OCTOBER 2019 # 58

the Medicine Maker™

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Online this Month

Last Chance to Nominate for the 2019 Innovation Awards!

Calling all vendors of pharmaceutical development and manufacturing technologies – nominations for The Medicine Maker 2019 Innovation Awards will close on October 25, 2019.

The Innovation Awards offer vendors the opportunity to showcase their newest products to be released onto the market, with the top technologies of 2019 being highlighted in the December issue of The Medicine Maker.

How do I enter?

Simply fill out the brief online nomination form available at tmm.txp.to/innovations19-nom

You'll need to provide a few details about the innovation you are nominating, including the release date and the impact you think this technology could have on pharma development and manufacturing.

All types of technologies are eligible, including, but not limited to: machinery, instruments, consumables, software, drug delivery devices, formulation technologies and ingredients.

The rules?

The technology must have been released (or will be released) between January 2019 and December 2019.

If I have questions…?

Contact the Editor: stephanie.sutton@texerepublishing.com

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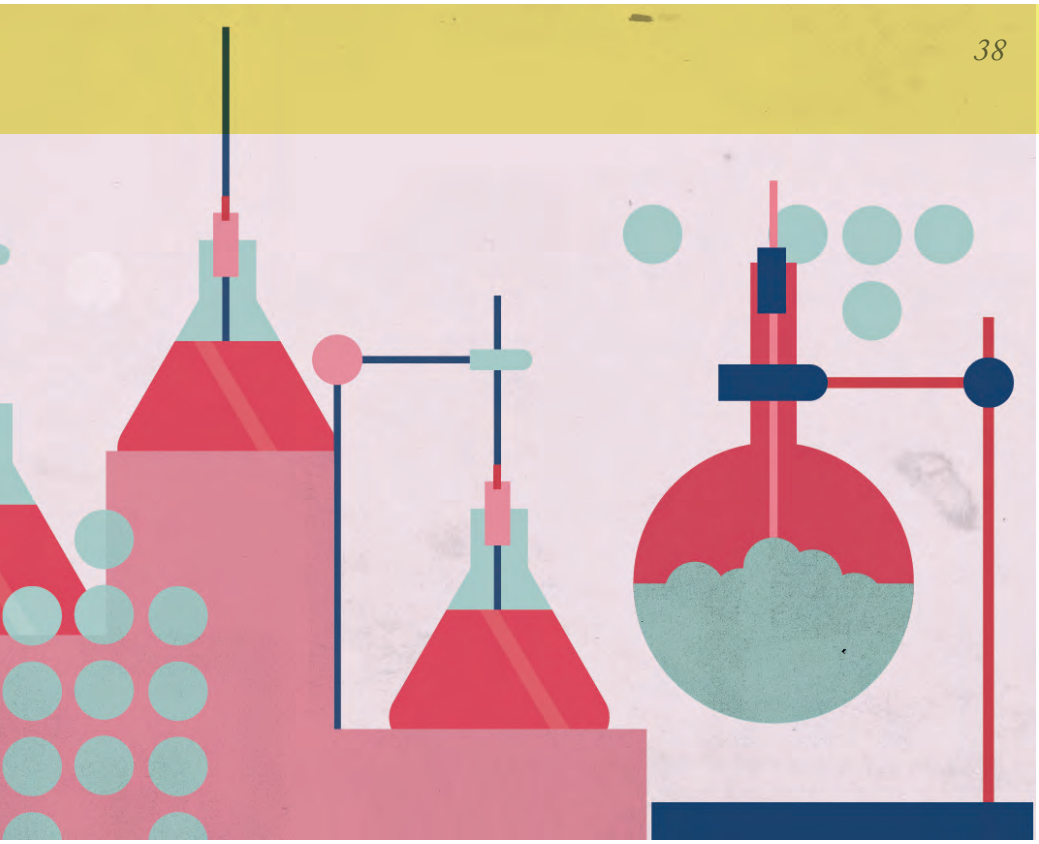

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Man Allegedly Praises Pharmaceutical Companies...

If this is news, perhaps the industry is in deeper trouble than we thought.

The man in question? Joe Biden – well known for speaking up against drug prices in the US. The headline that actually appeared in my news feed? "Joe Biden Reportedly Praises Pharmaceutical Companies." Other media outlets ran with similar headlines, seemingly unable to resist taking a pop at Biden and pharma in one go. It must have been a slow news day.

Biden apparently dared say there were "great drug companies out there – except for a couple of opioid outfits." Some have criticized Biden for praising companies that are "greedy, corrupt, and engaged in price fixing." (1, 2)

A new Gallup poll claims that, in the USA, big pharma is viewed with more distaste than any other industry (3). Even the Federal government has a better reputation than the drug industry. The high-profile situation with opioids will not have helped the industry's image (look forward to an in-depth report on opioids in the November issue of The Medicine Maker).

We've said it before, but pharma must do more to promote the industry's good side. In a recent conversation, I was told that pharma's negative reputation could have a negative effect on attracting talent; young scientists will likely be more attracted to medicine and healthcare rather than drug development. And the pharma industry needs (and deserves) great talent to fuel R&D.

Rather more worryingly, politicians appear to be somewhat ignorant of how the wheels of the pharma industry turn. For example, in late September, Jeremy Corbyn – leader of the UK's Labour Party – announced that he wants to seize patent rights from companies and establish a state-run operation to produce generic drugs (4). Read more on page 12.

We all want improved access to medicines but nothing comes for free. Corbyn's plans could completely disincentivize drug development. The announcement does, however, highlight the mounting anger and desperation on drug pricing. If pharma itself doesn't come up with workable solutions quickly (the recent announcement about a vaccines subscription from the NHS is one example of a more intriguing approach to the challenges of drug costs), then drug pricing will continue to feature on political agendas. And proposed solutions could be become even more radical.

Stephanie Sutton
Editor

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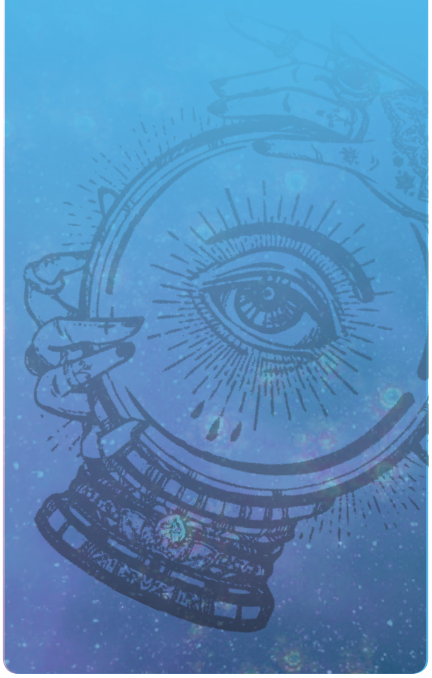
Upfront

Reporting on research, personalities, policies and partnerships that are shaping pharmaceutical development and manufacture.

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com



Predicting All Outcomes

A machine learning algorithm aims to take the "what ifs" out of chemical synthesis

Synthetic chemists who want to conduct novel reactions typically turn to the results of previous experiments to help ascertain the optimal conditions for enantioselectivity – and the likelihood of success. But it's a time-consuming and error-prone process. Matthew Sigman, a chemist at the University of Utah, estimates that there can be anywhere between seven and ten variables in a typical pharmaceutical reaction. "With billions of possibilities, you cannot cover all the variable space with any type of high throughput operation," he says.

Tapping into the power of AI and machine learning, Sigman and Jolene Reid – another chemist at Utah – have been able to predict the outcome of chemical reactions by analyzing previously published chemical reaction data (1).

"We hope our research will allow chemists to make informed decisions about reaction conditions before

beginning experimentation, effectively streamlining the drug discovery process," says Reid. "Previously, such predictive models were generated for single reactions; however, our research shows that selectivity models can be built and generalized over a range of reactions without affecting the accuracy in prediction."

Enantioselectivity is sensitive to any reaction component, including temperature and the type of solvent used, and so the team used multivariate linear regression, a machine learning algorithm, to dig into the impact of all reaction parameters by analyzing 367 data entries collected from 17 literature reports on the enantioselectivity of imines. Reid explains that imines are synthetically important molecules with lots of data available on their reactions types – a prerequisite for the team's analysis. The resulting model was able to predict the outcome of 15 reactions involving one reactant that wasn't in the original set, and the team went on to predict 13 more reactions, whose reactants and catalyst were not included in the original data.

Now, the team's goal is to create more general models that would enable the prediction of experiments with reaction conditions that look very different to those in the original set. They also plan to use their tools to better understand the limitations of predictive models, so that chemists will know the reliability of predictions that are used to guide optimal experimental conditions.

Reference

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For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
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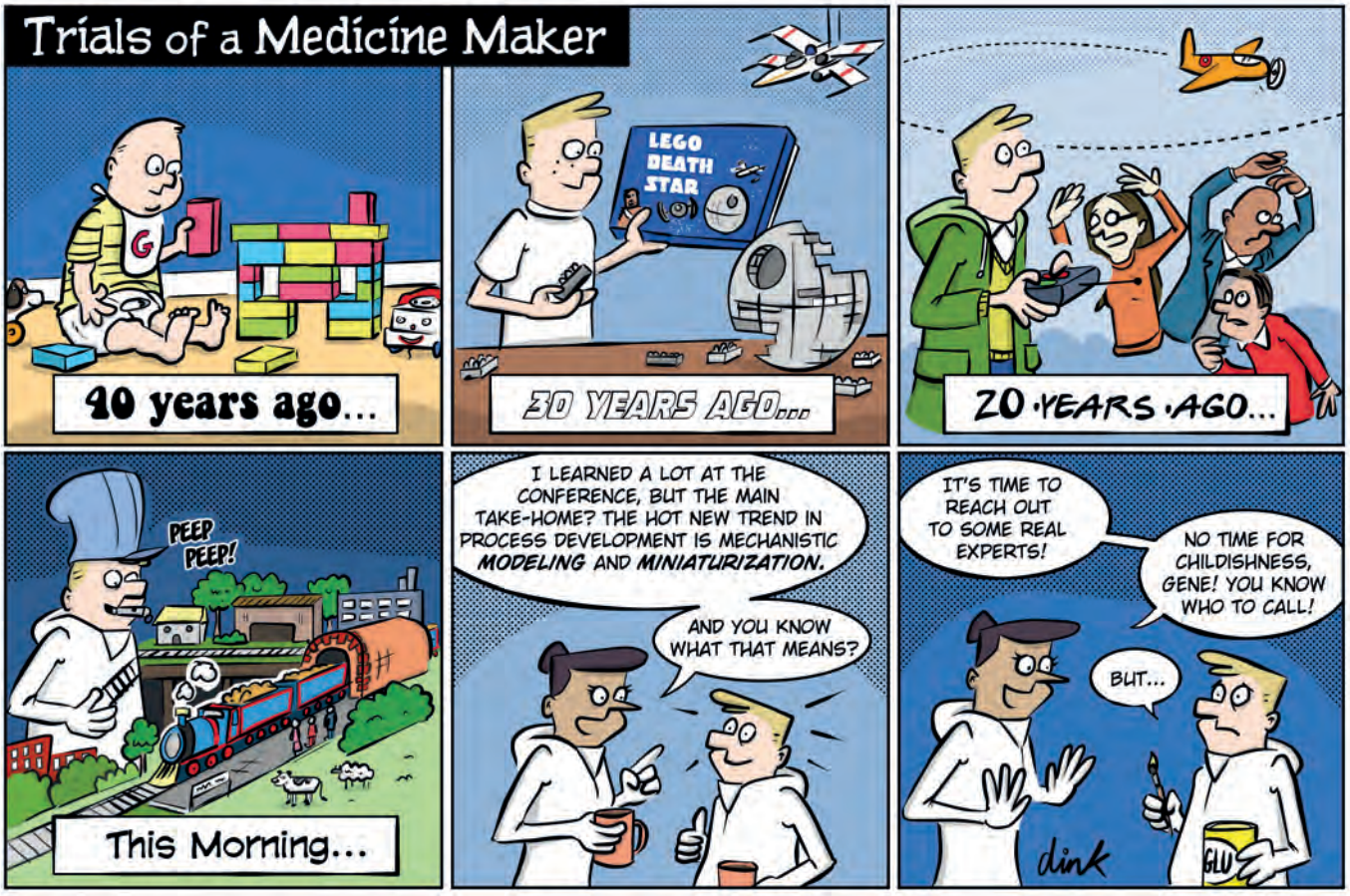

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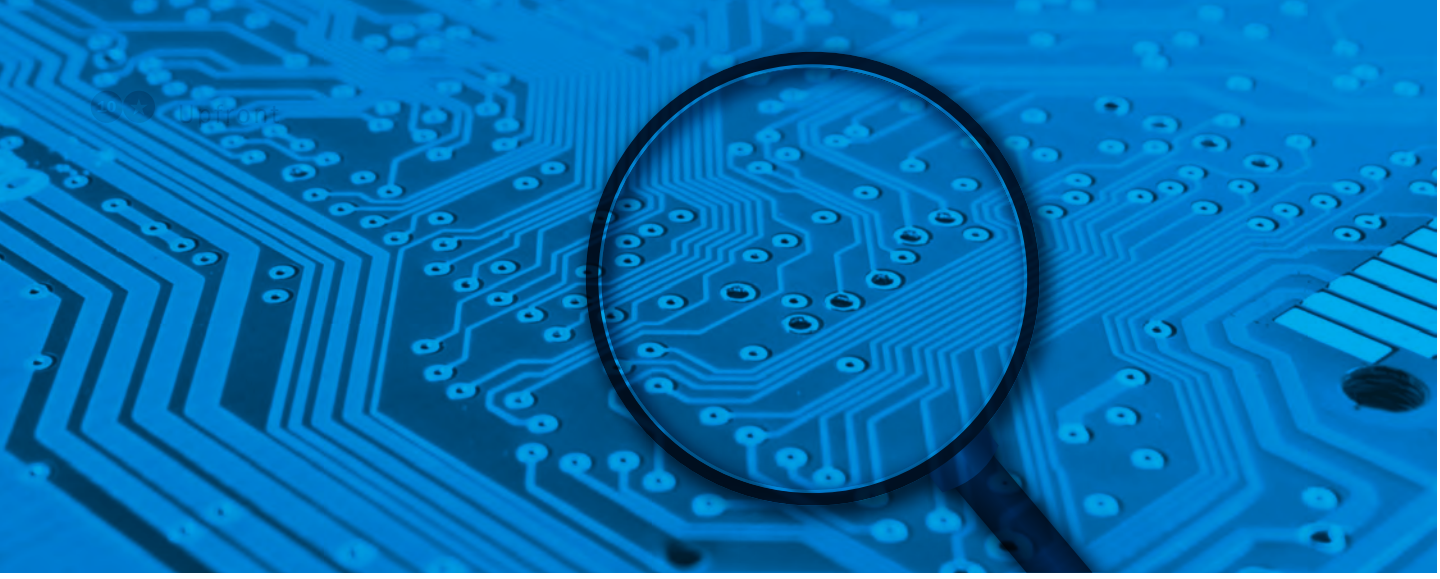

Solutions in… Automated Quality Reporting

Could an AI tool help stakeholders from the scientific community address the current state of reproducibility in scientific results?

Reproducibility is at the heart of scientific research – or at least it should be. Not only does it prove the rigor of research, it lays the foundations for the transparency and credibility of projects conducted. But there is growing concern about the number of studies with irreproducible results. Digital Science portfolio company, Ripeta, has developed an AI tool that scans manuscripts for the proper reporting of scientific method components to detect and predict the reproducibility of scientific research. Here, we speak to Leslie McIntosh, CEO of Ripeta, to find out how such tools can help advance scientific research.

