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ROYAL SOCIETY OF CHEMISTRY

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Sustainability Spotlight

In support of the UN Sustainable Development Goals—particularly SDG 3 (Good Health and Well-Being), SDG 9 (Industry, Innovation and Infrastructure), SDG 12 (Responsible Consumption and Production), and SDG 13 (Climate Action)—the pharmaceutical industry is increasingly advancing Net Zero commitments aligned with the Paris Agreement to help mitigate climate change while delivering more sustainable medicines to patients. Achieving these goals requires the integration of green and sustainable chemistry throughout drug development. In this context, this paper highlights the Pfizer Green Chemistry team's approach on its 25th anniversary, showcasing priority areas spanning discovery, process development, manufacturing, and waste treatment across the small molecule portfolio, with emphasis on performance metrics, enabling technologies, and cross-industry collaboration.

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ARTICLE

Sustainable Chemistry in Pharma: Pfizer Green Chemistry Team's Perspective

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In the last few years, many pharmaceutical companies have shared publicly Net Zero goals aligned with Paris agreement in order to curve climate change and deliver greener medicines to patients. To achieve these ambitious objectives, embedding green and sustainable chemistry concepts into drug development strategies will be of high importance. Herein, we cover the approach taken by the Pfizer Green Chemistry team on its 25th anniversary, highlighting key areas of focus from discovery to manufacturing waste treatment within our small molecule portfolio, while encompassing metrics, new technologies and cross-industry consortia initiatives.

Introduction

In the past years ***net zero*** has emerged as an important concept in pharmaceutical industries due to global warming, and the urgency to combat climate change.[1] To limit global warming below 1.5°C threshold and maintain a liveable planet as designated by the Paris Agreement, CO_2 emissions must reach net zero (or net-negative) by mid-century.[2,3] This immense humankind challenge goes beyond the pharmaceutical sector and calls for nothing less than a complete transformation of the way we produce, consume, and transport goods. Replacing coal, gas and oil-fired power with energy from renewable sources, such as wind or solar, would dramatically reduce carbon emissions. A change of mindset is critical.[4,5,6]

The chemical industry is responsible for about 5% of global CO_2 emissions, and the use of renewable biomass, leveraging circular economy and reducing greenhouse gas (GHG) emission will be key to decarbonize the industry.[7,8,9]

Conscious of this reality, pharmaceutical companies started to publicly announce Net Zero goals and Pfizer set its aggressive target by 2040.[10,11] And while an overarching and supportive corporate strategy is essential to be successful, green and sustainable chemistry will reside at the heart of the solution.[12]

According to US EPA, **Green chemistry (GC)** is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances.[13,14] And while closely related, **Sustainable chemistry (SC)** expands its focus to encompass a broader life-cycle analysis approach.[15,16,17] It includes reduction of GHG emissions, considers resource efficiency, renewable materials and sets broader goals aligned with the Industry's environmental responsibilities.[18,19,20]

Pfizer embraced early the GC concept and principles[21,22] and created back in 2001 its own Green Chemistry initiative.[23] This matrix team continues to support many actions nowadays across all stages of drug development. From discovery to commercial process design, from drug safety studies to manufacturing sites, this group of colleagues educates around green chemistry, participates in external consortia and supports internal initiatives.[24,25,26] Among these, metrics holds an important place to assess our processes and evaluate new technologies, and all these aspects will be discussed in this perspective.[27,28] At the outset, it is important to acknowledge that while Pfizer is active in multiple therapeutic modalities such as monoclonal antibodies and vaccines, this primary focus of this perspective is small molecules. The rationale behind this is because this modality has represented a constant for the Pfizer Green Chemistry team over the past 25 years, though it is important to stress that there is considerable emphasis currently placed within our team on the larger molecule (biologics) space particularly given the perception that their development faces larger sustainability issues than traditional small molecules. Tangible evidence of progress that we have made with this goal in mind with regard to vaccines is provided in the recent account of the development of our COVID-19 vaccine.[29]

Pfizer Green Chemistry Team

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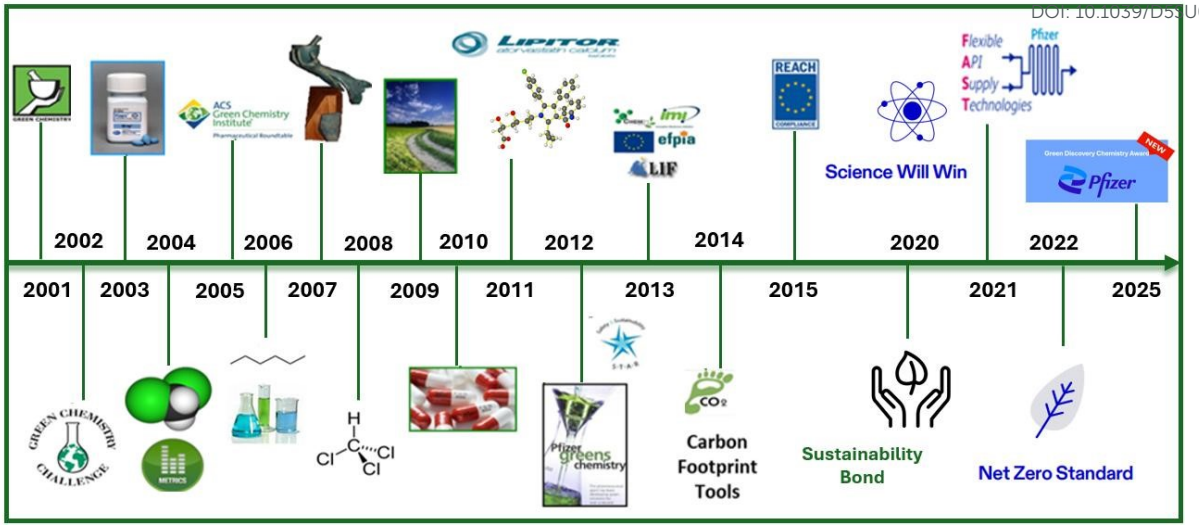

Figure 1. Timeline and Accomplishments of Pfizer's Green Chemistry Team

Origins of the Pfizer Green Chemistry Team can be traced back to 2001 at the Groton, CT site. Dr. Buzz Cue, the Vice President of Chemical Research and Development at the time, had put together a team that focused on the implementation of procedures to reduce chemical waste among the drug development pipeline. After getting support from Senior Leaders within Pfizer, they were then able to officially start the team in 2002. This led to an expansion of their efforts to additional R&D groups at both the La Jolla, CA and Sandwich, UK sites. A steering committee was formed for the team in 2003, which was made to work on implementing corporate level changes within the company. Since the establishment of the group, the overall goal of the team has been to interweave the 12 Principles of Green Chemistry into Pfizer's own green chemistry initiatives.[30]

As the team evolved over the years, their goals were developed to fit the need of where they felt their efforts were best placed. Initially, a major focus was on spreading the word of green chemistry internally while also promoting it externally. They then worked on building internal tools and resources to incorporate green chemistry into the stages of drug design and manufacturing.[31] The growing team allowed for priorities to be concentrated on the tracking of green chemistry metrics within the company and finding ways to improve them. The current focus of the team is analysing the carbon footprint and the direct influences the company has on the external environment (Figure 1).

There is now a diverse collection of chemists and engineers from all different points along the drug development pipeline who are a part of the Green Chemistry team. With extended expertise in green chemistry, there are more refined ideas when implementing the company's GC goals. A strength within Pfizer's team is its strong relationship between its commercial manufacturing partners, and the utilization of a green chemistry team leads. From the point of first synthesis to the drug reaching commercial status, there are countless sustainability benefits realized that can be attributed to efforts made by Pfizer's Green Chemistry Team.[32]

Pfizer Corporate Goals – Roadmap to NetZero

At Pfizer, we acknowledge global climate change as a significant challenge that necessitates collaborative efforts to address the potential risks it presents.[33] These risks include heightened adverse effects on human health and reduced accessibility to essential medicines and vaccines, which may result from value chain disruptions caused by the increasing frequency of severe weather events.[34]

As such, in 2022, Pfizer announced its intention to achieve the voluntary Net Zero Standard by 2040, a decade ahead of the standard's recommended timeline.[35] Recognizing the imperative for decisive action, Pfizer is dedicated to reducing greenhouse gas (GHG) emissions by 46% by 2030, using 2019 as the baseline year.[36] This objective supports global initiatives to limit temperature increases to 1.5°C above pre-industrial levels. By 2040, the company aims to reduce its direct GHG emissions by 95% and value chain emissions by 90%, compared to 2019 figures. These targets will be pursued through lowering energy consumption in operations, transitioning to renewable energy sources, and collaborating with suppliers to promote similar actions across the value chain.[37]

As part of our strategic vision to address this issue, Pfizer is dedicated to developing medicines that enhance patient health while minimizing environmental impact across the entire product lifecycle, in comparison to conventional research, development, manufacturing, and supply practices. Drawing on our longstanding commitment to green chemistry principles, we are advancing innovation in our R&D and commercial operations. Our comprehensive approach encompasses every

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stage of the product lifecycle—from early research through manufacturing to end-of-life management. We are embedding sustainable design principles into our R&D processes to reduce energy usage, reduce consumption of water, and raw materials, minimize waste, eliminate the use of chemical of concerns and adopt circular solutions wherever feasible. Additionally, we prioritize ongoing education for our colleagues, the establishment of key metrics and performance targets, and the promotion of innovation through collaboration and partnerships, all these at the core value of our green chemistry program.[38]

Sustainability Vision Across Development Lines

Discovery Chemistry: Emerging Initiatives/Design for Degradation

The initial stage in the drug development pipeline involves the discovery and design of molecules.[39] While a range of drug modalities are considered, most of Pfizer's early research efforts is currently focused on small molecule discovery.[40] In terms of our sustainability efforts, this provides the opportunity to influence not only the molecules that we make but also the ways in which we synthesize them.[41] The drug discovery process often starts with the evaluation of thousands of molecules to successfully identify a compound, which will then emerge as a clinical candidate and potentially a marketed medicine. One of the major challenges throughout the industry has been the development of innovative methods to streamline and expedite the discovery of such lead compounds.[42] From a Green Chemistry standpoint, this reduces an organization's environmental burden as from a simple perspective, the less compounds that an organization must make, the less chemical waste that they will generate.[43] This has also led to growth in numerous areas including hit identification through DNA-encoded libraries,[44] a plethora of in silico tools for the evaluation of compounds, structure-based drug design platforms focusing on X-ray crystallography and/or cryo-EM,[45] miniaturization of synthetic methodologies[46] and multiparameter optimization strategies focusing on minimizing compound dose.[47] Given space constraints, we will only consider several initiatives that we have pursued within our Discovery chemistry teams here at Pfizer.[48]

Designing for degradation, one of the Principles of Green Chemistry, represents somewhat of a dichotomy in the Drug Discovery paradigm. Metabolic degradation presents a challenge for drug design, and a common strategy is often to block these metabolic hot spots within a molecule to prevent rapid in vivo deactivation even though this can have an adverse overall environmental effect with the long-term build-up of pharmaceuticals in the environment.[49] For antibiotics, this also poses a threat to human health from antimicrobial resistance. While Pfizer is committed to responsibly managing wastewater discharges from our sites to assure that the research, development, manufacture, use and disposal of our medicines does not adversely affect human health or the environment, we in the Discovery phase judiciously employ in silico tools to balance both the dose and metabolic liabilities of the compounds that we design to try to balance metabolic stability with their long term potential for degradation in the environment. Furthermore, there is a growing interest in new targeted modalities that naturally degrade and are thus removed from the body and the environment more quickly. For instance, there has been expanded interest in the utilization of PROTACs and PEG linkers. This is a very direct way of designing for degradation since their level of degradation is wholly linked to their potency—in designing a potent compound, we are simultaneously designing one that will degrade quickly.[50] This is an overall greener method of synthesizing drugs produced at Pfizer, and targets nature's strengths to create a more efficient process.

While there have been significant developments in computational tools to predict physicochemical properties and enable preliminary triaging of compound collections for synthesis, there has also been large strides made in the development and implementation of artificial intelligence retrosynthesis programs that draws information from literature, Pfizer's internal notebooks and compounds, and patents. These tools offer multiples routes to a compound of interest, with the ability to rank the results based on several factors including predicted cost of goods, route complexity, precedence of proposed steps and scalability. While synthetic chemists are far from being wholly reliant on this technology to carry out their work, it does aid in fostering new synthetic ideas based on the large catalogue of precedent that would normally take a significant amount of time to sift through. The user experience of the AI retrosynthetic tools is constantly improving based on feedback from scientists to make the programs better fit their needs and feasibility of the generated reaction routes. These programs also offer the user the opportunity to select routes that enable a specific disconnection and set filter that eliminate specific undesirable reagents and/or transformations thus allowing a preliminary filter to assess potential greenness. The use of less toxic reagents in the first stages of synthesis leads to a jumpstart in the development of more environmentally friendly process and commercial routes. Members of the Pfizer Green Chemistry team have put together and distributed in-house guides and publications to help direct scientists to alternatives for undesired reagents and solvents. There is coordination between the Pfizer EHS team, the GC team, and research site procurement to facilitate better availability of these alternative chemical choices. The workflow for early discovery chemists has them executing synthesis on an experimental scale that is of an adequate size to test out their hypotheses, but not large enough to consistently waste chemicals and lab resources. Route design is a key factor to consider within the Discovery phase with an aspirational goal being to develop a route that enables not only expeditious SAR studies to be carried out but also can be utilized for the scale-up of a target compound. This is the basis of the concept of the development of a "Proactive Synthetic Route" as opposed to a "Target-Oriented Route" (*vide supra*).[51]

Parallel Medicinal Chemistry (PMC) is a major synthetic technology that Pfizer has had great successes in launching the ideas of early discovery programs.[52] A library building tool has also been launched that pulls monomers from both vendors and Pfizer's internally registered compounds. Embedded within this tool is the ability to virtually assay a proposed collection of compounds, and filter based on predicted properties as well as to ensure maximal coverage of the desired chemical space. Coupled with this, the utilization of the in-house PMC labs saves significant time and resources that would otherwise be lost through exclusively outsourcing these efforts. By having the capabilities to carry out PMC at the microscale (2 µmol), analytical (10 µmol), and traditional (100 µmol) scales, the needs of the various project teams and libraries can be met on an as-needed and material-sparing basis. Sending these plates of compounds to the on-site purification labs allows for high efficiency in the submission of the synthesized analogues to the assays for biological or biophysical testing.[53] In comparing the purification of the traditional PMC scale to an analytical PMC scale, the smaller analytical scale requires 90% less solvent overall, and results in a reduced cycle time of about 3-4 days.

