Supplementary Information for the Article

Designing Greener Active Pharmaceutical Ingredients: Insights from Pharmaceutical Industry into Drug Discovery and Development

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Content:

[1] Questionnaire with Q1 - Q10

Questionnaire for medicinal chemists / development chemists of PREMIER industry partners

PREMIER (Prioritisation and Risk Evaluation of Medicines in the EnviRonment; 2020-2026) is an Innovative Medicines Initiative (IMI) project, funded by the European Commission and members of the European Federation of Pharmaceutical Industry Association (EFPIA). PREMIER consists of 10 EFPIA companies, the European Medicines Agency, universities, research institutes, and small-to-medium-enterprises.

The overall goal of PREMIER Work Package 4.2 is to find ways to include environmental aspects within the drug discovery and development process to highlight potential concerns earlier for drugs of the future. The document *Pharmaceuticals in the Environment – Understanding the Feasibility of Designing Greener Drugs* ("two-pager") provides some background on the topic of pharmaceuticals in the environment and on the research process in PREMIER Work Package 4.2.

The R&D Process (Q1 - Q5)

Q1: In your company, does the drug discovery and drug development workflow follow the process depicted in the figure? Are there any deviations in your company's processes? If yes, which processes are different, and for which reasons?

Workflow of a common R&D process inspired by [1] [1].

Q2: Beyond the decision points included in Figure 1, are there additional important decision points in your drug discovery and drug development processes?

Q3: Are the decision points affected (i.e. do they play out differently) when iterating ('going back' to a 'previous phase') in the process?

Q4: Which criteria play a role in the decision points, and how? Examples: on-target = potency, physicochemical properties, ADME(T), PK, PK/PD, *in vitro; in vivo* efficacy, off-target effects and toxicity, stability (chemical, plasma, shelf life), developability, intellectual property, ect.

Q5: Could you summarize your company's use of a target-product profile?

Environmental considerations (Q6 - Q10)

Q6: Do environmental considerations currently play a role in any phase of the API discovery and drug development process? Which and where?

Q7: Can environmental considerations be included amongst other criteria in the target product profile (TPP, explanation provided by Lambert (2010))?

Q8: (a) In which phase(s) of the API discovery and drug development process do you see opportunities for taking up the following environmental aspects as criteria? (b) Which criteria could be suitable for take-up?

I. no/reduced environmental exposure,
II. environmental (bio)degradability,
III. no/reduced adverse environmental effects,
IV. no/reduced undesirable moieties (e.g. PFAS moieties CF_2 and CF_3)
V. other

Q9: Which would be key attributes for any environmental screening models/assays for future integration in the API discovery and drug development process?

Q10: Which incentives could in your opinion play a role in leading to greener APIs?

[2] Background information on the pharmaceutical R&D process

A good overview of the overall process and its basic principles is provided, for example, by [2] [2] and [3] [3]. Based on their description, we can differentiate six phases starting with target selection and ending in the clinical studies that are required for the new drug application (cf. figure in [1] Questionnaire). The first four phases – from target selection to candidate selection, which aim to discover an API candidate – are placed under the label drug discovery (**R**esearch, i.e. the R in R&D). The last two phases, i.e. preclinical and clinical studies, deal with the development of the formulated drug (drug **D**evelopment, i.e. the D in R&D). Explanation of the terminologies 'target', 'hit', 'lead' and 'candidate' can be found elsewhere [1].

Between one phase and the next there is typically a 'stage-gate', i.e. a formal decision-making moment where decisions concerning the project are taken, such as progressing a number of compounds to the next phase, returning to a previous phase, or terminating a project. These decision-making moments are data-driven, with the available data for the compounds under analysis typically plays a significant role.

The number of compounds screened or evaluated in a certain phase of the process is usually very significantly higher (typically several orders of magnitude) in the early phases of the R&D process than in the later ones, to which only a handful of molecules progress (Figure 1~~Figure 1~~). Many compounds do not make it to the end of the process because of efficacy or safety issues which are initially identified during these steps (Blass, 2015).

