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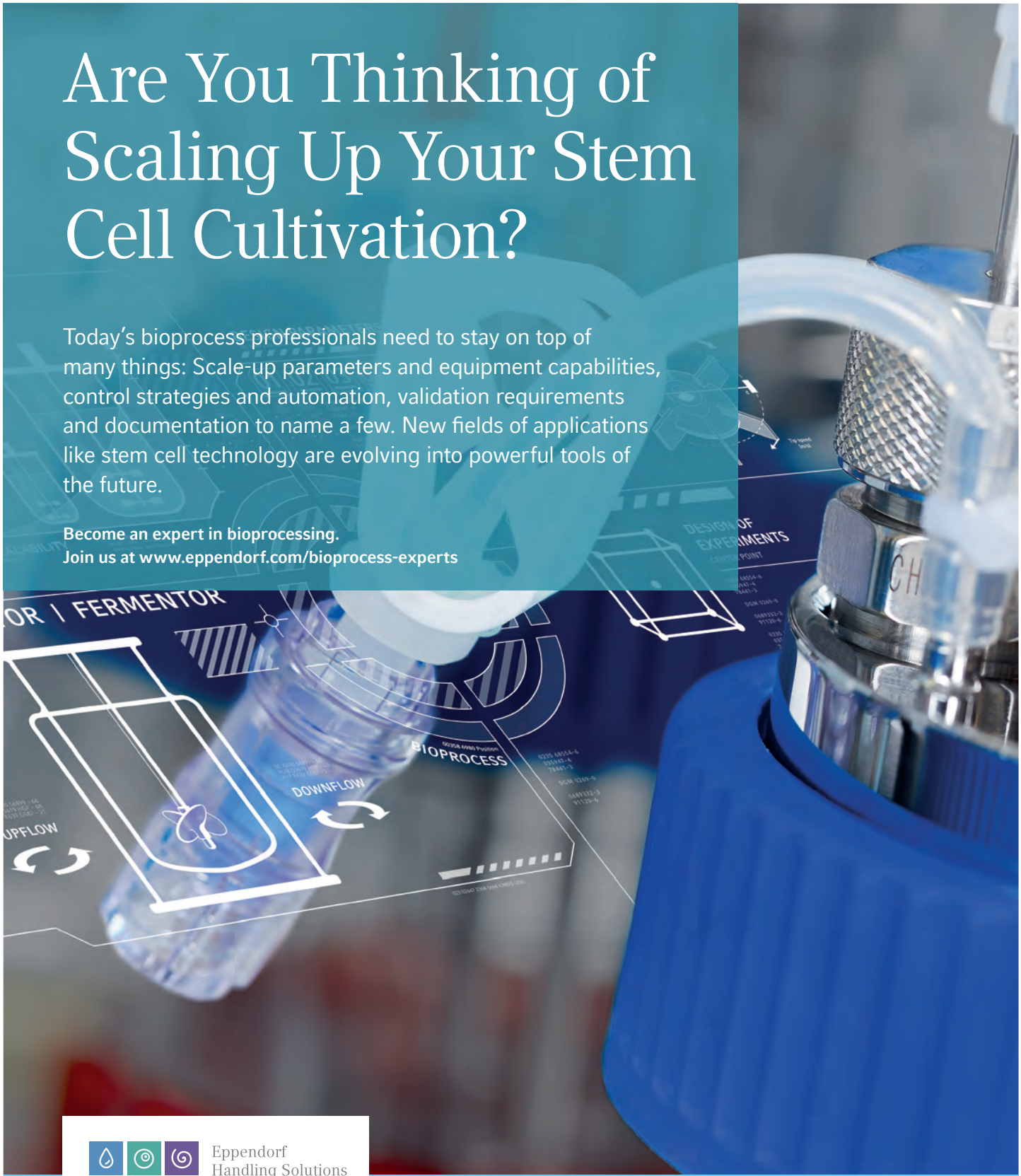

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Online this Month

A Good Citizen

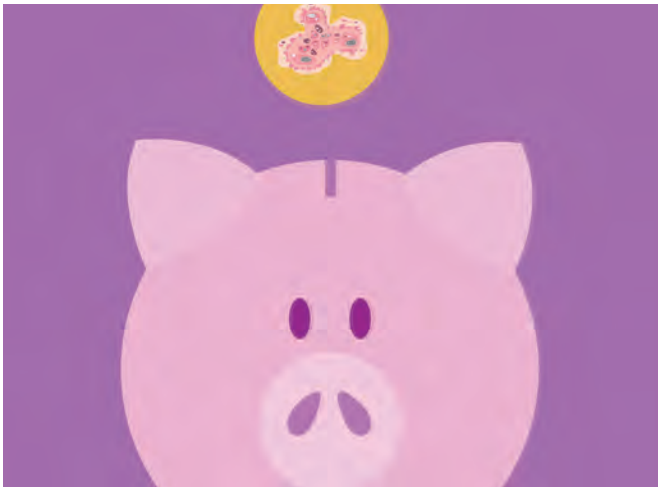
Pharmaceutical philanthropy is the topic of this month's cover feature on page 20, but there's more online, where Susanne Stormer, VP Sustainability Management & Reporting at Novo Nordisk, explains why "being a good corporate citizen is simply the right thing to do".

