Small Molecules, Global Challenges

From AI-driven design to counterfeit detection; here's how innovation is reshaping the world of small molecules

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Isotopic Fingerprints: A Forensic Frontier for Drug Product Authentication

Stable isotope ratio mass spectrometry used to assess drug authenticity and consistency.

Counterfeit and substandard medicines remain an ongoing threat, which is why the development of precision tools that can ensure drug authenticity and manufacturing integrity remain crucial. A study by researchers at Stanford University and the University of Copenhagen introduces a method using stable isotope ratio mass spectrometry to profile the isotopic signatures of pharmaceutical products.

Focusing on ibuprofen drug products and commonly used excipients, the study highlights how stable isotope ratios can serve as forensic markers to detect counterfeits and assess manufacturing consistency.

Stable isotope ratio mass spectrometry (IRMS) is a mainstay in geochemistry and food traceability, but is considerably less well known in the pharmaceutical world. The researchers analyzed 27 ibuprofen drug products sourced from six countries, alongside 27 widely used excipients, and found that each drug product exhibited a unique multi-isotope fingerprint, shaped by its formulation, manufacturing conditions, and raw material origins.

Through thermal combustion elemental analysis (TC/EA-IRMS), the team measured isotope ratios with high reproducibility using only ~150 µg of sample material – an amount small enough to leave the tablet essentially intact.

Insights into consistency

Among the key findings was insight into isotopic consistency across multiple batches of the same branded product. For example, nine different batches of GSK's Advil purchased in California, and varying in expiration dates, bulk sizes, and packaging, showed minimal isotopic variability, suggesting a high level of production control and supply chain integrity.

Drug products produced by the same manufacturer but with different dosages (e.g., 200 mg versus 400 mg ibuprofen) displayed distinguishable isotopic profiles. These differences are likely due to variation in excipient composition and processing, further emphasizing the sensitivity of isotope ratios to formulation changes.

Using 3D isotopic plots, the research visually separated ibuprofen products by brand and by country of origin. While overlapping excipient types were common among products from Europe, the isotopic profiles remained distinct, reflecting subtle but traceable formulation or raw material sourcing differences.

Of note, products from Japan and South Korea exhibited the most negative δ^2H values, meaning that the hydrogen within is less heavy than the standard and likely indicative of regional manufacturing practices or ingredient origins. For example, these tablets included caffeine or anhydrous calcium phosphate, which may have influenced their isotope profiles.

While the United States Pharmacopeia currently references isotopic characterization as a potential application of mass spectrometry, it has not yet formalized IRMS for drug authentication. However, the "United States Pharmacopeia describes the potential application of stable light isotopes under section ⟨1736⟩ Applications of Mass Spectrometry, 7.1.3. Isotopic Characterization, where authentication and identification of contaminants in drug products and raw ingredients are highlighted as some of the strengths of IRMS analysis, but no monographs utilize the isotopic methodology," the authors state.

By identifying both inter- and intra-manufacturer variations with a high degree of specificity, stable isotope profiling offers an added layer of traceability that could complement existing chemical and physical QC methods, particularly in global supply chains where counterfeiting is rife and raw material provenance is obscured.

The study concludes: "stable light isotopic analysis, thus, is a powerful tool for health authorities and pharmaceutical manufacturers to detect falsified and substandard drug products, protect against patent infringement, and evaluate raw material supply lines to ensure high-quality products."

EU Maintains Use of Titanium Dioxide in Medicines Amid Lack of Viable Alternatives

The EMA has maintained its faith in the safe use of titanium dioxide for pharmaceutical applications, but suggests that companies should look into alternatives.

After reviewing the 2024 EMA analysis, the European Commission concluded that titanium dioxide (TiO2) remains essential for the quality, safety, and efficacy of many medicines, and that no feasible replacement currently exists. The Commission will therefore maintain its use in medicinal products under Regulation (EU) 2022/63.

The decision acknowledges the pharmaceutical industry's role in tracking scientific advances and adapting formulations where justified. Companies are encouraged to continue evaluating excipients, including TiO2, when developing new products, ensuring that excipient choices are scientifically sound and regulatory compliant.

Industry feedback to the EU Commission's Quality Working Party experts states that "Establishing the [permitted daily exposure] will reassure patients that TiO2 use is actively monitored and controlled at safe levels". For now, titanium dioxide remains a fixture in the EU pharmaceutical landscape, but the conversation about its future use is not over.

TiO2 has long been a staple in medicinal products, valued for its whitening, opacifying, and protective properties. Found in more than 91,000 human and 1,600 veterinary medicines, it helps ensure uniform tablet color, improves product identification, shields active ingredients from light, and maintains visual appeal over a product's shelf life.

However, the safety of TiO2 has come under scrutiny in recent years. In 2021, the European Food Safety Authority (EFSA) concluded that concerns about genotoxicity could not be ruled out, leading to its ban as a food additive in 2022. While this ban did not extend to medicinal products, the European Commission tasked the European Medicines Agency (EMA) with assessing whether replacement was feasible without compromising quality, safety, efficacy, or availability.

The feasibility challenge

The EMA's first analysis in September 2021 acknowledged the potential to find alternatives but warned that any substitution would present major technical challenges and disrupt medicine supply chains. The updated 2024 analysis, informed by industry data, confirms those concerns.

The industry and EMA assessed TiO2-free coatings against key performance indicators (KPIs). All tested alternatives fell short in at least one critical area. For example TiO2's strong opacity helps achieve uniform coverage, even on differently colored tablet cores. Without it, alternatives often require more intense pigments, altering the product's visual identity, which is an important factor for patient compliance. TiO2 also offers superior light protection. Alternatives often require additional protective packaging to prevent degradation of light-sensitive medicines.