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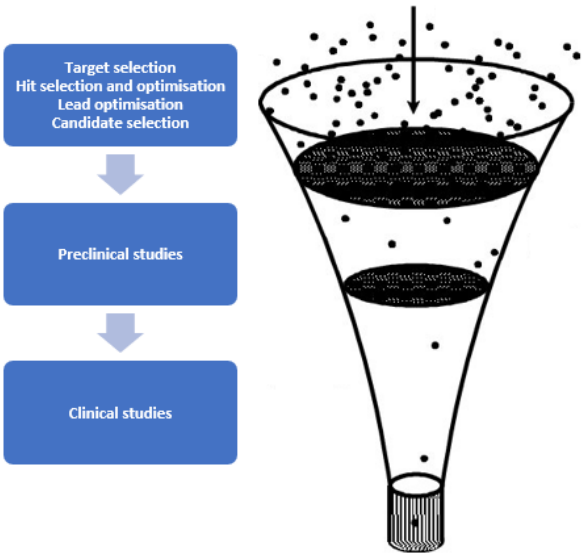

Figure 1: Funnel visualising that large compound collections are screened, further investigated, and optimized to bring a single drug to the market (taken from [4] [4]). Many compounds do not make it to the end of the process because of efficacy or safety issues which are initially identified during these steps [2].

[3] Two-page background summary for interviewees

Pharmaceuticals in the Environment – Understanding the Feasibility of Designing Greener Drugs

Authors: *Leuphana University, Ecologic Institute, March 2021*

This paper aims to kick off the exchange between medicinal chemists / development chemists (such as PK scientists) within PREMIER industry partners and PREMIER public partners. It provides some background of the significance of the topic "Pharmaceuticals in the environment" for future drug discovery and development and an overview of the planned involvement of industry.

Introduction

Human Medicinal Products are a unique class of chemicals within Europe as they are currently approved for patient use irrespective of their environmental hazard and risk. Although an environmental risk assessment (ERA) is required in the authorisation process, ERA results currently do not affect the decision to approve a medicine.

Active Pharmaceutical Ingredients (APIs) and their metabolites are excreted into wastewater subsequent to patient use. Most APIs are only partly removed by wastewater treatment and thus enter surface waters. Their continued presence in a range of surface waters and groundwaters as well as soils and sediments is driving increased stakeholder concern. Ecotoxicological effects of APIs have been shown using laboratory experiments with environmentally relevant concentrations. Also, effects of sewage treatment effluent (which includes pharmaceutical residues and other micropollutants) on populations of organisms in surface water have been shown. Such findings have led to public, stakeholder and regulatory concerns about risks of pharmaceuticals to the environment. There are also growing concerns about the presence of pharmaceutical residues in drinking water sources.

Because of these concerns, several EU strategies and resolutions as well as global initiatives have focused on addressing pharmaceuticals in the environment. Within the European Green Deal's Chemicals Strategy for Sustainability, which is part of the EU's Zero Pollution ambition, an increasing number of APIs will be monitored under the EU's Water Framework Directive. In 2019 the EU developed a 'Strategic Approach to Pharmaceuticals in the Environment' in response to these developments and increasing pressures and activities carried out by EU Parliament, EU Member States, and global entities (e.g. by UNEP, WHO, OECD). These initiatives all confirm the increased regulatory and wider stakeholder focus on this issue, and it is being discussed whether environmental hazard and risk should be included within the approval procedure of new medicinal products.

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Design of greener drugs

One way to address the presence of APIs in the environment could be to design greener drugs. PREMIER explores the feasibility and potential of various approaches for reducing pharmaceutical residues in the environment. Possible approaches could include precision or personalized medicines, biologics, nano-based medicines, antibody drug conjugates and other innovative therapies. Reduced environmental impact can also be achieved by including environmental criteria in the selection of drug candidates. Examples of greener APIs are compounds that, after their introduction into the aquatic environment, are degradable (*Benign by Design* or *Design for the Environment*) and will not accumulate, or that have a more favourable environmental risk profile.

The overall goal of PREMIER Work Package 4.2 is to find ways to include environmental aspects within the drug discovery and development process to highlight potential concerns earlier for drugs of the future. Within this work package, we will perform an analysis of the feasibility of incorporating environmental considerations into the principles that underlie the design and delivery of safe and

effective APIs for patient use. This analysis will be scientifically up to date, should capture on-going innovation in the pharmaceutical industry, and be based on real-world drug-design processes. **For this reason, we need the input of medicinal chemists, "*in silico*" experts and development chemists such as PK scientists of the PREMIER industry partners.**

Out of scope of this project are greener production methods and the use of sustainable and renewable materials within the drug discovery and development process itself.

What do we expect from industry experts?