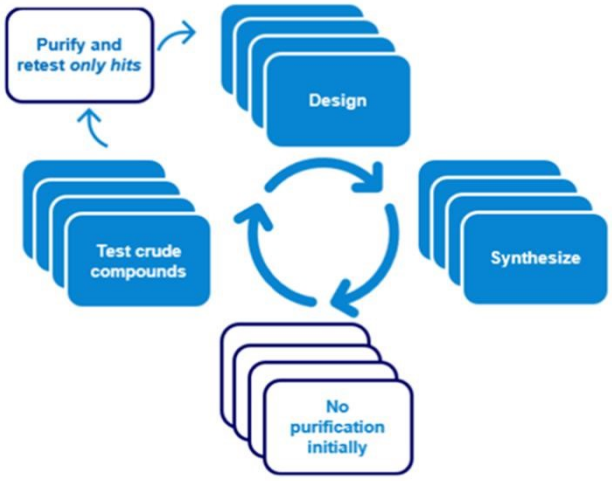

Figure 2: Schematic Representing "Direct to Biology" Workflow

A recent expansion in Pfizer's PMC space is the implementation of a Direct to Biology (D2B) workflow.[54] In running these microscale libraries, there is a significant decrease in the amount of template, reagents, and solvent needed for this process. In early-stage projects where there is a major focus on rapidly generating SAR data, this is a valuable system to get design-based questions answered in a manner that is less impactful to the environment. The D2B process eliminates the need for purification of inactive compounds by testing their crude mixtures and only triggering the purification of those that read out as a hit in the project's assay (Figure 2). Thousands of compounds have been synthesized using this approach, saving the significant amount of resourcing that would have been needed to make these on a singleton scale.[55]

Practical considerations within our medicinal chemistry laboratories also play a broad role in ensuring the sustainability of our operations. For instance, rotovaps are broadly employed for the removal/evaporation of volatile solvents after most synthetic procedures. Within a discovery chemistry environment, nowhere is their use more pronounced than in an Analytical/Purification group in which after a chromatographic separation, product-containing fractions are subsequently pooled, and the solvent removed to afford the desired neat sample. Replacement of the conventional "cold-finger" condensers on the rotovaps with an innovative new Ecochyll-XI unit, leads to improvements in cooling efficiency, energy savings while eliminating > 95% of dry ice from the laboratory (evidenced by a dramatic decrease in dry ice costs across the site) while also mitigating safety issues concerning the asphyxiation hazards associated with its use.[56,57] In a similar manner, chromatography plays a key role within Discovery chemistry and is a major contributor to the volumes of organic solvents being used in this space. While reverse-phase systems are often employed for the purification of final compounds, the removal of aqueous-based solvent mixtures often requires significant amounts of energy and lyophilization. While significant efforts have been made in providing alternatives to chlorinated solvents for this purpose, we have looked to implement SFC (supercritical fluid chromatography) systems not only within our expert purification group (primarily for chiral purifications) but also in an open access mode for the broader chemistry community. Utilization of supercritical carbon dioxide as a component of the mobile phase leads to a > 85% reduction in the organic solvent volumes used in a purification with a further benefit being less energy required for drying of the desired sample.[58]

Herein, we have provided details of several of the initiatives that we have implemented in our Medicinal chemistry groups though one of the key attributes of our Green Chemistry program is that it encompasses all departments and enables a seamless integration of new technologies and sustainability principles as a project progresses into development.

In addition, Pfizer works closely with external partners from early discovery through development to supplement our internal synthesis efforts for the synthesis of intermediates and analogues for lead development, optimization and early processes development.[59] Throughout this process from vendor selection to executing Pfizer projects, Pfizer sourcing teams work closely with our partners to ensure they not only comply with Pfizer EHS policies but also have a strong commitment to green chemistry and sustainability in their operations and follow green chemistry practices during execution of projects.[60] As a part of this process Pfizer shares Green Chemistry tools and practices with our partners and collect Green Chemistry Metrics for Pfizer projects. This includes setting up workflows for miniaturized HTS for reaction optimization, solubility screen and singleton array to minimize the material and solvent usages. However, the requirements and the rigour may vary with different stages of the program. In early discovery, speed is most important business requirement and may need to

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balance the use of Green Chemistry, for example, use of chromatography to purify materials on small scale is common practice, however as program progress towards scale-ups, chromatography separations are highly discouraged. Similarly, chiral resolutions are often used for small scale, whereas chiral synthesis using sustainable methods (Biocatalysis, use of chiral building blocks and chiral synthesis) are more common for scale-ups. Similarly, use of flow or photoredox technology are highly encouraged to minimize the hazard and to make processes more efficient.

API Supply: Commercial Process Development

The focus of pharmaceutical development is to enable the transition of drug candidates to launched medicines that treat indications and improve people's lives. At the core of this effort is the creation of processes suitable for commercial production of new chemical entities, a creative activity that requires inventiveness, leverages consistency and necessitates cross-functional partnerships. To address these needs Pfizer has developed a platformed approach to facilitate progression of molecules from early development through to launch and post-market, integrating the concept of Quality and Sustainability by Design (QSbD).[61]

The production methods used to transform commodity chemicals into finished drug substance directly influences the ability to manufacture in an economic manner, ensure quality supply and minimize environmental burdens.[62,63] The synthetic starting point from which to begin work and initiate scrutiny is important. Within pharmaceutical development identification of regulatory starting materials (RSM) can distinguish value steps from precursor steps, essentially biasing a focus only on final transformations. A critical deviation from this status quo is that Pfizer considers the entire sequence, effectively starting from basic building blocks when applying green chemistry. For example, the cost of RSM's is only one of several criteria by which we compare routes and drive commercial process development.[64,65] Our approach progresses from the traditional cost, quality, speed triangle to a cost, quality, speed and sustainability square where the fulfilment of each pillar is prioritized. This comprehensive approach to creating a launched commercial process is carried out in stages (Figure 3). In addition to cross-discipline collaboration to bring a process forward, the sustainability team connects into each activity through focus teams.

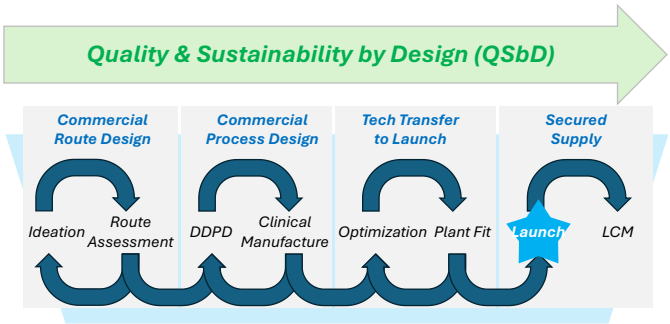

Figure 3: Approach for Development of a Commercial Route

Pfizer's approach to commercial process development operates through four phases with green chemistry being applied throughout: 1. Commercial Route Design, 2. Commercial Process Design, 3. Tech Transfer to Launch and 4. Secured Supply. Each workflow targets specific milestones and research goals that has embedded a manufacturing and sustainability component. Transitioning through all workflows results in a robust commercial process that can confidently produce a medicine using the best available technology to meet demand at necessary scales. In the complex field of pharmaceuticals, where changes to launched commercial processes outside of filed process descriptions has a high bar, an emphasis on crafting the right process the first time through is significant. Implementation of QSbD across workflows is essential to ensure both regulatory commitments are met while attaining a high level of environmental stewardship.

Commercial Route Design: The challenge for structurally complex targets is navigating the many disconnections and potential routes of synthesis; pharmaceutical drug substances are no exception. Within the application of QSbD to development we've established 'Commercial Route Design' as the first workflow. Diverging from medicinal chemistry, where rapid access to diverse material for study is important, the commercial route must meet a different set of criteria: long-term robustness, scalability and economic viability. Through the lens of sustainability this workflow aims to identify the intermediates used to transform commodity starting materials to final API through low step count, high convergency and implementation of strategic transformations. The application of chemical technology to disrupt and displace established approaches with leap-frogged efficiency are highly sought here. The mantra of good enough has been replaced by a continued drive for excellence and is supported by *ideation* and *route assessment* activities.

Commercial Route Design to prepare a single compound in a highly effective manner begins with *ideation*. Department brainstorming is leveraged to ensure capture of all possible disconnections and perspectives for taking alpha-raw materials to API. These ideas are assembled into a study plan that serves as the initial foray of prioritize activities. A challenge when targeting dramatic chemical improvements in highly complex settings is being unlikely to fully rely on established precedence. While this challenge serves as inspiration to synthetic chemists, cross-disciplinary exposure into technologies like biocatalysis, and the ever-increasing sophistication of retrosynthetic tools are important to help expand ideation past traditional transformations.[66] We've collaborated heavily with partners to continuously elevate the performance of retrosynthetic software in the face of ever-increasing structural complexity of API's and are keen to adopt strategies that identify unique previously unnoticed disconnections.[67]

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Route design is an experimental science and robustly pursued within the scope of *route assessment*, where paper ideation exercises are converted into practice. Prioritized routes are explored for feasibility, where surprised may lead to new opportunities and inspirations not conceived at the outset. This exploration is facilitated by high-throughput experimentation (HTE) to ensure enough reaction condition scope is covered for key bond forming transformations.[68,69] Although reaction conditions, unit operations and isolations are not nominated at this point, reasonable processability is required to establish a first-best process. To underwrite a nominated commercial route design sustainability considerations like step count, convergency, solvent choice and intermediate physical properties are made, with tools from the ACS GCI being implemented.[70]

Ensuring teams are provided with time, focus and resourcing to collect chemical information is essential to delivering the best commercial route design. The ability for teams to work without impending material demands is important to enable wider evaluation of chemistry both via planned engagement and serendipitous discovery.[71] 'Commercial Route Design' is therefore pursued in parallel to continued clinical manufacturing. First scale-up processes or supply route modifications that target specific gaps in robustness are carried out to meet clinical demand while assets are evaluated in this phase of development. Upon nomination of a commercial route, teams transition into commercial process design.

Commercial Process Design: Upon identifying route intermediates, focus pivots to 'Commercial Process Design', where processing details for each step are determined. The objective of this workflow is to select reagents, solvents, unit operations and isolation points. During this stage of development, the team integrates strongly with engineering and manufacturing colleagues to create a process suitable for commercial manufacturing.

The first activities in Commercial Process Design is *data-driven process design (DDPD)*, which leverages exhaustive HTE and data-rich experimentation to extensively explore reaction, workup and isolation space. Integration of solvent and reagent selection tools facilitate incorporation of green chemistry and sustainability into this workflow.[72] Parallel isolation work and hit validations continue to influence the screening activities in an iterative fashion. Elimination of unit operations such as distillations and narrowing on only essential unit operations is key to improving sustainability. A conscious effort to generate low-PMI, low burdensome, and robust processes is made in a data dependent strategy.[73] The 12 principles of green chemistry are strongly leveraged to ensure green decision making. Tools like Pfizer's ELN-PMI tool or internally developed modelling programs support teams to continuously monitor progress against goals for ensuring the best process is designed.

Within 'Commercial Process Design' vendor engagement for developing RSM manufacturing solutions is progressed. Pfizer aligns with the Pharmaceutical Supply Chain Initiative to ensure partners operate environmental consciously and we work to meet our Net Zero goals. Our commitment to sustainability includes collaborating with partners that share an aligned approach to incorporating green chemistry into process manufacturing. In this regard, it is important to realize that numerous external partners are based within manufacturing geographies (particularly in Asia and India) that still rely heavily on coal-based energy thus contributing significantly to Scope 3 emissions for Pfizer. While our direct control is somewhat limited in this space given that energy-use initiatives are driven by governments, Pfizer uses sustainability and ESG as part of our supplier assessments as noted to ensure vendor commitment to invest and implement sustainability goals, which include emissions from their operations. Metrics associated with these goals are often tracked on an annual basis by Ecovadis score and SBTi (Science-Based Targets initiative) with the data shared with the vendors to ensure both engagement and that progress is being made towards meeting the set goals. As also noted, Pfizer works with vendors to provide them education, tools and guidance to achieve these goals. Fundamental development of processes is conducted in collaboration, where green chemistry best-practices are shared and emphasized. These exchanges help contribute to achieving scope 3 sustainability objectives.

