery without compromising the proprietary research models required in industry. Finally, the significant amount of freely accessible, high-quality data generated within this consortium will be a rich source for future analyses by data scientists. Artificial intelligence and machine learning applications using high-quality data on highly diverse compounds across many pharmacological mechanisms will spur research in new fields of biology and generate a source of targets for proprietary projects in various therapeutic areas.

Open access – additional dissemination obligation

Considering the specific nature of this topic, it foresees application of an additional dissemination obligation (IMI2 JU MGA art. 29.1). All results of this project will be made available to the scientific community by open access (i.e. unencumbered, pre-publication, and free from restriction on use). Open access parameters include not only the right to publish findings using these tools, but also the right to disseminate the tools, results, assay protocols, and all the associated data packages, including cell-based assays.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts.

Therefore, the synergies with the following past and ongoing IMI1 & IMI2 projects could be considered by the applicants:

- Unrestricted Leveraging of Targets for Research Advancement and Drug Discovery (ULTRA-DD): https://www.imi.europa.eu/projects-results/project-factsheets/ultra-dd
- Research Empowerment on Solute carriers (ReSOLUTE): https://re-solute.eu/
- Open PHACTS (terminated): https://www.imi.europa.eu/projects-results/project-factsheets/open-phacts

Please note that during the project implementation phase the applicants could also consider other potential knowledge generated by the forthcoming projects under IMI2 JU:

- European Screening Centre: unique library for attractive biology (ESCulab): https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call12_CallText.pdf
- Development of a platform for federated and privacy-preserving machine learning in support of drug discovery: https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF

Synergies with the following European and international initiatives could also be highly relevant:

- Structural Genomics Consortium (SGC, https://www.thesgc.org/) that has in depth expertise concerning all aspects of this proposal;
- US National Institutes of Health initiative, Illuminating the Druggable Genome (https://ncats.nih.gov/idg), which will provide the bioinformatics tools to help improve the understanding of the properties and functions of proteins that are currently not well studied within commonly drug-targeted protein families;
- European Bioinformatics Institute (EMBL-EBI, https://www.ebi.ac.uk/) for data handling and analyses;
- Open Targets (https://www.opentargets.org/) for target identification;
- H2020 iNEXT consortium (https://cordis.europa.eu/project/rcn/194892_fr.html) for fragment screening;
- H2020 OpenRiskNet (https://cordis.europa.eu/project/rcn/206759_fr.html) for compound design;
- ERIC EU-OPENSCREEN (www.eu-openscreen.eu) for screening;
- ESFRI-consortium ELIXIR (www.elixir-europe.org) for sustainable infrastructure for biological information;
- ERIC INSTRUCT (www.instruct-eric.eu) for structural biology infrastructure.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Bayer (project co-lead)
- Boehringer Ingelheim (project co-lead)
- Pfizer
- Servier
- Takeda

As part of this endeavour, each pharmaceutical industry partner is willing to contribute at least 10 high-quality chemical probe compounds from their current or previously terminated R&D projects; at least 50 chemogenomics tool compounds from their own compound collections; and support the development of a minimum of 5 chemical probes by in-kind (especially chemistry).

In addition, the industry consortium includes the following IMI2 Associated Partners:

- Diamond Light Source (UK)
- Ontario Institute for Cancer Research (Canada)
- The Montreal Neurological Institute at McGill University (Canada)
- The Royal Institute of Technology (Sweden)

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 30 257 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 23 800 000, of which EUR 9 930 000 financial contribution to the beneficiaries receiving JU funding in the selected action and an indicative IMI2 JU Associated Partners in-kind contribution of EUR 6 457 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 27 935 000.

Applicant consortium

The applicant consortium (academic groups and SMEs) is expected to demonstrate expertise, leadership and a proven track record in all scientific areas addressed in the topic, including:

- adherence to open-access principles, and expertise in developing and managing open-access projects, which are essential to provide unencumbered and pre-publication access to the chemogenomics tools, chemical probes, patient-derived assays, and associated data packages to the scientific community free of any restrictions on use;
- expression, characterisation and structure determination of soluble proteins, integral membrane proteins, and protein complexes in an integrated project at large scale;
- assay development across a large number of different proteins and protein classes, including cell-based target engagement assays;
- screening compound libraries at scale, using a variety of approaches including high-throughput, focused, computational, fragment and DNA-encoded libraries;
- 'hit-to-probe' capabilities, including using structure-guided methods to improve efficiency and systematic characterisation in relevant biophysical, biochemical, and especially cellular/phenotypic assays;
- strategies to systematically map the knowledge space of protein families, including developing computational approaches and physical reagents to facilitate cross-screening;
- generation, characterisation and dissemination of chemogenomics libraries, including systematic compound characterisation *in vitro* and in cells;
- establish quality-control metrics and both demonstrate and record their use in practice, including mechanisms to solicit independent input into quality;
- development of innovative technologies to speed up the generation of tool compounds, and innovative approaches to accelerate their wider adoption in academia and industry;
- development of strategies to ensure that chemical probes are appropriately used by the community in biological assays;
- track record of scientific success in partnerships with clinical centres, and success in managing contracts and ethical issues;
- track-record of obtaining project-specific ethical approvals for clinical research collaborations;
- using patient-derived samples to advance drug discovery in close cooperation with industrial partners, including the development of novel assays.

SMEs can be of great benefit to IMI2 JU actions and can strengthen the competitiveness and industrial leadership of the European Union. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the funded action. For these reasons, applicants should consider engaging SMEs throughout the proposal. For example, under this topic, the contribution of SMEs would be considered beneficial for broad profiling of chemogenomics compounds and chemical probes.

Members of the applicant consortium are also expected to demonstrate excellence and a proven record of accomplishment (evidenced by collaborative publications) in establishing networks of recognised thought leaders in all relevant sectors indicated in the topic, including:

- a global network that spans medicinal chemistry, biological assays, human biology, experimental medicine and clinical research;
- proven track record of achieving high-value/high-impact outcomes catalysing research in pioneer target areas of drug discovery;
- ability and history of leveraging additional funds with diverse and international organisations, including patient groups, foundations, philanthropy and SMEs;
- history of making research output widely available and evidenced commitment to open science principles;
- mechanism in place to efficiently and effectively disseminate chemical and biological research materials (e.g. chemical probes, protein constructs, antibodies).

Members of the applicant consortium are expected to have successfully collaborated with a network of scientific researchers especially with industry and should demonstrate:

- previous impact on launching or adding value to internal drug discovery projects in the pharmaceutical industry;
- previous impact on providing the foundation for experimental medicine studies in the public sector;
- previous success in collaborations among networks of academics and SMEs – as evidenced through shared projects and co-authored publications;
- previous success in governing and managing large projects, including e.g. finance, intellectual property and inter-institutional contracts;
- a track record of consistently achieving (or even exceeding) milestones and deliverables on time and within budget;
- a track record of making new technologies widely available, for example as generally accessible platforms or commercial products;
- experience in managing varying interests of multiple stakeholders.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal that includes their suggestions for creating the full proposal architecture, taking into consideration the industry contributions and expertise provided below.