http://tmm.txp.to/0717/Stormer

The Passing of Raymond Sackler

Pharmaceutical entrepreneur and philanthropist, Raymond Sackler, passed away in July, aged 97. Sackler was one of three brothers who founded Purdue Pharma in Connecticut, after acquiring Purdue Frederick in 1952. The company's most well-known product is the opioid, OxyContin.

http://tmm.txp.to/0717/Sackler



Foundations for R&D Success

The recent BIO congress in San Diego included a panel discussion, moderated by Richard Soll, Senior Vice President of the Research Service Division at WuXi AppTec, on the role that disease-focused foundations are having on drug discovery and development in bridging the translational gap. Traditionally, foundations have acted as funding agencies for basic scientific research and therapy areas – with limited involvement outside of financing projects. However, a disease foundation is now, in many cases, absolutely fundamental to the research and development process. You can read an overview of the panel online.

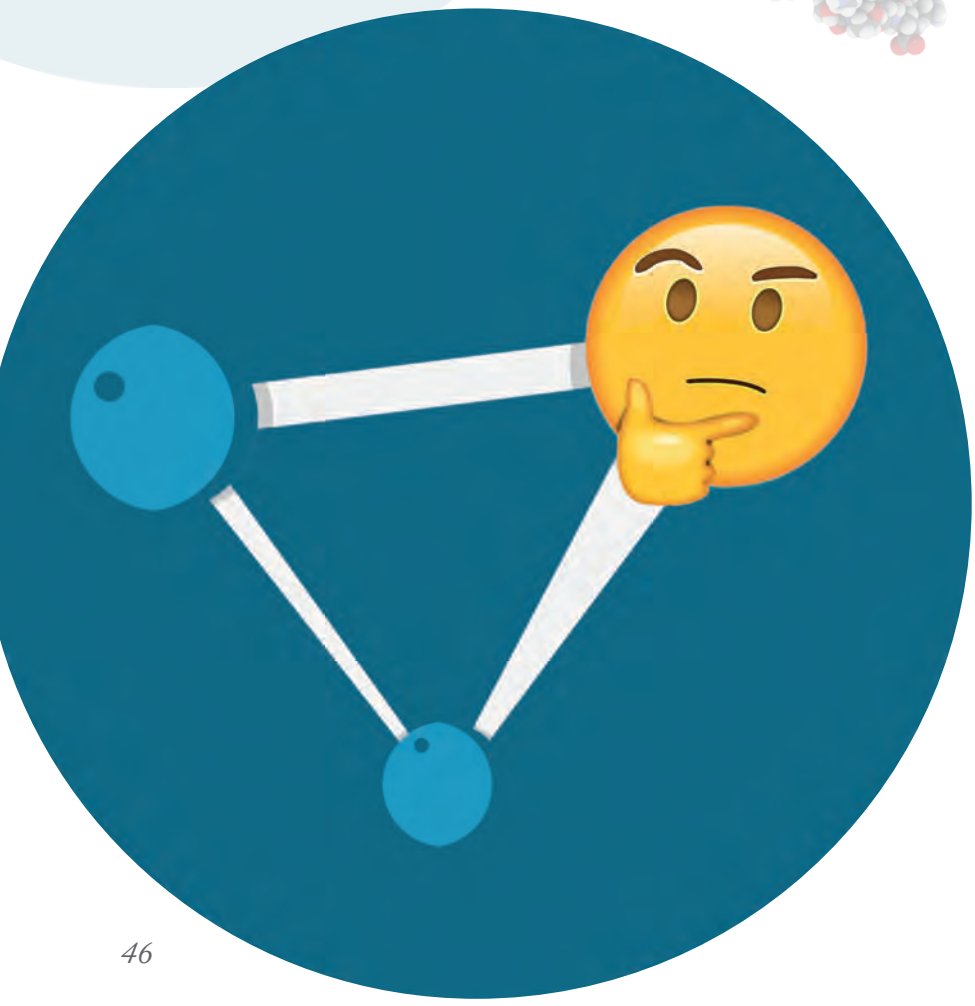
http://tmm.txp.to/0717/Foundations

Don't Forget!

Nominations for the 2017 Innovation Awards are now open at *http://tmm.txp.to/innovation-form2017*

Nominations are also open for the 2018 Power List at *http://tmm.txp.to/2018/powerlist*

Contents



46

50

On The Cover

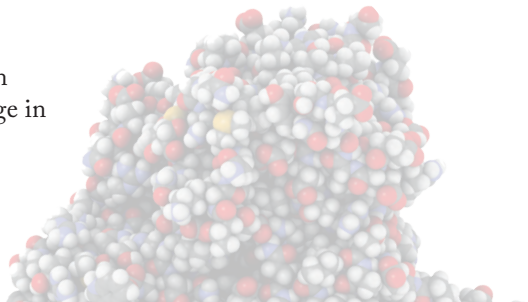
Making a difference – beyond medicine making.