Separately, in March 2025 the EMA reviewed new safety data submitted by an industry consortium. Although not a full re-evaluation, the assessment – supported by the European Chemicals Agency (ECHA) and EFSA – found that any carcinogenic risk from titanium dioxide in medicines is negligible, reflecting both the pharmaceutical-grade purity and the small quantities used.

TiO2 is deeply embedded in pharmaceutical development pipelines, used from the earliest formulation stages through clinical trials. The EMA estimates that even if a suitable alternative were found, reformulating a company's full product portfolio would take 7-12 years due to staggered reformulation schedules, manufacturing adjustments, and regulatory approvals.

Implementing Green Chemistry into API Manufacturing

Early API development can drive environmental gains without sacrificing speed or yield.

The path from preclinical research to API drug commercialization is fraught with risk and complexity, with thousands of compounds narrowing down to a single drug suitable for patient use. The intense scrutiny in this process often puts sustainability on the back seat, especially during early phases. But this is exactly when sustainability should come to the forefront. By embedding green chemistry principles from the outset, pharmaceutical developers have the opportunity to reduce their environmental impact and design processes that are scalable, cost-effective, and compliant with evolving regulatory expectations.

We spoke with Axel Zimmermann, Director, Process Development Services, Pharma Services, and Peter McDonald, Director, Process Development Services, Pharma Services, both at Thermo Fisher Scientific, to find out more about greener API manufacturing.

Why is early-stage API development ideal for embedding sustainability principles?

API supply for early phase clinical trials and underlying tox batches typically relies on synthetic approaches, which are designed for the divergent synthesis of compound libraries, tolerating a broad substrate scope. Green chemistry aspects, waste reduction by process intensification, solvent recovery, water conservation, or the use of starting materials from renewable sources, play a subordinate role.

Generally, companies begin to consider the switch to a commercially viable and sustainable synthetic route towards the end of phase II. By this stage, the medchem route is often no longer scalable, or is becoming too expensive to supply sufficient material for later stage trials. At the same time, efficacy and safety have been established sufficiently to justify the investment in developing a scalable and cost-effective manufacturing process.

Switching the synthetic route at this point still allows sufficient time to develop, optimize, and validate a sustainable and commercially viable process before large-scale production for phase III trials and regulatory approval.

Implementing green chemistry and scalability aspects at later stages of the clinical development program can lead to significant costs and delays during product commercialization. For example, new impurities that may arise from the commercial manufacturing route will potentially require extensive bridging studies to validate the new route, and ensure it meets safety and efficacy standards.

Scale-up, as well as thermal process risks, are becoming prominent if detected late in the process development. Scaling from lab to commercial production may reveal inefficiencies and inconsistencies, leading to production delays, increased costs, and logistic supply during the transport and storage of hazardous reagents. Ultimately, speed to market can be delayed as the transition requires time for scale-up and validation, potentially leading to missed market opportunities.

Axel Zimmerman

How can green chemistry approaches be integrated without compromising yield, scalability, or time-to-market?

In general, green chemistry principles are not contradictory to the development of viable commercial synthetic processes; they are foundational to it. A well-designed, scalable, and intensified commercial manufacturing process that starts with raw materials originating from renewable feedstocks is intrinsically green. It prevents waste rather than treating or cleaning up waste, uses non-hazardous raw materials and reagents at low consumption levels, and operates at high space-time yields, thereby minimizing energy consumption.

Additionally, processes designed with green chemistry principles in mind are often more scalable and require less adaptation towards regulatory approval, ensuring significant time and cost savings on the path to product commercialization. For example, technologies such as continuous flow chemistry enhance reaction control, reduce scale-up issues, and improve safety, leading to faster development

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Implementing Green Chemistry into API Manufacturing (cont...)

times and more efficient processes. Optimizing reactions to minimize by-products and waste, along with in-line monitoring, maintains high yields and reduces the need for extensive purification.

Furthermore, aligning green chemistry principles with regulatory requirements and engaging with regulatory bodies early helps integrate these practices without causing delays.

What role do solvents play in the overall environmental footprint of API production?

The demand for drugs, with improved target specificity, results in APIs with increasing molecular complexity. Consequently, these molecules require additional synthetic steps, specialized reagents and reaction conditions, and extensive purification. All of these factors lead to increased solvent consumption and complex solvent systems that are difficult to purify for later reuse or external recycling.

Beyond environmental and cost considerations, the handling of solvents and resulting waste streams can pose significant logistical disposal issues if not adequately addressed. With Process mass intensity values ranging from 150 to 1,000, this is particularly critical for pharmaceutical manufacturing processes.

Peter McDonald

To minimize the use of solvents in pharmaceutical manufacturing, a "refuse, reduce, reuse, recycle" strategy can be applied. This involves designing efficient synthetic routes with fewer steps and simpler solvent systems. By doing so, not only are the volumes of solvents reduced, but the recovery and reuse of recycled solvents in the manufacturing process are facilitated. Such a proactive design strategy ensures that solvent use is minimized from the outset, making the entire process more sustainable.

When changes to the manufacturing process are no longer feasible at a late stage of clinical development, the focus shifts to "reduce." Underlying manufacturing processes can be optimized in terms of space-time yield to enhance throughput while simultaneously reducing waste and energy costs.

The third pillar is the "recycle" approach, which involves the reuse of purified solvent streams within the same manufacturing process or their external recycling in less regulated processes. Since the reuse of solvents often requires purification, which incurs significant costs for personnel and energy (e.g., through distillation columns), it is crucial to develop processes with simple solvent compositions. Such compositions can significantly ease the purification of solvent streams, making the recycling process more efficient and cost-effective. Focusing on solvent recovery and reuse, the industry can further reduce its environmental impact and resource consumption.

How has Thermo Fisher implemented circular economy principles in API development or manufacturing?