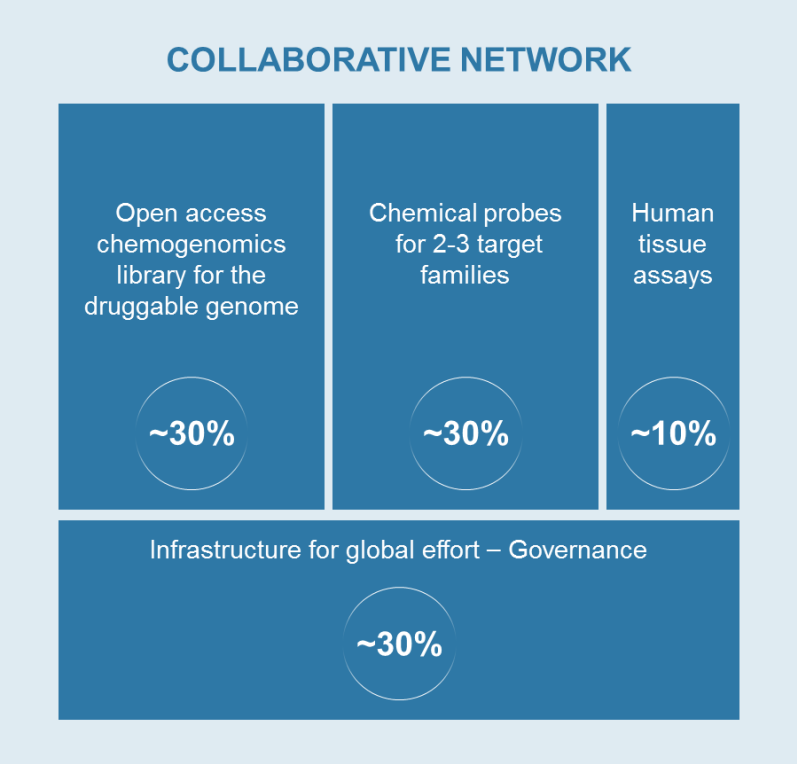
In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The full consortium will define project aspects such as governance, guiding principles and project plan. The architecture below for the full proposal is a suggestion.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The planned endeavour consists of four parallel pillars that include an underlying sustainable network infrastructure. The expected resource distribution to the four pillars is indicated below (% of overall resources):



Pillar 1 – Open-access chemogenomics library for the druggable genome

In the first pillar, it is planned to establish a chemogenomics library consisting of compounds meeting predefined target-specific criteria (biochemical activity, selectivity, physico-chemical profile sufficient for cell-based assays, evidence of cellular target engagement and no general cytotoxicity). To ensure transparency and quality, acceptance of compounds into this library will be governed by an arm's length committee of independent experts from academia. The acceptance criteria for Pillar 1 compounds (e.g. selectivity, potency) will not be as stringent as for chemical probes (Pillar 2 compounds), but because of the extensive annotation, Pillar 1 compounds will be very valuable for target prioritisation, target deconvolution, and as starting point for chemical probes. They will also enable a fast-track approach to develop drug leads for exciting new targets.

The following work packages are planned to achieve Pillar 1 goals:

Work package 1 – Collection of available compounds from academia and industry

Deliverables: 30-100 mg of pure material for ~2 000 compounds identified and collected from the following sources meeting predefined criteria:

- compounds (1 000-2 000 compounds covering a variety of targets) identified and collected from known literature compounds;
- inclusion of openly available chemogenomics compound sets that fulfil stringent quality criteria;

- acquisition of compounds provided by participating pharmaceutical companies (at least 50 per participating EFPIA partner);
- compounds for selected target families generated within this IMI2 project (see Pillar 2);
- establish an independent review mechanism to assess the quality of the compound to be included in the set.

Work package 2 – Annotation of library compounds

Deliverables:

- data packages necessary to enable use of the compounds in pre-clinical studies by scientists globally;
- making data available to the scientific community via a publicly accessible database (see Pillar 4, work package 10), either generated within the consortium, or in collaboration with an existing public partnership.

Work package 3 – New methods for chemogenomics compound generation and profiling

Deliverables:

- protocols for novel and broadly applicable assay principles for biochemical, biophysical and cell-based assays to speed up generation of chemogenomics compounds and their characterisation;
- broadly applicable, novel technological and experimental approaches with the potential to speed up the hit-to-probe process by more than 6 months;
- generation of the remaining 2 000 to 3 000 compounds needed to cover one third of the druggable genome (assumption: 5 000 compounds needed to cover 1 000 targets, i.e. 1/3 of the druggable genome);
- establishing the strongest possible chemogenomics open source network of collaborations, allowing efficient sourcing of externally generated high-quality chemogenomics compounds and sets.

Industry and Associated Partner contribution to Pillar 1:

- provide at least 50 chemogenomics compounds per EFPIA partner from proprietary compound collections as open access chemogenomics compounds; solid material for testing;
- compound profiling in established assay panels that are available within the companies;
- access (free of charge) to the Diamond Light Source (Associated Partner) platforms for external groups contributing to the project deliverables;
- membership in scientific and decision-making committees (e.g. definition of target family-specific criteria and assessment of candidate compounds).

Expected applicant consortium contribution to Pillar 1:

- develop tools to identify chemogenomics compounds from patents, scientific publications and other sources;
- synthesis to provide solid material of chemogenomics compounds for testing;
- provide compound profiling to confirm that they meet the agreed upon criteria;
- experience in high-throughput, fragment-based screening;
- experience in covalent-ligand chemoproteomics approaches;
- assemble the remaining 2 000 to 3 000 chemogenomics compounds to cover one third of the druggable genome via internal activities or through collaborations and/or crowdsourcing;

- characterise selected compounds by determining three-dimensional protein-small molecule complex structures to high resolution and accuracy;
- membership in scientific and decision-making committees (definition of target family specific criteria; assessment of candidate compounds);
- manage independent peer-review mechanism to assess suitability of compounds for inclusion in the set.

Pillar 2 – Chemical probes for 2 – 3 emerging target families

For the second pillar, the aim will be to generate chemical probes for proteins within a minimum of 2-3 priority target families of high therapeutic interest. The initial priority will be on E3 ligases and solute carriers (SLCs), although we will not limit the scope to these target families. E3 ligases and SLCs were selected as initial priority families due to their high therapeutic importance, coupled with their relative intractability. This combination makes them ideally suited for a consortium-based approach for developing high-quality chemical tools. The inclusion of other target families will be agreed jointly by the consortium.

The number of chemical probes generated per family will depend on a number of considerations, including the strength of the genetic links to disease, experimental feasibility, therapeutic potential, as well as the number of members of the target family class. While working on probe projects, the consortium will also generate compounds that may not meet the stringent probe criteria but will be valuable as chemogenomics compounds thereby enriching the collection described in Pillar 1.

The following work packages are planned to achieve Pillar 2 goals:

Work package 4 – Protein production

Deliverables:

Validated protein expression clones, protein purification protocols, recombinant proteins for assay development and for 3D-structure determination; recombinant antibodies to facilitate assay development.

Work package 5 – Assay development for target engagement

Deliverables:

- protocols for target-specific biophysical, biochemical and cell-based assays and use of those assays for probe generation and confirming target engagement;
- genetically-engineered cell lines (such as knockout cells) to inform on target selectivity.