Upfront

In My View

Feature

20



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One Century On

In 100 years, healthcare and medicine are likely to be vastly different to what we can predict – or even imagine.

Speculating about the future makes for fascinating conversation. And because we all want to live long and healthy lives – and want the same for our loved ones – we are probably unified in the hope for a future where the risk of death by disease is very much reduced.

New medicines are emerging all the time, but although many improve the quality and length of life, far fewer offer complete cures. Some in the industry hope that gene and cell therapies will revolutionize medicine, but it's perhaps too early to tell (read more in the supplement to this month's issue, which can be found on our website www.themedicinemaker.com).

Others envision the future of medicine going far beyond curing disease. At a recent event, a scientist confessed that he'd had a conversation with other delegates about how to prevent the aging process. It sounds like science fiction, but a number of studies are underway (1-3). And it wouldn't be the first time that science fiction has accurately predicted the future. In Aldous Huxley's 1932 novel Brave New World, the citizens of London are kept sane with mood-altering medicine; anti-depressants became the subject of experimentation in the 1950s...

Earlier this year, Kaleidoscope Health & Care launched a global competition for short science fiction stories about healthcare in the year 2100. The aim? To generate new creative thinking around healthcare. "In a world where five years counts as long-term, we need to think differently. Thinking about the real long-term in health is exceptionally limited – this means governments and the NHS are flying blind as to where we're headed," states the competition home page (4).

To some extent, we can predict the near future – but as the writer William Gibson once said, "the future is not Google-able." And one hundred years from now, we can at least predict that the world will be very different. As Kaleidoscope's competition page notes, "Some 83 years ago, child mortality was high, hunger was rife, and the NHS non-existent. Yet within 40 years, babies were being born with the help of test tubes, and 40 years later, the human genome had been mapped, and more people were eating too much than too little."

As a fan of science fiction, I'm looking forward to reading the winning entries. But in the meantime, I'd be curious to hear your "shots in the dark" about the long-term future of healthcare, advanced medicine, and the pharma industry: stephanie.sutton@texerepublishing.com

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

When the Stars Align

Multistep continuous-flow manufacturing is easier said than done – especially under cGMP. But Eli Lilly has found a way with prexasertib

The next wave of highly potent and tailored small molecule drugs poses a serious challenge to the current batch manufacturing infrastructure; frequently, oversized equipment is simply unsuitable for lower volumes. And that's why companies such as Eli Lilly – with a number of potent cancer treatments that target small patient populations in its pipeline – are considering continuous manufacturing.

Although many groups have been able to continuously manufacture APIs, achieving cGMP and strict regulatory compliance can be challenging. In a recent study (1), Eli Lilly report the development of a multistep continuous process that produced 24 kg of prexasertib monolactate monohydrate under cGMP. Eight continuous unit operations were conducted to produce the target at roughly 3 kg per day. Kevin Cole, Principal Research Scientist at Eli Lilly and Company, tells us more.

Why focus on prexasertib?

The main technical drivers specific to prexasertib were improved process performance and safety relative to the batch process, both for the step using hydrazine and the ability to control formic acid using distillation, which enabled isolation of the monolactate monohydrate. Continuous manufacturing also makes sense for materials that require high containment, such as prexasertib, because the equipment can either be dedicated to an individual product or disposed of after use.

There is a strong desire within the company and the industry at large to modernize pharmaceutical manufacturing so, to some extent, this was also a test case to assess the feasibility of continuous manufacturing. For a long time, we've wanted to run a manufacturing process in this way, and the "stars aligned" in terms of an active clinical project that had material needs and could be developed for flow.

How does your process improve upon current methods of manufacturing prexasertib?

It was a completely new process in terms of the chemical route used, as well as the salt form that was isolated. We believe that the monolactate monohydrate salt could be produced from a batch process, but we have not substantially investigated that option. Currently, the continuous process enables removal of formic acid solvent by distillation, which has been shown not to work in batch mode due to stability and mass transfer limitations.

There are several significant benefits derived from the new chemistry route: it is two steps shorter, there was a late stage coupling step in the old route that used undesirable reagents and showed high performance variability, it can be more easily scaled up, uses a much less expensive pyrazine starting material, and offers better control in the later steps in terms of solubility. Specifically, in the previous route, there was a step where the insoluble product crystallized from solution uncontrollably. Some of these benefits are due to inherently better chemistry, while others are benefits of continuous processing.

Are there any limitations to continuous processing?

There are currently several challenging areas that we deal with routinely:

1. The formation of solids in a continuous reactor. We need to understand the solubility of all the reaction components to avoid

undesired formation of solids in a continuous reactor (which can cause plugging) and develop high performance reactor types that are more tolerant towards solids.

2. Challenging implementation of continuous processing in the contract manufacturing network because of limited capacity/ability in the external network.
3. Very long reactions that cannot be sped up by heating. As your continuous reactor gets bigger and bigger to accommodate a long reaction, it starts to look more like a batch reactor.
4. Development timelines and the amount of data needed for a continuous process are improving as we gain experience; however, there is substantial operational complexity to linking flow unit operations with process analytical testing that operate simultaneously – advanced process modeling is required to ensure sufficient understanding of the system.