Upon completion of DDPD, first implementation of a new chemical process through *clinical manufacturing* is conducted. This manufacturing enables teams to demonstrate the designed processes and implement essential changes before committing to registration. At this stage a control strategy takes shape and understanding the impurity landscape leads to potential for telescoping, thereby removing burdens associated with isolations.[74] With an end-to-end process demonstrated and secured teams transition into tech transfer to launch.

Tech Transfer to Launch: With the framework of a commercial process in place the next step is 'Tech Transfer to Launch.' The rigorous implementation of green chemistry and sustainability fundamentals in QSbD through the design phases ensures an elevated level of decision making was conducted, where final adjustments for long term supply can be met. Here the application of optimization and plant fit ensures the intended process rises to the robustness and understanding required for filing. Process intensification is a significant feature of this workflow. Defining the boundaries of acceptability informs manufacturing practices in an optimal space. This departure from theoretical claims to real implementation is a unified effort, requiring input and balance across departments. Green engineering regarding equipment, function and processing support plant execution. A well design process that lacks optimization and plant fit fundamentals will not ensure supply of the medicine it is intending to produce and in turn also a drag on sustainability. From successful launch a program moves into secured supply of the medicine.

Secured Supply: Even after launch, the process parameters and design space are leveraged to support life cycle management

(LCM) efforts. Further process refinement that maintains the bounds of the process description is made to drive sustainability further while staying within established quality commitments.[75,76] In addition, our second gen synthesis group continuously reviews opportunities for new RSM syntheses or routes with an ever-increasing focus on sustainability metrics. Overall, the implementation of QSbD ensures strong alignment with sustainability for the production of commercial API and provides an elevated level of development knowledge for LCM.

Green Principles in Drug Safety

Drug Safety represents a key function that is intrinsically linked both to the Discovery and Development functions with an onus also placed on analytical and formulation groups to develop processes and procedures to enable access the compounds for *in vitro* and *in vivo* studies for safety assessments.[77,78] Key within these activities is to drive decision-making as much as possible through either *in vitro* or *in silico*-based assays though when necessary, the amounts of compound require for studies Is relatively level particularly when compared to API manufacturing campaigns, and as such green initiatives in the Drug Safety space focus on different aspects to other areas. In addition to material-sparing (or in silico assays), compound requirements are optimized/minimized through strategic study designs with a minor excess requested to cover unanticipated events such as additional samples/subjects or an updated study design. Furthermore, study durations around early toxicological assessments have when appropriate being shortened from 14 to 7 days leading also to a reduction in compound requirements leading to waste reductions both up- and down-stream.

Of growing importance specifically with the current pending regulatory restrictions around PFAS, toxicology teams work closely with chemical concern teams within Pfizer globally for forever chemicals, their association to certain safety concerns, acceptable intakes and alternative chemicals.[79,80]For PFAS, this is notably relevant given the reliance of TFA in both core methodologies for the synthesis of ADCs and peptides and as a key additive within mobile phases for HPLC within our analytical chemistry labs.[81,82] Critically, these issues impact not only Pfizer but also the broader industry as a whole, and as such groups such as the ACS GCIPR and the IQ consortium have been active in issuing grants and white papers focused on developing alternatives to TFA for specific applications.[83] Furthermore, as an organization, we proactively track the rapidly evolving proposed regulations around PFAS noting critically how it will impact both our internal development operations as well as our supply chain partners while also critically evaluating academic laboratories for innovative, emerging technologies that can mitigate the challenges associated with PFAS (enzymatic, photo-/electrochemistry). [84,85,86]

Sustainability Metrics

API manufacturing generates substantial amount of waste that are estimated to cost tens of billions of dollars in disposal every year across the Industry.[87] This represents both an ecological and an economical challenge for the business. Consequently, pharmaceutical and agrochemical companies are constantly looking for ways to measure the sustainability of their processes. One of the key metrics adopted by most is cumulated Process Mass Intensity (PMI)[88] which is highly accurate and represents a good proxy for waste. However, molecular complexity plays a crucial role in PMI of APIs and is challenging to measure. Consequently, estimating PMI target for a given API remains complicate despite recent efforts in this space, notably from the IQ Green Chemistry group on iGAL 2.0.[89] In addition, all waste is not equal from a greenhouse gas emission standpoint and the last few years have seen the emergence of new PMI-Life Cycle Analysis (LCA) tools to better capture the environmental impact of processes.[90]

In 2022, Pfizer decided to start capturing all clinical campaigns manufacturing across its entire Small Molecules portfolio in a systematic way.[91] The focus has been made on key data to drive sustainability as early as possible during development: PMI, cost, energy and Global Warming Potential (GWP). Over three years of data collection has led to an emerging workflow on data compilation, benefitting internal R&D processes, portfolio-wide trend comprehension, and support of external ACS-Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) projects.

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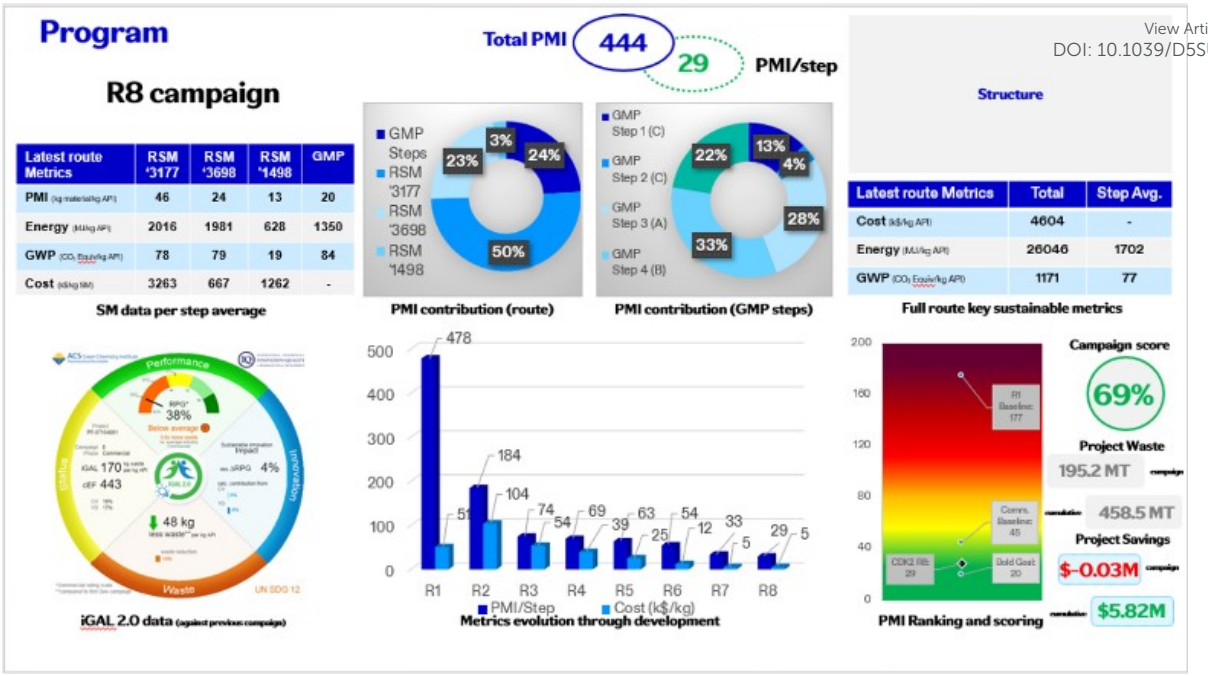

Figure 4: High-Level Metrics Campaign Dashboard

The sustainability workflow has focused on baselining and influencing trends within the process chemistry group. All manufacturing campaigns supporting clinical trials and products launch are now being systematically monitored, with data coalesced from batch records, vendor reports, and other documents. Raw data is entered into the ACS-GCI LCA tool to calculate PMI, GWP, and energy while an internal tool focuses PMI and cost. Both tools provide data quality assurance by cross-referencing PMI. Afterwards, data is stored into databases that help define baselines based on stage of development, giving insights on project trends, savings, and opportunities. Each campaign data is compiled into a single slide campaign dashboard and presented to the project team, highlighting hotspots and achievements (Figure 4). Most importantly, this visualization of metrics is a key driver of sustainability by bringing colleagues onboard and changing mindset during drug development.

Data is also used to create quarterly and annual dashboards to summarize waste, savings, and key performance indicators for Pfizer Chemical Research & Development Organization.

Over two years of data capturing has cumulated to 118 campaigns and 1657 steps. Yearly delivery is heavily dependent on portfolio demands, however it is consistently around 30 campaigns and 20 projects (Figure 5a). This is divided by both year and stage of development. Benchmarks for development are the first enabling route (R1), pre-proof-of-concept (pre-POC), post-proof-of-concept (post-POC), and the validation process. In each of these respective spaces, there are currently 41 R1, 42 pre-POC, 21 post-POC, and 11 validations (Figure 5b). Some are not categorized.

Internally, baselining has enabled goal setting, ensuring alignment with Pfizer's net zero goals. Goals were set prior to the data-baselining initiative, and with proper workflows on sustainability metrics created clarity on the path forward was gained. It was found that first clinical supply campaigns start around 175 PMI per step, decreasing quickly as the project develops. With continue refinement and collection, new trends will emerge and provide further clarity on campaign, project, and portfolio trends.

The systematic collection of data has significantly enhanced decision-making throughout the development of current assets. However, despite notable advancements, certain gaps remain

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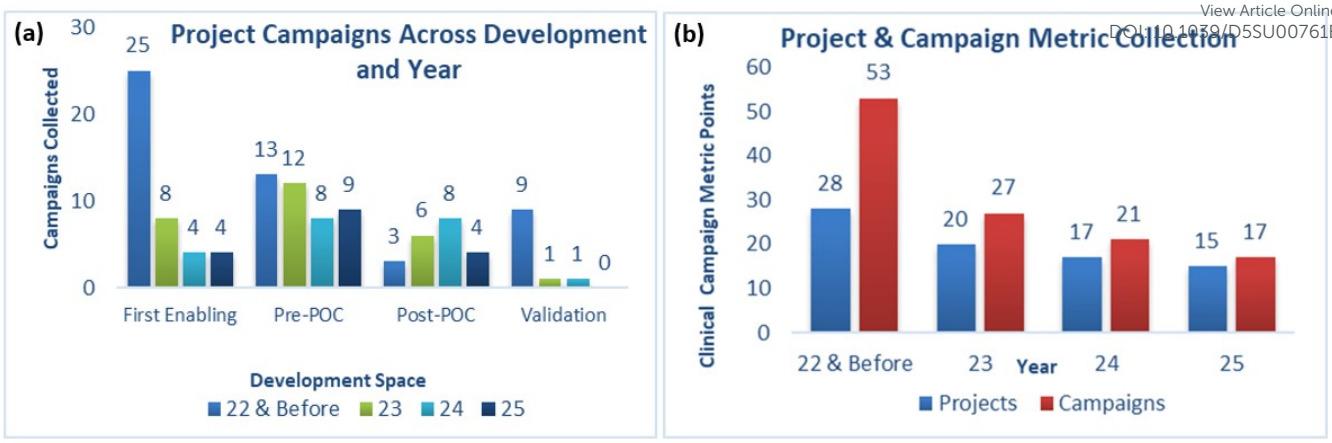


Figure 5(a): Number of Project Campaigns/Year; (b) Metrics Collection by Project/Campaign.

and should be addressed during data analysis. At present, energy and Global Warming Potential (GWP) values lack the level of accuracy achieved with Process Mass Intensity (PMI).

While most analytical tools rely on the EcoInvent database to access relevant data, a comprehensive inventory of all chemicals utilized is yet to be established.[92] Additionally, widely used industry tools, such as the ACS GCIPR PMI-LCA, are limited to assessing the energy consumption and carbon footprint of input materials. Currently, the energy use—and consequently GWP—associated with various unit of operations (including agitation, heating, cooling, distillation, and drying) is not captured in these analyses. Furthermore, collecting GWP data related to downstream waste treatment remains complex, as it varies with the type of waste produced.[93] This aspect is critical given that the predominant method for waste management continues to be energy-intensive incineration. The associated costs must also be considered when evaluating alternative synthetic pathways, which particularly benefits processes characterized by low PMI.

Developing new tools or improving existing ones will be required to address these gaps and better support sustainable metrics in the pharmaceutical industry. Upcoming considerations for greener manufacturing, including solvent recycling, optimized reactor cleaning, and the use of renewable material sources, will need to be integrated into future tools used in the sector.

Technology and Innovation

Aiming to design synthetic routes that transform commodity chemicals into the desired drug with the greenest conditions possible, process chemists face imperious challenges that require out-of-the-box creative thinking and introduction of new technologies. A handful of tools considered state-of-the-art technologies in past decades have been successfully transitioned to industry. Flow chemistry, High-throughput experimentation (HTE) and computational and predictive sciences are nowadays used in most of the pharmaceutical programs helping reactivity identification, mechanistic understanding and significantly reducing waste, decreasing time for development and tech transfer, and reducing cost.

