Workshop Report

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 PREMIER/TransPharm 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 with around 100 participants.

During interactive small group sessions, the following topics were discussed in depth:

1. Moving towards the design of APIs with less impact on the environment after use – Needs of actors in drug R&D and the health care sector
2. Environmental criteria for APIs to reduce their impact after use
3. Implementation of environmental criteria in drug discovery and design of small molecules
4. Criteria for greener production of pharmaceutical products – Is there a business case?
5. Sustainability assessment of pharmaceutical products – 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.

"It is a mammoth task to develop a system that measures all aspects of sustainability", concluded host Ad Ragas 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."

1. Moving towards the design of active pharmaceutical ingredients (APIs) with less impact on the environment after use (Day 1)

The topic of the first workshop day was the design of APIs with less impact on the environment after use and associated needs for actors in R&D and health care. In two parallel sessions, this topic was discussed from the perspective of actors close to R&D processes: *what do they need to start to change their processes so that greener APIs play a role in their decision-making?* There were two other parallel sessions to discuss the question from the perspective of actors in the health care sector: *what do they need to start implement/stimulate the use of green APIs?*

In the R&D session, it was discussed what the needs are that would enable industry to move towards designing greener active pharmaceutical ingredients and prioritised them in a bulls-eye chart (Figure 1). The answers covered a huge number of aspects such as a clear definition of what constitutes a "green" pharmaceutical, clear definition of the parameters to be modelled/ measured, the existence of high-throughput and cost-effective assays to measure these parameters, a compelling story that justifies to medicinal chemists and upper management such a transformation, and incentives (e.g. financial or legal) to facilitate that transformation of industry.

Participants then proceeded to identify their priority needs 1-4. Collaboration was mentioned often as a solution for these needs. Other examples are guidance and training.

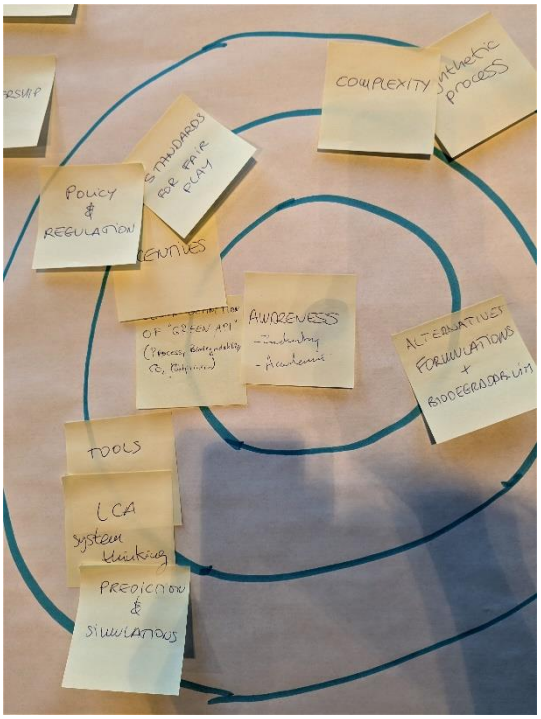

Figure 1: Example of a bullseye on needs of R&D organizations to embrace challenges to design greener APIs.

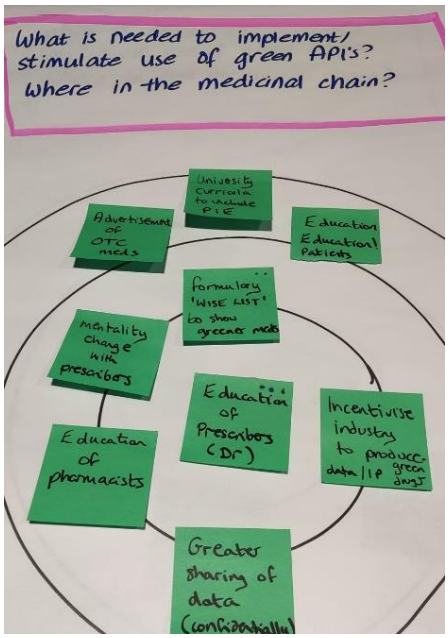

Figure 2: Example of a bullseye on needs of the health care sector.

In the health care session, it was first discussed what a green API is. Different answers showed different ways of approaching this (e.g., regarding biodegradability, metabolites/by-products, toxicity in the environment, but also carbon footprint and process intensification). On bulls-eye posters (Figure 2), the main needs were identified which need to be met in order to implement/stimulate use of green APIs. The most important aspects were green procurement, education and awareness of prescribers (and others) to prescribe green APIs, criteria to define/assess green APIs and data to do so, R&D and development of green APIs. Incentives and regulation are needed to create push and green market access.

