Sustainable Chemistry and Engineering in Pharma

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Editorial

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Active pharmaceutical ingredients (APIs) and their starting materials are highly complex synthetic constructs and consequently accumulate a relatively high environmental footprint, for instance, as measured in terms of high E-factors[1] or process mass intensity,[2] along with their multistep syntheses. Redesigning the manufacturing routes to established medicines and producing the next generation therapies utilizing greener methods offers the possibility of significantly improving their sustainability. By addressing some examples in the field, this editorial aims to provide the readers and authors of *ACS Sustainable Chemistry & Engineering* an introduction to the topic and is intended to serve as a starting point for discussion on the challenges the pharma industry faces, as well as collaborative efforts that can be utilized to achieve improved sustainability in the industry.

Government funding agencies across the world support sustainable chemistry and engineering of relevance to the pharmaceutical industry through a panoply of mechanisms, ranging from grants supporting individual Ph.D. projects through to support for multimillion-dollar research centers. Individual pharmaceutical companies collaborate with individual projects or offer support to larger endeavors. Also, consortia of pharmaceutical companies have combined efforts to amplify the voice of the industry to emphasize precompetitive topics of interest to all members. For instance, the American Chemical Society (ACS) Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) has been exploring avenues to expand more sustainable science and engineering within the industry since 2005. As a precompetitive consortium of international companies in the pharma/biotech and affiliated space, substantial efforts have been made to enable chemists and chemical engineers to contribute toward global sustainability and provide solutions for all. This has occurred by sharing existing knowledge (e.g., via compiled reagent and solvent selection guides) as well as designing metrics and tools to gauge performance and outline improvements (e.g., process mass intensity (PMI) calculator, PMI predictor). The Roundtable advocates for targeted green chemistry and engineering backing to academic and government laboratories from U.S. federal and international funding agencies. In addition, since 2007, the GCIPR has also provided funding to academic groups to address sustainability gaps identified by the precompetitive consortium members. These knowledge gaps are needs that all members and the greater scientific community would benefit from filling. They often involve addressing old-school, workhorse chemistry and engineering practices that were designed at another time and require updating for a more sustainable future. In total, the GCIPR has funded over 30 projects to a level greater than $2.4 million. This support helps advance novel ideas with sustainability implications but also provides training and advancement to scientists, many of whom will go on to be the academics and industry employees of tomorrow.[3]

Consortia of companies can also participate through public−private partnerships, as in the case of the EU's Innovative Medicines Initiative (IMI), where projects such as CHEM21[4] brought together six European Federation of Pharmaceutical Industries and Associations (EFPIA) companies; eight universities, research organizations, public bodies, and non-profit groups; five small and medium enterprises (SMEs); and two third parties. Another example is Mistra SafeChem, a Swedish research program that aims to create a sustainable chemical industry and reduce exposure to hazardous substances. Mistra SafeChem is financed by Mistra, The Swedish Foundation for Strategic Environmental Research, and it engages researchers from the IVL Swedish Environmental Research Institute, different units of RISE (Research Institutes of Sweden), seven university departments, and no less than 12 industry partners.[5]

It is perhaps inevitable that strong working partnerships can develop between individual companies and particular institutions. These include high profile collaborations between Virginia Commonwealth University, where Frank Gupton has received over $40 million from the Bill and Melinda Gates Foundation and the Novartis-MIT Center for Continuous Manufacturing. In the UK, the Accelerated Discovery and Development of New Medicines: Prosperity Partnership for a Healthier Nation, brings together the pharmaceutical industry in the form of a company (GSK) with academia, building on the company's long-standing existing collaborations with the University of Nottingham and University of Strathclyde using their respective unique strengths on research topics of interest across the full range of drug discovery and development, including sustainable processes and process intensification.[6]

The link between industry and academia in sustainable chemistry and engineering is in many ways embodied by one of the buildings in which Prosperity Partnership research is conducted. The GSK-Carbon Neutral Laboratory at the University of Nottingham, funded by a £12 million donation from GSK, incorporates the latest technologies in order

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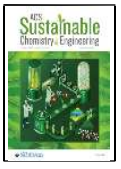

achieve carbon neutrality over its lifetime. The building acts as a catalyst for new industry collaborations and research within focuses on world-leading "clean and green" research in sustainable chemistry. The center is also a regional hub for chemistry education, giving local schools and colleges access to working laboratories and technical support.

