NEWSLETTER N° 01

TransPharm Press

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Christian Stevens, Professor at Ghent University and TransPharm coordinator

It is always a big effort to prepare a proposal for a Horizon Europe project, certainly when most of the work needs to be performed in a vacation period (which was the case for this project). However, I was amazed by the eagerness of the contacted colleagues to get involved in the project on transforming pharmaceutical production into a more sustainable process related to different application levels.

To me, it means this is an extremely important topic which is highly relevant for society. This became also apparent during our first meetings of the TransPharm project. It really matters to our partners; people want to do an effort to make it work and to get over the hurdle that separates the care for patients and the care for our environment.

It was also refreshing to experience that the five EU granted projects clearly expressed the desire to work together along the common lines of sustainability in the production of API's. Even though the chemical and pharmaceutical sector is almost constantly under societal pressure, I am delighted to be able to work together with an excellent and highly motivated team of partners that want to make a difference for the future of pharmaceutical production and engineering. Trying to bring back this production to Europe in order to increase the security of supply of APIs for our patients is a challenge, but we are convinced we are able to make an important contribution towards this exciting goal.

GREENER PHARMACEUTICALS: A MAJOR SOCIETAL CHALLENGE

Pharmaceutical innovations improve the lives through its contributions to public healthcare and wider societal benefits. Medicines are essential to human health, and as such they are important in realising the UN's Sustainable Development Goal (UNSDG) of 'Good Health and Well-Being". At the same time healthcare contributes to world-wide greenhouse gas emissions. Also, the active pharmaceutical ingredients (APIs) themselves can cause environmental impacts. Thus, although medicines are essential for human health, they impact the environment, which is also vitally important to human health and part of the UNSDGs of 'Life under Water' and 'Clean Water and Sanitation'. Until recently, the environmental impact of pharmaceuticals has largely been ignored.

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The environmental impact of medicines is determined by their design and their production. After use, their molecular design determines the burden of their residues to the environment. Studies have shown that **APIs are ubiquitous in the environment**, including both aquatic and terrestrial ecosystems. The EU Commission has addressed the increasing problem of environmental pollution due to pharmaceuticals throughout their life cycle. *A* circular economy is a major building block, however, it is evident that pharmaceuticals, **cannot be circulated or recycled after their use**.

TRANSPHARM KEY FEATURES

- 11 partners
- 8 countries
- 7.5 M€ total budget funded by EC
- 48 months

In TransPharm, we aim to support strategies to reduce the environmental impact of pharmaceuticals by working along two lines:
(1) **developing environmentally friendlier APIs**, and
(2) **reducing the environmental impact of the manufacturing process.**

A new concept related to a **"green pharmacy" approach** is being envisaged, which can be defined as the sum of all measures and tools that should be taken in order to minimize the environmental impact of pharmaceuticals, regarding products as well as APIs, during all pharmaceutical activities, from designing new molecules to manufacturing, distribution, dispensing, use and disposal. One of the key approaches to limit environmental pollution by APIs is to **design them for fast and complete environmental degradation** whilst ensuring practical shelf-life, pharmacological safety and efficacy in humans. Next, the **creation of "rules for telescoped reactions**" could lead to an immense step forward in the sustainability of pharmaceutical production.

To be fully prepared for the future, **tools for an integrated assessment** of sustainability benefits will be developed, as well as the general concepts within the business cases on how to bring more sustainable pharmaceuticals to the market.

TRANSPHARM MAJOR OBJECTIVES

- Optimize the use of existing and new data for greening drug synthesis and development
- Identify greener and more sustainable-by-design APIs as proof of concept.
- Reduce the inputs and outputs of API synthesis through introducing shortcuts in API synthesis schemes.
- Provide new methodologies to assess the sustainability of pharmaceuticals over their entire life cycle.

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WHAT OUR ADVISORY BOARD MEMBERS SAY

Dr Kirsty Reid, Director Science Policy, EFPIA

« The pharmaceutical industry is committed to making a positive impact on the lives of patients while operating sustainably. Our member companies are constantly seeking ways to minimise their environmental impact by mitigating climate change and transitioning to circularity. We welcome the TransPharm project objectives and will work with them towards a sustainable European pharmaceutical industry. »

Frank Roschangar, Boehringer Ingelheim Pharmaceuticals, Inc.

« I am excited about contributing to TransPharm and help develop environmentally friendlier APIs by addressing the environmental challenges we face today for a sustainable future. »

Wouter De Soete, Sr. Manager Environmental Sustainability & LCA, Janssen Pharmaceutica

« TransPharm is a European flagship project aiming at developing greener active pharmaceutical compounds, manufactured in the most sustainable way. In order to achieve such ambition, adequate measurement should be in place. I look forward to collaborating on the development of an industrial applicable, holistic sustainability assessment methodology for pharmaceutical products. »

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HOW ARTIFICIAL INTELLIGENCE CAN HELP GREENING PHARMACEUTICALS PRODUCTION?

Synthetic chemistry plays a central role in the research and development of pharmaceuticals. Despite great breakthroughs in synthetic methods, the production technology is still relying on round-bottom flasks and batch reactors with a large environmental footprint. Making the transition to smarter processes in continuous flow will make pharmaceutical production greener. Researchers at the Laboratory for Chemical Technology at Ghent University (Belgium) are investigating how chemical processes can be intensified using artificial intelligence and cheminformatics.