What issues are caused by a lack of reproducibility in scientific papers?

Non-reproducible research questions the science. It is actually intriguing on one hand, as there may be something in the scientific process that has not been identified, such as variables that haven't been identified or taken into account, that positively influence the science. However, far too many variables exist that could influence research outcomes. Ultimately, having reproducible research builds (or weakens) trust in the scientific work. Effective reproducibility lies at the heart of the scientific method.

Is the scientific community doing enough to support the quality of its research and reporting?

The scientific community is an ecosystem made up of stakeholders from varying backgrounds. Researchers, funders, institutions, and publishers must take some responsibility in improving the reporting of research. However, no single stakeholder is fully responsible for making a change. Improvement in research quality will come when multiple actors in this network decide to make changes – including aligning incentives for researcher promotion with conducting and reporting better quality research.

Lastly, good research should be a commitment towards transparency even when accessibility of all pieces is not possible. As mentioned in our "Making Science Better" report (1), if we start from a simple construct of what good research is, then it starts with a well defined study objective or hypothesis.

How can AI tools help improve the current standards of reporting quality?

Most peer reviewers are not reviewing manuscripts for aspects such as data availability statements – and some authors do not even realize it is needed; reviewers tend to focus on the scientific question and conclusions. Yet, having data availability statements improves the quality of science and has become a requirement for most publications and many funders. Ripeta improves the quality of reporting research by using AI to rapidly check scientific manuscripts for crucial elements of reproducibility. For example, do the authors use proper scientific reporting and scientific method components? Ultimately, tools like this will help improve the quality of manuscripts and enable more robust scientific reporting.

What's next for this project?

There are a few exciting things in the works. One is to expand what we have automated to include other variables and to also provide contextual feedback to help authors make improvements with less work. For example, if they stated their software but don't cite it, the tool can offer a suggested citation or point towards how to find the citation. In addition to analyzing one paper, we are currently summarizing the results across a grouping (for example, multiple articles from one journal, research topic, company) and creating reports. The aggregated data will eventually be displayed through a dashboard for easier viewing.

Reference

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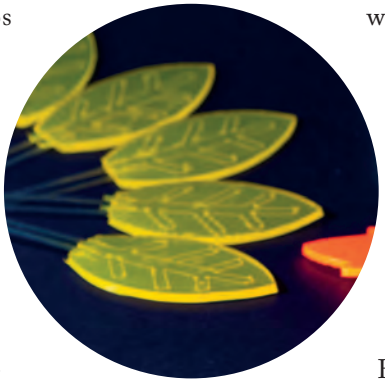
A (Green) Dream Realized

Chemical reactors fueled by sunlight could push pharma towards a more sustainable future

Inspired by the way leaves, algae and some bacteria absorb light and focus energy, researchers at the University of Eindhoven in the Netherlands are harnessing solar energy to drive chemical reactions. The team, led by Timothy Noël, has developed a mini-reactor made of polymeric material that absorbs sunlight and converts it into a single color, which can then be directed towards reaction channels (similar to the veins of a leaf) (1). Raw chemical products are fed through the channels and the solar-derived energy facilitates the reaction necessary to create drug molecules.



Noël, an associate professor, who joined the University of Eindhoven in 2012, has been investigating the potential of conducting reactions using light. And though he and his research group initially used LEDs for this purpose, they soon began to explore how more natural sources of energy, such as sunlight, could be used to initiate chemical reactions. A prototype reactor was developed in 2016 and the team has since enhanced its design using PMMA plates and PFA capillaries, a solvent-resistant plastic, and has also incorporated stable dyes to help with the conversion of solar light.

As with any natural resource, sunlight is subject to natural variability, but the team has found a solution. "On a cloudy day, we have less light to work with than on a bright one. To combat this, we created a mini-feedback system that works to keep the conversion and yield the same level," says Noël. By detecting changes in light intensity in real time, the system can adjust the flow rate of products passing through the reactor channels.

To demonstrate the versatility of the device, the team has produced two drugs – artemisinin (an antimalarial) and ascaridole (an antiparasitic) – but, according to Noël, such reactors could be used to produce a wide variety of different therapeutic products.

"In 1912, an Italian photochemist, Giacomo Luigi Ciamician, described the world's need to transition from fossil fuels to renewable energy. He also challenged the scientific community to imagine a chemical industry run on solar energy," says Noël. "With our current understanding of environmental issues, it is clear that we must address this now. But analogous to the mass implementation of solar cells for electricity production, a political push and financial incentives will also be required for the implementation of solar energy in the chemical and pharmaceutical industries."

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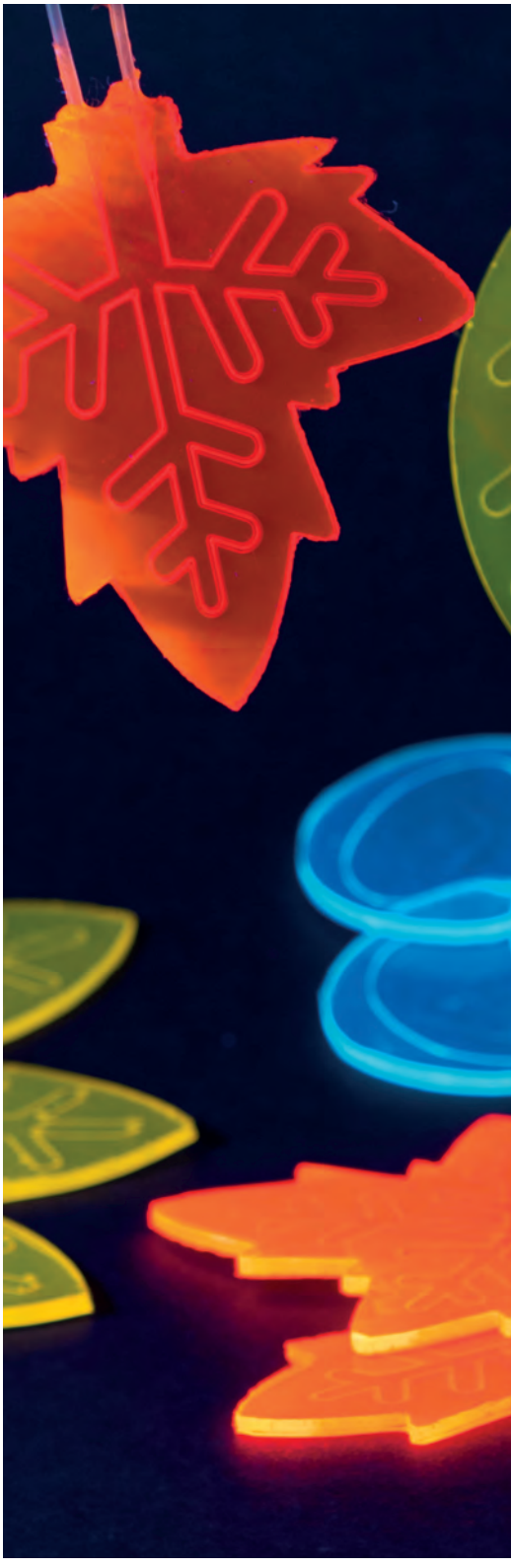

The Patent Snatchers

Can't offer an "affordable" price? Then say goodbye to market exclusivity

The UK Labour Party has set out its plans to put "public health before private profit" and ensure that "pharmaceutical companies make vital drugs available at prices that the National Health Service (NHS) can afford." The proposals include making public funding for research conditional on the resultant drugs being priced affordably and the creation of a new, publicly-owned generic drugs manufacturer to supply cheaper medicines to the NHS.

Perhaps most controversially, a Labour government would also issue Crown- or compulsory-use licenses when the NHS isn't being offered an "affordable price for a medicine." A compulsory use license enables a government to issue a license to another manufacturer (private or public) to produce a generic version of a patented drug at a lower price – without the consent of the patent holder.

The proposals are compatible with international patent law; namely Article 31 of The World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). According to Article 31 of TRIPS, governments have the right to grant compulsory licenses on virtually any ground – including public interest, anticompetitive conduct, or for noncommercial government use.

However, the TRIPS Agreement does subject the exercise of this power to certain preconditions, including that manufacturers should be "paid adequate remuneration in the circumstances of each case."

Ellen 't Hoen, Director of Medicines Law & Policy and researcher at the Global Health Unit of the University Medical Centre at the University of Groningen, The Netherlands, explains that, ultimately, "the government sets a royalty rate." Though there is guidance for setting remuneration from the WHO/UNDP (2).

't Hoen, has documented the use of compulsory-use licenses since 2001 (3). She found that between 2001 and 2016, there were 100 instances of the possible use of compulsory licences or public noncommercial use licences, predominantly concerning medicines for HIV. Only eight were issued by "developed" nations. For example, in 2005, the Italian Competition Authority forced Merck to grant free licences to allow the manufacture and sale of Finasteride in Italy, two years before the patent was set to expire in 2009. The royalty paid to Merck wasn't disclosed.

Some governments have faced international political pressure for making use of the "TRIPS flexibilities." In 2016, US officials threatened to withdraw financial support for Colombia's peace process after the country issued a compulsory licence for the cancer drug imatinib (4), for example. But, as 't Hoen's research shows, the majority of TRIPS flexibilities invoked were successfully implemented.

't Hoen also points out that a credible threat of a compulsory-use license can lead to a better price offer or a voluntary license. Bayer drastically lowered its price for ciprofloxacin in 2001 after the US threatened to issue a compulsory license, for example (4).

This Crown use was relatively commonplace in the UK during the 60s and 70s. "Between 1953 and 1971, the UK issued 20 compulsory licenses for medicines," says 't Hoen. "The famous British IP scholar, Stephen Ladas, commented in 1975: 'Although this power of the Ministry of Health to purchase drugs and medicines from sources independent of the patentee has been much criticized by the pharmaceutical industry, it is not likely to be affected by such criticism. Such power will be exercised if the patentee is alleged to maintain unduly high prices for these products.'"

One potential problem for the Labour Party is section 57A of the UK Patent Act (added in 1977), which implies that companies should be compensated based on profits lost as a result of a government issuing a Crown-use licence. The Labour plan says that this "creates ambiguity on the need to offer compensation to the patent holder" and that, though this hasn't been tested in court, "there may be a need to revise the law to make it clear there is no responsibility to pay such compensation in such cases."

Labour's proposal also states that Brexit may "present an opportunity" for the UK to "move away" from EU rules covering

data exclusivity, marketing exclusivity and Supplementary Protection, which they argue lead to higher prices.

The response from pharma has, to say the least, been disapproving. Richard Torbett, Executive Director of Commercial Policy at the Association of the British Pharmaceutical Industry, referred to compulsory licensing as "the seizure of new research" and warned that "it would completely undermine the system for developing new medicines. It would send a hugely negative signal to British scientists and would discourage research in a country that wants to be a leader in innovation" (5).

Steve Bates, Chief Executive of the Bioindustry Association, added: "NHS patients and the UK economy would both lose the chance of new life saving treatments if the UK becomes a hostile environment for intellectual property" (6).

The proposal does not specify exactly how frequently compulsory licences would be issued. But one example cited was the recent case of the cystic fibrosis drug Orkambi, which NHS England refused to purchase from US-based Vertex because the price was "unaffordable." And if the plan is to issue a compulsory license in any circumstance when the NHS isn't being offered an "affordable" price, then the UK's intellectual property environment could be rather different under a Labour government.

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Anti-VEGF: Is Breast Always Best?

Drugs used to treat retinal disorders appear to pass into breast milk, posing a potential risk to the normal development of nursing infants

Mothers are typically advised to breastfeed their newborns, but for those who live with medical conditions, managing the symptoms of their illnesses while nursing can present challenges. Research led by St. Michael's Hospital in Toronto, Canada, indicates that the anti-vascular endothelial growth factor (anti-VEGF) drugs ranibizumab and aflibercept (injected intravitreally to treat retinal disease) are able to enter the breast milk of breastfeeding mothers, potentially raising concerns about possible adverse events in the developing infant (1). Notably, according to the labels on both drugs, it is unknown if the molecules are excreted in human breast milk.

The team found that the anti-VEGFs studied were able to reach a mother's systemic circulation in the first few days following intravitreal injection – and, from there, enter the breast milk of lactating patients. Rajeev Muni, a vitreoretinal surgeon, and Verena Juncal, a retinal fellow, who co-led the first-of-its-kind study, do not know exactly how anti-VEGF drugs enter into breast milk, but it appears to be dependent on several variables, including drug lipophilicity, molecular size and drug levels in maternal blood.

"Though the mechanism that allows anti-VEGF agents to enter the bloodstream hasn't been fully elucidated, it is known that large amounts of VEGF are present in breastmilk and that it binds to specific receptors in the intestinal epithelium of newborns," says Muni. "The binding of VEGF at these sites is thought to play an immunomodulatory role in the newborn's intestine, and, in the systemic circulation, VEGF plays a role in angiogenesis and vascular permeability."

Juncal explains the importance of the finding: "The main concern is not only that the baby is constantly receiving breast milk with reduced VEGF levels for a long period of time, but also that the baby could be absorbing the drug into the systemic circulation and, thereby, causing suppression of VEGF systemically."

In three women included in the study, one continued to breastfeed while receiving intravitreal ranibizumab therapy, one discontinued nursing immediately before receiving a ranibizumab injection, and the third chose not to breastfeed at all and was started on intravitreal aflibercept. Both ranibizumab and aflibercept were detected in the breast milk of the patients who were not actively breastfeeding. In the mother who continuously breastfed, drug levels were not detected – likely because the drug in the breast milk was constantly excreted and ingested by the infant and never accumulated sufficiently.

The lack of controlled data about anti-VEGF drugs in human pregnancy means that they are considered category C drugs, implying that potential effects to the fetus cannot be ruled out. However, while other treatment options exist, anti-VEGF drugs cannot always be avoided for the treatment of certain conditions. Indeed, some mothers may choose to breastfeed while requiring months, or in some cases, years of treatment.

The researchers admit the sample size is small, due to the fact that this situation does not frequently present itself. However, they explained that if the drug reaches the breast milk in a small number of patients, the same would happen in a larger number as the biological process is the same. "It would have been very difficult to find a large cohort of patients, but every retina specialist will likely face this situation at some point in their career. With these three patients, we have definitively shown that the drugs reach the breast milk with a corresponding decline in breast milk VEGF levels," says Muni.

Juncal went on to express the importance of updating product labelling to ensure patients and physicians were aware of the potential effects of these drugs.