As another example enabling the development of sustainable chemistry and engineering in the pharmaceutical domain, the aim of the research at Nelson Mandela University is to reduce the cost of generic APIs in low- and middle-income countries. This approach is thereby focusing on sustainable approaches. South Africa's pharmaceutical sector is worth approximately R20 billion (ca. $1.4 billion) annually; however, local producers play a limited role in the overall value chain. All companies essentially purchase the APIs from overseas and formulate them into finished products. This has left South Africa, and other less-developed countries (e.g., India), vulnerable to disruptions in supply chains. An unfortunate real-world example of this vulnerability is currently unfolding as a result of the COVID-19 pandemic.

While there is a transparent market for the local manufacture of APIs, especially for the treatment of AIDS, TB, and malaria, there are various barriers to entry. One of the key issues is that existing formulators are reluctant to work with start-up companies due to the high costs associated with the establishment of a commercial good manufacturing practices (GMP)-approved manufacturing facility, putting in question the price competitiveness of local API manufacturing compared to existing generic manufacturers in Asia.

At the Nelson Mandela University, the vision is to utilize the most sustainable chemistry and technology to define the lowest-cost manufacturing route to APIs. In recent years, much attention has been given to continuous processing, and the advantages of flow chemistry are well documented from a green and/or sustainable perspective.[7] Regarding drug discovery itself, Professor Kelly Chibale is founder of Africa's first drug discovery and development center (H3D) at the University of Cape Town, which focuses on affordable treatments for tuberculosis and malaria. H3D is well known for its pioneering research into a single-dose treatment against malaria;[8] however, to produce medicines for the local population would require a qualified nearby manufacturing facility.

It is worthwhile to understand where in the world activities in this area are being undertaken. Equipment suppliers, mostly based in Europe, and supported by various funding programs, were eager to develop innovative technology to improve the competitiveness of the industry. This has, however, led to the present challenge in Europe and America that a lot of custom manufacturers now have excess batch capacity. As such, from a financial perspective, the driver is to better use their existing infrastructure. In comparison, one advantage in less developed countries, such as South Africa, is that there are very few chemical manufacturers and as such very little existing infrastructure. Consequently, if companies are interested in establishing capacity, they have the freedom to select the best sustainable technology from both cost and performance perspectives: starting from nothing is an advantage in some cases.

Overall, it is essential for universities to drive sustainable innovation in order to help society by working with start-up companies in collaboration with the existing formulation industry to provide guaranteed access to low-cost medicines.

Apart from the aforementioned infrastructure, the accessibility to APIs vastly relies on the availability of synthetic methods. Catalysis has played a crucial role in the synthesis of pharmaceuticals or drug-like compounds by providing new or better reactions. The last century has witnessed an explosion of new synthetic methods that have enabled chemical reactions unlikely to occur in the absence of a catalyst. A major challenge is that the catalyst may not be as efficient or selective enough when applied to APIs,[9] for instance, due to functional groups present in the molecule, resulting in an increased environmental footprint. However, a major burden for academics is the lack of access, or permits to work, with biologically active compounds in some jurisdictions. While this might be common practice for some academic disciplines, it is not common in the majority of (organic) chemistry laboratories. This burden can once again be overcome through academia−industry collaborations, and this symbiosis is key to promote innovation.

A remaining challenge for the catalytic synthesis of APIs remains catalyst immobilization, both for the purpose of potential catalyst recycling as well as minimizing product contamination due to residual homogeneous transition metals. Generally, using heterogeneous catalysts is considered a promising approach, because solid catalysts are cheaper, easy to handle, exhibit excellent chemical and thermal stability, and can be completely recovered after the reaction. However, the presence of weak catalyst−reactant interactions in heterogeneous catalysis due to the phase difference of reactants (liquid) and catalysts (solid) limits the application of solid catalysts in the pharmaceutical industry. Because of this weak catalyst−reactant interaction, it is challenging to control the reaction mechanism; i.e., conversion as well as selectivity are often lower in heterogeneous catalysis. As a result, multiple workup steps are needed to separate the desired product, and this will increase waste generation as well as the production cost. One of the potential solutions to this problem is immobilizing typically used homogeneous catalysts (transition metal complexes) for drug synthesis on a solid material (e.g., polymer, carbon, silica). The resulting immobilized catalyst can provide the benefits of both homogeneous and heterogeneous catalysts.