Work package 6 – Structure determination and chemical starting matter

Deliverables:

Generation of protein structures necessary to support probe generation. Depending on the target families selected, protein structures for both soluble and membrane proteins will be required. All protein structures generated in this project will be deposited in the Protein Data Bank (https://www.wwpdb.org/). In addition, fragment screens will be conducted to identify starting points for probe generation.

Work package 7 – Generation of chemical probes

Deliverable:

At least 100 well-characterised chemical probes, meeting stringent criteria for potency, selectivity and with demonstrated on-target effects in cells. This WP includes medicinal chemistry capabilities.

Work package 8 – Technology development

Deliverables:

Development of transferrable technologies for broadly applicable methods to speed up probe development and characterisation along the whole value chain from target selection to probe characterisation. This will include (but not exclusively) automation approaches, cloud-computing platforms, algorithms, parallelisation, reagents, devices, protocols and documentation.

Industry and Associated Partner contribution to Pillar 2:

- design and access to fragment or other bespoke libraries;
- access to larger compound screening collections;
- high-throughput screening (HTS) or focused screens to identify hits;
- crystal-based fragment screening at Diamond Light Source (Associated Partner);
- access (free of charge) to the Diamond platforms for external groups contributing to the project deliverables;
- expertise in triage and validation of screening hits;
- design and synthesis of research chemical probes;
- medicinal chemistry to optimise hits;
- protein expression and purification for selected priority targets;
- assays (e.g. selectivity screening panels) and structure determination to support probe development;
- establish quantitative chemical probe criteria, in conjunction with the applicant consortium.

Expected applicant consortium contribution to Pillar 2:

- ability to access chemical libraries from leading academic chemists and chemical biologists;
- small- and medium-scale screening of EFPIA partner chemical libraries;
- secondary biochemical screens to validate and prioritise hits;
- off-target biochemical and cell-based screens;
- crystallographic fragment screening and protein-ligand structure determination to support probe development;
- design and synthesis of chemical probes;
- medicinal chemistry to optimise hits;
- assays (e.g. selectivity screening panels) and 3D-structure determination to support probe development;
- high-throughput cloning, expression, purification, and novel 3D structure solution (if necessary);
- established quantitative chemical probe criteria, in conjunction with industry;
- technology development to improve quality and speed up the development and dissemination of chemogenomics compounds and of chemical probes.

Pillar 3 – Human tissue assays

All chemical probes and selected chemical tools will be subjected to unbiased phenotypic screening in patient-cell-derived assays for target validation in the human disease context. Specific assays will be in new and emerging areas of immunology (e.g. inflammatory bowel disease, scleroderma, interstitial lung disease, lupus, arthritis, and fibrosis in different organs), oncology (including immuno-oncology) or neurological areas (e.g. neuroinflammation and neurodegeneration). Assays developed previously in the Ultra-DD and other IMI programs might be leveraged and expanded to include new and emerging areas of research.

The following work packages are planned to achieve Pillar 3 goals:

Work package 9 – Human tissue assays

Deliverables:

- develop at least 20 novel human tissue-derived assays in three major therapeutic areas of immunology, oncology (including immune-oncology) and neuroscience. Selected established high-quality translational assays will be optimised and miniaturised and others (such as more complex co-culture systems) will be developed within the project;
- validate these assays by using tool molecules and test chemical probes, including gold-standard positive and negative controls. The cell-based assays will be derived from human material, such as blood and tissue biopsies;
- when possible and if scientifically appropriate, the consortium will convert primary cells into a renewable resource, such as human stem cells and spheroids as well as organoids;
- both primary and stem-cell derived cells will be deeply characterised phenotypically, and to the extent possible within the funding frame, also characterised by deep -omics technologies.

Industry and Associated Partner contribution to Pillar 3:

- contribute high-quality compounds for screening in these biological assays;
- provide scientific expertise and advice to support setup and develop the human tissue assays (including details on protocols, throughput formats and patient-genetic stratification for sample collection as needed);
- access to patient-derived assays for neurodegeneration;
- profile the compounds emerging from Pillars 1 and 2 above into assays and generate target validation data packages collaboratively with the consortium partners.

Expected applicant consortium contribution to Pillar 3:

- network of target and disease experts to profile each probe in disease-relevant assays (e.g. immunology, cancer and neurology);
- access to patient-derived human material (fluids, blood, tissue, other);
- ethical and legal frameworks to engage in such collaborations;
- strategies to include genotyping and deep phenotyping of patient-derived cells and tissue;
- mechanism to characterise probes in other consortia with panels of cell-based assays, e.g.
  Sanger Institute (https://www.sanger.ac.uk/)
  NCI panel (https://dtp.cancer.gov/discovery_development/nci-60/cell_list.htm)
  BTCure (https://www.imi.europa.eu/projects-results/project-factsheets/btcure)
  STEMBANCC (https://www.imi.europa.eu/projects-results/project-factsheets/stembancc);

- engage additional collaborators who are leading the field in functional cell assays and disease models for particular targets;
- mechanism to access additional, relevant phenotypic assay panels in priority areas.

Pillar 4 – Infrastructure and governance to lay the foundation for a global effort on the whole druggable genome

To establish an efficient and coordinated effort within this project, an additional goal of the fourth pillar is to align this project with similar projects or individual efforts globally, in order to reduce duplication of effort and to leverage the IMI investment. The consortium will work with global efforts to adopt such standards, and to this end, will establish or implement standardised, broad cell-based and biochemical assay panels to characterise chemogenomics compounds and chemical probes. The consortium will also establish a database for all data generated, as well as a central compound store and compound logistics (e.g. via a contract service organisation). The intention is for the chemogenomics library and the corresponding sustainable infrastructure to form the nucleus of a coordinated, worldwide, open-access effort to put together a reference compound library covering the entire druggable genome. Consequently, an important aspect of this project will be to provide leadership and a governance structure for the network, which will include investigators not only within the IMI consortium but also from complementary projects around the world. Although many members of the network will be working independently, and with independent funding, the aim is for all partners within the network to follow a jointly agreed masterplan to maximise synergies. In addition to the network, the consortium will find innovative ways to add compounds to the library, including e.g. setting up competitions for young scientists via crowdsourcing to add to the project deliverables. In summary, it is essential for the consortium to develop an international partnership comprising screening centres and chemical biologists around the world. We plan to encourage open-access publication of the results of the research in open-access scientific journals, help create platforms to share results, and work with commercial vendors to make the physical samples of tool compounds available for years to come to the biomedical community.

The following work packages are planned to achieve Pillar 4 goals:

Work package 10 – Infrastructure and platforms

Deliverables:

- compound logistics to handle distribution of all chemogenomics compounds and probes as well as compound exchange between partners;
- more than 500 assays established/accessible to annotate chemogenomics compounds and probes generated within this project with a potential to test compounds from network;
- easily accessible database containing all data generated within this project with a potential to hold data from related endeavours; format suitable for chemists and biologists; these data will be generated and made accessible according to FAIR (findable, accessible, interoperable, reusable) principles;
- long-lived platforms and transferrable infrastructure (e.g. open source code, commercially available services, cloud-hosted servers) to make the new technologies available to a wide audience beyond the consortium;
- open access and dissemination framework established.