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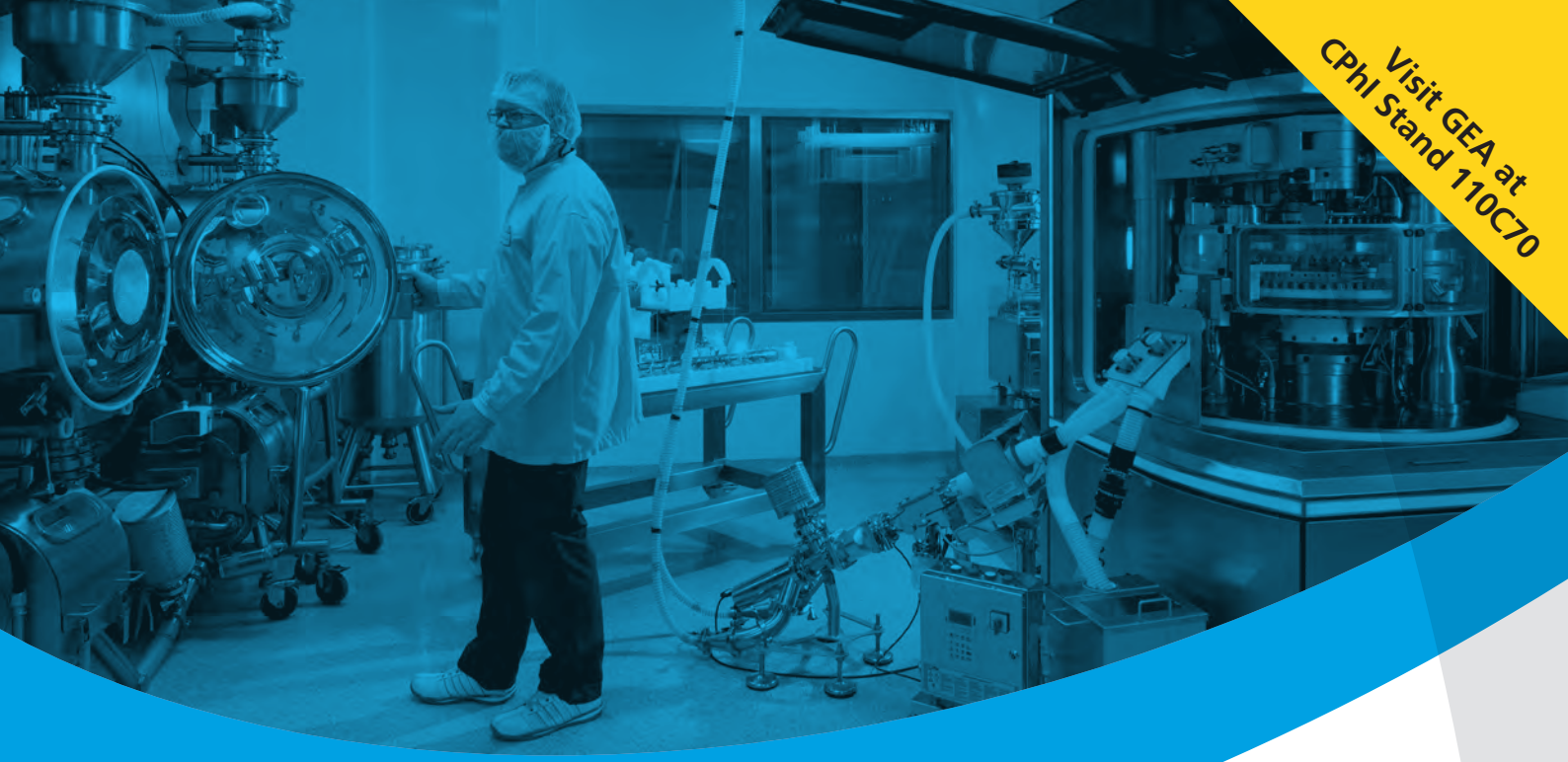

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Staying On Trend

From patient-centric design to speciality excipients and security of supply; what are the latest trends in formulation strategies?

By Dr Ali Rajabi-Siahboomi

If you want to create a patient-centric medicine with the best chances of compliance, then paying attention to the design of your tablet is crucial. But as well as keeping patients in mind, it's also important to consider manufacturing – decisions made about a tablet and its formulation, including its coating finish, can have a significant impact on production efficiency (1, 2). In short, your formulation strategy matters for many different reasons.

Over the past two decades with Colorcon, I have seen a lot of change in terms of formulation needs as companies strive to be more efficient and deliver better medicines. Importantly, our customers' requirements need solutions to match their business challenges and production needs, as well as the needs of patients. Colorcon is a unique company in that it is extremely innovative and agile, even though we operate within a tightly regulated market. This is important, as it means we can respond as market needs change, providing exceptional products, local technical support and regional production capabilities. Today, for example, many pharma companies have regional manufacturing facilities and require the same raw materials at the same consistency and quality for use across these different geographical territories. Through expansion of our global footprint, Colorcon now has capabilities in strategic locations around the world to enable easy, local access and supply for our customers. Our industry expertise has continued to deepen over the years. While Colorcon's focus has always been in film coating and speciality excipients, through our alliance with DuPont we also represent an extensive line of excipients for modified release applications. This is important expertise that pharma companies are looking for in a long-term partner.

Patient centricity combined with safety

One topic that is becoming increasingly recognized by healthcare providers and brand owners is patient centricity. When developing a new product, manufacturers want to meet the treatment goals but they are now increasingly looking to improve patient experience and adherence.

Making it easier for patients to take their medicine is one of the best things you can do! There are a number of solutions out there to help with this. Tablet shape, size and color should all be considered from the patient's perspective. Tablets that are too large, for example, can impede swallowability, while tablets that are too small can also be a problem since they may be difficult to handle. Colorcon's Brand Enhancement service helps to visualize what a dosage will look like as a tablet. We have also developed coating formulations (Opadry EZ) that improve swallowability, through making the tablet very slippery when in contact with just a small amount of water. A positive patient experience is key to improving medication adherence.

Another key trend that companies should not ignore is product authentication. Fake and diverted

medicines are a huge problem (and cost) around the world, and many countries now mandate the use of serialization or other on-packaging security measures to ensure the authenticity of medicines. With anything on the packaging, however, there is still a risk that it can be copied. Now, there is also growing interest in physical chemical identifiers (PCIDs) that can be incorporated into a tablet coating to enable individual tablets to be authenticated. The FDA is very interested in this technology because it will be almost impossible for counterfeiters to copy. The agency is currently conducting a review process for on-dose identifiers.

Keeping pace with market trends

All companies want to reduce their development times, get to market as quickly as possible and manufacture efficiently. In addition, it is important to mitigate potential risks, both from regulatory registration as well as product robustness – no one wants to put something on the market that they then must call back! In terms of registration, we offer directly accessible online regulatory documentation to support dossier submission. Delays often occur when information is missing from dossiers – and when manufacturing, packaging and other areas are ready to get moving, the last thing you want is a delay caused by regulators asking questions. We also help customers to de-risk with our business continuity plans for security of supply; we have manufacturing plants in multiple locations around the globe, and the materials and products are interchangeable from one facility to another – so if there is ever an interruption at one plant we simply manufacture and ship from an alternative site.

To reduce development time and help with product robustness, we provide R&D with access to HyperStart, a starting formulation service. Through this confidential service, we collate information about the properties of the API, drug, solubility, dose, particle size, shape and so on – and then we present the customer with a start-up formulation. We aim to get it first time right – this can be challenging to do but it certainly helps to reduce the number of iterations that the customer would otherwise have to do.

And for the future?

The marketplace is changing. The large centralized R&D model has changed, with innovation instead being led by smaller start-ups and CROs, which often don't have significant experience in formulation or commercial production. Through our global network, we're able to actively support development with these smaller companies; providing formulation and excipient expertise, access to facilities and regulatory support.

When designing new products and services, we focus on our customer's challenges – what's holding them up? As always, manufacturers are seeking to reduce costs and increase productivity, so looking at how we can help our customers to improve the efficiency of their manufacturing operations – while still being patient centric – is key for us. For example, we developed the first high solids level dispersion, Opadry QX, a PVA-PEG copolymer based coating system that delivers significant process efficiencies. Our sugar coating system, Opadry SGR, reduces production time from days to hours by allowing for the use of automation (traditionally, sugar coating is a manual process). Recently launched, StarTab, directly compressible starch, is proving to be game changer, slashing the number of excipients needed for tableting and making direct compression even easier. Choosing your excipients to streamline or buy back production time can be significantly more cost effective than upgrading to more high-capacity equipment.

We also aim to keep up to speed with the new and emerging technologies our customers are using so that we can provide the right support for them. Key topics that people are currently talking about are continuous manufacturing and 3D printing. We've been active in the area of continuous processing for some time, leading the development of excipients and coating formulations that provide unique benefits in this area. With 3D printing, we continue to investigate and have partnered with universities and other experts to learn more in terms of what excipients are suitable for this technology. It's all about supporting customers both now and in the future as their needs continue to evolve.

Continuing education

For over 30 years, Colorcon has run Coating and Formulation Schools, which combine theoretical and hands-on training, plus regulatory understanding in the areas of film coating, core formulation, excipient selection and controlled release of solid dosage forms. The courses come with a certificate of attendance and we find many customers send their staff as part of their continuous training and professional development.

Now together with the Innovation Program, these educational events are under the umbrella of the Colorcon Academy.

Dr Ali Rajabi-Siahboomi is Chief Scientific Officer at Colorcon.

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Putting Patients First

Oncology research has come a long way over the past 30 years, but we must transform outdated practices to further improve drug discovery innovation

By Carlo Toniatti, Chief Scientific Officer at IRBM, Pomezia, Rome, Italy

My career began in the late 1980s as a physician, where I spent a few years working in internal medicine. Treatment options for cancer were incredibly limited at the time, with heartbreaking consequences. Our knowledge of both treating and preventing cancer was still in its infancy. Great progress has been made from those days; efficacious targeted therapies have since followed, and today we're seeing the emergence of personalized cancer therapies.

However, despite recent success, the development of novel and efficacious cancer therapies remains an extremely difficult task. Only about 10 percent of the targeted oncology drugs entering phase 1 of the clinical development pipeline are eventually approved, and just a minor subset of them exert a strong therapeutic effect as measured by patients' life prolongation (1). It is a shared view that the success rate in clinical development could be increased by developing more predictive and reliable preclinical models of cancer. This would allow us to ensure that we only provide patients with high-quality agents by designing innovative, biomarker-driven and patient-tailored clinical trials.

However, we have to admit that one – if not the key – reason why oncology drug development is so challenging is our limited understanding of cancer biology. This, in turn, restricts our capability to match a targeted therapy with the patient population that would benefit from it. We not only need to identify novel targets, but must also understand the context in which they are critical for tumor establishment, survival

"Only about 10 percent of the targeted oncology drugs entering phase 1 of the clinical development pipeline are eventually approved."

and progression. Only at the end of this process can we eventually develop novel and efficacious drugs against these validated targets.

Traditionally, target discovery and validation are carried out in academia, with big pharma and biotech in charge of developing and advancing novel drugs. The collaborative force of academia working with the pharma industry – where I have worked for the past 25 years – deserves a lot of credit for how oncology therapy has progressed. I believe there is considerable scope for improving how the two organizations work together, circumventing not only cultural barriers, but also finding appropriate answers to long-standing practical issues, such as the management of intellectual property. An efficient and closer collaboration between the two is particularly necessary in current times, where the pharmaceutical industry is reducing internal R&D budgets and working on less risky targets, while different competing companies perform several trials with comparable drugs acting on the same targets.

Several models have been proposed and established to improve the collaboration between academia and industry. Of note, an increasing number of academic centers are investing in drug discovery efforts. This is achieved through establishing internal R&D capabilities or leveraging the support of either charity foundations or not-for-profit-organizations that are specifically focused on advancing the early stage programs started in academia. In both cases, I believe that in order to succeed, it is critical to avoid a handoff procedure between different stages. Experienced teams of industry scientists should lead the drug discovery efforts while maintaining close – preferentially daily – contact with the scientists who discovered the target and have a deep knowledge of its underlying biology.

Another significant issue that must be solved to improve the interaction between academia and industry is the reproducibility crisis within biomedical science. Reports from companies such as Amgen and Bayer HealthCare have suggested that between 65 and 90 percent of academic literature cannot be replicated within the pharmaceutical industry (2, 3). I can say that these numbers roughly match with my personal experience in industry of being unable to reproduce published cancer biology data in about 50 percent of cases.

"Several models have been proposed and established to improve the collaboration between academia and industry."

This lack of reproducibility impacts the entire ecosystem: on one side, this does not help in increasing reciprocal trust, and on the other side, it also escalates financial cost because of the money wasted during a drug discovery program trying to replicate external data.

It is intrinsically difficult to find a single definition of irreproducibility, but problems can occur due to differences in reagents, laboratory protocols, data analysis, and study design. I personally believe that one of the major issues is the tremendous pressure towards publishing positive results in the academic environment. Can a researcher launch a successful career with a long list of negative data? Could a young scientist ever make a name for themselves without a great paper demonstrating the efficacy of a treatment for their PhD or postdoc? Linking research eminence with the publication of positive results will create a bias towards a positive story. Researchers are, therefore, incentivized to select the best possible data to publish in the best possible journal – at the cost of ignoring potentially meaningful, but negative, data.

While positive results are, of course, applauded within industry, failure is also built into the pipeline as an important consideration. Within drug discovery, organizations, like my own, employ a 'first to fail' approach to help ensure that resources are efficiently managed. Predefined go/no-go points are included in workflows, which allow for calculated risks to be built into programs. This provides researchers with early exit points if a program is showing unanticipated issues or has problems that cannot be addressed. By rapidly reaching these risk points through robust processes, researchers quickly know whether or not a project is worth advancing. Perhaps some practices within academia could take note from this to help transform how they perceive success.

Several proposals have been made to address the reproducibility issue and there is not a single solution for a complex problem, but a more rigorous review process before publication, the adoption of standardized study design, and transparent sharing of protocol and methods can certainly help. One example of a program aimed at verifying the reproducibility of seminal findings published in Nature, Science and Cell is 'Reproducibility Project: Cancer Biology', which was launched in 2013. This theoretically goes in the right direction, but the reported results have

added confusion rather than clearing the water! The initial plan to reproduce 50 high-impact cancers manuscripts was reduced to 37, then to 25, and now to 18; not only because of budget constraints, but also because the detailed protocols and reagents used in the original labs were not always available and it would have taken too long to optimize every single experiment. Of the 14 replication studies completed and reported so far, five have substantially reproduced the original papers; four have reproduced some parts of the original papers but did not reproduce other parts; two of the studies could not be interpreted; and three studies did not reproduce the original findings but in some cases the very original has been confirmed in other labs, instead… (4). It goes without saying that the authors of unconfirmed data challenge the new results and attribute the lack of reproducibility to the different experimental settings used in the original versus the replication studies. So here we are, back to square one.

A lot is left to the initiative of the singular institution, lab and scientist – we need a cultural change to tackle the reproducibility crisis. Senior scientists need to dedicate time to the training and mentoring of their graduate students. We need to ensure that researchers who find that something doesn't work are acknowledged with funding or credits towards tenure, and that 'negative' data are published in highly ranked journal when appropriate. By failing to corroborate findings, we are potentially halting or slowing progress within drug discovery that will improve the lives of cancer patients everywhere.

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Time to Pop It In!

Sometimes patients need gentle, digital prods to ensure medical compliance

By Timo Heikkilä, COO at Popit, Finland

Digital devices have become a part of our personal ecosystems. Wherever we go, smartphones or and other digital devices are there to help us navigate our daily lives and the challenges we face. And in healthcare environments too, digital technology is seeing increased uptake, but we need to do more, particularly when it comes to tackling patient compliance.

Patient compliance with prescriptions is poor. For a variety of reasons, including poor communication, difficulty opening packaging and a lack of understanding, patients can find it difficult to adhere to their medical courses. My friend and colleague, Janne Sahlman, co-founder of Popit and medical doctor at Kuopio University Hospital, had mentioned that many of his patients would return for multiple surgeries due to noncompliance with post-surgery prescriptions. And though I knew that there were methods of identifying and quantifying patient compliance with solid medications in smart pill bottles, such solutions were not readily available in all areas. In Europe and Asia, for example, around 80 percent of solid drugs distributed and sold are in blisters and there isn't a technology to determine when pill consumption occurs. In reality, the industry knows very little about how patients take their pills on a daily basis.