Identifying and elaborating on priority needs showed that e.g. factoring the environmental impact into the price, a cultural/behavioural change, stakeholder engagements, and funding are key to solve the identified needs.

2. Environmental criteria for active pharmaceutical ingredients to reduce their impact after use (Day 2 – morning)

After plenary presentations on criteria to reduce the environmental impact of APIs after use (environmental persistence, ecotoxicity, bioaccumulation and mobility, summarized in PREMIER report D4.6), subgroups discussed these criteria focusing on the following questions:

- How did you experience the plenary presentations? Missing criteria?
- What criteria to reduce the environmental impact of APIs after use would be feasible to implement in the R&D process and what not?
- What do you see as the window(s) of opportunity to implement these criteria?

It was concluded that it is possible to take up environmental considerations in (early) drug R&D, but there are also some challenges. The most important condition is that criteria, tools and cut-off values are clear. They must be robust and reliable to allow stop/go decisions to be made. Which topic(s) these criteria are about is of lesser importance to R&D specialists. Most of the screening should be performed *in silico*, early in the R&D process.

Screens for environmental mobility and bioaccumulation are seen as quite feasible to implement in drug R&D, as there might be an overlap with already existing screening methods. Environmental persistence/biodegradability was considered a key criterion. It can be designed in with the other key properties, but this requires clear-cut prerequisites or reference points. Principles/rules of thumb could support the design. Persistence/biodegradability may be factored in at the point of selecting the scaffold substance.

From an environmental perspective, the focus should be on avoiding PFAS molecular groups. However, this is hard from an R&D perspective. Therefore, a more detailed consideration on the consequences of different kinds of fluorination is needed. Cultural changes are expected to lead to higher awareness and demand for greener products, and eventually incentives to the industry. A good (reliable and proven) example is needed to get the ball rolling.

3. Implementation of environmental criteria in drug discovery and design of small molecules (PREMIER Parallel session, Day 2 – afternoon)

Participants in this session were R&D experts from pharmaceutical companies and the PREMIER project partners working on greener pharmaceuticals and ecotoxicological assays.

The process of incorporating sustainability aspects in (early) drug R&D is seen as complex, but not unfeasible (Figure 3).

Figure 3: Examples of actors' view on the process of incorporating green aspects in early drug R&D. *Actors chose a picture card and explained why: "The roof is leaking when the green tiles are missing" (left), "The long and winding road." (right).*

Currently, there is a lack of awareness and clearly defined criteria. The first can be solved by providing education on environmental impacts to R&D experts and decision makers. A 'green' company image may also increase marketing value. Besides this, there should be incentives regarding regulatory processes and budget. This calls for an action plan with a compelling story.

Criteria should be well-defined and have a clear relation with actual environmental hazards and risks. R&D needs a toolbox with easy to use, simple, meaningful assays, which are high throughput and fit within the appropriate stages of R&D. The test endpoints should be selective and specific, with clear cut-off values. There also needs to be a system for ranking/weighing of criteria, against each other but also against other R&D criteria. Off-target effects identified in drug R&D may help to identify which environmental organisms may be at risks. The field of bioaccumulation may be the easiest area to start to work together, as this is usually not a good property for patients as well as the environment. Tools to assess bioconcentration in the environment are well developed and may be of use in early pre-clinical development. Successful cooperation between R&D experts and environmental scientists in bioaccumulation studies could stimulate further progress.

4. Criteria for greener production of pharmaceutical products – Is there a business case? (TransPharm Parallel session, Day 2 – afternoon)

During the PREMIER/TransPharm workshop, a Mentimeter quiz was organized on the topic "Is there a business case for green pharmaceuticals?". It consisted of 8 questions. The questions were posed during a plenary session, chaired by Caroline Moermond to 36 attendants. Their responses are summarized below.