Work Package 11 – Global framework

Deliverables:

- the framework for a global network with partners around the world that work on related goals, established with a governance structure that supports efficient collaboration and sustainability;

- partnership agreements with major European and international efforts in screening assay development; patient-derived cell assays, chemical screening, chemical probe generation and compound profiling;
- a process for recruitment and rigorous triage of external activity and contributions.

Work package 12 – Project management

Deliverables:

A management and governance structure which ensures that the project completes all deliverables in a timely and efficient manner.

Industry and Associated Partner contribution to Pillar 4:

- director or senior scientist/manager to represent company on joint steering committee;
- experts in drug discovery to manage collaborations in specific scientific areas or on specific targets/target families;
- contributions to collaborative scientific meetings, management of internal versus external activities;
- advice, involvement or secondment on infrastructure development, e.g. compound management, database, platform technologies, partnering opportunities and governance framework.

Expected Applicant consortium contribution to Pillar 4:

- experienced managers to ensure that the key consortium deliverables are completed;
- senior scientists to manage project deliverables, to disseminate the project outputs and to engage in collaborations to maximise impact;
- database, loader and visualisation tools to enable open access use of all data generated in this project and within related initiatives; partnering with public databases (e.g. ChEMBL) if possible;
- development of compound logistics for this project and for related initiatives to enable easy access to the chemogenomics compounds and the chemical probes, e.g. in collaboration with established SMEs;
- management of finance, valuation of deliverables, communication etc;
- create international alliance of screening, probe generation and compound profiling initiatives and align toward consortium objectives;
- dissemination of results in the form of publications, meeting presentations, and via the consortium's website;
- screening assays for broad profiling, e.g. broad panels for kinases, G-protein-coupled receptors (GPCRs); assays for cell permeability and unspecific toxicity;
- plan for sustainability of infrastructure after the end of this project, e.g. via partnering with contract research organisations (CROs), national facilities and vendors.

Sustainability

Sustainability measures beyond the duration of the proposed action should be considered based on the expected results generated by the action. At stage 2 the full consortium would have to propose a sustainability plan to be implemented during the project duration and including relevant resources and budget. Sustainability is of utmost importance for this project.

- The chemogenomics library and the chemical probes, and the existing and new data from their use, should be easily accessible on a continuous basis. The applicant consortium should have a convincing plan how to

achieve this, e.g. via non-exclusive access to the synthetic routes of these compounds to vendors be they large, mid-size or even start-ups, that are willing to distribute the chemogenomics library and/or chemical probes and their controls.

- A significant investment in hardware, software and expertise for compound logistics, database and assay panels will be needed to make this project a success. To make best use of the investment, the applicant consortium should already have an initial plan for sustainability.
- This project is planned as part of a global initiative for creating an open-access chemogenomics library for the entire druggable genome. This ambitious goal, which is beyond the scope of this particular call, will not be achieved within the timeframe of this IMI project, thus, sustainability of the infrastructure and platforms is of utmost importance for the overall mission.

The applicant consortium should already have an initial plan for sustainability, e.g. via CROs that are interested to continue operations as part of their business or via letters of intent from universities or other research organisations concerning the continued use of the research tools and the infrastructure. A detailed plan will be developed and implemented within the project.

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Topic 3: Intelligent prediction and identification of environmental risks posed by human medicinal products

Topic details

Topic code	IMI2-2019-17-03
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Pharmaceuticals are present in the environment as a consequence of patient use, manufacture, and improper disposal. They predominantly enter the aquatic environment via patient use and are typically found in concentrations from sub-ng/l to a few µg/l [1].

In the European Union (EU) an environmental risk assessment (ERA) is required as part of the marketing application and approval for new drugs [2]. Currently the ERA is conducted late in drug development and often parallel to Phase III clinical trials and after significant investment. An ERA is triggered if the predicted environmental concentration (PEC) exceeds 0.01 µg/l. More focused, exposure-independent environmental assessments are also required if (i) the drug is highly lipophilic (logD ≥4.5) and could fulfil the criteria for a persistent, bioaccumulative and toxic (PBT) chemical, and/or (ii) the drug is a potential endocrine disruptor that acts on the reproductive axis requiring tailored assessment. Chronic sub-lethal ecotoxicity testing has only been required since 2006 in the EU [2].

The growing regulatory and scientific concerns regarding pharmaceuticals in the environment have reached the point where some stakeholders are advocating:

- the inclusion of environmental hazard and risk within the patient-benefit evaluation that underpins the marketing authorisation of a drug;
- a catch-up scheme for medicines authorised for use prior to 2006 that lack comprehensive environmental assessments;
- increased transparency of environmental data;
- increased consideration of environmental properties in drug development (i.e. greener drug design).

The inclusion of environmental hazard and risks in the patient-benefit analysis challenges the current drug development paradigm where environmental testing is conducted parallel to Phase III clinical trials. Without validated tools to predict environmental risk earlier in drug development this could impact the availability of life-changing medicines to patients within Europe and impact the competitiveness of the industry. These tools can also be used to prioritise established pharmaceuticals for testing and tailor specific test requirements to conclude on environmental risk in an effective and efficient manner. Many of these concerns are captured within the current European Commission (EC) strategic review of pharmaceuticals in the environment (PiE) [3] and they form the foundation for this IMI2 JU topic.

Burns et al. (2018) [4] have already demonstrated that prioritisation approaches need to consider consumption, environmental exposure potential (generic and spatially explicit exposure), lipophilicity, mode of action, pharmacological potency, target conservation and read-across, in order to identify drugs of potential environmental concern and ensure that the right species are chosen for a tailored environmental assessment. The availability of tools and models to assist with the prioritisation of approximately 1500 legacy drugs that lack any environmental data for tailored ERAs has the potential to deliver significant animal welfare benefits and cost savings without compromising environmental protection. It is also important that a database of environmental information on active pharmaceutical ingredients (APIs) is maintained, developed and populated within iPiE-25 in a manner that

maximises the transparency of ERA data to all external stakeholders, in order to help inform ongoing environmental monitoring campaigns and other scientific and regulatory activities. The availability of these data in the public domain would also reduce unnecessary duplication of testing, including some vertebrate testing on fish, and reduce the number of conflicting environmental risk assessments that exist for some compounds. Additionally, the same tools and models used for prioritisation could be used to predict the risk of human metabolites of APIs.