The next generation of emerging technologies comprises electrochemistry, photochemistry and biocatalysis. These tools allow access to new bond disconnections, expanding the chemical space, as well as shortening synthetic routes

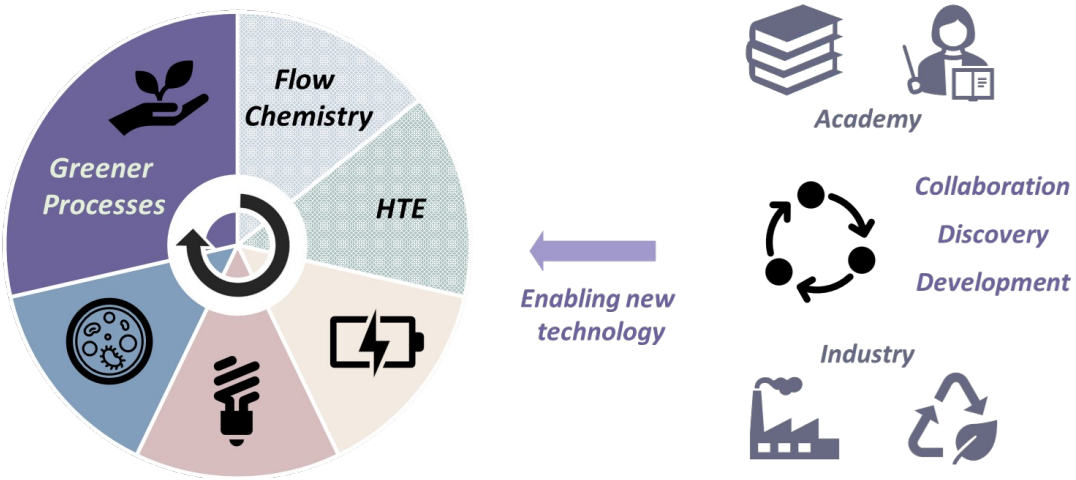


Figure 6: Academic-Industrial Collaborations to Enable New Technologies for Greener Processes

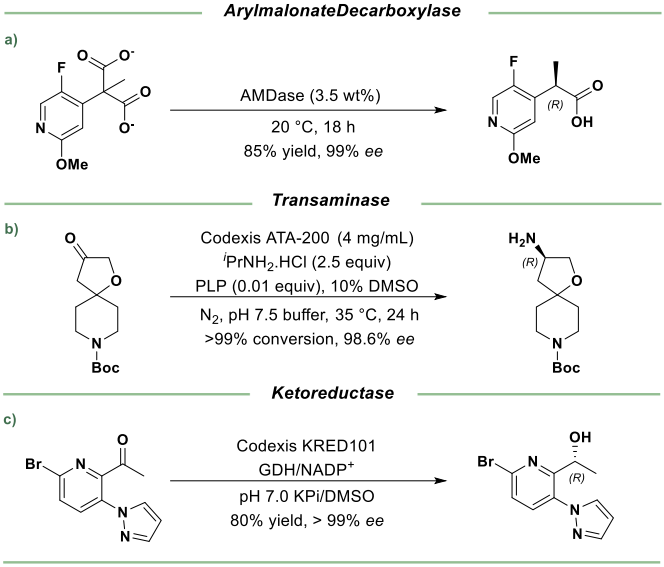
consequently minimizing waste and processing time, and substitute hazardous or toxic reagents or energy sources used in classical transformations, affording greener processes. Key for the success, implementation and enabling these new technologies is a close partnership with academic scientists and interaction with industrial peers (Figure 6).[94,95,96,97,98]

Biocatalysis

Biocatalysis, the use of enzymes as catalysts, has arisen as an extremely useful and sustainable technology in chemistry innovation. This technology enables chemical reactions with unmatched enantio-, regio- and chemo-control, moreover, it has been acknowledged in the 2018 Nobel Prize for Chemistry. Key advantages of enzymes compared to conventional transition metal catalysis are typically faster catalytic rates, the substitution of toxic reagents in their preparation, the abundance of sourcing materials, the use of aqueous solutions and mild temperatures.[99] Biocatalytic processes have been successfully implemented in the pharmaceutical industry, mainly because of the above-described advantages and because biocatalysis is more scalable compared to electrochemistry or photochemistry.[100,101] Most processes relying on biocatalysis are performed in conventional reactors using either whole-cell or recombinantly produced unpurified enzymes. Effective removal of residual proteins remains a significant challenge, particularly in multi-enzyme cascade reactions where the presence of numerous biocatalysts complicates downstream purification. Chemical and engineering solutions such as precipitation and filtration after denaturation, extraction, and other separation methods are being developed. Biocatalysis is seeing a renaissance due to its compatibility in engaging multiple enzyme-catalyzed steps in one-pot, significantly accelerating processing times and reducing PMI of synthetic routes.[102]

Pfizer regularly employs biocatalysis both in the early-stage drug discovery and development as well as in the late-stage development and API manufacturing. The most common enzyme classes used are hydrolases, keto-reductases, imine-reductases, ene-reductase, transaminases, and oxygenase enzymes. Three recent examples of biocatalysis implementation in the early-space drug development include: a arylmalonate decarboxylase for enantioselective synthesis of (R)-α-aryl propionic acid derivatives,[103] the use of a Codexis transaminase to generate a chirally pure spirocyclic ring containing compound, 1-oxa-8-azaspiro[4.5]decan-3-amine,[104] and an efficient keto-reductase process that enabled the synthesis of molecules used to build a sickle cell disease clinical candidate PF-07059013 (Scheme 1).[105]

In the late-stage drug development a recent example includes the use of a keto-reductase in the development of a small molecule therapeutical targeting the protein EZH2 involved in cancer growth and proliferation. The initial process involved had a 360 kg PMI of the step, total route PMI of 4004 kg, and GWP of 593 kg CO_2e, and after the implementation of a biocatalytic step the PMI/GWP was improved to 72 kg (80% decrease), 1675 kg (58% decrease), and 52 kg CO_2e (91% decrease). The enzymatic reaction was scaled up to 55 kg and resulted in 91% isolated yield with 99% enantiomeric purity (Scheme 2a).[106]



Scheme 1: Use of Biocatalysis in Early Drug Development

Another example involved the use of Candida Antarctica lipase B (CalB), for enzymatic ester amidation. This enzymatic step was the 2nd step in a five-step process to the synthesize a valuable 3,8-diazabicyclo[3.2.1]octane derivative.[107] The enzymatic amidation yielded >90% conversion in the span of 48-72 hours on a 110 kg scale and required molecular sieves to minimize the formation of biproducts (Scheme 2b).

While the aforementioned enzymatic reactions mostly include examples of well-established enzyme classes, Pfizer has recently employed a novel class of enzymes, reductive aminases, on multi-kilogram scales. Aleku and colleagues identified a novel imine reductase (IRED) from *Aspergillus oryzae* that exhibits dual catalytic functionality.[108] In addition to catalyzing the stereoselective reduction of imines, this enzyme also facilitates the in-situ formation of imines via the condensation of ketones and amines, thereby enabling a one-pot reductive amination process.[109] This subclass of IREDs has been dubbed as reductive aminases (RedAms). Pfizer has recently disclosed two examples of this type of enzyme used in large-scale biocatalytic processes.

The first example relates to the development of an investigational cyclin-dependent kinase (CDK) inhibitor. The enzyme used in the process was an engineered RedAm from *Amycolatopsis azurea,* while benzylamine was used as a nucleophile amine donor. The optimized process was scaled up to 50 g and characterized with 35% isolated yield and %ee of 98.4 (Scheme 2c).[110]

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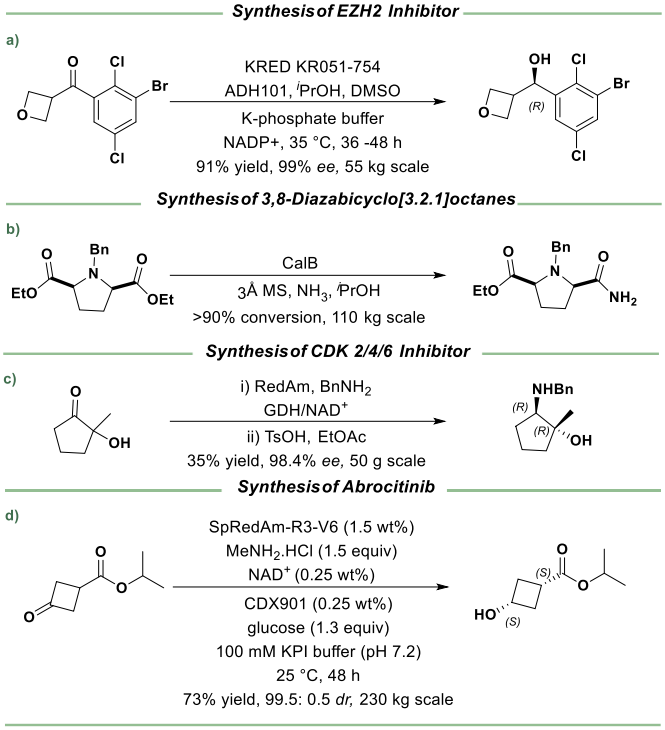
The second example of the use of a reductive aminase involved the reductive amination of isopropyl 3-ketocyclobutylcarboxylate, yielding a key intermediate in the synthetic route to abrocitinib.[111] The initial process involved a step PMI of 61 kg, a total route PMI of 657 kg, and a total GWP of 1916 kg CO_2e, and after the implementation of a biocatalytic step this decreased to 41 kg (32% decrease), 356 kg (46% decrease), and 494 kg CO_2e (74% decrease). Process intensification and enzyme engineering of SpRedAm enabled a scale-up to 230 kg, with substrate loading of 125 g/L and enzyme loading of 1.5 wt%. Under these optimized conditions, the reaction achieved a 92% assay yield, a 73% isolated yield, and a diastereomeric ratio of 99.5:0 (Scheme 2d).



Scheme 2: Example of Biocatalysis in Late-Stage Drug Development

As biocatalysis continues to gain traction in pharmaceutical manufacturing, several catalytic gaps remain. Enzymatic amide bond formation, central to many drug molecules remains challenging, though recent progress with ligases shows promise.[112,113,114] Carboxylic acid reductases (CARs) offer untapped potential for converting carboxylic acids into amines and alcohols, yet their ATP-dependent nature demands further enzyme engineering and expression optimization.[115] Halogenases, despite their relevance to halogen-rich drug scaffolds, are limited by narrow substrate scope and low turnover.[116, 117] Similarly, biocatalysts for chiral amines, sulfoxides, carboxylic acids, and amino acid analogs remain underutilized due to poor activity and specificity.[118] Finally, enzymatic C–C bond formation remains underdeveloped; while lyases have shown isolated success, broader discovery of robust carboligases is needed.[119] The expansion of reaction space in all enzyme classes is increasingly supported by computational tools that mine growing enzyme databases for novel biocatalytic functions.[120,121]

Non-Precious Metal Catalysis

In continuing to build on sustainable synthesis at Pfizer, nonprecious metal catalysis (NPMC) remains a cornerstone of scientific interest and innovation for us.[122,123] While palladium-catalyzed transformations continue to play a central role in synthetic chemistry, increasing attention is being directed toward more earth-abundant and cost-effective alternatives. Catalysts based on copper (Cu), nickel (Ni), and iron (Fe) not only offer a sustainable replacement for palladium in well-established reactions such as the Suzuki–Miyaura coupling but also enable access to novel transformations that engage a broader range of functional groups and reactivity patterns.[124, 125,126,127,128] One area of research is the discovery of new and novel ligands for Ni catalysis which are essential for controlling reactivity and selectivity of reactions.

In 2016, in a Pfizer-academic collaboration with Professor Weix the team developed an approach to identify new ligands from a library of pharmaceutical heterocycles at Pfizer.[129] Recognizing that there is broad availability of phosphine ligands available, these do not perform as well as those based upon nitrogen and oxygen for Ni-catalyzed cross-electrophile coupling[130] or Cu-mediated C-N bond formations, the collaboration sought to speed ligand discovery through screening Pfizer's compound collection, which contains *ca*. 3 million compounds and is rich in diversity specifically with regard to N-substituted heterocyclic motifs. Initially filtering for compounds containing a [(2-pyridyl)-C-X] motif (X = N, O, S) led to over 1500 compounds even when further constraints were added around material availability (> 2g) and limiting X to be N. More focused screening evaluating different steric/electronic properties of the ligands as well as prioritizing low MW and non-proprietary compounds provided a collection of 82 ligands to be developed, which could be evaluated utilizing standard high-throughput experimentation-based protocols. This initial screen allowed identification of primary pyridyl-2-carboxamidines (PyCam) and (2-pyridyl)-substituted aliphatic N-heterocycles as promising ligand motifs thus allowing a second screening of the Pfizer file to be carried out focusing on these core metal-binding structures. This led to the identification of 31 potential ligands, which could then be profiled through screening, with seven showing better results when benchmarked against the best, commercially accessible ligand 4,4'-dimethoxy-2,2'-bipyridine (dmbpy). Key to this improvement in desired reactivity was the observation that the new ligand systems significantly suppressed the major side reaction (formation of biaryl derivatives) seen with the dmbpy ligand.