Industry partners will provide general insights into the drug discovery and development process and into the design principles commonly used in the development of new molecular entities. This will include an analysis of the workflows, processes, key decision points and associated criteria, and economic considerations involved. This way PREMIER aims to understand (i) the key drivers for candidate progression and decision-making, (ii) how and where environmental considerations could be embedded into the process, (iii) key criteria that any tools or assay must fulfil in order to be deemed 'fit for purpose', and (iv) the barriers for the integration of environmental considerations within drug development.

First interview round – April to June 2021

From April to July 2021 *Leuphana University* and *Ecologic Institute* will be performing structured interviews with industry partners on these topics. A first round of interviews is aimed to get a good understanding of the overall drug discovery and development process and its challenges. Industry partners will be asked to identify decision points where environmental considerations could play a role within drug development, to identify future opportunities to integrate environmental tools and models, and to identify necessary attributes for these environmental screening tools/models/*in vitro* assays.

These interviews (ca. 2 hours per company/interview) will be performed with representatives of industry partners – medicinal chemists, "*in silico*" experts and PK scientists. Industry's environmental experts can sit in on the interviews with the chemists of their respective company. Each interview will be held separately with representatives of a single company. We welcome the presence of more than one representative from an individual company from the groups mentioned above, as this typically provides for more in-depth responses. The questionnaire will be provided at least one week before the interview.

Overview of industry involvement in PREMIER WP 4.2

The following table summarises the involvement of industry chemists / experts in PREMIER WP 4.2.

What	Who	Why	When
1st round of interviews	medicinal chemists, "*in silico*" experts, PK scientists and environmental experts of EFPIA partners	to reach a common description and understanding of the general drug design and development process	Apr - June 2021
1st PREMIER workshop		to share and discuss the outputs of interviews	September 2021
2nd round of interviews		to understand fundamental drug design principles and their environmental significance	First half of 2022
2nd PREMIER workshop	Stakeholders across the product life cycle of an API	to present and discuss concepts to be taken up in common understanding of the feasibility of designing greener APIs	Second half of 2023

Research outputs will be summarized by academia (Leuphana University) and industry (AstraZeneca) in four reports. If needed, non-disclosure agreements can be agreed upon and signed.

For further reading:

- *Report on environmental risks posed by medicinal products, by BIO IS for the EU Commission*
- *EU Commission's Strategic Approach on Pharmaceuticals in the Environment*
- *Publication on design of pharmaceuticals for environmental biodegradability (Klaus Kümmerer)*

Key publication on ecological risks of pharmaceuticals

[4] Information on parameters, discussed during interviews also in an environmental context, based on literature data.

	Generic info	**When during the R&D process?**	**How investigated?**
Potency	Reflects the sensitivity of the organ or tissue to a drug, expressed as a concentration needed for a certain biological response [5]	Start of an extensive screening cascade → An important consideration in the process	Within pharmacological *in vitro* screening, potency can be defined using various assays. Examples are biochemical assays, biophysical assays, and cellular functional assays [6]. Highly potent compounds tend to be more lipophilic [7]. Sufficient potency and further properties are needed for efficacy in patient [2].
Physico-chemical properties	Standard endpoints are solubility (in biorelevant media), lipophilicity (log D), stability (chemical and photo), ionization (depending on ambient pH) and pK_a [6]. Key to identifying compounds with a drug-like profile.	Predictions early in discovery process	Structural descriptors (e.g. molecular weight, nr of aromatic rings, hydrogen bonds) easily calculated and helpful to predict phys-chem properties. Computational tools used to predict e.g. log P. Appropriate simplistic prediction used for property-based drug design to increase likelihood that a drug will have drug-like properties [8]. Not drug-like compounds can be avoided already in design phase, and predictions confirmed experimentally. Rules or guidelines developed to search for biologically suitable (drug-like) compounds: Lipinski's rule of 5 [9], the rule of 3 [10], Ghose filter [11] and Veber's rule [12]
ADME and PK studies	Absorption, Distribution, Metabolism and Excretion; Studies performed to understand the time course of drug concentration in the body, drug bioavailability, metabolic pathways and potential for drug interactions [5].	Depending on the assay Studies with labelled compounds are performed *in vivo* for very advanced molecules [6]. Note, distribution studies are conducted late with very few compounds (if at all).	Several *in vitro* tests to understand ADME profile, e.g. permeability & transport, P450 inhibition, protein binding, microsomal stability. More on stability: - EMA guideline defines exemplary stability data package, but leaves flexibility to consider varying practical situations due to specific scientific reasons. Typically, impact of temperature, humidity, photoirradiation, acids & bases on chemical structure and ionization state is tested in drug discovery. In drug development, shelf-life of the product is assessed [13] - Pharmacopoeia (in EU: European Pharmacopoeia) – a single reference work for quality control of medicines) – contains official legally binding standards providing a scientific basis for quality control [14].
Target selectivity & off-target effects	Sufficient target selectivity needed to avoid/minimize off-target effects → key criterion.	Once potent compounds with appropriate phys-chem are selected	Screened against a broad range of potential unintended targets (receptors, ion channels, enzymes, transporters) to reduce safety-related attrition rates through *in vivo* studies [2,6,15]