"If pharma companies focus more on the benefits of digital technology for patient compliance then an 'Internet of Pills' could become reality."

Sahlman, myself and others founded Popit, a MedTech startup, to help track and improve compliance, and our first product targets blister packaging – and it was featured by the

European Commission's WATIFY (an awareness-raising campaign to push the modernization of European industry). But how do we apply the smart pill bottle concept to blisters? Popit Sense is a smart device that can be clipped to a blister pack, where it uses a variety of sensors and patented technology to determine when a medication has been extracted, gathering real-world evidence.

When a pill is popped out from the blister packaging, information is sent to a smartphone app via Bluetooth. According to clinical pilot results (2), Popit Sense was able to improve compliance in 24 women taking a daily birth control pill over the course of two months by over 80 percent. When developing the device and app, we were wary of reminder fatigue, a phenomenon that involves patients ignoring prompts to comply. Our approach: patients only get an alert if a dose is missed. Our results were exciting in that they seemed to indicate that patients began to learn and adopt improved behaviors for taking medications.

Recently, we launched a project in collaboration with Pfizer to help patients with rheumatoid arthritis to take their Xeljanz medicine on time. We're a small Finnish biotech so it was very exciting for us to partner with such a big company! Upon discussion, Pfizer had already identified patients in some therapeutic groups who felt that they weren't receiving sufficient support in-between visits to the doctor, contributing to their noncompliance. Our solution was a perfect fit for this need, as we make it possible to send contextually relevant "boost" messages to the patient's smartphone based on the treatment stage and individual level of adherence. Because of this collaboration, the solution will be rolled out in Finland, Sweden and Norway, providing patients with the Popit Sense device, the app and tailored support messages that take adherence and treatment stage into account. We're also in negotiations with other companies to provide solutions for different therapeutic areas.

For many patients, health is already digital. People can track their sleep, water intake and refill prescriptions at the touch of a button (or screen) and, therefore, have the expectation that support with medical compliance should also come through this channel. By making the leap to the digital domain, the entire pharma industry can do much better to improve adherence and get the patient (and the healthcare provider) to feel like the treatment as a whole is providing the best possible outcomes.

If pharma companies focus more on the benefits of digital technology for patient compliance then an "Internet of Pills" could become reality. When medication is connected, it is possible to combine the inputs of how medication is taken to the outputs that are already easy to track, such as electrocardiogram, heart rate or blood pressure. Once you have this set of information, it is easier to gather real world evidence, obtain the best possible treatment outcomes and understand how medication is really working.

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Plug and Play for the Future

Key to unlocking the benefits of Industry 4.0 and achieving Plug and Play is leveraging standard, open, modular automation architectures that allow fast and accurate data flow from the factory floor to other technology layers, without the need for top down integration. But this can only come about through collaboration.

By Daniel McCarthy

Single-use biotech process equipment is already making use of technology to automate processes and the level of complexity is increasing. As companies try to bring together a growing number of disparate process elements, integration becomes key to unlocking the full cost and efficiency gains of digitalization or Industry 4.0. For example, individual pieces of equipment generate important data related to the quality of the product they are manufacturing, but unless that data is comparable across different unit operations and accessible from different technology layers and systems, it cannot inform users about important performance insights of the process.

Traditionally, companies would opt for system integration to ensure that all of their processing equipment was able to share data and communicate with one another seamlessly, but this is time consuming and expensive, especially when you consider the level of customization and range of software platforms that pharmaceutical companies often want. For example, some companies may favor a site-wide Distributed Control System (DCS), while others may opt for a different automation architecture, perhaps one where autonomy is given to the local control system on the equipment. The second option permits the equipment supplier to leverage their expertise in exactly how best to operate the equipment. Differences in approach tend to come down to philosophy, which is often a function of size: larger companies, producing the same product in large batches might favor a more centralized system; while smaller companies may require greater flexibility, which can make integration especially difficult. Even within the same company, no two plants will have the exact same automation architecture.

There are several additional automation challenges that companies face:

- Integrating equipment. How do you make sure the various pieces of equipment, from different vendors, interact with your automation systems in exactly the same way?
- Testing and validation. The more customized a system is, the more the burden of test and validation effort is increased, which delays getting the drug to market.
- Obsolescence management. Often the underlying operating systems will become obsolete on a much shorter timeframe than the hardware will (Windows® 7 is a recent example). This raises the question of how can you keep your operating systems current without costly hardware and software updates? How do you ensure you have the latest security patches on isolated systems, for example?
- Expanding or updating processes. If you have developed a process using one manufacturer's equipment, how do you scale up for commercial manufacturing, which may use wildly different systems and equipment?
- Training operators to use different HMIs (human-machine interfaces) for visualizing and controlling your process. If different pieces of equipment contain different HMI designs with varying degrees of user-friendliness, then you will have to spend the time and money to train your operators to use each of them independently and effectively without errors.

Standardization will allow greater, quicker levels of integration

There is one key factor that will reduce the time and cost required to integrate automation systems: standardization. By using automation systems that adhere to standards and embrace plug-and-play concepts, different process equipment can interact with other systems quickly and without errors – or the need to integrate them from the top down. Standardization of HMI layouts with a focus on usability and operator work flows will ensure the systems are intuitive and easy to use for operators, allowing them to take the right action by providing the right information at the right time.

Crucially, by building features and abilities, for instance following an integration standard that allows equipment to be easily interfaced into your underlying automation architecture ("plug-and-play"), you set the foundations for Industry 4.0. Any automation architecture and the standards it follows must be agile to leverage the future possibilities that come with Industry 4.0. It will become possible to use deep and machine learning to monitor

Easy as MTP

By Michel Claes

For the last year, the Siemens team and Pall have been participating heavily in the BPOG automated facility initiative.

One of the main discussion points was how to standardize equipment and processes so that it would be easier to integrate various unit operations from different vendors into an overlying structure. We looked at a standard called VDI-2658 by Namur, the German user association of automation technology in process industries. They began an initiative to more easily integrate "modules" into an overlying architecture, which they called the "process orchestration layer." The idea is that each "module" (which could be something as small as a motor or as large as factory) would be intelligent in its own right, but could also be interconnected to a wider network. In our use-case, the typical module would be a single-use bioreactor. It would be intelligent enough to work alone, but at the same time could also be controlled by a Distributed Control System (DCS), such as Siemens' SIMATIC PCS 7 or Emerson's DeltaV.

The objective is to standardize the process by which modules can be integrated into the supervisory process architecture, which includes control, visualization, alarming and reporting. This requires communicating over an open communication protocol, OPC UA, as well as defining vendor agnostic standard communication interfaces for all the objects in the system, rather than everyone designing their own proprietary systems. Thereby ensuring everything is speaking the same language. The complete interface of a module can be packaged in specially structured XML file, called the Module Type Package (MTP) file. The integration of the module into a DCS is reduced to the automatic ingestion of this file.

Within BPOG, we have advocated for the use of VDI-2658, commonly named MTP, as standard so that biopharmaceutical unit operations can simply be imported into any orchestration system, ready to run without delay. We believe that these standardized solutions will be a key enabler of industry 4.0. principles, such as Interoperability, Information Transparency and Decentralized Decision.

Michel Claes is a Senior Industry Consultant for the Pharmaceutical Industry and part of Siemens' Pharmaceutical Concepts and Technology team.

the process and make autonomous decisions to optimize production in real time, to feed this information into and refine advanced process models. The next logical step in the future is to use artificial intelligence so that equipment can reason and adapt in even smarter and more human-like ways. To glean meaningful insights from ever increasing amounts of multivariate data sets being generated using process analytics, a system architecture must have the right capabilities built in at the network level to handle data and pass it through the layers. Standardization will better enable the necessary integration – both vertically and horizontally.

Future automation architectures should embrace virtualization: hosting virtual instances of software that are abstracted and independent of the actual physical hardware, rather than having separate operating systems and several applications on individual local machines. Building this functionality into our automation architectures will smooth the move of automation software to a cloud based system, or allows companies to integrate automation software from an equipment supplier onto their own IT infrastructure. This would reduce the labor and expertise required to maintain and upgrade systems – reducing downtimes. Or open up new possibilities such as software as a service or allowing seamless remote access for support.

Collaboration enables standardization

Overall, standardization is a key enabler of fast and trouble-free integration of equipment systems. It will allow more flexibility between equipment and automation vendors, reduce time to market and improve quality by simplifying testing and validation. But how do we achieve standardization across the industry? The key is collaboration – something Pall has strongly supported. And it isn't just Pall that has championed standardization of automation systems in biopharma processes; equipment manufacturers, technology suppliers and industry organizations (for example, among the many, the BioPhorum Operations Group, BPOG) have also advocated for industry-wide standards (see sidebar: "Easy as MPT" for an interesting example). Having been involved with standards-creation within BPOG, it really goes beyond discussing issues and making comments on drafts – a common procedure in many traditional standard-setting organizations. In one room, you will find several automation technology vendors and equipment suppliers, in many cases competitors with one another, setting their differences aside and working together with end users to define a standard that works for everyone.

In my 20 years working in this field, I have never seen collaboration quite like it. And I think this speaks to the importance of standardization and automation in enabling Industry 4.0 – for the industry as a whole.

Daniel McCarthy is a Principal Automation Engineer at Pall. He works within the Analytics and Controls strategic program supporting new product development for the life sciences.

SUSTAINABILITY AND RESPONSIBILITY – *Beyond Buzzwords*

The pharma industry actively works towards improving human wellbeing, but we only have one planet on which to enjoy good health. What is pharma doing to reduce its environmental impact?

By Maryam Mahdi

When it feels like our relationship with the environment is at breaking point, every aspect of our lives becomes a reminder of the link between our behavior and the wellbeing of our planet. Whether we choose to support brands that are among the world's largest polluters or choose to do nothing as forest fires consume the Amazon, we often find ourselves at crossroads that allow us to make changes for the better or see us continue along a disastrous path.

A significant amount of attention is given to the emissions produced by the mining, energy and automotive industries but for some time the pharma industry has been flying under the radar, despite its substantial impact on the environment. For example, a 2012 study by the Sustainable Development Commission of the NHS found that pharmaceuticals accounted for 16 percent of all emissions produced by the UK's health and care sector. And though there is scant data detailing the US pharma industry's role in producing carbon emissions, it has been reported that the industry as a whole produces 55 percent more carbon emissions than the automotive sector (2).

Pharma's carbon footprint is just one part of the story. The discharge from the 100,000 metric tons of pharmaceuticals produced and consumed each year can affect both wildlife and human health. In 2014, it was reported that a drug manufacturer in Patancheru, India, released an estimated 44 kg of broad-spectrum antibiotics into the environment – enough to treat 44,000 people (3). Though this case is extreme, it should give us all pause for thought.

Fortunately, many companies are taking steps toward change – from introducing renewable energy, to new wastewater strategies, to sustainable packaging options. Here, we present a few good examples of how players in the pharma industry are trying to make a difference.

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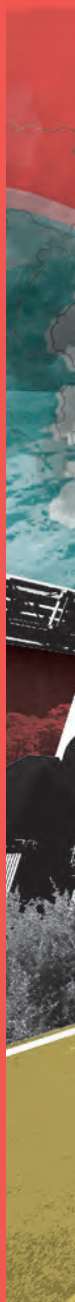


THE GREEN FACILITIES OF THE FUTURE?

We only have one planet. We must play a responsible role when it comes to its care.

By Thomas Otto

In late July, António Gutteres, Secretary-General of the United Nations, penned letters to all heads of state urging them to set out clear plans for achieving carbon-neutrality by 2050. The move comes amid increasing conversation about the state of the climate and the future of the increasingly polluted planet that younger generations will inherit. Though the letters were addressed to the most senior members of our governments, the message is pertinent to all of us. We only have one planet to live on and we should all feel compelled to play an ongoing responsible role in its care.

The pharmaceutical industry, like all sectors, must take a clear stance on its corporate social responsibility. We collectively contribute to the betterment of patient lives worldwide and as a professional who works in pharma I am privy to the dedicated work carried out by the men and women who work in all areas of the drug development and supply chain processes. But pharma must also show the same level of dedication when it comes to our commitment to protecting the environment.

Sustainability should be a central pillar of corporate philosophy. For approximately the last decade, my company has been certified according to the International Organization for Standardization's (ISO) environmental protection standard, ISO 140001. The framework outlined by the standard supports companies and organizations in setting up environmental management systems and can be applied to businesses regardless of the sector they may fall under. In 2014, we also adopted ISO 50001, a standard for energy management. By adhering to these international guidelines, we have been able to introduce carbon-neutral energy derived from certified renewable sources to all of our German-based sites this year. We intend to offset our company-wide use of natural gas within the next ten years and invest in recognized, high quality climate protection projects, such as those involving reforestation for the unavoidable carbon dioxide emissions we produce.

Vetter was privileged enough to be awarded a Facility of the Future award for our Ravensburg-based Center for Visual Inspection and Logistics in the 2018 International Society for Pharmaceutical Engineering (ISPE) Facility of the Year Awards (FOYA). The site consequently realizes a sustainable energy concept and includes the operation of a modern, environmentally-friendly block heating and power plant, the use of geothermal energy and the comprehensive use of excess energy, as well as photovoltaic systems, all of which are combined in an energy-efficient manner. While we were honored to receive the prize, we – like all CDMOs – have work to do to keep up with the evolving pharmaceutical market.

Beyond our facility design and our strategies to minimize our carbon output, we continuously monitor our energy consumption, enabling us to identify areas for improvement in our operations. Sometimes, it is the little things that can make a big difference. For example, by digitizing many of our processes, including the replacement of paper-based procedures and opting for video call software to facilitate "face-to-face" meetings, we are incrementally reducing our impact on the planet. Though these may seem like small changes in the grand scheme of things, they are helping to retrain and prepare our employees for the fast-changing field of sustainability.

> *"The pharmaceutical industry, like all sectors, must take a clear stance on its corporate social responsibility."*

In parallel to our internal campaigns, we have also formed initiatives with the city administration and local organizations to help decrease the environmental impact of commuters, motivating our employees to seek alternative transport when traveling to and from work.

It is important to recognize that the ability of any given company to reach (or go beyond) the milestones I've outlined here may be limited by the regional mindsets of governments and institutions. I have observed stark differences in the attitude of organizations outside of the EU region when compared with those within it in regard to the adoption of green practices. Regulation also limits what companies are able to achieve in this space. The difference between simply renting a site and owning it are huge when it comes to what eco-friendly practices can be adopted. If, we, as an industry, were able to harmonize our standards for eco-friendly resource usage, the barriers to progress that many companies come up against could be broken down.

As a CDMO in the field of aseptic manufacturing of injectables, we understand how resource-intensive the production process can be. Automated air circulation, water and electricity are all necessities in the creation of high-quality drug products. However, we as a sector need to be able to rethink the ways in which we use the resources at our disposal and encourage the adoption of innovative strategies that will help mitigate our footprints and bring us closer to carbon-neutrality. It is worthwhile trying to verify and realize options to harmonize regulatory requirements with environmental-friendly usage of resources. Generally, CDMOs need to embrace cleaner technologies in the near future to help reduce their environmental impact. The introduction of these technologies should be considered not only when companies are purchasing or acquiring new facilities, but also when expanding existing facilities to have the most significant impact.