In 2021, Thermo Fisher Scientific was awarded the contract for manufacturing a high-volume API, which was under significant time constraints for its product launch. A critical transformation in the synthetic process involved a complex solvent system for the reaction and subsequent work-up, necessitating the handling of approximately 1,500 metric tons of a waste stream containing a ternary solvent mixture within a two-month production window.

The associated costs and logistical challenges of managing this solvent waste prompted the development of a reuse strategy alongside the regular tech transfer and scale-up activities. This strategy utilized an entrainer to break different azeotropes in the ternary mixture, achieving a recovery rate of over 80 percent for the two key components. The initiative was executed in close collaboration with the client, including the establishment of a control strategy for the recycled solvents. This facilitated the sustainable production of the API without compromising the yield or quality target product profile.

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Implementing Green Chemistry into API Manufacturing (cont...)

How can pharmaceutical developers evaluate the trade-offs between process efficiency and environmental responsibility?
The sustainable design of a chemical manufacturing process not only addresses economic challenges, but also enhances ecological process characteristics. By integrating sustainability principles into process design, manufacturers can achieve cost savings through increased efficiency, reduced waste, and lower energy consumption.

Simultaneously, these practices contribute to environmental benefits such as decreased pollution, conservation of resources, and reduced carbon footprint. Thus, sustainable process design creates a synergy where economic and ecological advantages reinforce each other, leading to more responsible and effective manufacturing operations.

Are regulatory frameworks evolving to better support or incentivize sustainable practices in API development?
For decades, the pharmaceutical industry has transformed patient lives through the development of medicines. While quality, efficacy, and safety remain paramount, there is now a growing focus on sustainability, driven by initiatives such as net zero emissions, circular economy practices, and green chemistry. However, the implementation of sustainability-driven post-approval changes for launched products faces many challenges from a chemistry, manufacturing, and controls regulatory point of view, making it complex to improve sustainability for commercialized products.

With the ICH Q12 guideline, a globally agreed and harmonized framework for managing post-approval CMC changes is provided. While previous guidelines, such as ICH Q8(R2) and Q11, focus primarily on early-stage product development, registration, and launch, the ICH Q12 guideline offers a predictable and efficient regulatory framework that builds on the process knowledge of critical parameters, critical quality attributes (CQAs) and rationalized specification established during product launch (established conditions), thereby facilitating sustainable post-approval changes and complementing previous quality ICH guidelines.

The definition of established conditions can be challenging, however, as it requires a thorough understanding of what constitutes critical quality attributes and critical process parameters. The definition of established conditions can be critical – especially for older filings applying modern quality by design-based principles. Misinterpretation or misclassification of established conditions can also lead to compliance issues.

What innovations could drive greener API development over the next five to ten years?
The API manufacturing process has the most significant environmental impact within the pharmaceutical product supply chain. The prevention of waste streams by a sustainable design of synthetic routes and development of high yielding, intensified processes can have far more impact and treating waste after it has been produced.

Green chemistry principles using advanced technologies such as (bio)catalysis, synthetic biology, and flow chemistry approaches will play a larger role in enabling more sustainable drug synthesis. Advanced manufacturing technologies in combination with AI tools, such as model predictive control optimizations, can help to speed the optimization of chemical reactions, predict reaction outcomes, and identify greener solvents and catalysts, leading to more efficient and sustainable processes. Once a sustainable process is in place, the emphasis can then move to circular economy approaches, with a focus on "reuse" in the process and the external recycling of process streams.

The modelling of liquid-liquid separations will become crucial for optimizing separation processes, thereby enhancing the solvent quality for reuse in the process. In this context, machine learning, which integrates experimental and simulation data from computational fluid dynamics and thermodynamic modelling will be key to enhance model accuracy and predict distillation behavior.

Collaborative efforts with manufacturers, suppliers, and academic partners are all crucial to develop sustainability approaches and incorporate them early into the overall improvement process.

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Chemistry and Crazy Ideas: Getting to Know Ali Tavassoli

Learning more about the people behind this year's Power List: Ali Tavassoli, Chief Scientific Officer of Curve Therapeutics.

After making his Power List debut earlier this year, Ali Tavassoli's work on the high-throughput intracellular production and screening of cyclic peptide libraries has been recognized with the Royal Society of Chemistry's Interdisciplinary Prize.

Tavassoli's work on protein–protein interactions can potentially address one of the most challenging areas in drug discovery: targeting the complex surfaces where proteins bind to each other to regulate vital biological functions. Such interactions are involved in many diseases, including cancer and viral infections, but they have traditionally been considered challenging because small molecules often cannot effectively disrupt them.

Tavassoli has developed an innovative approach, using cyclic peptides generated inside cells using genetically encoded libraries, that can block protein-protein interactions with high specificity. This opens the door to targeting previously inaccessible disease mechanisms and could lead to entirely new classes of therapeutics. His work not only expands the pool of viable drug targets but also provides powerful tools for discovering novel compounds faster and more precisely.

Here, we speak with Tavassoli to find out more about his research.

Congratulations on your recent prize-winning ventures! How does it feel?

It feels good! But for me, this isn't just an award to myself, it's an award for everyone who has contributed over the years to our shared scientific vision. We've been working to show that it's possible to create libraries of compounds inside cells and carry out high-throughput screening and drug discovery in a disease-relevant environment, rather than traditional approaches that screen in a biochemical buffer with recombinant proteins.

When we started this back in 2003 or 2004, it really was a bit of a crazy idea! The technology just hadn't caught up with what we wanted to do. So, we began by engineering human proteins into bacteria and linking the survival of the bacterium to a human protein-protein interaction, then screening our compound libraries that way.