Need and opportunity for public-private collaborative research

A public-private collaborative research partnership is required to identify and manage the environmental risks of human medicinal products across the whole of their product life cycle as no single stakeholder can proactively manage and mitigate these risks alone. The holistic environmental stewardship of human medicines requires consensus across many stakeholders and technical experts, potentially including:

- regulatory agencies (i.e., European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), national environment agencies, European Commission's Directorate-General for Environment) may contribute publicly available information on registered APIs;
- EMA and the EC as key stakeholders can contribute to appropriate assessment designs to address the issue of PiE and deliver elements of the PiE strategy;
- inter-governmental organisations with responsibility for environmental health policy such as environmentally persistent pharmaceutical pollutants (e.g. United Nations Environmental Programme and the Strategic Approach to International Chemicals Management (SAICM), the Organisation for Economic Co-operation and Development (OECD));
- medicinal chemists and structural biologists to support ambitions for exploring the feasibility of greener drug design;
- specialised subject matter experts may identify and extract public data and populate a species diverse ecotoxicological database;
- academia may contribute by elaborating theoretical and hypothesis-driven experimental testing programmes to validate hazard or risk predictions, and define prioritisation parameters;
- experts in artificial intelligence and machine-learning specialists to support the identification of relationships at a systems-wide level that can act as predictors of environmental hazard and risk;
- environmental engineers including scientists from the waste water industry;
- social scientist community and socio-economists to determine the relative value society and patients place on safety, efficacy and environmental considerations versus access to medicines;
- patient-oriented organisations;
- physicians and pharmacists who have interests in the environmental impact of pharmaceuticals and association professional development training;
- independent consultants that may support the development of *in vivo*, *in vitro* and *in silico* tools for ecotox hazard identification, prioritisation and risk assessment;
- industry may provide input with reference to their large product portfolio, in particular test materials, pre-clinical and clinical data, unpublished ecological information, and contribute to experimental validation programmes.

Scope

The overall objective of this project is to ensure the environmental safety of human medicinal products through patient use by providing innovative and predictive tools to:

- identify environmental hazards and risks associated with candidates in drug development;

- screen and prioritise established, 'legacy' pharmaceuticals for a tailored environmental assessment;
- make environmental data for human medicinal products more transparent to all stakeholders through the development of a publicly available database.

This project aims to validate approaches to prioritise the risks of human medicinal products. A recent review of prioritisation approaches is described in Burns et al. (2018; [4]) that could form the basis for strategies employed in this project. It is important that the predictive *in silico*, *in vitro* and *in vivo* tools and models:

- are extended to include other targets and endpoints in a wider range of taxa and environmental compartments;
- have their predictive capability maximised at a systems level through the application of innovative machine learning approaches and artificial intelligence innovation;
- are validated to understand their predictive capability and applicability domain;
- are assessed for their feasibility to be integrated earlier into drug development to flag environmental concerns sooner than within the current industry model; and
- are applied to established APIs that lack comprehensive datasets to address and prioritise concerns about the environmental risks associated with legacy medicinal products.

Thus, the focus of this project will be on developing methods and guidance for targeting predictions and screening assays on the various types of compound classes represented in the area of human pharmaceuticals. Whilst this project is primarily focused on environmental exposure pathways and associated risks for human medicinal products, some of the project outputs could have potential use in the prioritisation of veterinary medicines. The tools and models developed could also be used to help screen or set safe discharge targets for API manufacturing sites. To deliver these objectives the following issues or themes fall within the scope of the project:

- to work across a broad group of stakeholders including the pharmaceutical industry to define what constitutes a greener API;
- to weigh the feasibility of designing greener APIs with the priorities of patient efficacy and safety;
- to drive innovative approaches to assess environmental risks. Such innovative approaches should include: (i) improving the predictability and applicability of the fish plasma model, (ii) providing three-dimensional *in vitro* cell culture approaches to assess API uptake, metabolism, elimination and toxicity in fish as a key priority for the pharmaceutical industry given the high level of drug target conservation in fish, and (iii) applying artificial intelligence and machine learning approaches to improve comparative toxicological predictions between preclinical and environmental safety assessments. The tools being developed must have the potential to be applied much earlier within drug development than existing environmental assessments and possibly be aligned with ongoing preclinical drug, safety and metabolism assessments;
- to consider environmental impacts in other environmental taxa and for other environmental compartments beyond surface waters, e.g. groundwater, secondary poisoning etc.;
- to address concerns with off-target effects and the environmental relevance of these effects;
- to assess and determine the validity of the tools and models for underrepresented mechanisms-of-action (MOA) classes of APIs and define the applicability domain for the each of the tools and models according to OECD standards;
- to apply and validate the tools, models and methodologies developed with an ambition to assess at least 25 legacy APIs, including key metabolites, selected in agreement with key external stakeholders. It is expected that any ERA data for priority APIs identified, generated and validated in this project will be made publicly available outside the iPiE-25 programme;

- to maximise the knowledge generation potential of a pharmaceutical ecotoxicology/environmental database including the integration of predictive capabilities and maximisation of data accessibility and transparency to all stakeholders;
- to enable the pharmaceutical ecotoxicology/environmental database to capture spatially refined exposure assessments and measured environmental concentrations for prioritised compounds and the integration of tools and models to provide probabilistic or semi-probabilistic approaches to ERA;
- to develop a database as a central resource for the collation of ERA supporting data with the support of the EMA and national competent authorities, in order to minimise duplicate testing, particularly on vertebrates, and remove any requirement for inefficient monograph type approaches.

APIs that are potential sex steroid receptor agonists and antagonists have a categorical inclusion, and require a tailored ERA, hence these fall outside the remit of this topic call. Also given that antibiotics have a mode of action largely restricted to prokaryotic organisms and only require limited testing to conclude on environmental risk they don't require further consideration within this topic call. Finally, due to complexity of investigating environmentally relevant mixtures of APIs and other chemicals models should be developed and validated based on exposure to single compound exposures. However, it should be recognised that many of the tools and models being developed and validated in this project could be applied to mixture assessments.

Expected key deliverables

The expected deliverables should be achieved during the 5-year duration of the funded project.

- Establish a clear definition of what constitutes a greener API and how feasible this ambition is relative to the priorities for patient efficacy and safety.
- Agreement on future ERA and risk prioritisation strategy with our key stakeholders (i.e. the EC and EMA) together with an associated socioeconomic impact assessment for the implementation of this strategy.
- Delivery of validated predictive models/tools together with supporting documentation and guidance that can (i) be integrated earlier within drug development and (ii) prioritise established or legacy APIs for a tailored ERA. The validated tools and models should be made publicly available and consider including:
    - clearly defined validity domain for each tool and model developed within the project and consideration of underrepresented classes of APIs within their validation;
    - the scientific basis for false negative and false positive predictions needs to be considered as do the different regulatory and industry tolerances for false predictions against regulatory decision making and its consequences for drug development;
    - tailored and definitive ERA data for approximately 25 APIs, including some key metabolites, that have been used to test, validate and refine the prioritisation framework and supporting guidance.
- An updated knowledge-driven ecotoxicology and ERA database with integrated software to support semi-probabilistic and probabilistic risk assessments. The fully transparent, long-term hosted and sustainable software should integrate mode of action/read across grouping with associated structural alerts, a wider coverage of APIs together with recommendations for an EU-wide Pharmaceutical Ecotoxicology Database supported by industry and the European Commission. These data are expected to be available in the public domain.

Expected impact

The overall aim of this project is to apply innovative approaches to ensure the environmental safety of human medicinal products such that both (i) environmental concerns do not become a barrier to patient access to medicines, and (ii) the intended use of medicines does not pose an unacceptable risk to the environment.