Late-stage functionalization (LSF)[10] is the chemoselective and often site-selective functionalization of complex molecules and a powerful tool in drug discovery. If a catalytic method can be applied to an advanced synthetic intermediate, analogues to drug targets would be more readily accessible. Such an approach would avoid embarking on individual syntheses of all analogues anew. LSF provides drug analogues with specific functional groups that moderate the sterics and/or electronic properties of the APIs, giving relatively easy access to new organic compounds ready for testing and with potentially improved biological activity. Finding appropriate reaction conditions for LSF requires an extensive number of optimization experiments, a task that can be facilitated by automated testing via high-throughput screening (HTS). HTS is eased by the use of commercially available catalysts that work under a noninert atmosphere (i.e., tolerate air and moisture). One of the most recent challenges in this area has been the direct functionalization of C−H bonds in drug-like molecules. C−H bonds are ubiquitous in organic compounds, and the development of catalytic methods that introduce a specific functional group in chemoselective and regioselective manners on a functionalized compound is of great importance.

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This area of research has recently been reviewed,[11] presenting important guiding principles. Current challenges include the use of accessible and earth-abundant metals as catalysts and to some extent avoiding the use of strong-donor ligands (i.e., P- and N-ligands), which normally require their own complex syntheses. Furthermore, the use of heterogeneous catalysts and of other reaction mediators based on earth-abundant metals is encouraged for the LSF of APIs, which may contribute to the sustainability of API production methodologies significantly.

Another challenge for the development of sustainable chemistry and engineering in the pharma industry is related to the use of solvents. Indeed, solvents are a primary contributor to the high E-factors,[2] partly due to the high purity and quality requirements for FDA-approved therapeutics. Aside from attempts to reduce the amount of solvent used for purification purposes, the large amounts of solvents used for the reactions could be reduced or eliminated. Indeed, techniques regularly used in the pharmaceutical industry to reduce particle size (ball milling and jet milling) or to shape solids (extrusion) can be used for synthesis purposes.[12] These synthesis techniques, gathered under the generic name of mechanochemistry, enable the running of reactions while drastically reducing (and sometimes eliminating) the use of solvents. One of the very first examples describing the use of such a technique for the production of an API was the synthesis of bismuth subsalicylate (also known as Pepto-Bismol) by ball milling.[13] In addition to enabling the production of the API with a very low amount of water, the previously used and toxic bismuth(III) nitrate could be replaced with innocuous bismuth oxide (Bi_2O_3). Although not yet directly applied to the synthesis of an API, it has also been shown that jet milling, a technique that allows particles to collide with each other via a high velocity gas jet, enabled the quantitative conversion of aldehydes and amines to imines at the kilogram scale, with very short reaction times (3 min).[14] One can easily imagine applying this continuous and solvent-free technique for the construction of API covalent bonds. Reactive extrusion, a technique to mix and convey the material through a die to give it a special shape, has also been used to produce APIs. The very first use of this technique to produce an API was reported in 2011 for the manufacturing of a cocrystal composed of the drug candidate AMG-517 with sorbic acid.[15] While enabling the elimination of solvents, this process also provided the cocrystal with superior mechanical properties than cocrystals produced by a solvent-based synthetic route.[16] This approach was further developed to create covalent bonds for the production of molecules of interest to the pharmaceutical industry, such as the dipeptide aspartame,[17] the hydrazone nitrofurantoin, and dantrolene.[18] In these cases, the utilization of reactive extrusion has enabled avoiding the use of undesirable solvents, while drastically improving the overall process efficiency when compared to conventional solvent-based routes. These examples clearly show that, in addition to reducing or totally suppressing the need for solvent, mechanochemical techniques, such as ball milling, jet milling, and reactive extrusion, can also improve efficiency, while offering additional advantages, such as for instance, expanding the scope of reactants or improved physical properties of the targeted solid material. Although highly attractive, these approaches are still limited by the lack of understanding of the underpinning mechanisms, as well as the dearth of knowledge on the role of the physicochemical properties of the reactants on the course of the reactions. Studies addressing limitations that inhibit wider dissemination of these techniques to the pharmaceutical industry, such as those listed above, would certainly help to improve the situation and overall use of such techniques.

The examples included in this editorial highlight the various opportunities for collaborations between the pharmaceutical industry and academia and how these collaborations can lead to more sustainable API production. Moreover, selected examples of underutilized but highly sustainable tools and approaches for API synthesis are discussed. We at *ACS Sustainable Chemistry & Engineering* would like to encourage our authors and readers to report on such collaborations and challenges in future editions of our journal, in addition to reports on more sustainable synthesis and production routes to APIs.

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Notes

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