While the pyridyl-2-carboxamidines was prevalent in the medicinal chemistry literature, their use in metal-mediated processes was unprecedented highlighting the advantage of mining pharmaceutically relevant compound libraries for competent ligands. In addition, these systems (in contrast to

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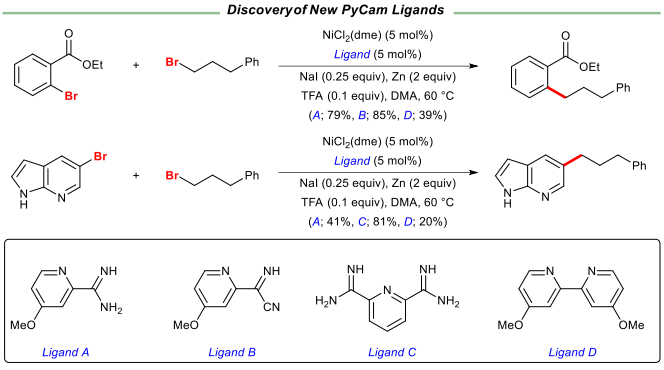
elaborated bipyridines and phenanthrolines) are easy to synthesize from 2-cyanopyridines allowing a further set of 17 ligands to be accessed for further screening.

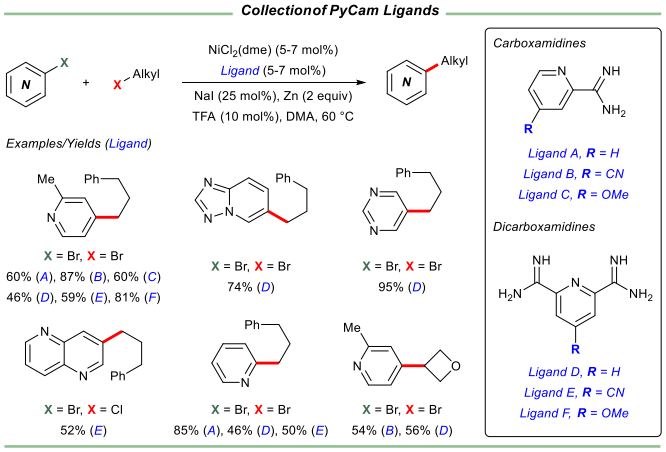
This compound-library derived ligand collection was further profiled against a series of five control ligands in two challenging cross-electrophile coupling scenarios namely the reaction of an aryl bromide featuring a coordinating functionality at the 2-position and in the reaction of 3-bromopyridine derivatives with alkyl halides. Studies on the first reaction showed that again amidine-based ligands performed better than the control cohort with these improvements again being attributed to an increase in the selectivity of the process. Further trends on the ligand structure could also be derived from the results with alkyl- and aryl-substitution on the amidine leading to lower yields. N-cyano-substituted amidines performed in an analogous manner to the unsubstituted derivatives while electron-donating groups at the 4- and 5-positions of the pyridine ring gave improved yields. For the reaction of 3-bromopyridine derivatives, it was observed that while the amidine-based ligands were in general superior to the controls, only the tridentate ligand (2,6-pyridinedicarboxamidine) gave high yields (> 70%) if the desired coupling products with again this superior outcome linked to a diminished amount of the homo-coupling in the reaction.



Scheme 3: Discovery of PyCam Ligands through HTS

To exploit these results, a set of four of the best amidine-derived ligands from these screens were further profiled in a series of reactions featuring pharmaceutically relevant substrates presenting the aforementioned motifs (2-bromosubstituted arenes and 3-bromopyridines). In all cases, the superior performance of the amidine systems over a conventional bipyridine ligand was demonstrated with the tridentate system again providing a further boost in yield for the 3-substituted pyridine derivatives.

While uncovering a new family of ligands represented a breakthrough, there remains a challenge in expanding the substrate scope and specifically effecting nickel-catalyzed cross-electrophile couplings of heteroaryl halides (key pharmaceutical fragments) with alkyl halides. Expanding on the previous observation on the unique reactivity of the sole tridentate ligand evaluated, variation of the electronic properties of the pyridine ring allowed a focused subset of ligands to be derived that were profiled (along with the analogous bidentate systems making a total of six ligands) in series of cross-coupling reactions involving a broad range of heterocyclic systems (including diversely substituted pyridines, pyrimidines, naphthyridines) with alkyl chlorides/bromides and iodides.[131] Despite these heterocyclic fragments being highly featured in the patent literature, only sparse examples of alkylative cross-couplings were reported with these typically featuring pre-formed organometallic reagents. While the success of the use of a specific ligand is dependent on the structure of both the heterocycle and the alkyl halide, and it was difficult to discern any general reactivity trends, the results demonstrated that it is possible to get synthetically useful yields using only a small collection of ligands. In addition, issues such as isomerization of secondary alkyl groups during cross-coupling processes were not encountered, though it should be noted that five-membered ring heterocycles including both bromopyrazoles and bromoimidazoles proved to be recalcitrant coupling partners using the current system.



Scheme 4: PyCam Ligand Collection Enables Diverse XECs

This approach of screening large compound libraries for the serendipitous discovery of new ligands capable of mediating metal-catalyzed reactions has been exploited by other organizations though presents several drawbacks most notably that it is unpredictable, inefficient, time-consuming and relies on having access to a large compound library of diverse chemical matter, which a large proportion of the synthetic community does not.[132,133,134] Given this, a new approach was developed to expedite ligand discovery/optimization which avoids either detailed experimental or computational mechanistic analysis though instead takes advantage of a qualitative computational evaluation of reactivity trends to select ligand systems for further study.[135] The proposed three step process involves initial evaluation of a set of known ligands in the reaction of interest followed by development of simple trends from the results of these focusing on ligand features that are crucial for success. These features can then be applied to further filter/prioritize potential ligands for screening. Applying this workflow to the nickel-mediated cross-electrophile

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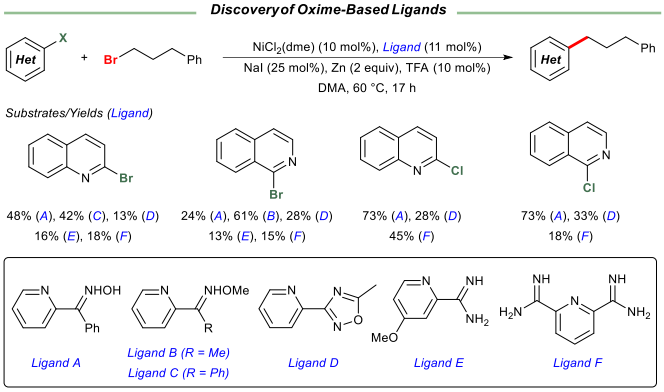
coupling, comparing a series PyCam ligands with the established bpy-ligands in the model coupling of ethyl 3-bromobenzoate with 1-bromo-3-phenyl propane demonstrated that not only were the PyCam ligands more effective but also highlighted that the differences in reactivity were largely due to charge effects. Based on this information, a correlation can be drawn between the observed reaction outcome and the computationally derived atomic charge (Mulliken charge), which strongly suggested that electron-poor amidine ligands performed better in the reaction. While this obviously represents a over-simplification of the factors involved, the development of this model is significantly more time-efficient than a more extensive computational analysis. To interrogate this simplistic model, a training set of previously evaluated PyCam-based ligands were studied in parallel to a series of sixteen commercially available compounds with similar structures to these with the overall ligand selection biased towards electron-deficient systems. The latter set of ligands were further divided into those predicted based on the model to give higher- or lower- yields. Evaluation of the assay yields showed that in general the somewhat crude predictions were validated with gratifyingly all the new ligands evaluated given a higher conversion than the reaction performed in the absence of ligand. A broader exploration of the reactivity of these sixteen ligands against a series of heteroaryl halide coupling partners (benchmarking against a standard set of PyCam ligands) allowed the identification of the pyridine-oxime as a privileged ligand structure. Given the ease of access to these derivatives, a small subset (PyOximes) could be rapidly accessed and profiled in the coupling of quinoline and isoquinoline electrophiles. Herein, this ligand system outperformed not only the conventional bpy-systems but also the previously disclosed PyCam ligands thus validating this simple semi-qualitative approach to the discovery of new ligands. The improvement in reactivity of these new ligands is hypothesized to be due to not only suppression of side reactions (dimerization) but also due to the facile postreductive elimination regeneration of the active Ni-species with these theories supported by the relative computed relative redox potentials of the Ni-complexes involved in these steps.

Flow – Continuous Manufacturing

In alignment with Pfizer's corporate sustainability strategy, sustainable manufacturing is now an essential component in delivering our products while meeting environmental, economic, and societal responsibilities.[136,137] Through the flow chemistry strategy, we employ both continuous and batch processing technologies to achieve these objectives.

The advantages of flow and continuous chemistry with respect to sustainability outcomes include cost-effective prototyping and fabrication, accelerated mixing processes, reduced waste generation, improved yields, enhanced thermal management, increased safety in reactions, shortened reaction times decreasing energy consumption, and the facilitation of intelligent, scalable systems through automation.[138,139] Flow chemistry is also aligned with advanced energy utilization technologies such as photochemistry[140] and electrochemistry.[141,142]

For Pfizer, this advanced manufacturing platform offers significant advantages by improving operational efficiency and enhancing product quality and consistency, while simultaneously reducing both manufacturing and environmental footprints as well as overall operational costs.[143] From an environmental perspective, this method promotes waste minimization, decreased energy consumption, and reduced raw material requirements.[144] Our objective is to implement continuous manufacturing process to advance green chemistry principles and minimize environmental metrics, including process mass intensity (PMI), GAL, and E-factor. This approach also aims to achieve substantial reductions in energy consumption throughout our operations, representing a key contribution toward reaching our NetZero targets.



Scheme 5: Discovery of PyOxime Ligands

High-Throughput Experimentation

The running of multiple reactions to optimize both the discrete and continuous parameters involved in a chemical transformation has long represented the cornerstone of process research.[145] However, with the development of and investment in automation, the past decade has seen the emergence of High Throughput Experimentation (HTE), which has allowed both an exponential increase in the number of reactions that can be run/analysed in parallel with a decrease in the requisite amount of substrate for each discrete experiment (Figure 7).[146] These two factors have a profound effect on how HTE as an enabling technology can impact the sustainability of our chemical operations.[147] Obviously, reductions in the amounts of materials required allows us to preserve key resources while an increase in the number of reactions allows a broader range of conditions to be evaluated with the inclusion of "more speculative" (greener reaction) conditions becoming a viable option. Automation has also enabled time savings in the overall HTE process which in tandem with the reduction in material requirements has accelerated the uptake of this technology within Discovery chemistry. Pivotal to the success of the miniaturization is the performance of the HTE-screens in a glovebox environment under air- and moisture-free conditions thus preserving the integrity of reactive catalyst systems through precise handling of microgram-

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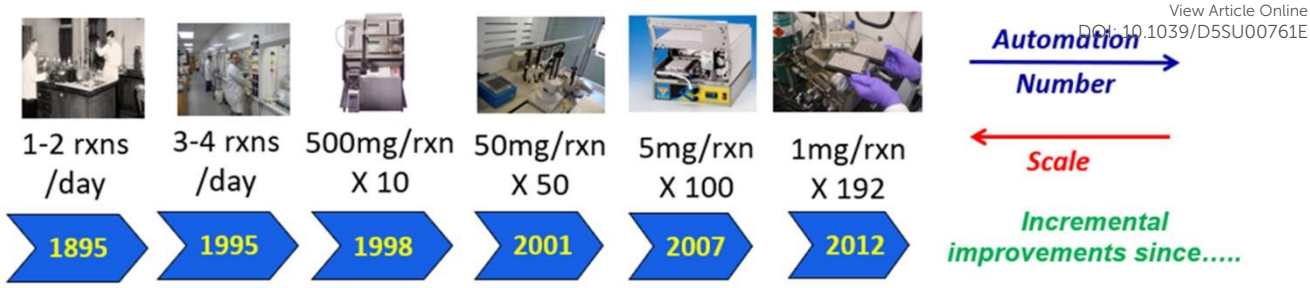

Figure 7: Impact of Automation on HTE

quantities in solution. From an economical perspective, this presents a further advantage with the ability to make up stock solutions of these materials that can be utilized on numerous occasions without any loss of performance.

In the Discovery environment, there are numerous advantages of running HTE campaigns to optimize specific reaction chemistries.[148] HTE rapidly provides the opportunity to either evaluate speculative or optimize key bond-forming reactions, which if successful not only serve to expedite the synthesis of analogues for SAR studies but also may be incorporated into a scale-up campaign for a particular lead compound. While failed HTE campaigns can also provide serendipitous observations around formation of by-products, more crucially, they allow approaches to a series of molecules to be eliminated enabling downstream resources to focus on more productive synthetic routes for a prospective scale-up or even commercial manufacturing process. One major disadvantage of the employment of HTE resources in Discovery chemistry is the high attrition rate of projects though this highlights the key to efficiently supplement these processes with seamless automated workflows. In addition, while resource represents time, strategically carrying out these studies in an early Discovery setting makes more sense despite the high attrition rate, as not only does it allow breakthroughs to be implemented throughout a compound's life cycle but also prevents resource being required in Development when timing of compound deliveries is on the critical path.