This project aims to determine the extent to which human medicinal products pose a risk to the environment and to provide innovative tools and models to assess environmental properties earlier within drug development. Current empirical approaches to identify environmental hazard and risk are not suitable for integration earlier within drug development; they are long in duration and require significant test material, hence bespoke models trained and validated on actual pharmaceuticals may offer a genuine alternative.

The current European guidelines for environment risk assessment came into force in 2006 [2]. Therefore, human medicinal products authorised before this date have incomplete environmental datasets and often lack long-term chronic ecotoxicology data. It is estimated that approximately 1500 active pharmaceutical ingredients lack sufficient environmental data to conclude on the risks that they pose to the environment. Within the recommendations made by Deloitte [3] as part of the European Commission strategic review on pharmaceuticals in the environment, an ERA catch-up procedure was advocated for (all) legacy pharmaceuticals that lack data. To conduct a full Phase II Tier A ERA on all medicines authorised before 2006 equates to about EUR 1 billion worth of ERA testing, a significant amount of vertebrate testing, and would saturate the environmental CRO capacity to conduct such studies, in addition to testing for new APIs, for decades. Therefore, an intelligent approach to prioritisation and testing is required. The validation and implementation of such an approach through iPiE-25 could save the pharmaceutical industry more than EUR 500 million without compromising environmental protection. This is serious money and a resource that can be invested in developing innovative medicines for patients, in particular where there is an unmet patient need. This project aims to refine, extend, validate and implement these prioritisation approaches to ensure the environmental safety of established medicinal products.

The transparency and accessibility of environmental data for human medicinal products remains a concern to many stakeholders [3] and the current lack of visibility is resulting in duplicated regulation testing by the pharmaceutical industry within marketing applications. To maximise the transparency of environmental data to all stakeholders this project aims to develop an EU-wide pharmaceutical ecotoxicology database. The availability of environmental data (e.g. ecotoxicological endpoints) in the public domain will (i) help all stakeholders better understand the risks posed to the environment by human medicinal products, (ii) allow environmental chemists to present their monitoring work in the context of risk, and (iii) reduce duplication of environmental testing across the industry. The database will also enable the environmental risks of a human medicinal product to be actively managed across its product life cycle and help facilitate the industry extended environmental risk assessment (eERA) model.

Applicants should also indicate how their proposal will impact the competitiveness and industrial leadership of the European Union by, for example, engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Possible synergies and collaborations could exist with:

- the IMI iPiE Project (http://i-pie.org/) and the iPiE-SUM database (https://ipiesum.eu/)
- the EcoDrug database (http://www.ecodrug.org)
- the IMI eTox project (http://www.etoxproject.eu/)
- the United Kingdom Water Industry Research (UKWIR) Chemicals Investigation Programme
- the NERC-Defra Chemicals in the Environment directed research programme
- the NORMAN Network (https://www.norman-network.net/)
- ChemPop Project funded in the UK which will consider correlations and possibly causations of historical aquatic and terrestrial faunistic and floristic data with historical micro-/macropollutant presence

- US FDA Environmental AssessmentsEuropean Medicines Agency and environmental data within European public assessment reports (EPAR)
- regulatory agencies developing the Japanese and Canadian ERA schemes
- Global Chemical Outlook of the UNEP (United Nations Environment Programme): https://www.unenvironment.org/
- EU Technology Plattform SusChem Europe: http://www.suschem.org/
- Start – Strategien zum Umgang mit Arzneimittelwirkstoffen im Trinkwasser: https://www.researchgate.net/project/start-Strategien-zum-Umgang-mit-Arzneimittelwirkstoffen-im-Trinkwasser

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- AstraZeneca (lead)
- Bayer
- BMS
- Eli Lilly
- GSK
- Novartis
- Roche
- Sanofi
- Servier

The industry consortium will contribute the following:

- expertise and experience in leading and managing large scale public-private partnerships;
- provide physico-chemical, ecotoxicology and environmental fate data that are regulatory compliant (provision of existing data by the industry partners does not count as in-kind support);
- drug discovery and development expertise;
- computational chemistry expertise;
- support for test compound selection and experimental design;
- synthesis of test materials (e.g. 14C API or metabolites) for validation work where existing material is not available;
- design and execution of environmental risk assessments that comply with EMA and FDA regulations;
- identification of appropriate assays to support tailored environmental assessments;
- techniques and statistical methodology development;
- expertise in regulatory sciences and in strategic approaches to collaborate with environmental authorities to introduce innovative environmental methodologies;
- legal expertise related to intellectual properties management and complex partnership co-development structures.

Specific industry contributions are listed under the relevant work packages (WPs) and need to be taken into account by the applicant consortia.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 4 550 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 4 550 000.

Applicant consortium

The applicant consortium will be selected based on the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in partnership with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. Applicant consortia could consist of members from academia, SMEs and subject matter experts in environmental fate, toxicity, modelling and risk assessment. SMEs could include contract research organisations (CROs) providing regulatory compliant studies to support the validation work; alternatively, they could provide tools, assays, models or database development to help deliver the topic objectives. Scientists from regulatory agencies are also actively encouraged within the consortium and wider regulatory engagement will be invited via the formation of a scientific advisory board for iPiE-25.

This requires mobilising, as appropriate:

- experience in leading, managing and measuring impact of public-private partnership consortia;
- expertise in programme management and professional provision of project management services, administration, governance and compliance;
- communication expertise, preferably for stakeholder management of large-scale consortia;
- expertise in ecotoxicology, environmental exposure assessment and environmental risk assessment;
- expertise in environmental exposure modelling and approaches for semi-probabilistic and probabilistic environmental risk assessment;
- proven ability to generate regulatory compliant environmental risk assessment studies;
- expertise in mode-of-action-driven ecotoxicology;
- expertise in data management and curation, database development, data visualisation;
- expertise in the development and implementation of evidence-based decision software;
- social science experience to support engagement with stakeholders across the product life cycle;
- expertise in analytical and environmental chemistry to support environmental assessments and environmental monitoring;
- statistics and statistical modelling expertise relevant for the design and analysis of ecotoxicology and environmental monitoring studies;

- expertise in artificial intelligence and machine learning approaches to big data analysis;
- expertise in drug discovery and drug development;
- proven ability to impact environmental policy and regulation;
- expertise in assessing and judging the quality and relevance of ERAs and supporting studies.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

Work package 1 – Determining the feasibility of greener drug design (year 1 and 2)

One of the options identified within the European Commission strategic review of pharmaceuticals in the environment recommended an EU/industry co-funded initiative to promote the design of APIs that pose lower risks to the environment (Option 3; [3]), so-called ‘green drugs’. The overall aim of this work package is to determine the feasibility of greener drug design.