			- [16] [16] recommend minimum panel of 44 off-targets and development of *in silico* models for an early profiling with the aim to lower attrition rates. Example of kinase selectivity demonstrates importance: ATP-binding motif is identical in most of the more than 500 known examples of kinases (catalyse phosphorylation), explained by natural evolution. If drug target of a research program is at ATP binding site, selectively targeting one kinase over the others can be challenging [2].
Toxicological & toxicokinetic studies (*in vivo*)	Information on toxicokinetic elsewhere [17].	Performed in healthy animals in preclinical studies, i.e. when a drug candidate with an attractive overall profile is identified [6].	Toxicological studies: animal health, e.g. body and organ weight, food consumption, eye function, histopathology (microscopic examination) of a wide range of tissues [2]. Toxicokinetic studies: the relationship between internal concentrations (typically in plasma but can be at tissues) and the gross safety liability *in vivo*, often linking *in vitro* off-target activity to resulting observable toxicity [6].

References

1 J. Messinger, L. Otsomaa and S. Rasku, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, ed. L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, The Royal Society of Chemistry, 2016, pp. 101–115.

2 B. Blass, *Basic Principles of Drug Discovery and Development*, Elsevier Science, Burlington, 2015.

3 L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, eds., *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016.

4 R. Boschi, *European Journal of Operational Research*, 1982, **10**, 250–259, https://www.sciencedirect.com/science/article/pii/0377221782902247.

5 N. H. G. Holford and L. B. Sheiner, *Clinical Pharmacokinetics*, 1981, **6**, 429–453.

6 A. Baxter, in *Reference Module in Biomedical Sciences*, Elsevier, 2021.

7 M. Stocks, in *Introduction to Biological and Small Molecule Drug Research and Development*, ed. R. Ganellin, S. Roberts and R. Jefferis, Elsevier, Oxford, 2013, pp. 81–126.

8 R. J. Young, D. V. Green, C. N. Luscombe and A. P. Hill, *Drug Discovery Today*, 2011, **16**, 822–830, https://www.sciencedirect.com/science/article/pii/S1359644611001796.

9 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Advanced drug delivery reviews*, 2001, **46**, 3–26.

10 M. Congreve, R. Carr, C. Murray and H. Jhoti, *Drug Discovery Today*, 2003, **8**, 876–877.

11 A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *Journal of Combinatorial Chemistry*, 1999, **1**, 55–68.

12 D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *Journal of Medicinal Chemistry*, 2002, **45**, 2615–2623.

13 EMA, *ICH Topic Q1A: Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (CPMP/ICH/380/95)*, available at: http://www.pharma.gally.ch/ich/q1a038095en.pdf, accessed 18 February 2021.

14 EDQM Council of Europe, *European-Pharmacopoeia - Background & Mission*, available at: https://www.edqm.eu/en/European-Pharmacopoeia-Background-Mission, accessed 9 February 2022.

15 J. P. Hughes, S. Rees, S. B. Kalindjian and K. L. Philpott, *British journal of pharmacology*, 2011, **162**, 1239–1249.

16 J. Bowes, A. J. Brown, J. Hamon, W. Jarolimek, A. Sridhar, G. Waldron and S. Whitebread, *Nature reviews. Drug discovery*, 2012, **11**, 909–922.

17 Laboratory Animal Science Association, *Guidance on dose level selection for regulatory general toxicology studies for pharmaceuticals, chapter 4.3 Toxicokinetics and saturation of exposure*, available at: http://www.lasa.co.uk/PDF/LASA-NC3RsDoseLevelSelection.pdf.