Speed represents a critical component in the implementation of HTE within Discovery chemistry with a screen typically processed within 2-3 days through a "design-execute-analyze-report" based cycle. As noted, reactions are run on sub-mg scale with solvent volumes of ~ 100-250 µL. While various options exist for running screens, we utilize discrete glass-vials with magnetic stirring in a 96-plate format as we believe that these offer the best option in terms of translation of reaction conditions/mass transfer to conventional glassware. For the cycle, design of the screen involves preparing the matrix of the reaction plate(s) selecting reaction conditions through literature precedents/statistical methods as well as knowledge gained from previous screens. The latter is of particular value as this data has been gained from screens run on pharmaceutically relevant substrates and can also be exploited in the development of AI/ML models owing to its precise formatting/curation as well as the presence of negative data.[149] The preparation/execution of the screen leverages automation in the set-up with preferably solution-handling through multi-channel pipettes utilized to prepare the plate. While solid weighing is possible, solution handling is more expeditious and highlights the importance of initial formatting of the plate with common solvents/reagents across rows/columns etc to minimize the number of transfer operations. Reactions are typically then agitated on hot-plate stirrers though more sophisticated options exist to evaluate gas chemistries, photoredox reactions etc. Upon completion, plates are typically diluted, centrifuged, then analysed using an ultrafast HPLC method, which allows a 96-well plate to be analysed in ~ 2 hours. Processing and reporting can present challenges as often authentic markers of the desired products are not available, though is facilitated through orthogonal analysis using both UV- and mass-channel analysis with deconvolution expedited through use of a range of software options and the results visualized through Spotfire, which allows convenient viewing and manipulation of the data. The rapid turnaround times enable screening groups to run 4 to 5 reaction screens/week. Common transformations like Pd-mediated Suzuki coupling, hydrogenation, C-N-,[150] C-O-, amide-bond formation allow templated-based screens to be established saving time in the design phase, while new reaction paradigms and solid-form evaluations (classical resolutions) provide opportunities to develop new workflows to maximize the amount of information obtained from each series of experiment.[151]

Synthetic planning paradigms represent a fundamental consideration throughout a pharmaceutical chemistry enterprise with two key assessments made within a Discovery chemistry setting that impact overall sustainability, specifically; (a) what is the minimum number of compounds of required complexity to answer a specific design hypothesis, and (b) can we develop efficient orthogonal chemistries to disconnect a molecule to enable late-stage modification of a common intermediate through a series of different SAR vectors ? Ideally, addressing (b) would also provide an advanced starting point for the crucial bond disconnections for the development of a scale-up route for a lead API. To illustrate this, and how HTE can facilitate this workflow in real project setting, consider the example of chemistry planned for the synthesis of a series of range of diversely substituted pyrimidines for a kinase-related program. The initial Route A is a "target-oriented" route, and while the desired materials can be accessed through this approach, several

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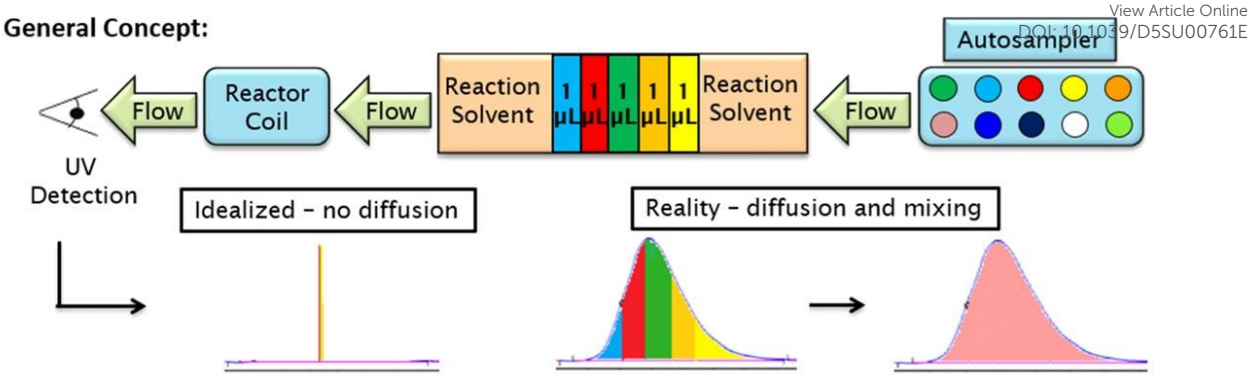
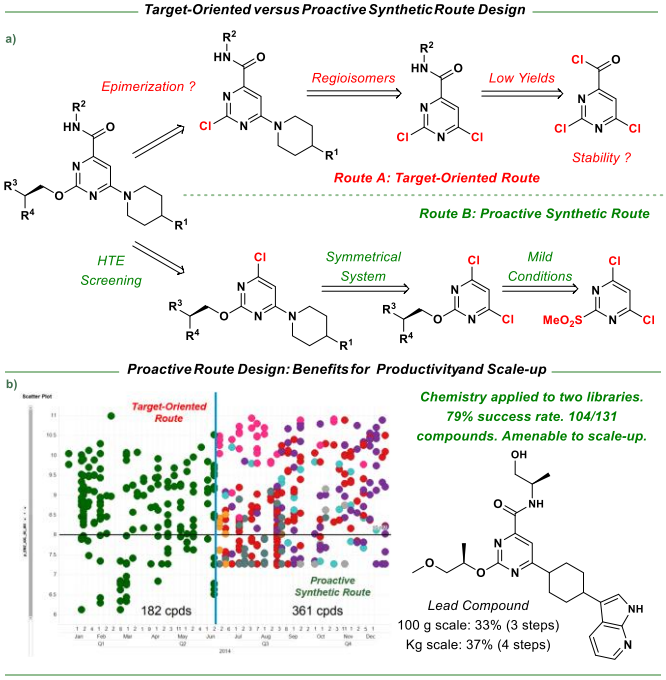


Figure 8: Concept of HTE Flow-Screening

drawbacks exist that limit its broad applicability and scalability. The starting acid chloride has limited availability in bulk, and is moisture sensitive to handle, while the initial S_NAr displacement while favouring the substitution of the 4-Cl leads to a mixture of regioisomers. The final substitution with the alcohol under forcing base-mediated conditions was also observed to lead to epimerization of the chiral center of the alcohols utilized. Route B highlights the implementation of a "proactive synthetic" route now starting from an alternative starting material, which is readily available on scale. Initial S_NAr displacement is favoured for the sulfone with leveraging of the better leaving group allowing milder conditions to be utilized thus avoiding epimerization. There are no issues with regioisomers for the S_NAr displacement with the amine as the molecule is symmetrical. The key step now involves developing robust conditions for the carboamidation of the 4-Cl to form the amide whilst minimizing direct S_NAr displacement. To achieve this, our HTE platform was leveraged to develop suitable conditions (24 catalyst/ligands vs 2 bases v 4 solvents = 192 reactions). The metrics indicate that upon switching to the proactive synthetic route, we were able to double analogue production in a similar timeframe and utilize the chemistry for library production as well as kilogram scale-up of the lead molecule (Scheme 6).

The evolution of HTE within Discovery has enabled numerous breakthroughs, while also providing a seamless bridge into optimization workflows within the Development group. However, chemical space for many of the transformations we evaluate continues to expand, and with our plate/vial-based approach, sub-mg represents the practical limit for this platform. Given this, we developed the next generation flow-based screening platform, that allows 1500 reactions to be evaluated in 24 hours using microgram amounts of materials.[152] The system was initially validated using a model Suzuki-Miyaura coupling with concentrated stock solutions of "Pd", "base", "ligand" and both "substrates" injected into a flowing solvent stream. Mixing allows reaction to occur while dispersion occurs allowing evaluation of solvent effects (Figure 8). Variation of both the potential electrophiles and nucleophiles for a specific coupling allowed a comprehensive analysis of the reaction to be assembled from ~ 6000 experiments in 3-4 days. While, the analysis relies on the initial reaction rate being maintained throughout the coupling, the system was subsequently validated through scaling the optimal conditions in both batch and flow. Further development of the system has been reported for its employment in photoredox-based couplings[153] with the vast amounts of data generated in a controlled, automated fashion providing the basis for exploitation in ML/AI-based reaction condition prediction models.[154]



Scheme 6: Target-Oriented vs. Proactive Synthetic Route Design

Electrochemistry

Electrochemistry, particularly organic electrosynthesis, has recently experienced a remarkable 300% increase in the number of publications, predominantly in academic settings, highlighting novel transformations driven by its tunability and chemoselectivity.[155,156,157,158]

Despite its application in specialized industries (Baizer Process, BASF, ECRC, CERCI, and Otsuka), its integration into the pharmaceutical industry remains rather limited. The development of novel electrochemical transformations for pharmaceutical use faces several challenges: concerns regarding safety and compliance, uncertainties in scalability,

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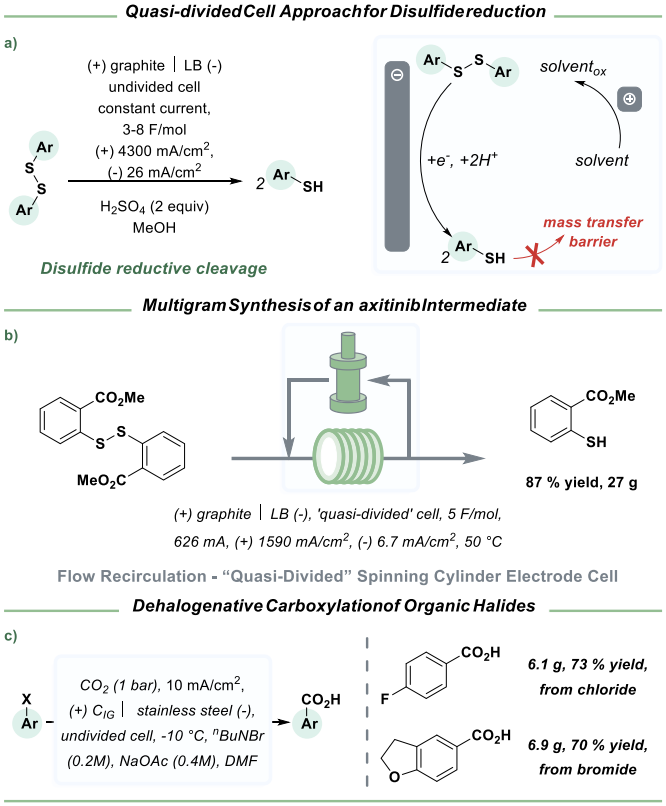
limited availability of manufacturing equipment compatible with organic solvents under cGMP conditions (which require specific controls such as voltage, current, and electrode material composition), and the design and commercial availability of reactions that meet productivity demands for commercial manufacturing.[159,160] Nevertheless, chemists and engineers are actively working towards enablement of electrochemistry for reactions that offer distinct advantages in hazard reduction, such as reductive processes like Birch-type reactions or entirely novel bond formations.

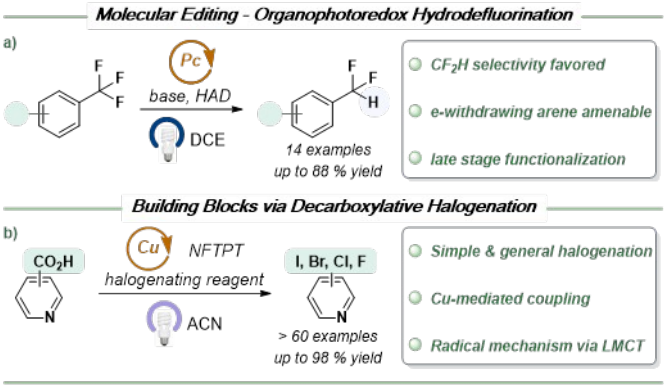


Scheme 7: Electrochemistry at Pfizer

At Pfizer, we are actively contributing to the advancement of the organic electrosynthesis field through collaborations with leading academic institutions and esteemed professors globally. In recent years, partnering with Professors Kappe and Cantillo,[161] we developed a sustainable electrochemical method for the reductive cleavage of disulfides that eliminates the need for divided cells or sacrificial anodes, establishing a 'quasi-divided' cell approach to electrochemical reductions. The method relies on generating a mass transfer barrier to prevent disulfide oxidation at the anode (Scheme 7a). In 2024, aiming to expand upon the 'quasi-divided' cell strategy, we collaborated again with Professors Kappe and Cantillo to design and develop a spinning cylinder electrode cell, offering precise mass transfer control for scale-up operations,[162] which enables the multigram synthesis of an axitinib intermediate (Scheme 7b). Very recently, in 2025, in a collaboration with the same academic group,[163] we designed an electrochemical strategy for the dehalogenative carboxylation of organic chlorides and bromides with CO_2 gas using a spinning cylinder electrode reactor. This methodology also leverages the non-sacrificial metal anodes approach, facilitating the transfer to multigram quantities in flow mode without depleting the anode material (Scheme 7c).

Photochemistry

Photoredox chemistry has emerged as a powerful tool to generate radical species with unique reactivity capable of engaging other molecules to forge new bonds (C-H, C-C, C-N, C-O, C-S, etc).[164,165,166,167] A significant attribute of photoredox chemistry is its selectivity in forming radical intermediates, which minimizes undesired pathways and reduces impurities. Compared to conventional methods, photoredox chemistry offers notable advantages, including reduced waste bypassing the need for stoichiometric redox agents, excellent chemoselectivity, atom economy and novel disconnections leading to shorter synthetic routes.The Pfizer team has engaged extensively with leading experts in photochemistry, including recent partnerships with renowned professors such as MacMillan,[168, 169, 170, 171] Yoon,[172] Wu,[173,174] Szymczak,[175] Musacchio,[176,177,178] among others.



Scheme 8: Photoredox Approaches to Molecular Editing and Building Block Synthesis

Photoredox catalysis is now widely used in both academic and industrial settings, especially in drug discovery and medicinal chemistry.[179] It has proven its utility in pivotal areas such as molecular editing, building blocks and bioisosters generation, and generally, in library synthesis and diversification.