The goals of this work package may include:

- Consulting with stakeholders across the product life cycle of a human medicinal product to identify what range of properties may constitute a greener drug and its relative importance versus patient efficacy and safety, of which latter must be fundamental for human medicines. This consultation should include medicinal chemists, drug discovery biologists, drug safety and metabolism experts, environmental risk assessors (regulatory and industrial), pharmacists, physicians and patient groups. The focus should be based on risk rather than hazard alone and should consider looking beyond the final active pharmaceutical ingredient to consider environmental impacts across the product life cycle. We anticipate a stakeholder workshop to disseminate, discuss and refine the findings of this review.
- Identifying the specific challenges of integrating environmental considerations earlier within the drug discovery and development cycle. Specific consideration should be given to current innovation and best practice in drug stabilisation and drug delivery strategies, particularly for oral therapy, versus what may constitute a ‘green drug’.
- Reviewing and quantifying the anticipated impact that innovations in personalised medicines, nano-based therapies and biologically-based pharmaceuticals may bring to the environment [5].
- Identifying a series of potential ‘green’ interventions and an associated roadmap for implementation where environmental considerations could be integrated across the product life cycle to proactively manage environmental risks of human medicinal products together with a health and socioeconomic impact assessment. This should be illustrated with potential case studies where possible.

Industry members of the project will bring their knowledge of drug discovery and development, together with relevant strategies to improve drug stability and delivery to help determine the feasibility of greener drug design. Industry will also describe the financial risks, levels of attrition and the criteria for model/ toolbox integration earlier within the development life cycle. Industry will also contribute its environmental knowledge into the activities to define a greener medicinal product and actively participate in stakeholder events and workshops.

Work package 2 – Development of an EU-wide Pharmaceutical Ecotoxicology Database (years 1–5)

To maximise the transparency of environmental data to all stakeholders this work package aims to develop an EU-wide pharmaceutical ecotoxicology and environmental fate database that captures (i) robust and reliable environmentally relevant toxicity thresholds for pharmaceuticals in a standardised format, and (ii) environmental risk assessments at an active substance rather than a product level to provide a view of environmental risk irrespective of product use.

The database should be knowledge-based and curated to ensure that the reliability and relevance of data is sufficient for regulatory decision-making. The database should also include decision-based reasoning and arguments for the inclusion/exclusion of data that can be open to scrutiny.

To help support a 'reality check' of predicted environmental concentration-based risk assessments, the database and associated software should support semi-probabilistic and probabilistic risk assessments that also include measured environmental concentrations and predictions from spatially explicit exposure modelling.

The fully transparent, long-term hosted and sustainable software should also integrate (i) mode of action/read across grouping with associated structural alerts, (ii) a wider coverage of pharmaceutical actives and (iii) recommendations for how it can be migrated to a sustainable EU-wide Pharmaceutical Ecotoxicology Database supported by industry and the European Commission.

Industry members of the project will provide environment data to support the development of the database. They will also contribute to the design of the database and help identify the types of visualisation tools and outputs that can be built into the functionality of the database and associated software. Industry will also work with the European Commission and the European Medicines Agency to ensure the wider sustainability of the EU-wide Pharmaceutical Ecotoxicology Database.

Work package 3 – Tool-box development and refinement (years 1–4)

This work package is focused on driving innovative approaches to (i) assess and identify environmental risk earlier within drug development and (ii) screen and prioritise the risks of established APIs that lack environmental data. It is expected that appropriate tools and models, such as the fish plasma model, will be extended to consider active pharmaceutical ingredients with a wider range of chemical properties and mechanisms of action. Such innovative approaches may include:

- improving the predictability and applicability of the fish plasma model through experimental validation accounting for plasma protein binding and availability [6];
- providing three-dimensional *in vitro* cell culture approaches or 'organs on a chip' to assess API uptake [7][8], metabolism [9], elimination and toxicity in fish as a key priority [10][11], given the high level of drug target conservation in fish [12];
- modelling internal API concentrations in wildlife species other than fish;
- applying artificial intelligence and machine learning approaches to improve comparative toxicological predictions between preclinical and environmental safety assessments [13][14]. Chronic ecotoxicity predictions integrating MOA would be particularly welcome. The tools being developed must have the potential to be applied much earlier within drug development than existing environmental assessment and possibly be aligned with ongoing preclinical drug, safety and metabolism assessments [15][16];

- considering environmental impacts in other MOA relevant environmental taxa and for other environmental compartments beyond surface waters, e.g. terrestrial risk assessment, irrigation and groundwater-related risks [17][18][19], secondary poisoning etc;
- addressing concerns with off-target effects and the environmental relevance of these effects;
- providing guidance how these tools can be integrated within a framework to prioritise established human medicinal products for a tailored environmental risk assessment.

Industry members of the project will partner across all aspects of the work package and provide appropriate expertise and generate test materials and where required new data to support model development. Industry will also help inform how the guidance can be pragmatically included within our existing business models.

Work package 4 – Validation of the prioritisation approach (years 1–5)

This work package should validate the prioritisation approaches advocated by work package 3. It is important that the predictive tools and models are validated such that they can be integrated with confidence earlier within drug development and used to effectively prioritise established or legacy APIs for a definitive or tailored ERA. The validated tools and models should include:

- tailored and definitive ERA data for approximately 25 APIs, including some key metabolites, that have been used to test, validate the toolbox and refine the prioritisation framework and supporting guidance;
- supporting documentation and guidance;
- clearly defined validity domain for each tool and model developed within the project and consideration of underrepresented classes of APIs within their validation;
- integrating the new experimental data into this project database, thereby strengthening its power and coverage;
- a consideration of the scientific basis for false negative and false positive predictions and the different regulatory and industry tolerances for false predictions and the consequences for regulatory decision-making and drug development.

Industry members of the project will contribute across all aspects of this work package. This may also include the generation of new tailored ERA data specifically designed to support the validation approach.

Work package 5 – Toolbox integration and guidance (year 2–5)

Once the prioritisation approach has been validated the toolbox needs to be integrated where appropriate within the drug discovery and drug development pipeline, and within a formal framework to prioritise established human medicinal products. This work package will engage with relevant stakeholders across the product life cycle to implement this guidance.

Industry members of the project will contribute across all aspects of this work package.

Work package 6 – Dissemination (possibly in conjunction with WP 7, year 1–5)

Dissemination of the project structure as a whole, of the descriptions of work for all work packages, of intermediate results and of the final tools that will be developed within this project, by means of:

- a regularly updated project website, reporting on progress of the project;
- collation of publications;
- congress posters and presentations by members of the different work packages;

- at least one final conference where the overall results and produced tools from iPiE-25 will be presented to both subject matter experts and the interested public at large.

Industry members of the project will contribute across all aspects of this work package.

Work package 7 – Coordination and management (year 1–5)

Appropriate coordination and management activities are key components for rounding up the work plan. Scientific coordination will deal with strategic direction by gathering and reacting to new scientific ideas, optimising the use made of the project committees, and supervising work package leaders as they execute their role. It will also comprise the definition of quality policies and continuing assessment of the project's degree of success. Management will put all the contractual, administrative and financial mechanisms in place to ensure a smooth workflow during the project lifetime.

Industry members of the project will be embedded in partnership throughout the coordination and management of the project, its work packages and agreed milestones and deliverables; it is anticipated that an industry partner will co-lead each work package. Industry will also work with key stakeholders in the EC and the wider pharmaceutical industry to ensure the long-term sustainability of the database.

