ECO-PHARMACO-STEWARDSHIP (EPS)

PILLAR 1 - RESEARCH & DEVELOPMENT: INTELLIGENCE-LED ASSESSMENT OF PHARMACEUTICALS IN THE ENVIRONMENT (iPiE)

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Background 3

Design of project and expected outcome 4

APPENDIX : List of IMI-projects related to Pharmaceuticals in the Environment 6

- **IMI Ongoing Projects** 6
- **Green Chemistry** 7
- **Anti-microbial resistance** 7
- **Additional example of an indirectly related project** 7

Background

During normal patient use of medicines, non-metabolised substances are excreted and emitted into the sewerage system following use. The compounds may then be released into surface waters or enter terrestrial ecosystems when sewage effluent is emitted to river systems or used for irrigation or where sewage sludge is applied as a fertilizer to agricultural land. Consequently, a variety of APIs have been detected in the natural environment across the world. Although reported concentrations are generally at trace levels, many APIs have been detected in a variety of hydrological, climatic, and land-use settings and some have the potential to persist in the environment for months to years.

APIs are biologically active compounds that are designed to interact with specific pathways and processes in target humans and animals. Concerns have therefore been raised about the potential effects of APIs in the environment on human and environmental health. Over the past 15 years, a substantial amount of work has been done to determine the occurrence, fate, effects, and resulting risks of APIs in the environment. Regulations have also been developed regarding the assessment of environmental risks of APIs and the pharmaceutical industry has conducted testing to meet these regulatory requirements.

Currently, environmental assessments of APIs are typically performed at the end of the development process, i.e. when the API is close to an application for market approval. Concerns have been raised over whether the standard Organisation for Economic Cooperation and Development (OECD) testing methods for examining chronic effects on organisms will identify ecologically important effects of specifically acting APIs. The effect of the non-steroidal, anti-inflammatory compound diclofenac on vulture populations in India is one example of an affected non-target organism that would not have been predicted from standard studies.

There is a need to address the environmental risks associated with legacy APIs. More than 3,000 APIs are currently in use and testing data is only available for a small proportion of these. While it would be beneficial to understand the potential effects of the untested APIs, the evidence to date suggests that the majority of medicines assessed pose no significant risk to the environment. Therefore, prioritisation is key so the resources (monitoring, testing and research) are focused on those medicines that might potentially pose the greatest concern. For example, evidence post 2006 appears to indicate that around 2%[1] of pharmaceutical substances are likely to pose a moderate to high risk. Ideally, these prioritisation approaches should not require extensive experimental testing but exploit a combination of the significant amount of data already generated on the fate and ecotoxicity of APIs,

[1]Environmental Classification of APIs on Fass.se, (12 March 2015): High (1) and Moderate (11) environmental risk substances represent 2% of all substances

some of the predictive models described above, and targeted experimentation. For example, a lot of information is available from physicochemical, preclinical and clinical studies on the properties and risks of APIs, which could be used to support predictions of the environmental impacts of an API.

In addition to addressing potential environmental risks of APIs in legacy products, another challenge is to identify potential environmental risks of new APIs during the early stages of the development process, thus ensuring such intelligent and efficient testing strategies can be defined. This can be realized by employing the models generated by IMI project iPiE based on preclinical and clinical pharmacological and toxicological data for existing APIs, or by using Quantitative Structure-Activity Relationships for environmental endpoints. For example, knowledge of the presence or absence of API targets across a wide range of taxa could be invaluable in identifying those organisms and life stages of organisms that are most likely to respond to exposure to an API and which should therefore be specifically targeted in the risk assessment process. Comparative biochemistry, genomics, and other "omic" technologies also offer potential tools for early identification of APIs of potential concern, as well as the most sensitive and vulnerable species.

By accessing the wealth of existing data and combining these with predictive models for environmental fate and hazards, it may be possible to establish with minimal experimental testing whether low levels of a pharmaceutical in the environment constitute a threat to environmental and human health. This will be an invaluable tool in the design of testing strategies and for prioritisation of legacy APIs for further ERA evaluation where deemed necessary.