I feel that none of the awards I've received are mine alone. Anyone who stands up to claim sole credit for what is clearly a team effort hasn't got it right. From the postdocs I worked with back when I was a postdoc, to those who trained me. This has always been a collaborative effort. Every student, every postdoc, every investor who believed in the vision has all played a part. The team at Curve Therapeutics now – our scientists, senior leaders, and investors – are all fantastic people who've chosen to come on this journey with us and dedicate themselves to this mission. The recognition belongs to all of them.

How has your approach advanced the identification of protein–protein interaction inhibitors?

Protein-protein interactions are thought to be difficult to inhibit. In some cases, there is a clear interaction between an alpha helix from one protein and a pocket in another protein, and in those cases, you can find inhibitors because there is a clear chemical motif that will point into the pocket from one protein to another.

But the majority of protein-protein interactions do not have

Chemistry and Crazy Ideas: Getting to Know Ali Tavassoli (cont...)

a clear and obvious hotspot and are thought to be flat and featureless. Finding small molecules against these is considered to be very challenging.

In conventional approaches, researchers often produce the protein target in bacteria using a recombinant system. If the target is a human protein, it will lack the correct post-translational modifications. The protein is then placed into a biochemical buffer, which typically renders it static. If it requires a chaperone or another factor to adopt its active conformation, that won't be present either.

Next, a screening method is applied – usually by washing a library over the protein. This could be a DNA-encoded library, phage display, or mRNA display. Compounds that bind are retained while others are washed away. After several rounds of washing, the remaining binders are identified by sequencing the DNA barcode or analyzing results from a multi-well plate assay. However, these assays often still use static protein in non-native conditions.

Our technique is fundamentally different. We use genetically encoded cyclic peptides that are cyclized head-to-tail through a process called intein splicing. The technique is called SICLOPPS and it enables us to generate libraries of hundreds of millions of cyclic peptides inside living cells. We also differ in the assays we use; rather than selecting hits based on binding affinity, we employ functional assays.

We express these libraries in disease-relevant mammalian cell lines, with each cell expressing one member of the library. We then engineer the system so that inhibition of a target – whether it's a transcription factor, a protein-protein interaction, autophagy, or any other process – produces a readable cellular phenotype. This lets us directly identify which cyclic peptides perturb the function of interest.

We separate the cells showing the desired phenotype and sequence the DNA in those cells to find the identity of the cyclic peptide that caused the desired effect. That peptide can be synthesized and tested independently, making our approach very different from traditional drug discovery.

Our cyclic peptides are just six amino acids in length, compared to the 12-20 amino acids typically found in mRNA or phage display peptides, which are already in "mini-protein" territory. This size difference matters because it's one reason cyclic peptides have struggled to make it to market. Despite decades of development, cyclic peptide discovered by these methods have not successfully reached the market. One that did was withdrawn a few years ago.

Our smaller ring peptides are more akin to traditional small molecules. This lets us apply the same design principles used for small molecules. For instance, our hexameric peptides bind their targets through a continuous di- or tri-peptide motif – a "pharmacophore." Thanks to the rigidity of the hexamer, we can model this pharmacophore effectively.

We can then "scaffold hop" by identifying small molecule backbones that mimic the cyclic peptide's pharmacophore conformation. This enables us to move from a peptide scaffold to a small molecule scaffold, bringing us closer to clinical viability.

As both a professor at the University of Southampton, UK, and the CSO of Curve Therapeutics, how do you balance academic research with the goals of a biotech company?

I really enjoy both roles. The academic side gave me the freedom to explore ideas that would be considered too crazy in industry because of risk and timeline constraints. Biotech tolerates risk, but long timelines not so much.

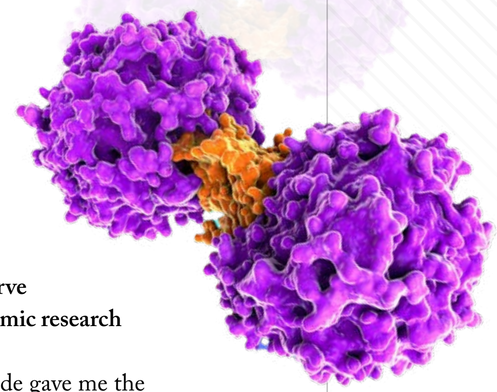
Academia is often the source of innovation for biotech and pharma, which then develop it into real-world therapies. I became an independent academic in 2006, and some of the concepts we developed simply couldn't have originated in a corporate setting.

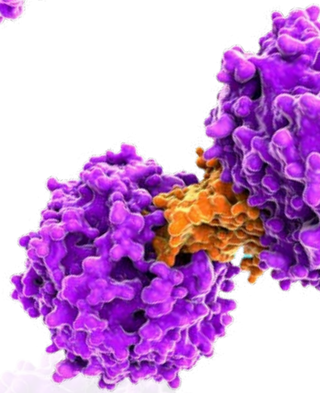
I started Curve six years ago, but I've kept a reduced academic group and still teach one undergraduate course. My main focus now is Curve. I didn't go into academia to do research for its own sake. I always wanted to apply what I did, and academia gave me the freedom to try the crazy stuff.

When I became a professor in 2014, I asked myself, "Is this it?" That's when I started thinking about focusing my efforts on translating my research into the world. Biotech is fast-paced and dynamic. You can get things done quickly. If I'd stayed in academia, it would've taken me my entire career to get where we are today with Curve, where in five or six years, we've made enormous strides.

Can you share insights into how your platform is being used in collaboration with Merck, Sharpe & Dohme (MSD)?

The platform is unique. Not just because it allows





Chemistry and Crazy Ideas: Getting to Know Ali Tavassoli (cont...)

screening inside cells, but because we use genetically encoded libraries. That means we can rapidly screen a billion cells with no robots required. That's a game-changer. And our modality is different. We're working with six-amino-acid cyclic peptides – Microcycles – that others can't easily use due to technical and chemical limitations.