Does continuous processing have a strong role in the industry's future?

There are a many different visions out there for what the future holds for pharma manufacturing – especially with regards to continuous processing. Certainly at Lilly, we envision the future for small molecule manufacturing to be different from the 2017 paradigm, which still primarily uses batch methods for production. We have invested aggressively in the development of continuous processing technologies – and we intend to use them! Our new continuous manufacturing building in Kinsale, Ireland, will allow us to pursue continuous processing much more. Batch processing is not going away, and there are certainly many instances where that method will be used in production. We want to use flow chemistry where it makes sense and provides an advantage. It will be interesting to see where some of the academic efforts in flow and additive manufacturing take us over the next few years. Finally, although Lilly isn't ready for it yet, the concept of a hand-held device that can make individual doses of medicines on-demand using continuous technology already exists – and it will be interesting to see if anything comes of that.

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Pharma Backs Blockchain

Will pharma adopt distributed ledger technology for data management within the next five years?

Blockchain – also known as "distributed ledger technology" (DLT) – is essentially a big record book. A DLT acts as a decentralized, digital journal where transactions and data are recorded across many computers or nodes, so records cannot be altered retroactively or individually. Data or transactions are stored in "blocks" on a blockchain, and it is considered a highly secure way of storing information. Blockchain technology was originally developed for use in the financial services industry, and is now piquing the interest of other sectors that require a secure and scalable system for data storage – such as pharma.

Some pharma companies are already using blockchain to safeguard drug provenance, manage inventories and provide an auditable drug trail. And in a recent Pistoia Alliance survey of life sciences leaders, over two thirds (68 percent) said that their organization is aware of blockchain or currently experimenting with its uses (1). As a result, a large majority (83 percent) of life science leaders believe blockchain will be adopted in the industry within the next five years. However, despite this early adoption, concerns remain over regulation and a lack of industry-wide standards. The survey found that the biggest barriers to blockchain adoption, as identified by life science leaders, are regulatory issues (45 percent), followed by concerns over data privacy (26 percent).

"In an industry conscious of the need to adhere to legislation, and cognizant of the very personal, sensitive data it has access to, it is the lack of regulation that is hampering adoption," says Nick Lynch, a Consultant at The Pistoia Alliance. Lynch argues that industry-wide standards will need to be developed and agreed to realize the potential of blockchain. "A patient's genomic data could be stored in 'blocks' on a blockchain. Standards for the format of its storage (i.e. how data is 'written') will be needed, or data will not be usable or interoperable," says Lynch. "Further, standards for access and sharing are essential to maintain security and privacy. The industry must come together and collaborate to develop these standards."

The survey also found that more than two thirds (68 percent) of life science leaders surveyed believe blockchain will have the greatest impact on the pharma supply chain. 60 percent of respondents believed blockchain will have the most use in storing medical records, including genomic data. "This is particularly notable given that genomic data is the fastest growing dataset in the world," says Lynch.

Lynch adds that the shift in power from medical practitioner to patient will also impact the uptake of blockchain. "Empowered patients have cheap and ready access to their genomic profile or ancestral history for as little as $100 – and they will want to manage this personal data the same way they manage their bank accounts," says Lynch. "Blockchain will support this by offering patients access to, and control over, how their data is used. In the future, patients could even monetize access to their personal data, giving individual companies access to 'blocks' of their data for research purposes. This shift is changing the entire model of healthcare from early R&D all the way to frontline delivery." *JS*

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Generating Generics Faster

The FDA aims to reduce drug prices with a more competitive market

Drug pricing remains a hot topic in the industry, with consumers urging manufacturers and regulatory bodies to bring down the cost of medicines. Now, the FDA are planning to help the consumers' cause. In a press release, FDA Commissioner Scott Gottlieb stated, (1) "Too many patients are being priced out of the medicines they need. While FDA doesn't have a direct role in drug pricing, we can take steps to help address this problem by facilitating increased competition in the market for prescription drugs through the approval of lower-cost, generic medicines."

The first steps toward this goal include speeding up the review of generic drug applications, and simplifying abbreviated new drug applications (ANDAs), allowing certain off-patent, off-exclusivity drugs to be accepted without prior discussion (2). The FDA are also teaming up with the Federal Trade Commission (FTC) to weed out the anti-competitive practices taking place in the market. Gottlieb's press release said, "We know that sometimes our regulatory rules might be 'gamed' in ways that may delay generic drug approvals […] One such example of such gaming is the increasing unavailability of certain branded products for comparative testing […] in some cases, branded companies may be using regulatory strategies or commercial techniques to deliberately try to block a generic company from getting access to test samples."

To gather more input on their plans, the FDA held a public meeting on July 18 and set out three main elements of its "Drug Competition Action Plan" (3), including:

- Looking for places where gaming of the system occurs, and changing rules where possible to ensure that the competition that Congress envisioned is taking place.
- Identifying potential scientific and regulatory obstacles that are hindering generic entry. The FDA aim to address these obstacles by ensuring that regulatory processes are in line with the most current advances in science.
- Focusing on the efficiency and throughput of the overall generic drug program, by ensuring that the FDA is evaluating new generic applications in an efficient manner.