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Cheminformatics is the use of computational and informational techniques to understand problems of chemistry, for instance in the in-silico mapping of chemical space – the theoretical space occupied by all possible chemicals and molecules. Cheminformatics strategies are useful in drug discovery and other efforts where large numbers of compounds are being evaluated for specific properties. Indeed, finding a synthetic route is a rate-limiting step in the development of a new drug. In the last couple of years, major efforts have been made to speed up this process by the creation of data-driven retrosynthetic software tools. Although the software is promising when it comes to predicting synthetic pathways, there is a big missing link between the software and the execution: suggesting appropriate reaction conditions. Even though recent research has attempted to address this problem, it quickly became clear that data-driven approaches fail for this task. The reason is twofold: the data is often incomplete or even wrong, and because of human bias specific conditions (e.g. solvents or reaction times) are much more popular than others. Machine learning models will simply reflect these trends.

Regarding flow chemistry, it is currently completely unfeasible due to lack of data. On the one hand a very limited number of reactions are performed or have been attempted in flow. On the other hand, most often the reported data are difficult to extract and consist of numerous steps where the used conditions and catalysts are typically not specified in full detail. Researchers in the group of Kevin Van Geem (LCT, Ghent University) calculated that less than 1 out of 1000 chemical reactions have ever been performed in continuous-flow reactors and that the synthetic toolboxes in flow and batch are very different. Hence, they embrace a physics-based artificial intelligence approach to research conditions using advanced cheminformatics tools. One such application is the suggestion of a solvent for the reaction. Until now, slow quantum chemical calculations were the most reliable option, but artificial intelligence tools can now be faster and more reliable. It is also essential in this context to accurately represent molecules, in such a way

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that even distinctions can be made between enantiomers. An additional challenge is to make sure that these algorithms can also learn to suggest not only the best but also the greenest alternative. Only then we come one step closer to sustainable pharmaceutical production processes.

WORKSHOP IN COLLABORATION WITH PREMIER PROJECT

PREMIER
PRIORITISATION AND RISK EVALUATION OF MEDICINES IN THE ENVIRONMENT

What is a sustainable pharmaceutical product? Can sustainability considerations be included in the discovery/design process of new active pharmaceutical ingredients (APIs)? And what information needs does the health sector have when it comes to the sustainability of pharmaceuticals? These are some of the questions discussed during the TransPharm/PREMIER workshop on 4-6 April in Nijmegen, the Netherlands. The workshop brought together a unique range of experts and professionals representing different stakeholders involved in the discovery, production, prescription, use and regulation of pharmaceuticals.

During interactive small group sessions, several topics were discussed in depth such as the need for a sustainability assessment system and the criteria to consider when designing such a system, as well as opportunities for education and awareness raising. Although there was a consensus on the urgency for sustainable pharmaceuticals, it is generally seen as a complex task. Communication and inclusion of the different disciplines will be key, in order to align the goals and vision, and to share knowledge and experiences. This workshop marked the start of bringing these disciplines together.

"Yes, we can!", was the conclusion when it comes to considering potential environmental impacts in the drug discovery and design process. *"But we need clear criteria, reliable predictive tools and some examples to inspire us."* The predictive tools that are being developed by the PREMIER project were welcomed as a promising starting point, but their usefulness remains to be demonstrated in practice. Hence, the need for inspiring examples.

To educate R&D scientists as well as healthcare professionals on sustainable pharmaceuticals there is a need for reliable and easy to understand evidence-based educational materials. Making pharmaceutical sustainability part of the formal educational curriculum is a next challenge.

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The call for clear criteria to assess the greenness of pharmaceutical products was echoed in the second part of the workshop. Industry, regulators, academics and representatives from the health expressed a clear need for sustainability information along the lifecycle of pharmaceuticals, e.g. to green production or to stimulate products that have a limited footprint. There was a broad consensus that sustainability assessment of pharmaceutical products should not only focus on production but also include other potential environmental impacts such as ecotoxicological effects after use and impacts related to the marketing and distribution of the products. In the end, this should lead to appropriate drug use while minimizing unintended consequences (e.g. reduced access to medicines). Country-specific and cultural differences such as sanitation, patient profiles, and access to medicine as well as regulatory aspects should be accounted for when moving further with this assessment system. The TransPharm project will use this input to further develop this concept.

"It is a mammoth task to develop a system that measures all aspects of sustainability",* concluded host Ad Ragas (Radboud University) at the end of the workshop. *"But let's not wait until we have perfect criteria on what constitutes a sustainable pharmaceutical. That discussion might take ages. We should move forwards and start experimenting. We will make mistakes, but we will learn from them. We need the courage to experiment and fail on our path to create more sustainable pharmaceuticals."

WE WERE THERE

- Workshop on sustainable solvents, GreenChem Network – September 2022, Ghent, Belgium
- GreenDigiPharma Kick Off Meeting – January 2023, Milano, Italy
- Flow Chemistry European Summit 2023 – March 2023, Rotterdam, Netherlands
- TransPharm/PREMIER workshop – April 2023, Nijmegen, the Netherlands
- SETAC Europe 33rd Annual Meeting – May 2023, Dublin, Ireland
- 7th Green and Sustainable Chemistry Conference – May 2023, Dresden, Germany

Contact us

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Upcoming events

- 9th Summer School on Sustainable Chemistry for Sustainable Development, Germany, July 2023
- GreenDigiPharma meeting with the University of Bari, Italy, September 2023
- The 11th International Conference on Life Cycle Management, France, September 2023
- TransPharm Workshop #2 in 2024

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