It's not just MSD – anyone who is interested in drug discovery against intracellular targets can see that this is different, and it's accessible. Even those without a specialist scientific background appreciate the difference between screening in a test tube with a static protein versus screening in a human cell that reflects real disease biology.

You co-authored a report on a dual HIF-1 and HIF-2 inhibitor using the SICLOPPS platform. What's the significance of that discovery?

HIF is crucial in solid tumors. It's the protein that tells your cells, "Hey, you're not getting enough oxygen. We need to adapt and send signals for new blood vessels." That's true for fetuses and tumors alike. Tumors grow quickly and outstrip their blood supply, known as hypoxia. HIF activation helps them survive and grow in this microenvironment.

HIF is a transcription factor with two subunits: HIF-alpha and HIF-beta. HIF-beta is constitutively expressed and always there, waiting in the nucleus. HIF-alpha is made and destroyed constantly – every few minutes – using oxygen-dependent hydroxylation as the signal for its degradation. When oxygen levels drop, HIF-alpha degradation stops and the protein is chaperoned into the nucleus, where it partners with HIF-beta, and changes the transcription of hundreds of genes to adapt to the low oxygen microenvironment.

From the moment it was discovered, HIF was recognized as a key cancer target. In 2013, we published the first HIF-1-specific inhibitor. Around the same time, a group in Texas published a HIF-2-specific inhibitor, which Merck eventually brought to market as belzutifan.

But many tumors are driven by both HIF-1 and HIF-2 – or they'll switch between them – so we aimed to develop a dual inhibitor. That way, we could fully shut down hypoxia response in tumors. Our dual HIF-1/HIF-2 inhibitor remains the only one that targets the HIF-alpha/HIF-beta PPI directly. It's one of the programs Curve is progressing toward the clinic.

How has your experience with the Royal Society of Chemistry influenced your research?

I was President of the Chemistry-Biology Interface Division at the Royal Society of Chemistry (RSC). I've always been drawn to multidisciplinary approaches to research. My PhD was in synthetic organic chemistry, then I did a postdoc using synthesis to understand biological mechanisms. This is how I got hooked on big-picture problem solving.

If you work in just one discipline, your tools are limited. But when you span fields, you can ask: "What's the best way to tackle this problem?"

I spent five years in Steve Benkovic's lab at Penn State University, for most of that time re-training in biology. When I joined Southampton in 2006 as an independent academic, they were forward-thinking enough to support cell culture labs in a chemistry department, which was rare at the time, that allowed my lab to take a multidisciplinary approach to our projects from the very start.

That mindset of bringing together the right tools regardless of discipline has guided my research since. Through my roles at the RSC, I've worked to highlight interdisciplinary science to funders and government. It's been personally enriching and, I hope, helpful to the community as well.

What future opportunities or challenges do you see in intracellular target discovery?

The academic group is still going strong! We're still doing crazy stuff and we have a few exciting papers coming out soon.

One involves using cyclic peptides to discover new antibiotics. Another explores targeted protein degradation. And there's a third project I can't talk about just yet, but trust me, it's exciting!

I would like to give credit to my students and postdocs who believed in these wild ideas and bring them to life. Without them, an idea remains just that. It is particularly satisfying that we're continuing to push the boundaries of what we do. I feel incredibly lucky to be surrounded by such amazing people who help turn these "crazy" ideas into reality.

The Multifaceted Future of Pharma

We asked over 100 industry professionals for their views on the future of pharma, including key disruptors and what can be improved… Here are two views focused on the small molecule space.

Small Molecules Are Still Here – and Still the Most Affordable – with Jordi Robinson, Chief Commercial Officer, Navin Molecular

One of the biggest changes that the industry has witnessed in the past 10 years has been the rise of biological-based drugs and the emergence of new modalities as therapies. With the promise of targeted delivery and improved safety profiles, the rise of biologics was seen to have the potential to replace traditional small molecule drugs and deliver better outcomes for patients. This drive has been exacerbated by legislative changes in the US, which favors the development of biologics over more conventional therapies, leading to a record year for biologics' approvals in 2023 – and a record number of large molecule therapies in drug companies' pipelines.

However, with hindsight, it could be questioned whether it is realistic to suggest that biologics are, in reality, 'replacing' small-molecules, which have been the mainstay of the pharmaceutical industry for more than a hundred years. Despite the obvious benefits that biologic drugs can bring, the economics of biological manufacturing simply do not add up when compared to small molecules; not just in relation to their manufacturing costs, which are often an order of magnitude greater without a similar elevation in efficacy; but also in relation to the size of the (potential) patient populations and – more importantly – the number of healthcare systems that can actually afford to approve biologics for use.

Similarly, the protocols of almost all global healthcare systems are predicated on the use of cheaper, small-molecules as first-line therapies. Unless a disease is exceptionally rare and/or no other therapies exist, it is highly unlikely that biologics would be used initially. Other issues with large molecules, such as the challenges of reproducible manufacturing, and the lack of capacity for manufacturing certain classes of biologics are easier to solve, but changing the majority of the world's healthcare providers' protocols for their prescription would appear to be a greater challenge for drug companies.

But perhaps the biggest 'threats' to the rise of biologics are not the size of patient populations or their manufacturing cost, but from the continued development of new small molecule therapies. The increased use of AI in drug discovery is leading to an explosion of new candidates being developed, and advances in manufacturing techniques mean that targets that were once considered either inaccessible – or at least uneconomical to produce at scale – are becoming viable. Similarly, the safety profiles of new small molecule drugs are significantly improved from those developed 20-30 years ago because of a much deeper understanding of the pharmacokinetics, and better manufacturing processes allowing the synthesis of exceptionally pure materials with a very high degree of reproducibility and control.