Gottlieb also outlined the submission of a new generic drug user fee program (GDUFA) to Congress, and the creation of a new manual of policies and procedures (MAPP). The proposed GDUFA II intends to reduce the number of review cycles needed for ANDA approval, and increase the communication between the FDA and applicants to boost the chances of approval within one review cycle, while the MAPP outlines simplified documentation for policies and procedures. Despite these steps to streamline the generic review process, Gottlieb also added that, "this efficiency doesn't mean lowering our standards." *WA*

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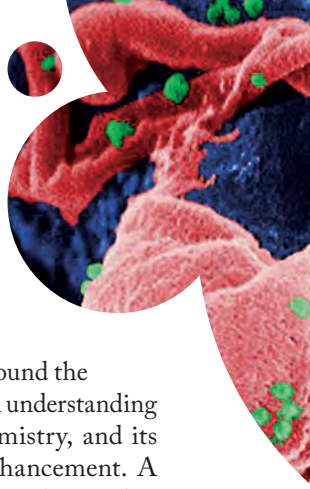

Salvagers of Solubility

High throughput excipient discovery looks set to boost oral bioavailability

A collaboration between the Dow Chemical Company and University of Minnesota has yielded a new method allowing the production of excipients that triple the oral bioavailability of drugs, when compared with commercial excipients (1). To further investigate their work, we speak with Theresa Reineke, a professor at the University of Minnesota.

Why is solubility such a problem for drug developers?

The drug discovery process for new chemical entities has shifted to increasingly less soluble APIs, which demand new methods and excipients for delivery. Coupled with the need to understand the mechanism of action in both solid and liquid states makes effective formulation a challenging analytical problem. To build a better foundational understanding of the systems, our work has combined the synthesis of polymers, use of industry standard processing (spray drying), and the development of improved analytical tools. As APIs cover a wide range of chemistries, it is unlikely that a single solution will work in all cases, so an integrated development approach offers the best opportunity for developing API specific solutions.

How did you find the solution to insolubility?

Our findings came about through our efforts to understand how variations in polymer chemistry affected drug solubility. We aimed to synthesize well-controlled copolymers that would allow us to study the structure/property relationships and interplay between an active drug and an excipient. During our research, several of the systems showed enhanced results when comparing the copolymers to polymers currently used in the field. An example of this was the NIPAm-DMA copolymer, which was highlighted in our recent publication (1). Through the application of high throughput (HTR) synthesis and API supersaturation screening, we found that the performance could be tailored to the excipient during API development, while working within a defined design space. A couple of graduates from the University of Minnesota collaborated with us to add to our original work, and synthesize an array of copolymers with a variety of monomers and compositions using HTR semi-continuous parallel polymerization reactors, then rapidly screen them using a parallel super-saturation test.

How long have you been developing high throughput capabilities?

We have been developing high throughput capabilities for close to two decades, and as part of those efforts we were able to miniaturize and parallelize the super-saturation test that allowed more rapid screening with the additional benefit of reduced volume materials. Techniques like these let researchers probe a larger experimental design space, and approach analytical questions more holistically.

What's next for your research?

Our next steps revolve around the initial research focused on understanding the role of polymer chemistry, and its relation to solubility enhancement. A key discovery from our work was that nano- and microstructures of polymer systems during dissolution play a critical role in solubility enhancement. We're building upon this finding by designing systems with controllable structures to more systematically probe these effects.

The university continues to be a strong partner to Dow, particularly when it comes to the areas of organic and analytical chemistries, polymers, and reaction engineering. As such, we remain focused on the future, looking for scientific breakthroughs and technologies.

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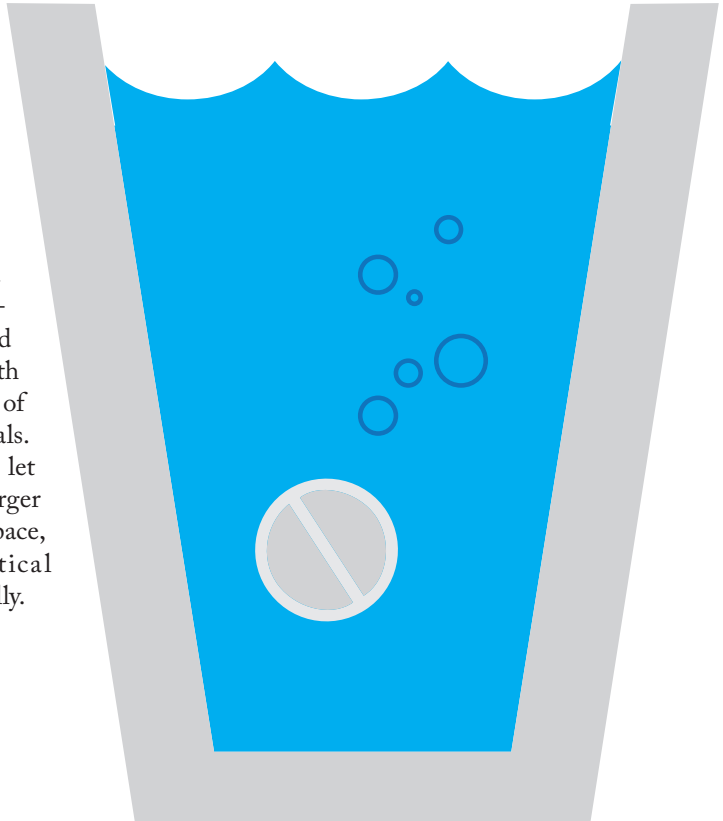