In 2020, in a multi-pharma collaboration with the academic groups of Gouverneur and Noël,[180] the team developed a molecular editing approach to access hydrodefluorination derivatives from trifluoromethylarenes, which are often perceived as possessing favorable pharmacokinetic characteristics for drug-like compounds. By employing an organophotocatalyst, a base, and a hydrogen atom donor (HAD) under blue light irradiation, the approach enables selective conversion of electron-poor trifluoromethylarenes into difluoromethylarenes (Scheme 8a). This method is tolerant to a range of functional groups and heteroarenes prevalent in medicinal chemistry campaigns, facilitating late-stage

functionalization of complex trifluoromethyl intermediates into their corresponding difluoromethyl analogs.

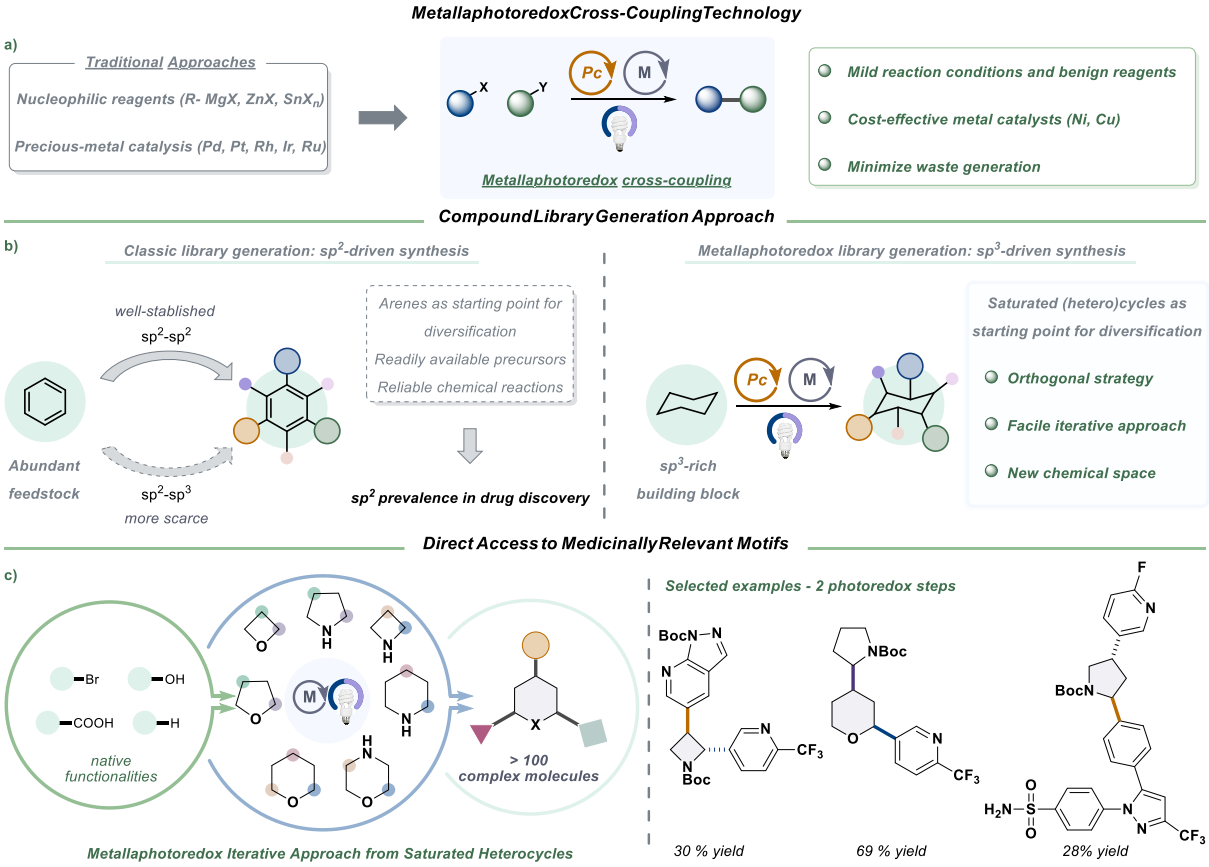
In 2022, through collaboration with the MacMillan group, the team developed an approach to access common building blocks, such as aryl halides, from readily available carboxylic acid precursors.[170] This unified approach to halodecarboxylation operates via a copper-LMCT (ligand to metal charge transfer) mechanism, utilizing common halogenation reagents like NIS, DBDMH, $ZnCl_2$, and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (NFTPT), which also serves as an oxidant (Scheme 8b). The protocol is compatible with prevalent heteroaromatic motifs in medicinal chemistry, demonstrating its efficacy in the late-stage functionalization of selected drug-like carboxylate derivatives.

A primary method for rapidly increasing molecular complexity is through cross-coupling reactions. Unlike traditional methods that use highly reactive organometallic nucleophilic coupling reagents, such as Grignards, zincates, and stannanes, or the later-developed precious metal-catalyzed couplings like Mizoroki-Heck and other Pd-mediated transformations, metallaphotoredox-mediated cross-couplings offer a safer and more sustainable alternative (Scheme 9a).

Traditionally, compound library generation has relied on the functionalization of aromatic cores using established coupling technologies such as Suzuki-Miyaura, S_NAr chemistry, or electrophilic aromatic substitution. However, this paradigm is shifting due to the rising interest in sp^3 character in drug-like molecules, which often confer advantages in pharmacokinetic properties, correlating with higher clinical success rates. Synthesizing such derivatives using traditional chemistry methods can be lengthy and sluggish, which is disadvantageous for the dynamic nature of drug discovery programs.

An alternative strategy for building these compound libraries involves starting with readily available saturated cores and functionalizing key molecular sites to form sp^2-sp^3 or sp^3-sp^3 bonds (Scheme 9b). Photochemistry enables the rapid direct functionalization of saturated heterocycles, and in collaboration with the MacMillan group, we demonstrated an iterative functionalization strategy of saturated heterocycles using photoredox chemistry. [168]

This method provides direct access to medicinally relevant motifs and was employed to synthesize mono-, bis-, or tris-functionalized derivatives of azetidine, oxetane, cyclobutane, pyrrolidine, tetrahydrofuran, tetrahydropyran, piperidine, morpholine, and piperazine, starting from native and readily available functionalities on the mentioned saturated cores.
By employing this photochemical iterative strategy, we successfully synthesized over a hundred highly functionalized derivatives, forming bonds such as Csp^3-Csp^3, Csp^3-Csp^2, C-F, C-CF_3, and C-N (Scheme 9c). This approach facilitates rapid access to complex targets under mild conditions, minimizing the number of reactions, isolations, and waste generation. It utilizes



Scheme 9: Applications of Metallaphotoredox Cross-Coupling

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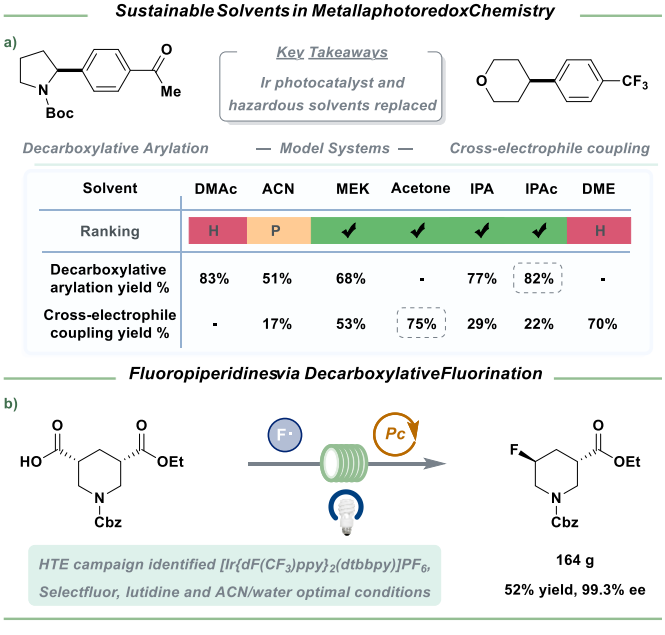
metals with low catalytic charges, while eliminating the need for hazardous redox agents.

As we advance towards incorporating photochemistry into the development stages of drug molecules, it is crucial to consider numerous factors often overlooked by methodology-focused academic groups. These include reactor configuration, precise temperature control, the choice of metal catalysts, reagents, and solvents, among others.[181] Our recent interests have focused on optimizing reaction conditions for two widely used cross-coupling reactions in both academic and industrial settings: decarboxylative arylations and cross-electrophile couplings. These transformations were initially conducted using process-unfriendly solvents like DME, dioxane, DMSO, DMF, and DMAc.[182] However, we have demonstrated comparable or improved results using more process-compatible solvents such as IPAc and acetone with model substrates (Scheme 10a). Additionally, we successfully replaced iridium polypyridyl photocatalyst systems with cost-effective organic photocatalysts, underscoring their potential for future scale-up applications.

Recently, Pfizer's team implemented photochemical decarboxylative fluorination at a multi-gram scale for a drug discovery program.[183] Through a high-throughput experimentation (HTE) campaign, the team identified optimal conditions to transform the chiral monoacid into the desired fluorinated derivative. Further optimization and flow application established conditions that yielded this derivative with 52% yield and 99.3% ee after purification (Scheme 10b). Subsequent processing delivered over 400 g of the single piperidine isomer (>98% de and >96% ee), which is a critical intermediate for a medicinal chemistry program.



Scheme 10: Metallaphotoredox Chemistry Using Sustainable Solvents

While the application of photochemistry in late-stage pharmaceutical development is still emerging, several successful large-scale implementations have been reported, heralding a bright future for photoredox chemistry in manufacturing applications.[184,185,186]

Mechanochemistry

Given the large contributions of solvents to PMI metrics in the pharma sector, mechanochemistry involving promoting reactions through imparting physical force on the substrates in the solid state (or utilizing minimal amounts of solvent) represents an attractive option from a sustainability perspective.[187,188,189,190,191,192] In addition to the reduction in solvent use, mechanochemistry provides several other advantages specifically the chance to reduce reaction times, to alter or enhance the selectivity of a reaction while also presenting the opportunity to carry out potentially sensitive reactions in a controlled setting.[193,194,195] While these factors present a compelling case to pursue this enabling technology, there are concerns to be addressed prior to mechanochemistry realizing broad adoption within the industry. While early issues around reaction reproducibility have largely been addressed through the development of robust, commercial instrumentation including ball- and planetary-mills, gaps still exist with regard to temperature control and assaying the force required to promote a specific mechanochemical process. Method development also presents a significant challenge given the difference in parameters that need to be optimized to enable a mechanochemical process (for example in ball-milling, size and number of balls, milling frequency, size of jar etc). While numerous successful examples of mechanochemical chemical reactions have been reported including some that provide innovative solutions to the issues of temperature control and condition selection, the major hurdle for this technology is regarding reaction safety.[196] Solvents as is well documented in combination with stirring ensure maximum reaction homogeneity while more importantly offer a means for thermal heat dissipation acting in this role as “heat sinks”. This is not the case for mechanochemistry with a further hazard being created in the pulverizing/grinding of potentially explosive/shock-sensitive solids. While factors around establishing protocols to allow mechanochemical processes to be safely investigated are still the subject of discussion, a preliminary evaluation cascade has been proposed based on a combination of structural features of a compound (oxygen balance, nitrogen% etc) and small-scale experimental testing (DSC, hammer test etc) that provide a level of confidence to perform such reactions on a laboratory scale.[197]

A further factor that is often cited with the emergence of novel technologies to promote reactions is potential scalability with challenges around achieving photoredox and electrochemical processes on a pharma-relevant scale being the subject of several reviews. In this respect, mixing of solids through techniques such as reactive extrusion presents the opportunity to overcome the limitation which is often cited to be a hurdle for other promising reaction manifolds in an expeditious manner using equipment which is already familiar to the pharma industry through its prevalent use in API formulation.[198,199] In addition to this, reactive extrusion is a multibillion-dollar industry and is broadly used in several industries.

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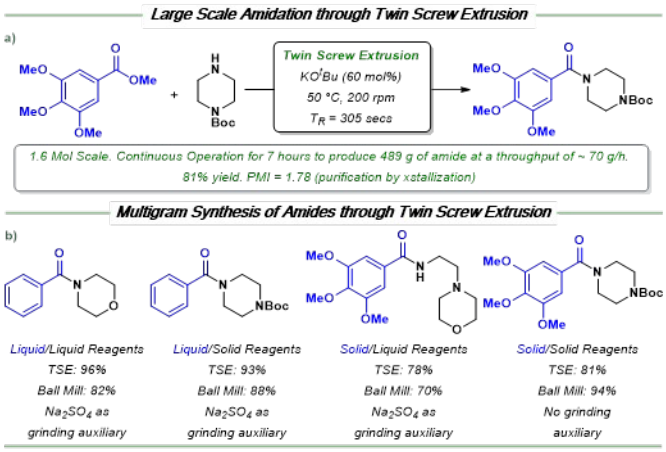
For mechanochemical applications, continuous extrusion also provides the opportunity to control the temperature of the reaction with high temperatures commonly utilized in the food sector to eliminate toxins/microorganisms to make food sources secure for utilization. Through the paradigm of heating reactions allows shortening of reaction times enabling the translation of a mechanochemical batch process to flow using extrusion techniques.