Although biologics have the potential to bring significant benefits to patients, the likelihood is that these will be unevenly distributed. Ultimately, despite many opinion pieces over the years claiming the opposite, small molecule therapies will be with us for the foreseeable future, and will almost certainly continue to be used as first-line therapies for the next 10 years. In the vast majority of global medicine, small molecule therapies are likely to be the sole therapy used in a patient's treatment, with biologics being more a medicine of last resort – and depending upon the nature of healthcare systems and payors.

So, although I have no doubts that pharmaceutical companies will continue to invest heavily in large molecule research and development over the next 10 years, I would prefer that, rather than eulogizing over the benefits of these therapies, perhaps the focus should be more about developing safe, effective medicines that can be accessed by the widest range of patients and, in the short to medium term, these will likely be traditional small molecules.

Optimizing Processes With AI – with Chad Telgenhof, Chief Commercial Officer, Sterling Pharma Solutions

As the pharmaceutical industry strives to create the drugs of the future, it is looking to open up new molecular space, and explore the potential of new modalities. Patient safety and quality remain paramount, and technology plays an important role in both the design of new drugs and their manufacture.

A significant improvement within the industry could be achieved through the widespread implementation of AI and ML

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The Multifaceted Future of Pharma (cont...)

throughout the lifecycle of a molecule. These would allow the design of new drugs to be undertaken much quicker, with the virtual evaluation of numerous parameters to assess physical properties, potential side effects, and efficacy.

Process optimization could be significantly enhanced, building on information from numerous sources to reduce the time spent undertaking real-time experiments. Screening processes in terms of hazard evaluation, and finding the optimal parameters with which to safely and efficiently manufacture products requires – and generates – vast amounts of data, and being able to concentrate the time spent by scientists and engineers to key steps will accelerate processes towards scale-up manufacturing.

In manufacturing, these technologies could monitor processes in real time to ensure quality control of products during synthesis, as well as the reactors and equipment being used, reducing human involvement in maintenance schedules. Supply chains and procurement could be automated to avoid stock availability issues for key reagents and intermediates, reducing delays and potential shut down of manufacturing, and maintaining operational and delivery schedules.

These technologies can dramatically accelerate the process of identifying and optimizing drug candidates, predicting clinical trial outcomes, and personalizing treatments, ultimately reducing costs, time, and improving the success rate of bringing new therapies to market.

There is application of AI and ML already within some areas of the industry, but the setup of the technologies requires significant capital expenditure, and the models are dependent on the amount and quality of data that are available for them to draw on. We are potentially some distance away from seeing universal adoption, but we are seeing major players in the industry harnessing the potential of existing technology, and building systems to grow as the amount of data that can be accessed increases. While there is no substitute for human interaction and experience, technology must be leveraged where possible to make the design and manufacture of drugs safer and more efficient.

Can AI Help Solve the Solubility Challenge?

We explore how AI-based tools are making a mark in formulation by improving solubility.

Every year, The Medicine Maker celebrates new drug development and manufacturing technologies through our Innovation Awards. In 2024, our winner was mPredict Co-Crystal Prediction Service from Merck KGaA, Darmstadt, Germany. The service uses AI to predict optimal co-formers for an API. The result? Co-crystals with improved solubility and stability.

Here, we speak with Daniel Price, Head of Excipients Business at the company, to find out more about pharma's solubility problem – and how the company came up with an AI-based approach.

The pharma industry has been talking about a solubility problem for years. Why are so many drugs in pipelines poorly soluble and what are the challenges of developing new solutions to address solubility problems?

With 70–90 percent of drugs currently under development being poorly soluble, addressing solubility challenges has never been more important.

Sophisticated drug discovery tools are being used to identify potential candidates to address the unmet needs of patients and treat rare/orphan diseases. These highly efficient tools – such as high-throughput screening and target-oriented drug discovery – can rapidly help medicinal chemists to identify and test a large number of promising drug candidates, but many of the identified candidates are complex chemical compounds that are hard to formulate and show poor solubility. In general, the size and molecular weight of APIs is also increasing, which further leads to poor aqueous solubility and poor permeability.

Solubility is critical as the drug must be soluble in the gastrointestinal fluids to pass through the intestinal membrane and into systemic circulation, where it can be delivered to the site of biological action. There are several chemical and formulation approaches to enhance solubility and dissolution of a drug depending on their subclass, but with several root causes and many potential solutions, selecting the best is often time consuming. Additionally, there is no one size fits all approach, and time and resource pressures in pharmaceutical development may mean that the best solution is not always found.

It was this combination of criticality and complexity that led us to begin exploring AI solutions for formulation screening of poorly soluble molecules.

Why is co-crystallization seen as a promising solubility-enhancing approach?

Co-crystallization is a relatively new chemical approach to enhance drug solubility, where an API is combined with a pharmaceutically acceptable co-former in a co-crystal structure. The resulting co-crystals have unique properties that can address challenges related to drug manufacturability, solubility, stability, and bioavailability – often resulting in significantly higher solubilities than the original API, without altering the chemical identity or reducing its biological activity. Additionally, co-crystallization is useful for substances without an ionizable functional group – as opposed to salt formation. Finally, co-crystallization within drug substance manufacturing is a simpler process compared to other solubility-enhancing technologies, such as enabling formulations.

In addition to the process and performance benefits of co-crystals, this strategy may also be used to extend the life cycle of an API, or even to bring generic versions of an API to market faster.

What role does the co-former play and why is selection so challenging?

The co-former interacts nonionically with the API to form a co-crystal via a solid-state bond. The co-former must be structurally compatible with and have a similar solubility to the API in various solvents. Therefore, co-former selection is dependent on API purity, structural features and physical properties. This diversity in the key success factors of drug-co-former interaction is what makes development of co-crystals so challenging, time consuming and expensive.