- Only few respondents (4 out of 36) consider environmental sustainability more important than security of supply. Most respondents either think it is equally important, are indifferent or think security of supply is more important than environmental sustainability.
- A large majority of the respondents (82-88%) thinks that a greener pharmaceutical product does not have to outperform conventional pharmaceutical products in other areas, e.g. clinical efficacy, safety for the patient (acceptable adverse effects), convenience of use, secure drug supply or shelf life.
- The respondents consider all environmental impacts related to pharmaceutical products more or less equally important (i.e., impacts of production and impacts after use).
- The respondents identified a lack of guidelines on what constitutes a greener API as the most important barrier to replace current APIs by greener ones, followed by (examples of) greener APIs and reducing the uncertainty on the reimbursement of costs/investments (Figure 4).
- The majority of the respondents (22 out of 36) thinks that the production of greener APIs and products should also be possible outside Europe.
- Respondents scored all proposed measures to stimulate greener APIs high, such as (1) fast track approval EMA/DRA, (2) a special label on packaging, (3) waivers during marketing authorization (reduced fees), (4) longer patent lifetime for greener products, or (5) reimbursement advantages. During the discussion, it was suggested to make use of positive branding and regulation (e.g., bans if better alternatives are available to stimulate greener APIs).
- A large majority (83%) of the respondents is in favour of sustainability certification by an independent third party, but it needs be clarified who will be paying for the costs.
- A large majority (67%) of the respondents thinks that a business case should also be possible if not all stakeholders are on board yet.

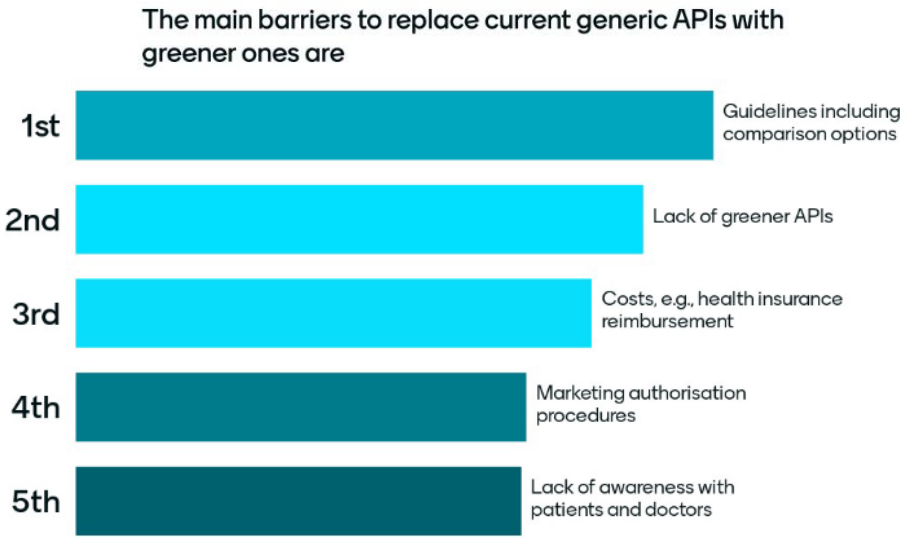

Figure 4: Mentimeter question 4/8 on the main barriers to replace current generic APIs with greener ones.

5. Sustainability assessment of pharmaceutical products (Day 3)

In four parallel sessions, participants discussed the question for whom and why **mapping the life cycle of pharmaceuticals and designing an assessment system** is needed. Participants found that sustainability assessment in daily work is complex, with many interconnections between actors and processes. The assessment should preferably be harmonized, resulting in one evaluation result that can be used by all members of the product chain, such as health insurance companies, clinicians, etc. It should lead to appropriate drug use. Unintended consequences should be minimalized (e.g., less access to medicines).

This assessment can be performed at all phases of the chain (Fig. 5), and should fit within existing frameworks. It should be part of formal regulations, but described in guidelines that can be more flexible to include new insights and country-specific aspects. Including the assessment in a benefit/risk analysis is a challenge, the balance should be right and societal benefits and individual benefits of the patient should then also be weighed. A full assessment includes health benefits and economic benefits. Environmental risks after use are estimated at market registration, but may change over time. LCA results (e.g., as a result of different distribution chains) change constantly. A cyclic process (conditional access) may solve this. Although a formal LCA may not be possible/appropriate at all stages (e.g. uncertainties in early stages), LCA thinking may be part of R&D and help to identify the largest hotspots within the chain, where sustainability matters most.

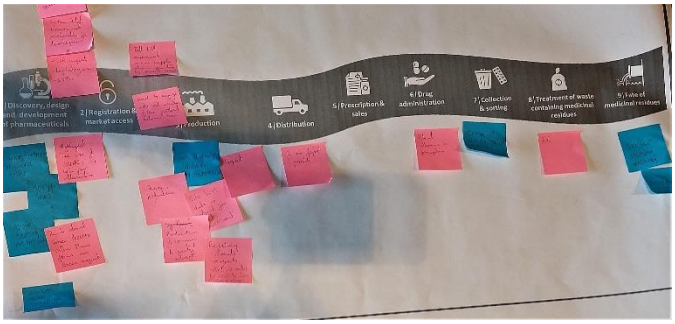

Fig. 5: Pharmaceutical Life Cycle & Needs for Assessment System.