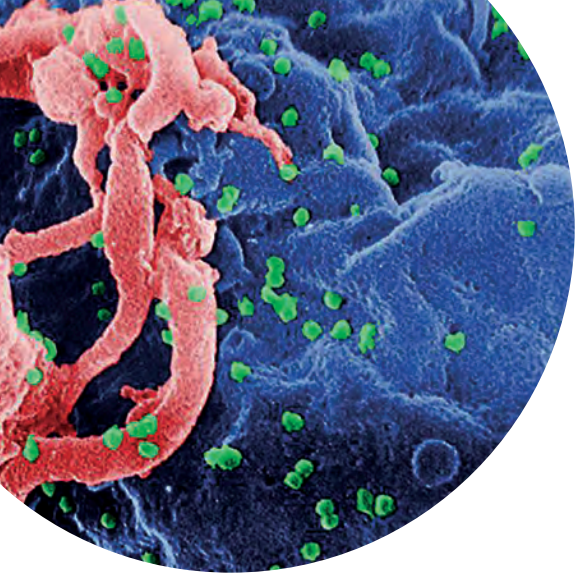

Reducing HIV Recurrence

A small molecule drug has shown the ability to diminish HIV reservoirs

Given HIV's ability to rapidly replicate and integrate itself into DNA from immune human cells and stay dormant for years, it remains a challenging infection to treat. "In the past, medicines have helped reduce the circulating virus to an undetectable level, but as soon as the patient stops taking the drug, the viral load comes back up," says Jean-Marc Steens, CMO of biotechnology company, Abivax.

To complicate matters, drug regime adherence is rarely – if ever – perfect. "Recent data presented at CROI (the Conference on Retroviruses and Opportunistic Infections) showed that in the US, many patients aren't taking their drugs as prescribed. From a public health perspective, these patients become infected again and could unknowingly transmit the disease, breaking down the whole paradigm we're working so hard to upkeep," says Steens.

So could public health risk be reduced by tackling the viral reservoirs that allow HIV to resurface? Abivax's small molecule – ABX464 – is the first drug to show a treatment-induced decrease in HIV blood reservoirs. Results from its recent phase IIa safety trial showed that eight of the 15 treated patients displayed a response to the drug (response was defined as a minimum reservoir decrease of 25 percent and absolute decrease of 50 copies / million PBMC's), while there were no placebo group responses to the drug (1).

"The 'father' of the molecule, Prof. Jamal Tazi, is the head of a collaborative lab between Abivax and CNRS (Le Centre National de la Recherche Scientifique), and he's been working on mechanisms of RNA biogenesis for 15 years, which resulted in investigating how different processes could impact RNA biogenesis, and if any pharmacological agents could affect it," says Steens.

Abivax is expanding the drug's role beyond the bloodstream by working on a study that investigates HIV reservoirs in the gut (data from first cohort of patients is expected by the end September 2017). Abivax also has plans to expand the capability of its platform beyond HIV. "ABX464 is specific for HIV because it targets the rev viral protein," says Steens, "But we do have other molecules in development – at a much earlier stage – that could target other viruses, such as dengue, chikungunya, and zika." *WA*

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Bad Brexit Risks Lives

An "unprecedented" joint letter from eight trade associations to Brexit negotiators warns of "supply disruptions to life-saving medicines"

Eight trade associations representing the European and British pharmaceutical industries have written to Brexit negotiators, Michel Barnier and David Davis, to underline the importance of close cooperation between the EU and the UK on medicines (1).

The letter warned against an "unorderly withdrawal" that would risk medicines being held up at EU/UK borders during customs checks or in warehouses as a result of new extensive retesting requirements. "This would lead to a severe disruption of most companies' supply chains, which would lead to potential supply disruptions of life-saving medicines," said the authors.

The Association of the British Pharmaceutical Industry (ABPI), one of the signatories, has described the letter as an "unprecedented step". The seven other signatories spanned the EU/UK pharmaceutical sector: the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio, Medicines for Europe, British Generic Manufacturers Association (BGMA), BioIndustry Association (BIA), and the Proprietary Association of Great Britain (PAGB).

The authors also called for an "implementation period" after the UK leaves the EU on March 30, 2019, so that pharma and biotech companies can transition to a new framework. The authors said, "This will allow companies time to make the necessary arrangements to avoid any unintended consequences on the availability of the medicines."