Design of project and expected outcome

The overall aim of this project is to develop predictive frameworks that utilise information from existing datasets on environmental fate and effects of APIs, toxicological studies, pharmacological mode of action and in silico models to support more intelligent environmental testing of pharmaceuticals in development, and to prioritise legacy pharmaceuticals for full environmental risk assessment and/or environmental (bio)monitoring. The aim will be delivered through the following specific objectives, each supported by a specific work package (WP):

1. To review existing approaches for prioritisation and mode of action based intelligent testing of APIs, in order to identify best practice and limitations in these approaches, and develop new and improved frameworks which are acceptable to potential end-users;

2. To establish a database with the appropriate quality assessment/quality control (QA/QC) mechanisms on the properties, environmental fate characteristics and ecotoxicity of APIs (and related compounds such as metabolites) and test species characteristics (e.g. presence/absence of API molecular targets, where available) and align this database with the existing IMI eTOX database[2] on toxicological properties of APIs;

[2] Link to the eTOX project website: http://www.e-tox.net/

3. To develop methods for predicting external (i.e. concentrations in the water) and internal (i.e. concentrations within organisms absorbed from the water) exposure to APIs and related compounds in the natural environment for different scenarios, based on data compiled in the database developed in Objective 2;

4. To develop methods and models for predicting aquatic and terrestrial ecotoxicological responses to APIs and related compounds, based on existing data compiled in the database developed in Objective 2;

5. To validate the models, concepts and frameworks developed in Work Packages (WPs) 1, 3 and 4 using targeted experiments and develop abbreviated in vivo assays;

6. To develop a software system, that integrates data and approaches developed in W1-5, to support intelligent testing and prioritisation of APIs in the environment. The system will be based on, and be fully compatible with, the IMI eTOXsys infrastructure for safety assessment of APIs;

7. To develop guidance on how the software system and associated predictive tools can be used in (i) early development programmes for new compounds and (ii) for prioritizing legacy products for experimental testing;

8. To engage with and exchange knowledge with stakeholder groups throughout the project to achieve broad acceptability of the approaches developed by the project and to ensure the sustainability of the database and software system into the future.

These objectives will be delivered through seven inter-related scientific WPs and one management WP by a world-leading consortium comprising experts in data management and computational modelling, pharmacology, ecotoxicology, environmental chemistry, predictive (eco)toxicology, prioritisation and intelligent testing methodologies and environmental risk assessment. A number of the WP leaders have established international reputations around the fate, effects and risks of APIs in the natural environment.

The result of the project should be an internationally accepted methodology for the prioritization of APIs for further ERA investigations. This methodology can be applied to select candidates of legacy products for detailed environmental testing and assessment, thus focusing the efforts of industry and regulators on those yet untested compounds having the highest potential for an environmental risk, and using testing methods for screening and testing which combine standard testing procedures such as established by the OECD with new innovative approaches specific to certain API properties. The application of this methodology will also help industry during the development of new APIs to provide information on potential environmental risks at an early stage.

The project started in January 2015 and will run until the end of 2018. It comprises 25 partners from academia, SMEs, industry, and regulators. So far, a scientific advisory board, consisting of many stakeholder groups, was established to provide a forum for discussions on the project progress and outcome.

APPENDIX : List of IMI-projects related to Pharmaceuticals in the Environment

The Innovative Medicines Initiative (IMI) is working to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. IMI is a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

During its first phase (2008-2013, IMI1), IMI had a budget of €2 billion, half of which came from the EU's Seventh Framework Program for research (FP7), and half of which came from in kind contributions by EFPIA companies. With a €3.3 billion budget for the period 2014-2024 (IMI2), IMI is the world's biggest public-private partnership (PPP) in the life sciences. Half of IMI's budget (€1.638 billion) comes from Horizon 2020, the EU's framework program for research and innovation. This will match €1.425 billion committed to the program by EFPIA companies, plus up to €213 million that could be committed by other life science industries or organisations that decide to contribute to IMI2 as members or associated partners in individual projects.