Several experimental screening techniques can be used for co-crystal formation, such as solvent crystallization, solvent assisted grinding, sublimation, slurrying and hot melt extrusion (DSC screening), but a scientist must identify which technique is most suitable.

Secondly, comprehensive experimental screening is rarely possible due to limited API availability, and lack of resources and time needed to conduct extensive experiments. It's also common that scientists will use co-former chemicals they are most familiar with, which limits the different co-crystal combinations they can generate. Although there are

Can AI Help Solve the Solubility Challenge? (cont...)

some guidelines to help guide co-former choice, these are somewhat rudimentary and limited to a smaller set of possible combinations. A much broader toolbox of potential co-formers could be explored if there was a more efficient and quick process for large-scale screening, avoiding the need for expensive and time-consuming experiments.

Tell me about the story behind the mPredict Co-Crystal Prediction Service; why was this area important to the company and how did you go about developing the AI tool for this service?

We have a strong background supporting our customers during drug development with a technically differentiated portfolio of excipients and raw materials for drug substance and drug product manufacturing. We have an innovation-driven culture and mindset and center our product and technology development on tackling the most difficult challenges in pharmaceutical development.

Hand-in-hand with this culture, we keep our finger on the pulse of new technology developments, emerging trends and new ideas. With AI now being such an important part of our daily lives and, increasingly, in drug discovery, we started with an ambition to bring drug formulation closer to digital technologies and AI. Given our extensive background in solubility, we applied various methodologies to several key challenges: co-crystallization prediction is one of our first success stories, but there are many more on the horizon!

To get more specific about co-crystallization, what we have developed is a new algorithm that combines computational chemistry, machine learning, and big data to calculate the likelihood of a successful co-crystal interaction between an API and co-former. We learned a lot during this process; for example, never underestimate the importance of data quality! After several failed attempts at mining literature data to build our model, we pivoted to developing all our data from scratch internally. This was a key learning, which we now apply to all our AI models under development and has significantly improved the reliability and predictability of our calculations. Additionally, our service delivers results 96 percent faster than traditional experimental screening.

Our Co-Crystal Prediction Service, a fantastic addition to the SAFC portfolio, is now live and being used to accurately and reliably predict the best co-crystal co-formers for a range of diverse and structurally interesting molecules – without the need for any prior experiments!

How accurate are the results and are there any success stories you can share?

During an extensive assessment of our model's prediction, we performed three independent validations using a "test dataset," which always contained different APIs from the training dataset. We initiated a comparison with current industry standard, alternative solutions and performed beta trials. The results were really encouraging. mPredict performed two times better than industry standard models, and our statistical analysis of the results shows an accuracy of 88 percent in the prediction of successful co-crystals.

These findings were supported in the results of our beta trials, where in one calculation, six out of seven predicted co-crystals were validated experimentally to form co-crystals with the test molecule – some of which had never been reported before in the scientific literature! This last point really underlines the potential in using AI for identifying new opportunities for product lifecycle extension.

What trends have you seen in the types of APIs that benefit most from co-crystallization?

Poorly water-soluble APIs without ionic functional groups, which have limited options for salt formation, are perfect candidates that could benefit from co-crystallization. Furthermore, co-crystallization may show improvement and better control over physical and chemical stability by minimizing polymorphism. The potential for co-crystallization as a product lifecycle expansion strategy really expands the potential of this approach to almost all small molecule drugs.

However, what we're seeing is that it's not only customers in large innovator pharmaceutical companies who are interested in this tool, but also smaller companies who cannot do extensive co-crystallization experiments, as well as companies producing generic drugs (non-branded medicines) who want to improve the formulation of an existing product and overcome intellectual property challenges.

Can AI Help Solve the Solubility Challenge? (cont...)

How do you think AI technologies will continue to improve and how will this shape the future of formulation?
We have seen broad adoption of AI in the drug discovery space, and within our organization we already have two solutions that support this. Our AIDDISON drug discovery software taps into the power of AI, machine learning, and CADD methods – providing a one-stop shop for AI-generative methods, virtual screening of large chemical spaces, and tools for hit-to-lead discovery and optimization. The software allows researchers to explore unbounded chemical space and generate ideas for entirely new compounds.

We also have our SYNTHIA retrosynthesis software, which is powered by sophisticated algorithms that can help experts access and make use of the vast amounts of data on chemical synthesis collated over decades of research which predicts whether it will be possible to make the compound through chemical synthesis.

However, in drug development generally, adoption of AI has been on a slower path. But with increasing pressure on pharmaceutical companies to reduce cost and time to market, the use of AI in formulation development has tremendous potential. It will not only help shorten time to market and bring new medicines to patients faster, but will also allow pharma companies to broaden their investigations to a wider range of chemicals and solutions by trying out things that go beyond the obvious.

Catching Up With Sebastián Arana, Head of Process Solutions, Millipore Sigma

How have your customers reacted to the launch of the mPredict Co-Crystal Prediction Service?
Very positively. At Process Solutions, we have a customer-centric culture that focuses on anticipating and shaping the future of pharma together with our customers as they develop, make, purify, formulate and assure the quality of their life-enhancing and life-saving drugs.

Our innovation is driven by their needs to problem solve – in the case of mPredict delivering results 96 percent faster than traditional experimental screening.

We have received a fantastic response from our customers after the launch of mPredict, and already have many active projects with a variety of molecules and needs.

Do you have any further plans to implement AI into your products and services?
As solutions providers, we facilitate the transition to digitally connected operations by offering innovative solutions that enhance operational efficiency, productivity, flexibility, data management, and compliance. At the Life Science business of Merck KGaA, Darmstadt, Germany, we are dedicated to delivering solutions that assist our partners achieving their goals of automated, data-driven and digitally connected operations.