It is also essential that companies keep their corporate social responsibility strategies as transparent as possible. Transparency goes hand in hand with trust and, for customers, clear and open corporate strategies can help dispel any doubts that they may have about the companies that they interact with. Transparency also helps open doors to collaboration with partners with similar goals and allows others to constructively critique the practices that they may adopt, allowing for continued growth and improvement.

Though it is necessary to assess the scope of work that needs to be done to improve pharma's impact from a company or organizational level, it is important that we as individuals remember to play our part. We all have the ability to look beyond our personal horizons and recognize the severity of our actions upon others, not only within our immediate surroundings, but in places further afield.

The pharma industry is ultimately a solutions-provider, contributing to the improved quality of life of patients. Given that climate change is rapidly changing the world around us, shouldn't we also take pride in being an influence and driving force in the move toward a greener future?

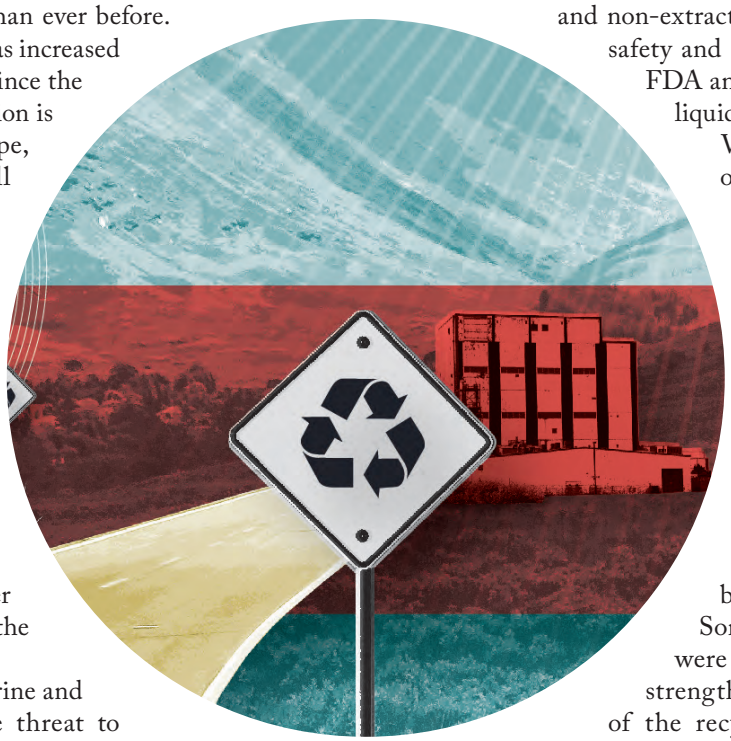
Thomas Otto is Managing Director at Vetter Pharma-Fertigung GmbH & Co. KG

COM(PET)ING WITH THE CONVENTIONAL

Being sustainable does not mean compromising on quality. With packaging, sustainable options can be just as good as traditional solutions, but we need more innovation in the field.

With Fabio Silvestri

The risk of a planet overwhelmed by plastic is a fast-approaching reality. The blame cannot be placed firmly at anyone's door as we have all contributed to the problem. In our daily lives, we consume more plastic than ever before. In fact, plastic production has increased by a staggering 60 percent since the 1960s and while its production is continually falling in Europe, the global landscape is still very bleak (1). In 2015 alone, 322 million tons of plastic were produced, with packaging accounting for 59 percent of all waste in the EU. This amount is set to double over the next two decades – so action is required now.



Pharmaceutical packaging accounts for a very small proportion of waste, but we can still take action in order to have a positive impact on the environment.

As plastics enter both marine and terrestrial ecosystems, the threat to human health increases in turn. One avenue that has not yet been tapped into in a meaningful way is recycling. In the EU, less than 30 percent of plastic waste is collected for recycling each year, with a large proportion of it shipped to other regions where the environmental standards may not necessarily reflect those held and adhered to by EU nations (1).

As the EU pushes for a more circular economy focused on reducing waste and making the most of the available resources, such measures must be given much greater consideration. After all, the EU has pledged its commitment to ensuring that all plastic packaging is recyclable by 2030. We, as an industry, cannot remain passive in sight of such a significant challenge. Ensuring that the packaging we provide is of a high standard, yet recyclable is imperative if we aim to uphold the reputation of the industry in a world where green thinking is growing in popularity.

PET Peeves

It would be nonsensical to envision foregoing pharmaceutical packaging because it ensures the integrity of drugs and helps the commercialization process. Though glass and aluminium are commonly used, plastic, particularly polyethylene terephthalate (PET), is also an essential component for packaging, prized for its strength and light weight. As PET is non-leaching and non-extractable in nature, it meets the safety and quality standards set by the FDA and is a suitable choice for oral liquid dosage forms.

While the growth in the use of this type of packaging has increased rapidly in recent years, it should be noted that PET is a non-biodegradable material that can be recycled. When PET is cleaned and shredded into pellets, it can then be crushed and made into new products. In the past, issues related to the features of recycled PET have prevented its adoption by mainstream pharma. Some of the major challenges were related to the mechanical strength, hardness and toughness of the recycled material, as well as regulatory red tape and requirements in place to safeguard drug stability and prevent contaminants from entering drug products. The FDA stipulated in 1999 that "post-consumer recycled plastic should not be used in the manufacture of a primary packaging component. If used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately," (2). However, in 2018 , the same authority publicly issued a letter of no objection confirming the capability of a producer's secondary recycling process to clean and produce post-consumer recycled PCR-PET suitable for food contact (3).

WORKING WITH WASTE

When considering pharmaceuticals and the environment, wastewater is a crucial topic. After installing new manufacturing capacity at its Karlskoga site in Sweden, Cambrex also opted to increase the site's wastewater processing capabilities. We spoke with Johan Karlsson, Manager of the Karlskoga Wastewater Treatment Plant at Cambrex to find out more.

For pharma and API companies, what are the challenges of dealing with wastewater?

In recent times, emissions requirements have become more stringent, which has led to the need to introduce additional purification steps for wastewater. For our site in Karlskoga, Sweden, as with other multi-purpose manufacturing facilities, there are several different waste streams that are being handled by the wastewater treatment plant (WWTP), so the volume, flow and levels of contaminants vary depending on which product is being produced at the time.

Any purification process is most efficient when the water flow and levels of contaminants are stable, but this is rarely the case in Karlskoga. The purification technique we have implemented in the WWTP uses carriers, which are designed to better withstand variations in flow and fluctuations of contaminants.

How can manufacturing discharge affect the environment?

The parameters that we primarily focus on are levels of nitrogen, total organic carbon (TOC), phosphorus and inorganic nitrogen. Nitrogen, inorganic nitrogen and phosphorus are important nutrients for plants, but if there is too much available nitrogen and phosphorus, they contribute to eutrophication, which can lead to algal blooms and decrease the quantity of oxygen in environments such as lakes and the sea. Too much release of TOC can lead to aquatic life being killed.

Why was it so important to increase the site's wastewater processing capabilities?

In recent years, the amount of nitrogen that the Karlskoga site has produced has increased, and so the WWTP has undergone a major refurbishment to break down more nitrogen. The new nitrification purification step that has been built is very sensitive, and steps have also been put in place to reduce TOC levels.

In Sweden, heavy rainfalls have become more common and this means that the variation of the inflow to the WWTP during certain periods increases. Investment has now been made so that we can maintain a high reduction rate, even under an increased load of rainwater into the treatment plant. We are constantly working to reduce the amount of storm water that enters the process sewage network, but this is a major challenge given the plant's location in a historic industrial area, with ageing pipe networks in the ground.

How is the wastewater treated?

The process wastewater is treated in several different stages with the most important steps being:

- Neutralization – the pH of incoming process water is low (acidic), so it is treated with lime to raise the pH
- Denitrification – converts nitrate into nitrogen gas
- TOC oxidation – organic material is treated with oxygen to emit carbon dioxide or fall as suspended material
- Nitrification – ammonium is broken down into two different steps
- Denitrification – nitrate formed in the nitrification step is converted into nitrogen gas
- TOC oxidation – takes care of any remaining organic material

Two different sedimentation basins are situated within the WWTP treatment plant. In the first stage, sludge is removed using polymers, and in the last step before the water leaves the treatment plant, polymers and iron chloride are added to remove any excess phosphorus that the treatment process itself has consumed.

"We are working to gain approval by 2023 to meet our own corporate and sustainability targets for developing greener plastic solutions."

We believe that it is possible to develop recycled and sustainable solutions that are appropriate for the pharma industry. As a first step, we have recently developed recycled PET packaging that complies with the European Pharmacopoeia. We now have bio-based polyethylene containers and BioPET bottles, containing, respectively, up to 100 percent for polyethylene and up to 30 percent for PET of raw materials from renewable sources. Being sustainable by no means results in a compromise on quality. In fact, the physical and mechanical properties of our recycled PET product line are comparable to virgin PET. We've also been developing measuring cups and spoons in food-grade PLA that are fully degradable within 60 days in industrial compost facilities – small solutions that still can make a big difference. We are confident that these materials would be compliant and approved by FDA.

We also have sustainable solutions for the food and cosmetics industries, but these have not yet received pharma certification. We are working to gain approval by 2023 to meet our own corporate and sustainability targets for developing greener plastic solutions.

The pharmaceutical industry must be highly regulated and though regulators are certainly strict, they are not rigid in their ideas or approach to innovation and are open to suggestions to improve the industry's sustainable packaging practices. We are not the only packaging company pushing for greener solutions in pharma, but more action is required. We must speak with the same voice and ensure that all the solutions we create are compliant with current pharmaceutical regulation if we truly want to affect change. The road to a sustainable future is long and winding and must be implemented in small, achievable steps. When speaking to pharma companies, I am filled with optimism by the willingness of the industry to undertake this journey. And though it may start slowly, its environmental impact will be huge.

Fabio Silvestri is Head of Product Strategy and Planning at Bormioli Pharma.

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ZERO IMPACT

What difference can circular systems make to the pharmaceutical industry's carbon footprint?

With Dorethe Nielson

It is estimated that by 2050 there will be more plastic in our seas than fish – a prediction which highlights our collective attitude toward the environment. Our patterns of behavior are shaping the future. Extreme weather events and rising sea levels are no longer the dramatic events used to frame science fiction films and novels depicting the world as it struggles to cope with natural disasters. These are now the realities faced by people across the globe. From wildfires in California to extreme flooding in Pakistan, it is evident that climate change is claiming lives and putting a massive strain on the world's economies. We can no longer afford to peer over the precipice debating whether we, within the pharmaceutical industry, have a role to play in this fight.

Rethinking our approach to the use of energy and resources could help transform our relationship with the environment. Innovation in material sciences, recyclable technologies and product design are helping us to steer away from the "take-make-dispose" industrial model employed in linear economies. At Novo Nordisk, we have the ambition of having zero environmental impact. Millions of people use our products each year and re-evaluating our use of energy and raw materials, as well as the production of carbon emissions is essential to mitigate our footprint.

"As we evaluate ways to reduce our carbon emissions by 2030, we must assess everything from transportation to the IT equipment we use."

Inspired by the former British sailor, Ellen MacArthur, we created a new initiative called "Circular for Zero" to make a circular economy (systems to eliminate waste and the continual use of resources) a reality. During her sailing career, MacArthur was astonished by the vast amount of plastics in our seas and oceans. Wanting to take action, she founded the Ellen MacArthur Foundation, a charity that aims to trigger a change in society through a circular economic system.

Circular for Zero was launched at the beginning of 2019 and is focused on minimising impact from the full value chain. As a company with global sites, we want to address areas of improvement across our value chain. We aim to be 100 percent

reliant on renewable energy by 2020, and we have employed different models to our sites to achieve this. A one-size-fits-all strategy cannot and will not work, so the key for us is to design a diverse renewable power grid. In the US, for example, we have introduced a 672-acre solar power installation at our North Carolina site, which will provide our entire American operation with solar energy. Meanwhile in Brazil, we are pursuing hydropower and in China, windmill parks. I think it is very exciting to be able to introduce solutions that best fit a given market.

Beyond our renewable energy goals, we have also begun to explore our capacity to address three fundamental questions:

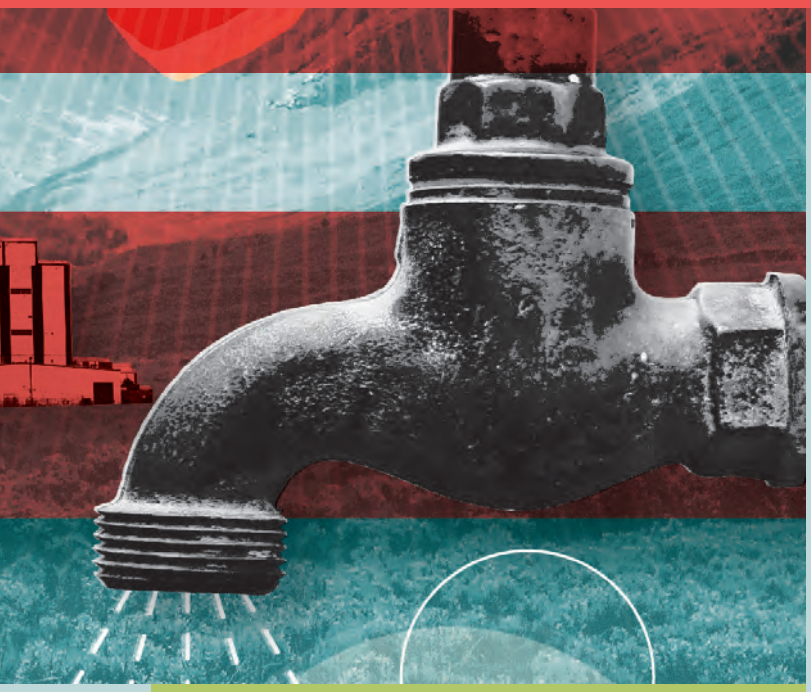
- How can we reduce the environmental impact from our global operations and transport to zero?
- How can we upgrade existing products and design new products that promote reuse and recycling?
- How can we improve collaborations with suppliers to switch towards circular sourcing and procurement?

As we evaluate ways to reduce our carbon emissions by 2030, we must assess everything from transportation to the IT equipment we use.

We are also working within OECD guidelines for extended producer responsibility (EPR). EPR is a policy approach that places responsibility on producers, financial and/or physical, for the treatment and disposal of post-consumer goods. We take this responsibility seriously, which has prompted us to look further into the development of solutions that will reduce environmental waste. As legislation varies from country to country, trying to develop the best possible solutions for our patients in the EU region and further afield will require further collaboration with governments, policy makers and the public. But in doing so, we hope to ensure that environmental considerations are an integral part of our future product design, affecting both drug products and packaging.

Though we adhere to ISO 14001 to ensure we have the correct environmental management systems in place, we are also working with our suppliers to optimize the way we source water, energy and raw materials. A few years ago, it was difficult to get people to understand the importance of environmentally responsible sourcing, but now the industry is increasingly aware of its environmental responsibilities, so finding suppliers who also aim for a greener future is much easier than it used to be!

Most importantly, as individuals we must all have a vested interest in adopting environmentally-friendly practices and educating ourselves. The steps the pharmaceutical industry is taking to protect the environment at a corporate level will ultimately have the most impact when we all begin to recognize that caring for the environment is everybody's business.



"In my current role, I am determined to create the best possible outcomes for us as a company and for the patients."

IN CONVERSATION WITH... DORETHE NIELSON

As Novo Nordisk's Vice President of Corporate Environmental Strategy, Dorethe Nielson wants to see a transformation in business practices so that the best environmental outcomes can be realized.