During the interactive session on "**Aspects to consider for a holistic framework**" participants of four subgroups answered a series of questions on sustainability. Focus was the environmental dimension of sustainability, for which nine impact categories had been identified (Figure 6).

The participants' feedback in general showed that many of the aspects mentioned are already part of daily sustainability considerations for many decision-makers.

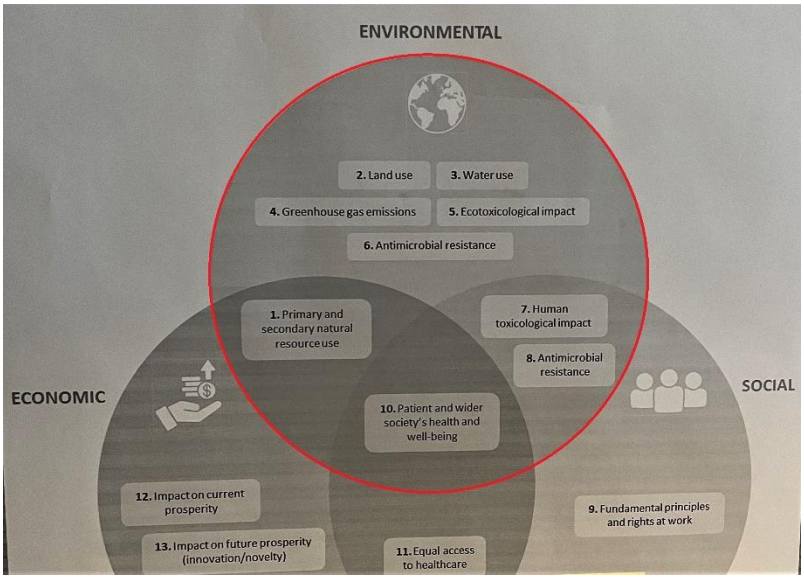

Figure 6: Assessment of Environmental Sustainability: Impact Categories.

Nonetheless, needs are diverging. For example, the level of aggregation of results of the sustainability assessment depends on the later use and also differs within one organization (for example the procurement team has other needs than the marketing team). Ecotoxicological impacts are already high on the agenda, while other impact categories such as land-use or prosperity are not yet widely anchored in stakeholders' minds. The topic of energy consumption popped up in several moments of the workshop and can be further considered in the project work along with the wide and detailed participant's feedback. Some aspects mentioned here are the need to i) consider the impact category "resource use" separately for the pharmaceutical's lifecycle (from production to end of life, e.g. for waste treatment) and their packaging, ii) define clearly what the difference is between human and environmental antimicrobial resistance and to iii) consider biodiversity as a separate environmental impact category. Another matter is the discussion how to better link to the UN SDGs.

In the last interactive session, two subgroups addressed **needs and opportunities for education and awareness raising in a) drug R&D and b) the health care sector**.

a) To educate students in drug R&D, several study programs are organised along EU countries. The programs are still new and the number of students might increase in the upcoming years. The focus differs per program, but aims to inform students on sustainable chemistry, green future or sustainable and high-quality pharmaceutical products. The programs emphasize a strong connection with the industry. Life-long learning is recognised to be important, in which the support of decision makers might be important.

b) To provide education modules to health care professionals and at universities as well as professional education, experts have taken initiative in many EU-member states. This is almost always ad-hoc, at single universities, and not harmonized country-wide or between countries. Making sustainability or PiE (Pharmaceuticals in the Environment) part of the formal curriculum is a next challenge. There is a clear need for good educational materials. Education materials should be evidence-based. Teachers need some reference (a textbook, either in print or online), which should be open-source. There is also a need for easy-to-understand material, e.g., an animation, some slides, infographics, that can be easily incorporated into existing education modules and create awareness. A slide deck should then also contain more detailed slides for those who wish to dive deeper into the materials.

6. Let's have fun!

The *Safe-by-Design Serious Game* (RIVM), played one evening after dinner, was helpful in making the complex topic a little easier to digest and applying the day's input with fun.

PREMIER/TransPharm

We are looking forward exchanging views in other settings or workshops. Please join our newsletters [PREMIER, TransPharm] for regular updates on the results of the PREMIER and TransPharm projects.