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

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

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:

(i) The inclusion of environmental hazard and risk within the patient-benefit evaluation that underpins the marketing authorisation of a drug;
(ii) A catch-up scheme for medicines authorised for use prior to 2006 that lack comprehensive environmental assessments;
(iii) Increased transparency of environmental data;
(iv) 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 requirement 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 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;

Specialized subject matter experts may identify and extract public data and populate a species diverse ecotoxicological data base;

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:

(i) identify environmental hazards and risks associated with candidates in drug development;

(ii) to screen and prioritise established, 'legacy' pharmaceuticals for a tailored environmental assessment;
(iii) 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:

(i) are extended to include other targets and endpoints in a wider range of taxa and environmental compartments;

(ii) have their predictive capability maximised at a systems level through the application of innovative machine learning approaches and artificial intelligence innovation;

(iii) are validated to understand their predictive capability and applicability domain;

(iv) are assessed for their feasibility to be integrated earlier into drug development to flag environmental concerns sooner than within the current industry model; and

(v) 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. 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;

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 assessment 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 the a pharmaceutical ecotoxicology/environmental database including the integration of predictive capabilities and maximisation of data accessibility and transparency to all stakeholders;

Enabling 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 adatabase 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 and remove any requirement for inefficient monograph type approaches.

As APIs that are potential sex steroid receptor agonists and antagonists have a categorical inclusion, and require a tailored ERA, 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) patient access to 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.

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 pharmaceuticals that lack data. To conduct a full Phase II Tier A ERA on all medicines authorised before 2006 equates to about 1B Euro 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 >500M Euro without compromising environmental protection. This is money and 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 medical product to be actively managed across its product lifecycle 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 Europe 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 UKWIR Chemicals Investigation Programme

The NERC-Defra Chemicals in the Environment directed research programme.

The NORMAN Network

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 EAs,

Regulatory agencies developing the Japanese and Canadian ERA schemes

Industry consortium

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 date 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 hazard and risk assessments that comply with FDA and EMA regulations;

identification, development and validation 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.

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 develop 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 evidenced-based decision software;

social science experience to support engagement with stakeholders across the product lifecycle;

expertise in analytical and environmental chemistry to support environmental assessments and environmental monitoring;

statistical 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; different innovative project designs are welcome, if properly justified.

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 lifecycle. 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 positive 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 lifecycle to proactively manage environmental risks of human medicinal products together with a health and socioeconomic impact assessment.

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/ tool-box integration earlier within the development lifecycle. 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;

Provide 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 – Tool-box integration and guidance (Year 2-5)

Once the prioritisation approach has been validated the tool box 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 both 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, and 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 working flow 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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