Digital and AI are at the core of our product and development roadmap. In the API processing space specifically, the mPredict co-crystal service is a key success story. In parallel, our expert team has been working on several additional use cases in the drug formulation space, such as similar models to predict optimal polymer selection in amorphous solid dispersion technologies. We are also developing a digital platform to support parenteral formulation development, buffer selection, and cell culture media optimization.

We are committed to delivering solutions in a stepwise manner, ensuring that we effectively meet the present needs and future ambitions of our customers, recognizing that each partner's ambitions are unique.

Thoughts on the future?
The future looks very bright for the use of AI and digital in pharmaceutical development, especially as this will directly benefit patients waiting for new therapeutics. We take our role in this transformation very seriously and will continue to provide cutting-edge products and technologies to solve the toughest challenges in drug development. mPredict is our first step on the digitally enabled formulation journey, and we are very excited for what's coming on the horizon!

From Benchtop Chemist to CEO?

After his postdoc, Simon Tasker joined Colorcon as a bench chemist – and never left. Today, he's the company's CEO. Here's how his career unfolded as he grew within the company he now leads.

You started out working for Colorcon in the UK. What led you to the US?

I was born in the UK, where I studied at university and then started work with Colorcon in 1996. My first role within Colorcon was as a bench chemist, helping to develop new products to support the pharmaceutical industry. I approached my manager at the time about the possibility of transferring to the US – and fortunately, they were looking for technical expertise there so it was a very natural transition. I took on a technical support role, working closely with our customers, traveling all over the country, as well as to Latin America and other regions. In 2004, I was offered the opportunity to transfer into a technical marketing and market development role, which I accepted.

Several years later, when I was interviewed for the CEO position at Colorcon, I was asked: "Why do you think you're well suited to do this job?" My reply was simply, "Because I know how these products smell and taste. I've held so many roles within this organization that it's in my DNA at this point."

Colorcon has had many stories similar to mine, with people who have grown their careers within the internal structure of the organization. I am just one of the people who represent this growth from within, which we value. Something we have worked hard to develop at Colorcon is fresh thinking and bold perspective, either from within the existing team or by bringing in new talent. It's all about balancing existing institutional knowledge with the evolution of ideas that come from new perspectives.

You've also spent time in China…

That's right. Around 2009, the president of our US organization approached me about working overseas. The question was amusing, given that I was a Brit working in the US. Colorcon was looking for a general manager for the China operation. My family and I relocated to China, and to say the experience was incredible is an understatement. We really enjoyed our time there.

I ran the business in China for four years, at which point my role expanded to include Japan, Korea, Southeast Asia and other areas within the region. The experience was remarkable with some fascinating places to visit. The intensity, hard work, passion and dedication of the people I met there was inspiring. It was an unforgettable chapter in my career.

How did you overcome the language barriers in China?

I went back to school. I've now developed a strong appreciation for reading and writing in Chinese. I find that if you take any person and drop them into a non-English speaking environment, they will pick it up. The beauty of this for me was that I could have a Chinese lesson and then walk out of class and put what I learned into practice. The learning curve was steep, and it was hard work, but it's surprising how easy you can pick it up.

From Benchtop Chemist to CEO? (cont...)

At what point did you realize you could potentially become the CEO of the company?
In 2016, I returned to the US to take on a global strategy role. Later, there was a need for someone to lead the Americas region, and I stepped into that position. From there, I eventually moved into the CEO role.

Being the CEO wasn't something I had necessarily aspired to, though. The first time I seriously considered becoming CEO was when my predecessor announced his retirement. He was a fantastic leader, so his departure was bittersweet for all of us. At that point, I thought, "Maybe I'm well-positioned to add value here."

Did you plan your career?
No, I've never spent much time thinking about the next job. My focus has always been on doing the best I can in the role I'm in. Of course, I've also tried to continuously develop my skillset and nurture my personal passions along the way. I've been fortunate to have incredible leaders and mentors around me.

I often say that as leaders, we need to spend a good portion of our time being talent scouts – identifying and supporting the good people around us and imagining where they might fit into the organization's future. I was lucky to have leaders who must have seen something in me.

People look at my career trajectory internally and think: "There was clearly a plan from here to there." But there was never a plan. I just did my best, kept my options open, and rarely said no to opportunities that came my way.

For me, it's never been about chasing titles or positions. I've always just tried to do work that I enjoyed and found meaningful. And I've been fortunate to work with great people. Of course, there were challenges – it's not always smooth sailing – but the hard work is balanced with fun. This aspect is something I've always appreciated about Colorcon: the culture is strong and there's an emphasis on enjoying the work as you do it. It's something you can feel in every interaction with the team, both historically and today.

How competitive is the industry when it comes to recruiting new talent?
It really depends on how you segment different areas of the business and when you consider regional variance. Although we're a US-headquartered company, we've actively looked at how to harness talent outside the US and Europe, particularly in Asia.

In terms of challenges, like many in the industry, we've faced more difficulties in the operational space. Areas like manufacturing and operations are competitive since the needs in those areas have evolved toward skills such as programmable logic controls and managing automated technologies, which has created a different type of talent demand.

We've focused on ensuring the roles in operations are productive and meaningful without being burdensome. For younger generations entering the workforce, we want to create an environment where they see Colorcon as a place they'd like to work and grow.

Overall, we've been fortunate to retain people in critical areas. Retention is something we're very mindful of because the competition for talent is always changing. We actively think about how to create the right conditions for people to stay. And it's not about making promises, it's about showing that there are pathways open to employees in all stages of their career. That's something that's very focused in terms of our discussion of our needs around talent and talent development.

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