The MHRA's contribution to the work of the EMA was also highlighted, along with the potential for a loss of capacity and expertise within the EMA – both for the review of medicines and pharmacovigilance – should the UK withdraw from the European regulatory network. "A capacity building exercise would be needed, leading to duplication of assessment work at EU and national level," states the letter, which also notes that Qualified Persons Responsible for Pharmacovigilance (QPPVs) would need to be relocated or replaced – a consequence of the UK leaving the European Economic Area (as John Barber argued in last month's issue of The Medicine Maker) (2). "This would have an overall impact on the running of the systems that ensure the safety and efficacy of medicines treating EU patients," said the authors.

In January this year, UK health secretary Jeremy Hunt said that leaving the EU meant there would be "separate regulatory arrangements" and that he did not expect the UK to be a part of the EMA because it would entail being "subject to the European Court of Justice." He did not, however, rule out the possibility of a mutual recognition agreement between the EMA and the MHRA (3).

Hunt reiterated the government's desire to "work closely" with the EMA after Brexit in a letter to the Financial Times earlier in July (4). But the letter also went on to state that if the UK government does not achieve its "desired relationship" with the EU, it would set up a regulatory system that "protects the best interests of patients and supports the UK life science industry to go from strength to strength." *JS*

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The Significance of Solid Form Science

With approximately 80 percent of new drugs suffering from poor solubility and bioavailability, understanding solid form is more important than ever.

There are a number of ways to manipulate a molecule's solid form to achieve the optimal physiochemical properties, including solubility and bioavailability, for the chosen delivery method. Alan Chorlton has spent the best part of 25 years working in solid state science, and in 2003 he cofounded Pharmorphix – a company specializing in solid state pharmaceuticals. In 2015, Pharmorphix was acquired by Johnson Matthey, where Chorlton now works as a Commercial Director. Here, Chorlton gives an overview of the field and how solid form science has progressed in recent years.

Why is solid form optimization so important?

Once a pharmaceutical company has identified a molecule they want to move through to the clinic, understanding and choosing the right solid form is vital to give the product the best chance of future success. Manipulating the solid form can help enhance key properties, such as bioavailability and solubility, and facilitate synthesis and scale up. Different routes of administration all require different physicochemical properties – what works for an oral formulation is often different to what works for a dermal formulation, for example. Adjusting the solid state, by developing co-crystals of a drug molecule, for example, can make a big difference. We managed to transform a drug that caused dermal abrasion into a molecule (using co-crystals) that could permeate the skin, without irritation. It's also possible to use solid state science to control properties such as solubility and pH, which are important in ocular and intravenous formulations.

How can the solid form be optimized?

The first port of call is usually to manipulate the solid form by choosing the right salt. Around 80 to 90 percent of drugs on the market are ionized, which means researchers can make different salt forms. Choosing the right salt can lead to better stability and solubility, depending on the delivery method, so it's important to have a good salt selection process. Usually, a molecule is screened against 20-40 different salt types to try and establish the salt that has the best properties for the desired formulation, be that an oral drug or a dermal formulation.

Once you've identified one or two salts with the right physiochemical properties, the next step is to consider polymorphism – the ability of a drug to exist as two or more crystalline phases – which can affect stability, solubility, synthesis and scalability. It is critical (and a regulatory requirement) that your polymorph be stable to prevent it from changing during the drug's shelf life – in extreme cases, some drugs have been withdrawn from the market due to polymorphic changes. At an early stage of drug development, it's important to review the different polymorphic forms of your molecule to establish which is most suitable. Polymorphic forms can also be patented, offering the potential to extend a drug's lifecycle.

How is the field of solid state sciences advancing?

Advances in high-throughput screening technologies – as well as analytical systems – have made searching for polymorphs much faster. In the past, it might have taken a PhD chemist an hour to analyze a sample, but now hundreds of polymorphs can be analyzed with x-ray powder diffraction within hours. Another important technique is single crystal x-ray diffraction – which is currently the best way to identify your molecule's crystalline structure.

There have also been significant advances in the understanding of amorphous materials. Amorphous materials are non-crystalline solids that can help enhance bioavailability and solubility – making them good candidates for pharmaceuticals. Historically, pharma companies have been wary of amorphous forms because, unlike crystalline forms, they lack a specific crystalline order, which means they can destabilize at any time – a ticking time bomb for your approved drug! Over the past decade, advances in solid state science, along with the emergence of hot melt extrusion and spray drying, have allowed amorphous materials to be stabilized. Today, there are around 30 amorphous drugs on the market, which is a significant increase over the last decade.

What is the most important element of solid state science?

Integrating all the various aspects of solid state science is arguably the most important factor. Understanding a molecule's physiochemistry and being able to screen for and take forward the right salt forms is one thing, but you must also have the right processes in place to scale up and manufacture the drug to develop stable and effective formulations. You need to develop a crystallization process that allows the molecule to be synthesized and manufactured consistently and repeatedly, and implement control measures to get the right yield and purity.

I derive great satisfaction from the fact that many of the drugs we've worked on at Johnson Matthey at the early stage are now on the market. Without the expertise that went into choosing the right solid form, many of these drugs might not have made it.