Why are environmental issues so important to you?

As a newly graduated chemical engineer, my career began with several projects at coal-fired power plants in Poland. Witnessing the level of pollution produced from these plants sparked my interest in environmental responsibility and gave me the perspective on the potential for growth in green practices in industrial spaces.

In my current role, I am determined to create the best possible outcomes for us as a company and for the patients.

What are your biggest achievements to date?

We're on track to relying solely on renewable electricity by 2020! But the journey actually started in 2004. It's been a long process, but we've worked alongside great partners like WWF and Denmark's largest electricity supplier, Ørsted; managed to bring down our emissions by 10 percent; develop a windmill park in the North Sea and explore new avenues for green innovation.

Novo Nordisk is progressing along a long and grand path – but are there any "quick wins" for companies aiming for a greener future?

A good start would be to actively procure or invest in sources of renewable energy. Though there may be additional costs initially, it is a simple strategy that can have a significant impact on companies' carbon output, reduce expenses, and put them in good stead with their partners and customers.

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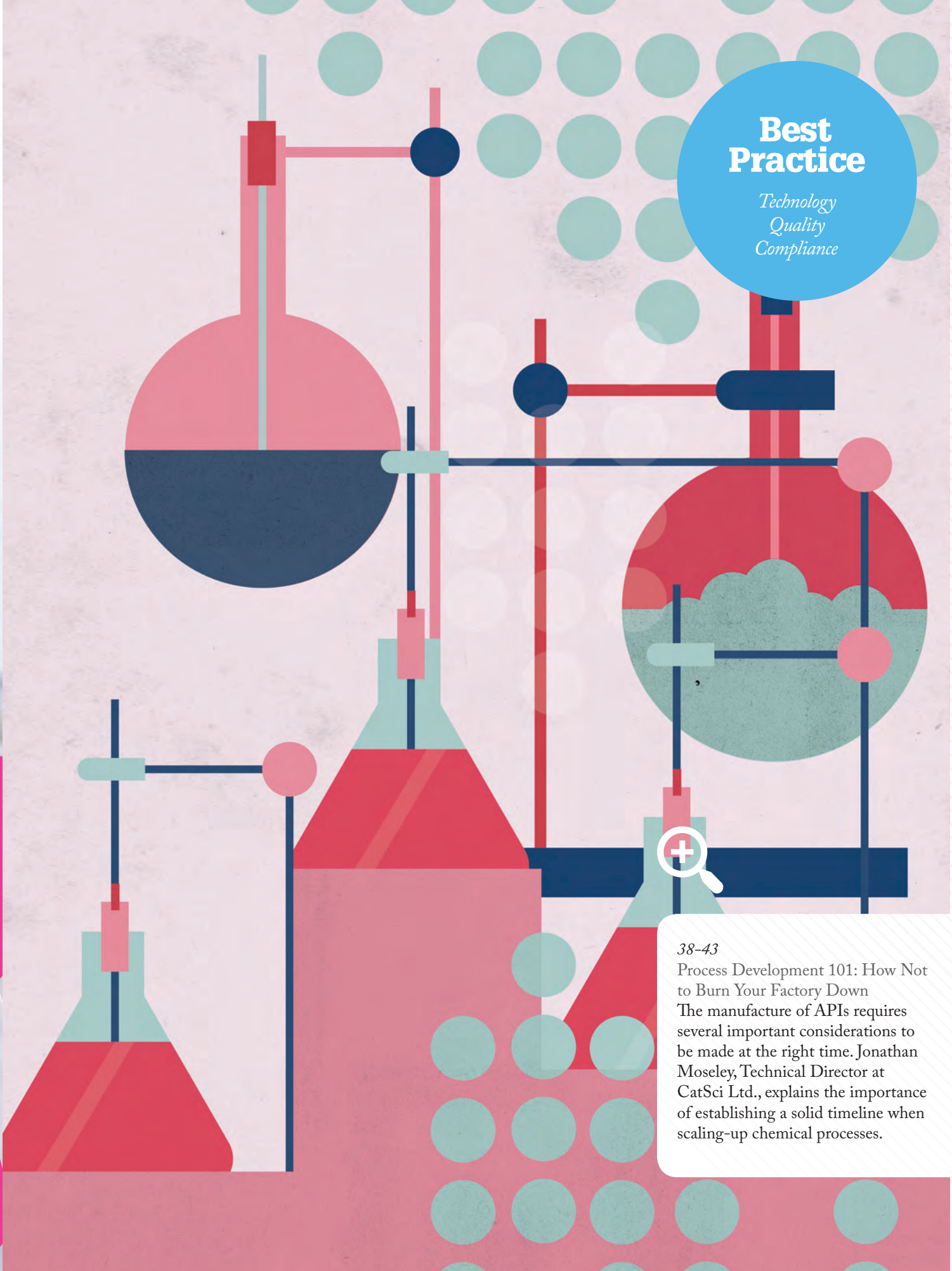
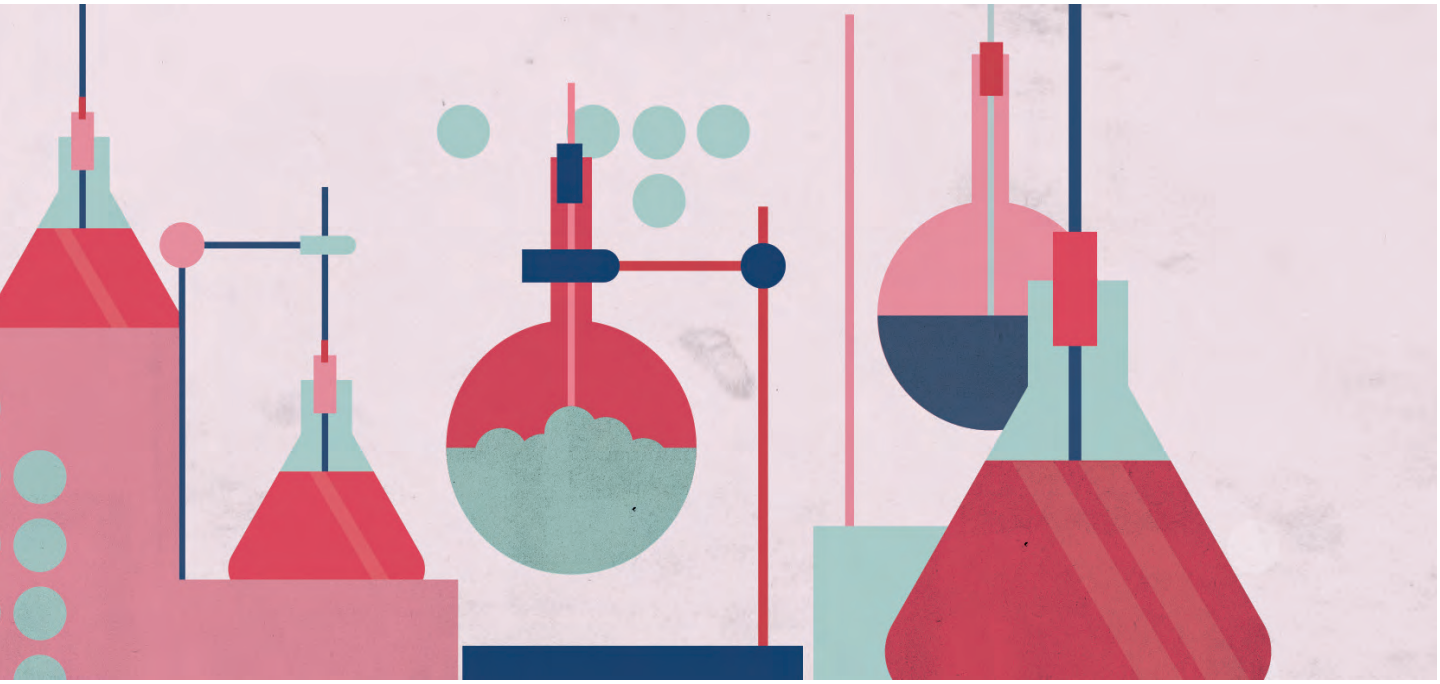


38–43
Process Development 101: How Not to Burn Your Factory Down
The manufacture of APIs requires several important considerations to be made at the right time. Jonathan Moseley, Technical Director at CatSci Ltd., explains the importance of establishing a solid timeline when scaling-up chemical processes.



Process Development 101: How Not to Burn Down Your Factory

Or... how to manufacture your API in the right quantity, at the right cost, and in the right time frame.

By Jonathan Moseley

Scaling-up chemical processes for the manufacture of small molecule pharmaceuticals is not simply about using a bigger reaction flask. Processes that can easily be accomplished at small scale in the laboratory are often not possible at large scale in factories without significant modification. And that's why process development is key. Process development serves two key functions. Firstly, to manufacture increasing quantities of the API – perhaps scaling from grams to tons over time – to support ongoing clinical testing of the experimental drug, and to support other development activities, such as formulation. Secondly, process development helps to improve the "recipe" to achieve these increasing scales of manufacture in a timely, safe and economic manner – all without polluting the environment, injuring anyone, or burning the factory down! Process development must consider chemical and physical safety; commercial concerns, such as time, cost, and availability of starting materials; chemical, analytical and engineering aspects; and legal and regulatory requirements.

"Once heat is generated faster than it can be removed, a 'runaway reaction' is inevitable – often with disastrous consequences!"

Chemical and physical considerations

The initial chemical route for any new API is likely to have been designed for the facile synthesis of many closely related structural analogues, which can be achieved by relying on late-stage functionalization, as shown schematically in Figure 1 (especially Step 6). For larger quantities, however,

the initial route may no longer be viable for a number of reasons. One common problem is that the initial starting material (A) may not be commercially available in sufficient quantities, necessitating additional steps from an earlier starting material (X) and adding expense. In another example, the hazards present in the initial route may be unsafe at a larger scale. The first priority, therefore, is to establish the commercial viability and operational safety of the chosen route. If this cannot be guaranteed, then another route will be required.

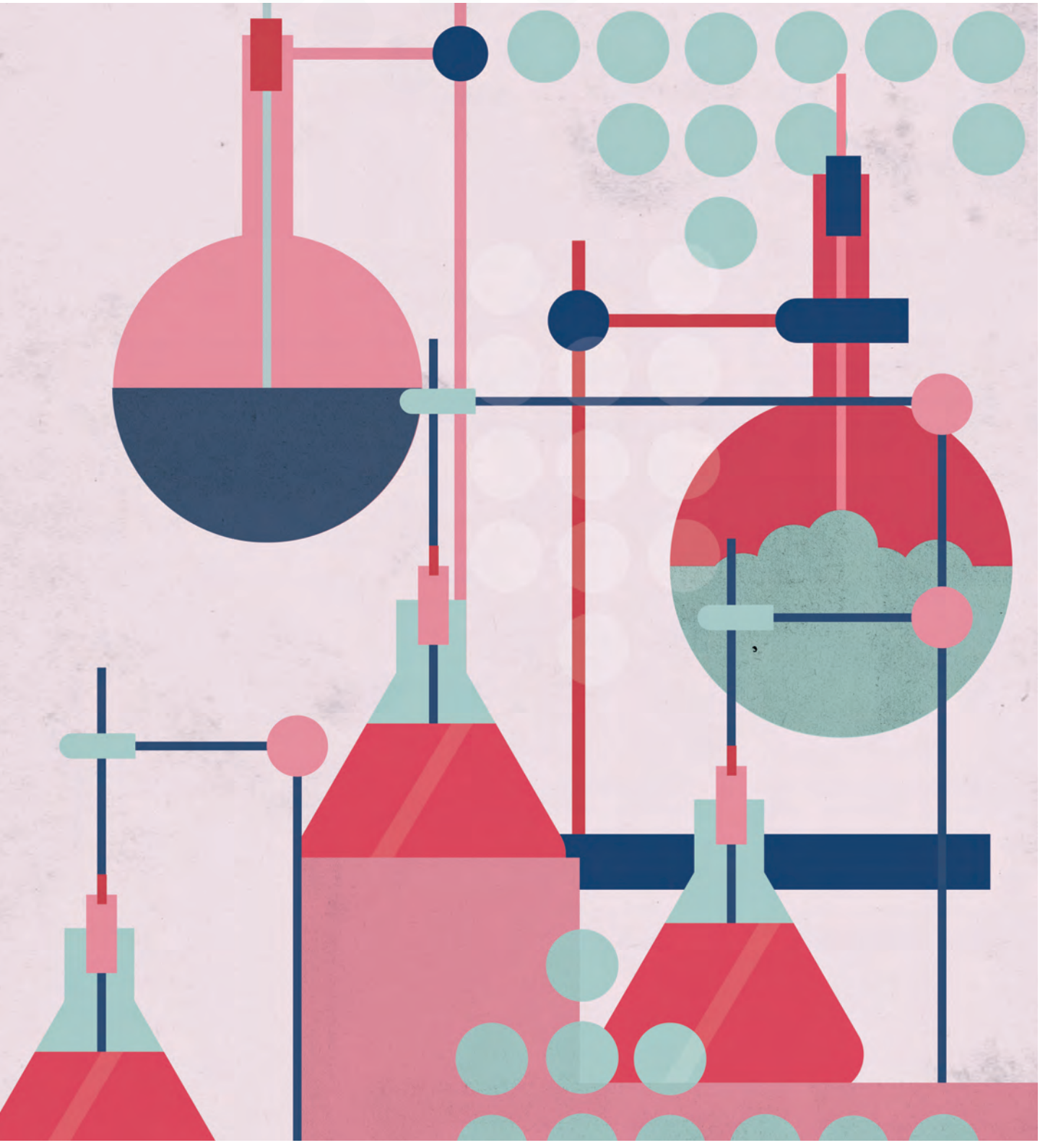
Even without these issues, it is likely that a shorter route using alternative, cheaper, and more readily available starting materials (bottom route of Figure 1) to produce the desired analogue will be more economical in the long term. At an early stage, it is beneficial to investigate and patent any other viable routes, even if not used (since it may also hinder competition in the long-term). Route selection is always a key priority.

After route selection comes chemical selection. Reagents need to be chosen for suitability, availability, safety, toxicity and expense. Costs that might be tolerated at small scale, as well as toxicity that can be contained within specialist laboratory equipment, may become unacceptable on larger scales. Chemical hazards can arise if the reaction generates excessive heat, for example, which can cause the reaction solvent to boil, potentially causing the vessel to rupture. Likewise, rapid production of gaseous by-products can burst reaction vessels. These and other factors may make some routes, reagents or laboratory techniques unviable for large-scale manufacture, so alternatives must be found.

In terms of physical conditions, the most important factor affecting scale-up results from the square-cube law, which explains how the surface area is inversely proportional to volume (SA/V) (Table 1). For reaction vessels of a similar shape, a 1000 L vessel has proportionately a 10-fold lower SA/V ratio than a 1 L vessel (Figure 2). This affects the rate at which heat can be added and, more importantly, removed from a reaction vessel – for example, during an exothermic reaction. Many chemical reactions generate heat as they progress and proceed faster at higher temperatures. Once heat is generated faster than it can be removed, a "runaway reaction" is inevitable – often with disastrous consequences! For this reason, scale-up is typically limited to 10-fold increments and careful measurement by chemical engineers of the heat produced (reaction calorimetry) is undertaken as scale increases to prevent this.