Given the potential to realize tangible reductions in PMI that mechanochemical-approaches offer, we have collaborated with the Browne group and ACS GCIPR to evaluate the feasibility of scaling a pharmaceutically relevant transformation in a continuous manner using a twin-screw extruder to conduct the reaction. At the outset, the base-mediated amidation of esters was considered with key goals involving; (i) applying the protocol to a diverse array of amines/esters with a focus on the physical form of the substrates (solid/liquid) as opposed to the steric and/or electronic properties, (ii) extending the methodology to a series of bioactive molecules, and (iii) providing a proof of concept translation from ball-mill to twin screw extruder to provide multigram quantities of a series of amides irrespective of the heterogeneity of the reaction partners.[200] The project initially sought to exploit the work describing the amidation of esters under ball-milling conditions utilizing potassium *tert*-butoxide as the base with initial experiments highlighting both the judicious balance between base loading and temperature in attaining optimal yields while enabling stoichiometric quantities of each of the substrates to be utilized. A new general set of conditions were developed that allowed for the synthesis of a matrix of 36 amides (including APIs moclobemide and flutamide) in modest to excellent yields irrespective of the rheology of the reagents. In addition, experiments were conducted on the efficiency of solid grinding auxiliaries in not only promoting the reactions of liquid substrates but also in minimizing hydrolysis of both ester and the base catalyst. These studies proved critical in translating the protocol from the ball mill to the twin screw extruder when liquid reagents were utilized. However, while successful multigram synthesis of a series of four amides was achieved using the extruder, these studies highlighted that translation of a methodology from the ball mill to a continuous mode of operation was not trivial specifically given a different range of parameters to optimize (screw speed, temperature of sectors, screw configuration etc).[201] The highlight though of this work was the exemplification of a seven-hour continuous amidation reaction of a solid amine and solid ester substrate leading to *ca*. 500 g of the desired amide product. This translates to a throughput of 1.5 kg of product per day with a STY of 4.74 x 10^3 kg m^{-3} day^{-1}. The sustainability impact of this approach is highlighted by a PMI for this process of 1.78 including the subsequent work-up and crystallization process (Scheme 11).

However, the last point raises a critical factor that must be kept in mind when considering utilization of mechanochemistry as an enabling technology to reduce solvent use. PMI (or related metrics) consider the amount of material utilized to deliver the pure product, and this consists of both the reaction component, work-up and purification.[202] While employing mechanochemistry/extrusion will have a profound impact on the PMI of the reaction through elimination of the solvent, the work-up/purification will likely remain unchanged and will likely use solvent-based techniques to both remove impurities and obtain the desired product that meets the purity specifications.



Scheme 11: Large-Scale Mechanochemistry Using Twin Screw Extrusion

Computational Chemistry – AI/ML

Computational tools based on emerging advances in artificial intelligence (AI) and machine learning (ML) have the potential within our industry to have a seismic effect in accelerating the design of environmentally friendly processes and products through a broad range of applications including predicting reaction outcomes, optimizing conditions reducing waste and energy requirements, and the design of novel, more potent molecules with better physicochemical properties that can prevent long-term accumulation in the environment.[203,204,205] One of the key benefits for our discovery and development groups is that the development of these tools provides the ultimate green chemistry benefit in reducing our reliance on expensive and wasteful (in both time and materials) trial-and-error lab experimentation through replacing these with robust, in silico-based analyses to drive portfolio-based decisions.

There have already been examples of our use of AI/ML-based retrosynthesis tools in the section on our Discovery group, though these are broadly utilized throughout our chemistry enterprise with a range of features (many of which are customized for proprietary use) exploited to ensure that each function gains maximum value from the output.[206] For example, within discovery, the emphasis is built on disconnections that enable the generation of maximal molecular diversity in the least number of steps from a readily, available starting material, with green chemistry principles promoted through filtering out reaction pathways that utilize hazardous reactions/reagents. Within development, the goal becomes more streamlined with searches now focused on routes towards a single target molecule. Herein, the tools serve as central resources for brainstorming sessions to ensure all possible disconnections have been considered while evaluating these focuses on cost of goods, number of steps, yields and importantly on the overall sustainability of the reaction conditions (solvents utilized etc). The major benefits of incorporating and streamlining these tools internally include the ability to incorporate our compound collections, and to further

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optimize the computational models through integrating reaction data from our electronic notebook repositories. The latter point is particularly advantageous as vast amounts of stringently curated reaction optimization information on pharmaceutically relevant substrates is included developed through high throughput experimentation campaigns while similarly reaction data developed using enabling technology paradigms such as electrochemistry, photochemistry can also be mined and accessed.[207] While we recognized the value of these emerging retrosynthesis tools, we also understand that it is critical to integrate them into our workflows in tandem with the expertise of practicing chemists to realize their true potential within the drug discovery/development space. This enables critical evaluation of machine-generated proposals to be seamlessly coupled with "real world" experience to allow a judicious decision-making in terms of which ideas should be tested in practice in the laboratory environment, and their potential overall value to the specific program from a big-picture perspective. Upon reduction of these chemistry ideas to practice, ML algorithms are also then broadly applied within development to fine-tune reaction parameters such as temperature and pressure with key objectives being optimization of yield, reduction of waste, and improving overall production efficiency.

AI/ML tools also play a pivotal role in the design and optimization of the structures of the drug candidates that we seek to access.[208,209] Proprietary internal data again enables our computational models to lever vast amounts of legacy information to build robustness into the predictions that are generated. Tools have been developed to forecast the efficacy of a compound against a specific target. Perhaps of greater utility at the current time within drug discovery is the development of AI-software that allows the visualization of complex protein structures with high levels of confidence, which can then be utilized to predict small molecule binding. The outcomes of these computational studies can then be enhanced in conjunction with experimental techniques such as X-ray and cryo-EM to provide a feedback loop to power the generation of precise-binding models to streamline and expedite compound design. The power of these models is emphasized through the ability to reliably forecast parameters such as binding energies, torsion angles, strain energies, and sites of residual waters within a predicted structure of a small molecule bound to a protein. Computationally-derived tools also play a significant role in the design space though filtering huge collections of proposed molecules through in silico predictions of physicochemical properties including solubility, lipophilicity, toxicity and stability to ensure that only a series of discrete compounds that have the potential to be clinical candidates are prioritized for synthesis. This represents one of the prime objectives of Green Chemistry within a Discovery setting in not only curtailing the amounts of compound to be made but also minimizing the actual number of analogues that need to be tested within a specific program.

Within our Green Chemistry program within Pfizer, we recognize the broad impact that AI/ML currently and continues to have within the pharmaceutical industry and the positive effects that this can have on not only our chemistry-focused but also our broader-based corporate sustainability objectives. We also realize that while we are fortunate to have access to vast amounts of both chemical and biological data derived from legacy projects over our history, the AI/ML space is rapidly evolving. Given this, while we do develop proprietary computational models internally, we also partner in a highly proactive manner (including sharing of data sets) within several consortia/focus groups (many of which have a specialist focus on the use of AI/ML to develop more sustainable drug discovery/development) as well as both expert companies and academic practitioners in this space.[210,211] In addition, the innovations from these partnerships are typically reported in the peer-reviewed literature to allow broader implementation of new AI/ML tools for greener chemistry throughout the industry. While our investments in the AI/ML/digitalization space are significant, given that these are relatively recent, it is challenging at the current time to quantify the benefits that these have realized in terms of cost, upstream emissions and overall operations specifically when offset against the necessary expansion of our AI infrastructure and its potential reliance on carbon-intensive electricity.

Participation in Consortia

The collaborative development of emerging green technologies and tools with the potential to become operational platforms within the next decade is a critical strategy for the pharmaceutical industry. In addition, fostering unique and innovative external business models to incubate or prototype promising technologies, as well as devising non-disruptive yet rapid commercialization approaches, are essential for effective implementation and sustained growth.

Several significant collaborations undertaken by Pfizer to influence the external environment include participation in the European Union's Horizon 2020 innovative research initiative, specifically under the Innovative Medicine Initiative (IMI) CHEM (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries).[212] Initiated in 2012, CHEM 21 was a public-private partnership that allocated €26.4 million toward the development of environmentally sustainable methods for drug development. These initiatives advanced both environmental goals and cost efficiency within the pharmaceutical industry. Most recently, Pfizer joined the IHI PHARMECO initiative, a European public-private partnership launched in November 2024.[213] This collaboration aims to support changes in pharmaceutical manufacturing by advancing sustainable technologies and reducing the industry's environmental footprint, while maintaining quality and patient safety standards. PHARMECO brings together pharmaceutical companies, universities, research organizations, small and medium-sized enterprises, and a government institute for a planned six-year multidisciplinary effort. The project is co-funded by the European Union, private members of the Innovative Health Initiative Joint Undertaking (IHI JU), and UK Research and Innovation (UKRI). Its primary objectives include enhancing production processes and developing standardized methods for evaluating sustainability.

Pfizer has also been a long-term participant in the ACS GCI Pharmaceutical Roundtable (ACS GCIPR), which was created in

2005 to support the integration of green chemistry and engineering principles within the pharmaceutical industry.[214] Initially established by Pfizer, Merck, and Eli Lilly, the roundtable expanded to over 50 members by 2025. Its three strategic priorities are: a) advancing the research agenda, b) developing tools and metrics to catalyze innovation, and c) educating students and influencing leaders. Regarding the ACS GCI PR, Pfizer has not only contributed through a leadership role within this consortium but also benefitted significantly from the learnings of peer organizations. This reciprocity is perhaps most easily demonstrated through the priority around developing tools and metrics. In this space, the concept and overall Venn diagram visualization of the Reagents Guide was provided originally by Pfizer, and has since been significantly expanded on through a focus team within the ACS GCI PR. In a similar manner, the Solvent Selection guide and PMI Predictor were based on original innovations from Astra Zeneca and BMS respectively and again have been further developed and made publicly available through the ACS GCI PR, whilst also being seamlessly integrated within our own internal workflows. Participation in both developing such tools, and exercises around benchmarking metrics also enable Pfizer as a chemistry organization to track our progress against the industry given that the data submitted from these endeavours are blinded through the ACS GCI. Working specifically in the pre-competitive space also enables the ACS GCIPR to identify common areas in which fundamental scientific research could potentially provide significant benefits in promoting sustainability benefits for the industry, and to partner in funding these as a collective as opposed to through individual company initiatives. As with tool development, providing grants to academic institutes enables not only distribution of the financial burden across partners, but also allows resources to be funnelled towards more ambitious projects that would face challenges in accessing funding from more established sources. Specifically, Roundtable grants have funded grants in emerging technologies including biocatalysis, electrochemistry, flow chemistry and mechanochemistry whilst also supporting research programs focused on more sustainable approaches to innovative therapeutics such as peptides and oligonucleotides. The latter represents a significant benefit for all member companies as enables the various chemistry communities to remain abreast of “cutting-edge” advances across modalities even if their own specific organization are not currently active in that area while also gaining insights from subject matter experts from within other Roundtable member companies. The Roundtable has been also actively involved in policy discussions, and the 2012 Swedish labelling scheme adopted the ACS GCIPR Tool for Eco-Foot printing. Each year representatives from the member companies were nominated for the position of Roundtable Chair with Pfizer having had the opportunity to lead the Roundtable on numerous occasions. In addition, Pfizer representatives participate and currently lead several of the Roundtable focus groups.

Additional collaborations include participation in the IQ Green Chemistry Working Group,[215] which advances the development of metrics and best practices, as well as engagement with the Pharmaceutical Supply Chain Initiative (PSCI)[216] and the Green ChemisTree Foundation[217]—both organizations dedicated to enhancing the sustainability performance of our global supply chain. With respect to the latter organization, participation in the biennial IGCW (International Green Chemistry World) convention in Asia provides the opportunity to engage directly with over 300 senior decision makers of the chemical industry with the remit to expand awareness and share technical expertise to facilitate the implementation of green and sustainable chemistry within India.

Conclusions

Global warming is fundamentally impacting human health, while increased frequency and intensity of climate-driven events disproportionately impact underserved communities. The time to act is rapidly closing and pharmaceutical company have a role to play in this battle.

Pfizer has set extremely ambitious Net Zero goals, 10 years earlier than the Paris Agreement, and has put in place an aggressive corporate strategy that is supported, in part, by its Green Chemistry team. Green chemistry will serve both as a foundation and a key platform to progress towards these Net Zero achievements. As presented herein through educational programs, metrics collection and strategic investments in new technologies, Pfizer is committed to addressing environmental, societal and economic issues associated with climate change. This pioneering and aspiring approach positions Pfizer as one of the leaders in the healthcare sector to combat global warming.

Author contributions

PR edited and collated the final manuscript. All authors were involved in the conceptualization and the writing of the various sub-sections.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this perspective.

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ARTICLE

Sustainable Chemistry in Pharma: Pfizer Green Chemistry Team's Perspective

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In the last few years, many pharmaceutical companies have shared publicly Net Zero goals aligned with Paris agreement in order to curve climate change and deliver greener medicines to patients. To achieve these ambitious objectives, embedding green and sustainable chemistry concepts into drug development strategies will be of high importance. Herein, we cover the approach taken by the Pfizer Green Chemistry team on its 25th anniversary, highlighting key areas of focus from discovery to manufacturing waste treatment, while encompassing metrics, new technologies and cross-industry consortia initiatives.

Data Availability Statement

No primary research results, software or code have been included, and no new data were generated or analysed as part of this perspective.