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Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 17 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents (e.g. IMI2 JU Model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2019-17-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**22 January 2019**
Stage 1 Submission start date	**22 January 2019**
Stage 1 Submission deadline	**25 April 2019 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**07 November 2019 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 43 108 139
From the IMI2 JU	EUR 40 786 000

Call Topics

IMI2-2019-17-01 **Optimising future obesity treatment**	The indicative contribution from EFPIA companies is EUR 7 100 000 The indicative IMI2 JU Associated Partners contribution is EUR 1 201 139 The financial contribution from IMI2 JU is a maximum of EUR 8 301 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2019-17-02 **Open access chemogenomics library and chemical probes for the druggable genome**	The indicative contribution from EFPIA companies is EUR 23 800 000 The indicative IMI2 JU Associated Partners contribution is EUR 6 457 000 The financial contribution from IMI2 JU is a maximum of EUR 27 935 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2019-17-03 **Intelligent prediction and identification of environmental risks posed by human medicinal products**	The indicative contribution from EFPIA companies is EUR 4 550 000 The financial contribution from IMI2 JU is a maximum of EUR 4 550 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

The following general conditions shall apply to this IMI2 JU Call for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[13].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[14] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

(a) legal entities established in a Member State or an associated country, or created under Union law; and

(b) which fall within one of the following categories:

(i) micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*,

(ii) secondary and higher education establishments,

(iii) non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations;

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI2 JU provided their participation is deemed essential for carrying out the action by the IMI2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[15].

STANDARD ADMISSIBILITY CONDITIONS, PAGES LIMITS AND SUPPORTING DOCUMENTS

Part B of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

In addition, page limits will apply to proposals as follows:

- at stage 1 of a two-stage call, the limit for RIA/IA short proposals is 30 pages;
- at stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages.

[13] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf

[14] Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking

[15] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

STANDARD ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall *apply mutatis mutandis* for the actions covered by this Call for proposals.

In addition, under all two-stage submission procedures the following additional condition applies:

The participants from EFPIA constituent entities and affiliated entities and Associated Partners which are pre-defined in the topics – under the section 'Industry consortium' – of a call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and Associated Partners.[16]

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

EVALUATION RULES

Part H of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals with the following additions:

Award criteria and scores:

Experts will evaluate the proposals on the basis of criteria of 'Excellence', 'Impact' and 'Quality and efficiency of the implementation' according to the submission stage and type of action, as follows:

Type of action	Excellence	Impact	Quality and efficiency of the implementation
RIA and IA 1st stage evaluation	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach;	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or international level: The expected impacts of the proposed approach as mentioned in the Call for proposals Added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where

[16] Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020"

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[17].	relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal; Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA 2nd stage evaluation	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or international level: The expected impacts of the proposed approach as mentioned in the Call for proposals; Added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[17]	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

[17] Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	the topic, ensure engagement of all relevant key stakeholders.	Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	

These evaluation criteria include scores and thresholds. Evaluation scores will be awarded for the criteria, and not for the different aspects listed in the above table. For all evaluated proposals, each criterion will be scored out of 5. Half marks may be given.

For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for each one of the two first criteria ('excellence' and 'impact') will be 3. There is no overall threshold. For the evaluation of second-stage proposals under a two-stage submission procedure; the threshold for individual criteria will be 3. The overall threshold, applying to the sum of the three individual scores, will be 10.

Following each evaluation stage, applicants will receive an ESR (Evaluation Summary Report) regarding the respective evaluated proposal.

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the Horizon 2020 Rules for Participation.[18]

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[19] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

Under the stage 2 preparation process, the applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited by the IMI2 JU, in priority order, for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. The IMI2 JU may explore this possibility if the first ranked applicant consortium and the industry consortium jointly notify the IMI2 JU that the preparation of a joint full proposal is not feasible. If this is the case, the first ranked consortium and the industry consortium shall notify IMI2 JU without delay, not later than within 30 days from the invitation to submit the stage 2 proposal. This notification must be accompanied by a joint report clearly stating the reasons why a stage 2 proposal is considered not feasible in order for the IMI2 JU to take the decision whether to invite the lower ranked consortium. In the absence of a joint notification within the deadline, it is deemed that the first ranked applicant consortium and the industry consortium are going to submit the joint stage 2 proposal. Accordingly, the second and third-ranked short proposals will be formally rejected.

Under the two-stage evaluation procedure, contacts or discussions about a given topic between potential applicant consortia (or any of their members) and any member of the relevant industry consortium are prohibited throughout the procedure until the results of the first stage evaluation are communicated to the applicants.

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to:

[18] https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/AWP_and_Budget_2019_adopted_on_12_December_2018.pdf

[19] In cases clearly identified in the relevant call for proposals where a given topic is composed of two or more sub-topics, one short proposal per sub-topic will be invited

- clarify the proposals and help the panel establish their final assessment and scores, or
- improve the experts' understanding of the proposal.

IMI2 JU evaluation procedure is confidential. The members of the applicant consortia shall avoid taking any actions that could jeopardise confidentiality.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (single stage, or first stage of a two-stages)	Information on the outcome of the evaluation (second stage of a two stages)	Indicative date for the signing of grant agreement
Two-stages	Maximum 5 months from the submission deadline at the first stage.	Maximum 5 months from the submission deadline at the second stage.	Maximum 8 months from the submission deadline at the second stage.

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions selected under topics covered by this Call for proposals.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

Part L of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

However, should a project 'opt-out' of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available under: https://www.imi.europa.eu/resources-projects/open-access-and-data-management-projects

SUBMISSION TOOL

Proposals in response to a topic of this IMI2 JU Call for proposals must be submitted online, before the call deadline, by the coordinator via the Submission Service section of the relevant topic page available under Funding & tender opportunities – Single Electronic Data Interchange Area (SEDIA).

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

In the first stage of a two-stage evaluation procedure, this template should not be submitted. However, applicants may integrate relevant aspects of this information in their short proposal (within the page limit). In the second stage of two-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected. [20]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[21] (see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020').

To ensure actions are implemented properly, at the time of the signature of the grant agreement, each selected consortia must have agreed upon a consortium agreement, i.e. the internal arrangements regarding their operation and co-ordination.

Two-stage full proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to this IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[22] (e.g. IMI2 JU model Grant Agreement).

[20] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[21] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006
[22] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

LIST OF ACRONYMS

Acronym	Meaning
API	active pharmaceutical ingredient
CRO	Contract research organisation
CV	Cardiovascular
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ERA	environmental risk assessment
EU	European Union
FDA	Food and Drug Administration
FP	Full Proposal
GA	Grant Agreement
GPCRs	G-protein-coupled receptors
H2020	Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020
HTS	High-throughput screening
IMI1 JU	Innovative Medicines Initiative 1Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2Joint Undertaking
IMI JU	Innovative Medicines Initiative Joint Undertaking
JDRF	Juvenile Diabetes Research Foundation
JU	Joint Undertaking
KM	Knowledge Management
MOA	mechanisms-of-action
OAC	Obesity Action Coalition
OECD	Organisation for Economic Co-operation and Development
PEC	Predicted Environmental Concentration
PBT	persistent, bioaccumulative and toxic
PiE	pharmaceuticals in the environment
R&D	Research and development
SAICM	Strategic Approach to International Chemicals Management
SMEs	Small and medium-sized enterprises
SLC	Solute carriers
SP	Short Proposal
SRA	Strategic Research Agenda
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World Health Organisation
WP(s)	Work Package(s)