Physical stirring also changes on scale-up. Magnetic stirrers work well in small reaction flasks, but are ineffective above the 1 L scale (Figure 2). Furthermore, much less solvent is typically used in scale-up reactions to increase throughput in plant-scale reaction vessels. This reduces processing times and costs for operations such as heating, cooling and distillation. However, concentrated processes are more likely to be heterogeneous (i.e., contain undissolved solids and liquid together), and even homogeneous reactions may be highly viscous.

Mechanical stirring must be used instead of magnetic stirring, but even so, it may not be fully effective as the scale increases. Different shapes of stirring blades may be needed on a larger scale, and baffles (flow-directing or obstructing panels) may also be introduced into the vessel to increase mixing, especially to lift heavy solids off the bottom of the reactor. It is difficult to predict and model the effects



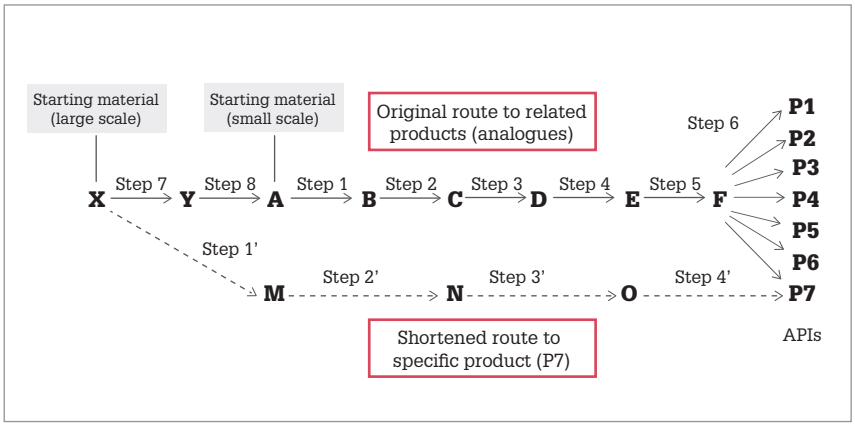


Figure 1: Schematic of route comparisons for original generic discovery route to prepare multiple analogues (top), and shorter bespoke scale-up route for a chosen product (bottom).

of stirring heterogeneous reactions on scale-up, but it's wise to be aware of the potential issues from an early stage. Collaboration with chemical engineers is strongly recommended to avoid potential problems.

Choose your solvent

After route and reagent comes solvent selection, although in practice all three are interdependent and investigated alongside one another. The solvent will be the largest single component in any reaction and its selection raises possibilities and challenges. Only a limited number of solvents are cheaply available on a large scale (and are mostly petrochemical derived). Environmental concerns and increasing regulation mean that fewer solvents are available for use, and restrictions are tightening all of the time. Many chlorinated solvents are now banned at full manufacturing scale, so even if laboratory studies are possible, there is little value in investigating them if their use is prohibited in large scale operations. Early identification of a preferred long-term solvent should be a priority.

Beyond expense and availability, solvents should dissolve substances to reduce the reaction volume needed and help minimize heterogeneity. The properties of the ideal solvent should fall in a "Goldilocks zone": it should dissolve reactants, but not the desired product so much that crystallizations become difficult. Low-boiling solvents limit the thermal range available for heating, which may slow the reaction rate (and time is money on a large scale!) and reduce the safety margin before boiling in the event of a thermal runaway. Such solvents often also have low flash points, and may generate static when pumped through glass-lined reaction vessels and industry-standard piping.

Conversely, high-boiling solvents offer a wider operating and safety window, but can be difficult to remove from desired products. Such solvents are often water miscible (allowing them to mix in all proportions), which can be advantageous. However, they can also have higher toxicities and costs, making them less desirable. Inevitably, solvent choice is a compromise between multiple factors.

Purifying the product

Lastly, for each step in the selected route, the intermediate product must be isolated and purified on a large scale. For small-scale reactions, intermediates are typically purified by

	Reactor Volume (L)	*Surface Area (m^2)*	*SA/V Ratio (m^2/L)*	*SA/V Ratio (to 1 L reactor)*
Test-tube scale	0.001	0.0004	0.407	9.3
Laboratory	1.0	0.044	0.044	1.00
Kilo-lab	10	0.209	0.021	0.48
Pilot plant	1000	4.75	0.0048	0.11
Production	10000	22.6	0.0026	0.05

Table 1: Comparison of surface area : volume (SA/V) ratio with reactor vessel scale.

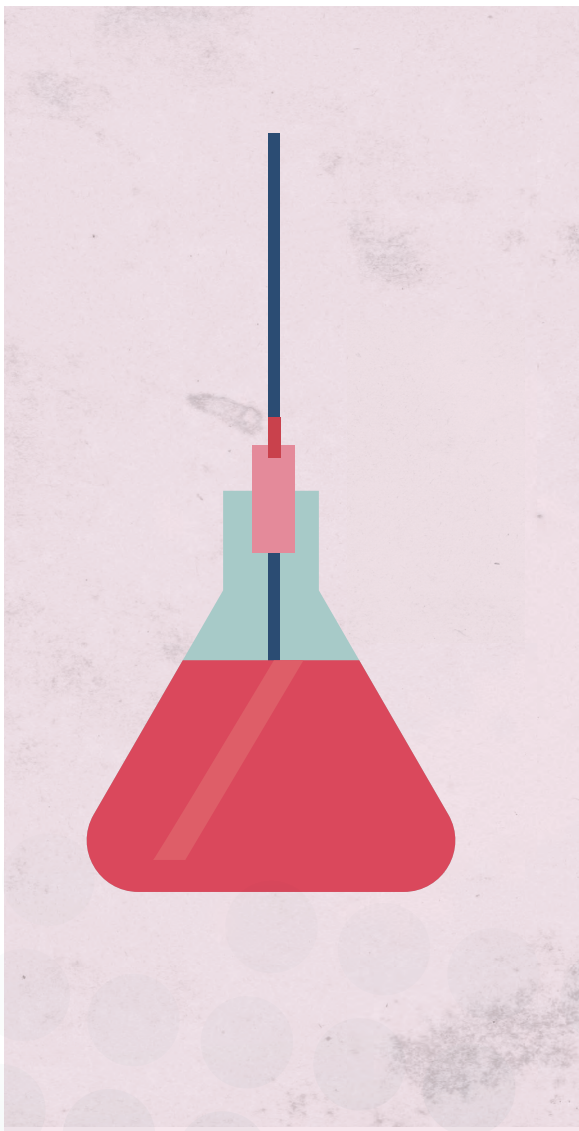


Figure 2: 1 L reactor vessel.

column chromatography. However, this powerful and ubiquitous laboratory technique is disproportionately difficult and expensive to conduct on a large scale – and almost always avoided!

Crystallization is the preferred method for isolation of solid products on a large scale, for which judicious choice of the solvent plays a part; in fact, the requirements of crystallization are more likely to have determined solvent choice over the reaction. Ideally, the desired product will crystallize directly from the reaction solvent at the end of the reaction, but this is rare. More commonly, another purification will first be required, typically involving additional operations such as extractions and washes. This will likely be followed by distillation, reducing the solvent volume before the more demanding crystallization can be attempted. Consequently, over half the time spent on optimizing a chemical reaction will typically be used to devise a robust and efficient isolation and purification process, rather than on the reaction itself.

Other forms of isolation are also possible. For high-boiling water-miscible solvents, an aqueous drown-out often works well. This involves adding a large volume of water to the reaction mixture, which precipitates the organic product and washes away the solvent and inorganic by-products from the process. However, this technique is inadvisable for late-stage intermediates in the route. It may precipitate all organic components in the reaction mixture, including structurally related organic impurities. Such impurities similar to the API could exhibit deleterious biological activity and so must be controlled to very low levels to protect the patient.

Analytical chemists help monitor and track impurities through the various steps across the project's lifetime, with increasing scrutiny of impurities at lower levels closer to the API. The process development chemist's challenge is to achieve increasing purification without recourse to all-powerful chromatography. Indeed, during the initial stages, the API should not be too pure, but have some typical impurities at moderate levels. If these batches are tested and proven clinically safe, any improved processes that follow with lower impurity levels should also be safe. However, the route, reagents and solvent should ideally be fixed before this, since even minor variations in processes can result in significant changes when considering impurities at <0.1 percent in the API.

As the drug candidate proceeds through development, the focus gradually changes from chemistry in the early stages, to engineering in the mid-phase, to analytical in the later stages. Safety remains paramount throughout, firstly for the researchers and operators involved, but ultimately for the patients receiving the new medicine. Commercial and environmental considerations increase in significance throughout the project's lifetime and it is both the challenge and responsibility of process development to ultimately deliver economically and environmentally sustainable chemical processes for manufacture, which are also high quality, safe and practicable to operate.

Jonathan Moseley is Technical Director at CatSci Ltd.

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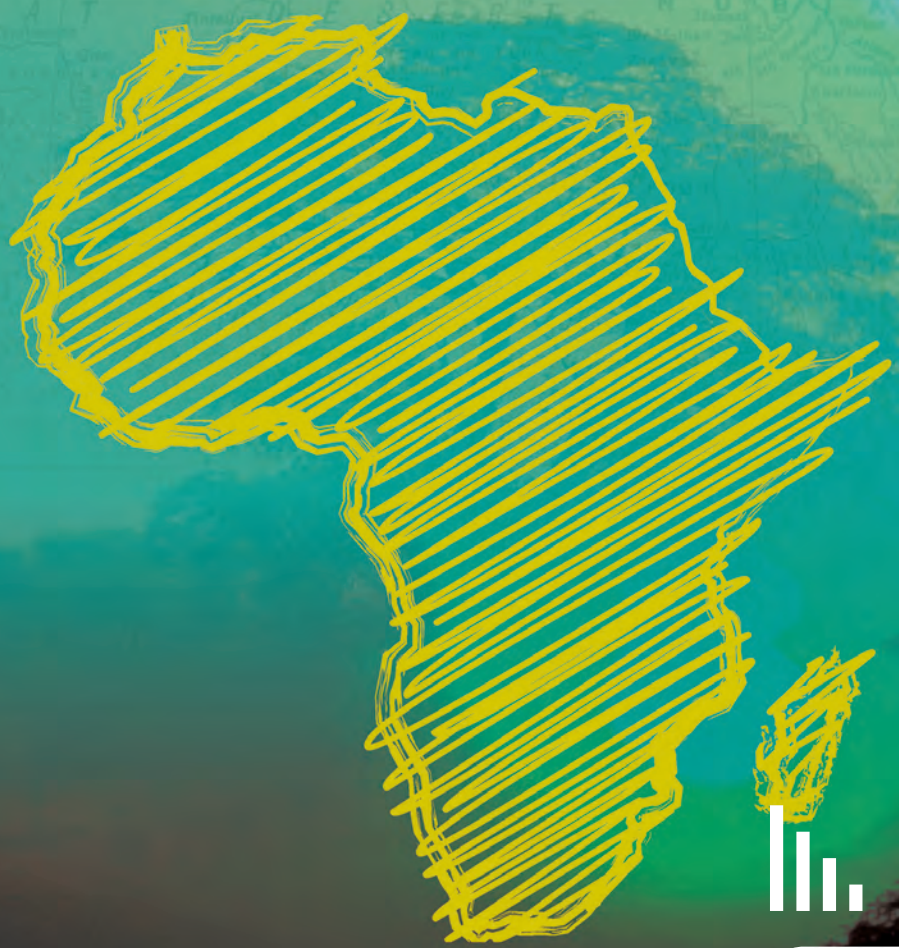


46–48
Dispelling the African Myth
What does African pharma have to offer the global pharmaceutical community? Kelly Chibale argues that the continent has more to offer than candidates for clinical trials.

Dispelling the African Myth

For too long, Africa has been viewed through a lens of afro-pessimism. It's time to rewrite the narrative.

With Kelly Chibale

When you think of Africa, what comes to mind?

Perhaps you view the continent as the next frontier in the global economy. Or perhaps the high morbidity and mortality rates dictate your point of view; the massive disease burden has made some believe that the continent is more suitable for providing candidates for clinical trials rather than leading them. It is true that, historically, Africa has lacked the infrastructure, trained staff and enabling technologies to contribute to the global drug discovery and development sectors, with the continent importing up to 70 percent of its drug products (1). There are many working tirelessly to change the perceptions of the continent and break down negative stereotypes; people who view Africa through the Western lens must be willing to accept that Africa is (and will continue to be) a source of healthcare and pharmaceutical innovation.

Afro-pessimism, or the notion that Africa has nothing to contribute, has plagued the pharmaceutical industry for too long – not only affecting those who live beyond the shores of the great land mass but also those born and raised there who pursued or are pursuing higher education and employment abroad, taking their skills and knowledge with them. Losing skilled professionals with the capacity to push Africa's pharmaceutical sector forward is detrimental to say the least. Countries are defined by their people and when so many African nations lose their highly-trained professionals to European, Asian and American institutions and organizations, they lose their ability to shine on the global stage and create the infrastructure so desperately needed to transform the face of African pharma.

However, this is not the case for all African nations. Rwanda, for example, has the capacity to train and retain its talent. In the years since the 1994 genocide, the country has had an astounding healthcare renaissance, with 90 percent of the country's population covered by national healthcare insurance. Life expectancy has increased and child and maternal mortality rates have plummeted (2, 3). The country has also adopted Zipline – an autonomous logistics network for the delivery of blood and drug products – to help address gaps in the healthcare and pharmaceutical systems.

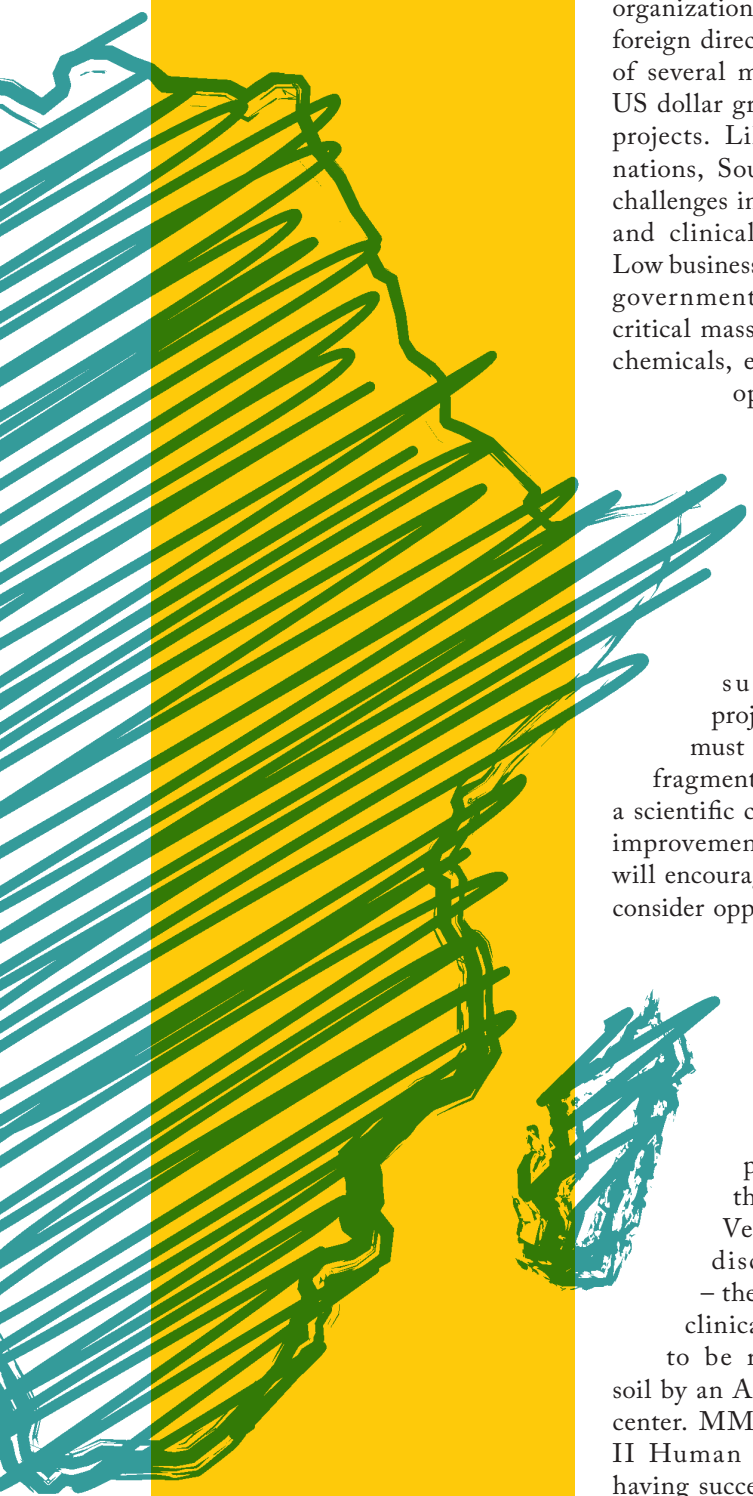
"Afro-pessimism, or the notion that Africa has nothing to contribute, has plagued the pharmaceutical industry for too long."