IMI Ongoing Projects (http://www.imi.europa.eu/content/ongoing-projects)

The Innovative Medicines Initiative (IMI) now has 47 projects that are up and running as a result of the successful launches of its first eight calls for proposals. Of those 47 projects, 8 projects, with a total budget of 455 Mio €, are shortly described below. The projects are closely or more remotely connected to areas of potential interest for the discussions regarding Pharmaceuticals in the Environment.

Risk assessments and toxicity predictions:

- **iPiE 10 Mio €**: Intelligence-led Assessment of Pharmaceuticals in the Environment: To develop predictive frameworks that utilize information from existing datasets on environmental fate and effects from APIs, toxicological studies, pharmacological mode of action and in silico models to support more intelligent environmental testing of pharmaceuticals in development and to prioritize legacy pharmaceuticals for full environmental risk assessment and/or environmental (bio) monitoring.

- **eTOX 13.9 Mio €**: Integrating bioinformatics and chemo-informatics allowing the in silico prediction of toxicities: To develop innovative strategies and novel software tools to better predict the safety and the side-effects of new candidate medicines for patients. Reliable prediction of side-effects in the initial phases of drug development lowers the failure rate in later phases, significantly reduces the number of animal tests needed and accelerates the development of new drugs.

Green Chemistry

- **CHEM21 26.4 Mio €**: Chemical manufacturing methods for the 21st century pharmaceutical industries: To generate a range of methods to make the drug development process more environmentally friendly. What's more, as well as being good for the planet, the methods developed by CHEM21 will also help the pharmaceutical industry to cut costs, resulting in cheaper medicines for patients.

Anti-microbial resistance

- **ND4BB**: New Drugs for Bad Bugs (umbrella project of COMBACTE, ENABLE, TRANSLOCATION): Antibiotic-resistant bacteria kill 25 000 people in the EU every year, and cost the economy €1.5 billion. IMI's New Drugs 4 Bad Bugs (ND4BB) program represents an unprecedented partnership between industry, academia and biotech organisations to combat antibiotic resistance in Europe by tackling the scientific, regulatory, and business challenges that are hampering the development of new antibiotics. The program currently comprises three projects.

  > **COMBACTE 250 Mio €**: Creating a pan-European network of clinical sites

  > **ENABLE 101 Mio €**: A drug-discovery platform for antibiotics

  > **TRANSLOCATION 29.3 Mio €**: Getting drugs into bugs (and keeping them there)

Additional example of an indirectly related project

- **ORBITO 24.5 Mio €**: Oral biopharmaceutics tools: Most drugs are taken orally, as tablets or capsules for example. However, designing these pharmaceutical products in such a way that the active ingredient is absorbed at an appropriate rate and extent by the gut is far from easy. The ORBITO project aims to enhance our understanding of how orally-administered drugs are taken up from the gastrointestinal tract into the body, and apply this knowledge to create new laboratory tests and computer models that will better predict the performance of these drugs in patients.

AESGP, the Association of the European Self-Medication Industry, is the representation of manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe. It is composed of national associations and the main multinational companies manufacturing self-care products. AESGP is the voice of more than 2,000 companies operating in the consumer healthcare sector in Europe, affiliated with AESGP directly or indirectly through the national associations.

www.aesgp.eu

European Federation of Pharmaceutical Industries and Associations

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

www.efpia.eu

The EGA (European Generic and Biosimilar medicines Association) represents the European generic and biosimilar medicines industries, which provide high-quality cost-competitive medicines to millions of European patients. Companies represented within the EGA provide over 160,000 skilled, high value direct jobs in Europe. Generic medicines save EU patients and healthcare systems over 40 billion each year and account for 55% of all dispensed medicines but for only 21% of the pharmaceutical expenditure in Europe.

www.egagenerics.com

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