Though it is too early for other African countries to adopt the Rwandan model, there is much to be learned from the East African nation and its willingness to embrace change.

Homecoming

As a Zambian scientist who pursued doctoral studies at the UK's University of Cambridge and University of Liverpool, and worked for the US-based Scripps institute, I was motivated to found a drug discovery and development institute to address some of the problems faced by the African pharma sector.

The Drug Discovery & Development Center (H3D) was set up at the University of Cape Town in 2011. Our research focuses on malaria, tuberculosis



and antibiotic-resistant microbial disease. In less than ten years, the organization has attracted significant foreign direct investment in the form of several multi-year, multi-million US dollar grants to conduct research projects. Like many other African nations, South Africa faces similar challenges in terms of drug discovery and clinical testing infrastructure. Low business R&D expenditure, poor government spending, insufficient critical mass to import consumables, chemicals, equipment and scant job opportunities mean that the country struggles to attract and keep young talent. Adding to the problem is the lack of continuity with respect to long-term funding and a sustained pipeline of projects. Drug development must be viewed not as a set of fragmented functional silos, but a scientific continuum of identifiable improvements. Through H3D, we will encourage more young people to consider opportunities in the African STEM community, by offering internships and career programs.

Outside of advocacy, a great achievement for H3D to date is our leading role in an international project in partnership with the Medicines for Malaria Venture (MMV), which discovered MMV390048 – the first ever small molecule clinical candidate for malaria to be researched on African soil by an African drug development center. MMV390048 entered Phase II Human clinical trials in 2017 having successfully completed Phase I Human clinical studies conducted through the UCT Clinical Research Centre (CRC) during the 2014/2015 period. Furthermore, H3D led the same international project team that additionally discovered UCT943 as a next generation malaria preclinical drug development candidate in 2016.

These milestones are positive, but we have no intention of resting on our laurels! We aim to develop research platforms that customize medicines to the needs of African patients who have varied responses to existing drug products because of genetic differences; for example, lower expression and activity of drug metabolizing enzymes. The H3D's African Drug Metabolism and Disposition project aims to validate a preclinical discovery tool that can be used to prioritize drug candidates based on their predicted pharmacological profile in African patients.

Changing perceptions

Regardless of how grand these breakthroughs are (or will be!), they are not enough to change the perception of Africa's role in pharma. Greater efforts to harmonize standards and regulations should significantly improve the continent's relationship with the industry and bring about multi-sectoral partnerships allowing for growth across industries. Unlike the EU's pharma industry, which is supported by the European Medicines Agency, the African pharma landscape has lacked an overarching regulatory authority with the same level of command. African countries develop and abide by conflicting legislation, which results in the sluggish approval of drugs, driving up the cost of much needed medicines – a cost that is passed onto patients.

A treaty for the establishment of a new regulatory authority, the African Medicines Agency (AMA),

was accepted by the African Union (AU) early this year during the 32nd Ordinary Session of Assembly held in Addis Ababa, Ethiopia. Once ratified by the 15 of the AU's 55 member states, AMA will be able to begin its operations. The newly formed agency intends to provide regulatory leadership and coordinate the activities of the AU to further strengthen the progress made in the pan-African healthcare and pharmaceutical sectors, giving the region a greater competitive edge.

African manufacturers, for example, should be able to reap the benefits of the newly developed system as their products will be able to stand up against imported drugs, which are subject to VAT and other logistical charges.

The pharmaceutical industries of countries including Ethiopia, Nigeria and South Africa are already on the rise and I am optimistic that others will follow suit. Though the road to success for African pharma is an uphill struggle, our goals are achievable – and within sight.

"African manufacturers, for example, should be able to reap the benefits of the newly developed system as their products will be able to stand up against imported drugs."

Kelly Chibale is the Founder and Director of the Drug Discovery & Development Center (H3D), The University of Cape Town, South Africa.

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The Advocate

Sitting Down With… Charles Gore, Executive Director, Medicines Patent Pool (MPP), Geneva, Switzerland.

What was the turning point for your career?

In my 20 years with the Hep C Trust, it was probably persuading the NHS in the UK to really get behind the idea of using peers as a central, indispensable component of hep C elimination. In my time with the World Hepatitis Alliance, which I set up in 2007, I guess I am most happy about three things: that we got hepatitis onto the global public health agenda by persuading 193 countries to make World Hepatitis Day an official WHO day (one of only four official disease specific WHO days); that we established the World Hepatitis Summit as a unique event, unlike all the existing medical conferences, that brought together governments, patient organisations and WHO to address all aspects of hepatitis; and that we got the elimination of viral hepatitis accepted as a global goal.

Why did you choose to move to the MPP?

I firmly believe that once a charity has served its purpose it should be shut down rather than morphing into something else. There are many people who are invested in creating new charities to bring awareness to a cause they feel passionate about rather than adding their expertise to existing organizations. Just as the Hep C Trust moved closer to achieving what it set out to do, an opportunity at the MPP came out of the blue. I chose to accept the Executive Director role because I felt I could do more for people here than at the Hep C Trust – there are an estimated two billion people in low- and middle-income countries without decent access to medical treatments and healthcare technologies, which, in my view, simply cannot be allowed to continue. Regardless of a country's economic status, its citizens deserve consistent access to medicines.

The MPP's role is to negotiate with patent holders to obtain licences to produce and distribute affordable but high-quality generic versions of life-saving medicines for low- and middle-income countries. The licences also enable the production of fixed-dose combinations and formulations for children. The MPP's manufacturing partners recently rolled out a first-line treatment for HIV, Dolutegravir, based on a licence with ViiV Healthcare, and we're beginning to see millions of people benefiting from it. Our most recent licence is with AbbVie to expand access for glecaprevir/pibrentasvir, which is a WHO-recommended first-line treatment for hepatitis C.

Why are companies turning to MPP?

The industry is beginning to recognize that, on a global scale, it needs to ensure better access to medicines for patients. I like to compare the situation to the current climate around electric cars. Car manufacturers recognize the importance of electric cars for a greener future. With complete certainty, many people, including myself, believe that petrol-engine cars will simply not exist in coming years. Pretending that they will is to deny an inevitable fact about the state of the industry and its trajectory. In the same way, pharma must acknowledge that medicine access is the future of the industry. It matters to advocacy groups and charities but most importantly it matters to patients. As the industry talks more about patient-centricity and meeting the needs of those it serves, this aspect of the sector has to be given greater consideration. What is the point of making medicines that are out of reach of the majority of patients in many parts of the world? By working with the MPP, companies are actively choosing to find strategies that genuinely help to put patients first, focusing on the most neglected patients living in low- and middle-income countries.

What are your future goals?

That no new medicine is launched without an access program, so that everyone who can benefit is able to do so. This may be through the MPP's public health licensing model, but not necessarily so. Our model is only one access model – and is only appropriate in certain circumstances. I also think we will need a means-assessed framework that outlines what governments should be paying for the medicines its citizens use. As countries become richer, they should contribute more to the cost of medicines. Cheap medicines are great, but governments around the world need to think about how they will expand their budgets so that they are making contributions befitting of their GDP; the issue is critical for the health and wellbeing of entire nations. If a country is capable of spending 10 percent of its GDP on healthcare (including medicines), why does it only spend three?

"We should be able to tackle some of the most pertinent issues faced by the pharma industry."

By giving governments the incentive to do this, we should be able to tackle some of the most pertinent issues faced by the pharma industry; escaping the drug discovery rut, creating the funds to foster innovation, and providing the means to tackle global crises, such as antimicrobial resistance – these can be better addressed if we have the right frameworks in place. The MPP is all about creating win-win solutions for patients, governments and pharma companies. Some have been sceptical about the MPP's role (some companies believed we were out to take the profits they made from patented drugs), but I think they are increasingly coming to understand our aim and vision. And the more we can change the industry's perspective on this issue, the closer MPP will get to achieving its goals.

SKIN SENSITIZATION SOLUTIONS

Skin sensitization is a common health issue. Humans frequently come into contact with chemicals that can cause contact dermatitis over time, including fragrances, sunscreens, certain jewelry and pharmaceuticals such as ointments. In the initial "induction phase," the contact between the skin's surface and skin sensitizers causes the immune system to develop specialized memory cells. An allergic reaction can occur weeks or even months after this initial exposure, causing memory cells to react to the offending substance in what is known as the "elicitation phase". This is clinically characterized as allergic contact dermatitis.

Pharmaceutical producers have a duty to establish toxicology profiles of any new chemical entity, including its potential to cause skin reactions. The classification of substances as skin sensitizers can be based on epidemiology, case studies, or on results from human sensitization patch tests, animal testing or in vitro testing. Toxicologists currently rely on a framework known as the Adverse Outcome Pathway (AOP) to gather, manage and organize data around key events and adverse outcomes. When it comes to skin sensitization, there are four key events of the AOP:

1. covalent binding of skin sensitizers to the skin proteins
2. activation of inflammatory markers in keratinocytes
3. activation of dendritic cells
4. activation and proliferation of T cells

A handful of in vitro skin sensitization tests have been developed, which have been internationally validated and are widely accepted by regulators. One example is the direct peptide reactivity assay DPRA test, which measures binding of chemicals with synthetic peptides that are used to mimic skin proteins (first event). The kerotinosens™ test can then be used to measure a substance's ability to activate an inflammatory response (second event). There are also the h-clat, U-SENS™ and IL-8 Luc assays, which assess dendritic cell activation potential (third event), and other tests based on genomic profiling are in the process of being validated.

However, there are limitations. There are still no in vitro tests available that comprehensively address T cell activation, and the qualitative nature of the AOP framework prevents it from providing in-depth data about molecular and cellular activities that take place within each of the known key events.

At SGS, we are performing in vitro testing to assess the chemical potential for sensitization. Whether it be through employment of existing technologies, or through the development of novel, high-throughput in vitro toxicology methods to investigate biomarker panels at a proteomic level.

Allergic contact dermatitis is a serious issue worldwide and better testing methods are needed – including those that do not rely on animal models. Europe and several other international regions have implemented a full ban on animal testing for cosmetics and cosmetic ingredients, and are further implementing 3Rs (replacement, reduction, refinement) framework in many product sectors. For skin sensitization tests, in particular, there are many alternatives. We have a team of toxicologists dedicated to contributing to the field of in vitro toxicology and can support our sponsors' testing needs with standard assays and custom-based approaches.

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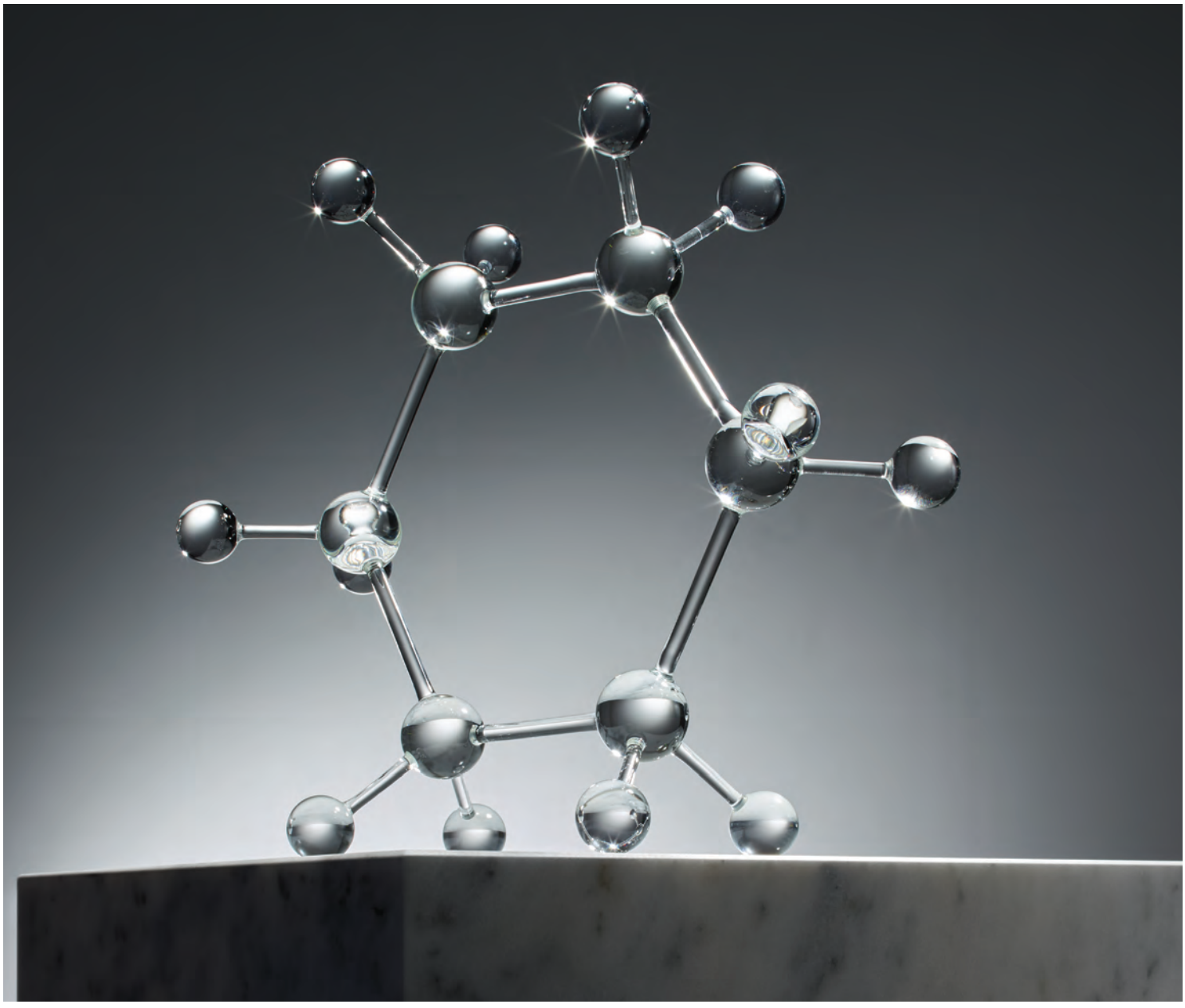

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