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

Continuous Control

If the pharma industry wants to replace conventional batch processing with continuous manufacturing, it must also employ control procedures to ensure quality.

By Jamie Clayton, Operations Director at Freeman Technology, UK.

According to the FDA, continuous manufacturing has many advantages... greater consistency in product quality, reduced inventory, lower capital costs, a smaller ecological footprint, minimized manual handling, shorter process times through integrated processing, the ability to employ real-time release testing approaches... In essence, continuous manufacturing supports Quality by Design (QbD) initiatives by allowing quality to be directly built into a process – and the FDA is encouraging companies to consider continuous technologies (1).

However, working with a truly continuous system within a highly-regulated sector incurs challenges. Consistent outputs depend entirely upon the quality of feed materials, as well as a comprehensive understanding of how those materials behave within the process, and how changes in process conditions might affect that behavior. You must know exactly which material parameters are critical to your process – after all, there's little benefit in generating multiple parameters if they have no relevance on what you're trying to achieve.

When it comes to powders, employing tests that simulate conditions within the process is key. Accurately building a design space within which optimum process performance can be maintained requires comprehensive characterization of the powders – and that characterization needs to be relevant to the process. Traditional powder characterization methods, such as angle of repose, flow through an orifice, and tapped density, have been shown to be limited when used to define design spaces representing continuous flow. Instead, dynamic testing, where the axial and rotational forces acting on a blade as it rotates through a powder sample, can directly evaluate powders in consolidated, conditioned, aerated, or fluidized states – just as they would be within a processing plant.

In a continuous manufacturing process, powder particles move as a highly-stratified flow stream in continuity. Inline testing, such as particle size and near-infrared (NIR) spectroscopy composition analysis, can help – enabling processes to be monitored in real time and operators to react accordingly – but there's no reason why samples can't be extracted and measured using appropriate offline techniques to ensure consistency with a pre-determined design space.

Consider granulation: the true implementation of QbD would be to associate the properties of the granules as early as possible with a critical quality attribute (CQA) of the final product (for example, tablet hardness, dissolution properties, or disintegration) – something that we can do reliably and efficiently using dynamic characterization methods. We took part in a collaborative study that used dynamic characterization to quantify the impact of process changes on properties of granules produced by a continuous high-shear wet granulation and drying system. And we demonstrated a direct relationship between the bulk flow properties of the granules at all stages of manufacture, as quantified by the basic flowability energy (BFE), and hardness of the resulting tablets (2).

Critical process parameters are those that contribute to that CQA, such as machine settings, process speeds and length of operation, and it is possible to target specific tablet properties using different combinations of process settings. Continuing to use the wet granulation process as an example, these will include mixing time, chopper and impeller speed, and water addition rate. If the wet granulate attains the target BFE, then tablet quality can be assured – and there's no need to take samples at every stage of the process.

Right now, continuous processing within the pharma industry is in its early days, but interest and uptake are growing, and lessons are being learned every day that will help optimize the technology. Many other industries already use continuous manufacturing for mass production and I believe it also has a strong future within pharma.

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Testing the Boundaries

Are you compliant with the new guidelines for elemental impurities? There's only six months left to get up to speed.

By Sarah James, Principal Scientist, CMC Analytical Services at LGC, UK.

In June 2016, the FDA announced new draft guidance on reducing elemental impurities in drug products. Elemental impurities can make their way into a drug product from various points in manufacturing processes – and in some cases can be a risk to patients. The aim of the guidance is to help manufacturers of both new and generic small-molecule drugs to comply with recent standards introduced by the International Council for Harmonization (ICH) and US Pharmacopeial Convention (USP). These standards, which are established in USP General Chapters <232> Elemental Impurities – Limits, and <233> Elemental Impurities – Procedures, as well as ICH Q3D – Guideline for Elemental Impurities, come into full effect at the start of 2018 and place drug elemental impurities into various new hazard categories based on their toxicity (permitted daily exposure [PDE]) and likelihood of occurrence in the drug product, which is derived from a number of factors including probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes, and the observed natural abundance of the element.

To comply with the new guidelines, companies will need to carry out a detailed risk assessment of their materials using the new categories. For non-experts, the subject of elemental impurities can be daunting; extensive expertise is needed to effectively characterize elemental impurities, including the development and validation of appropriate assays. Traditionally, wet chemical tests have been used for the determination of heavy metals in drug products but, in my view, inductively coupled plasma-optical emission spectroscopy (ICP-OES) and inductively coupled plasma-mass spectroscopy (ICP-MS) are much better approaches since they offer improved elemental specificity, accuracy, and sensitivity – as well as the added confidence that comes from targeted quantitative data. Not only are these techniques well placed to ensure that materials meet the new compliance criteria, they are also already well used in the industry.

But is the industry ready for the new guidelines and the increased use of these techniques? I am not so sure. The typical remit of today's pharmaceutical quality control laboratories does not normally include delivery of large volumes of ICP-OES/ICP-MS drug product testing. To succeed, experience and knowledge will be key. Scientists will need to understand how to develop both limit and quantitative test methodologies for a wide range of sample matrices, as well as being able to effectively use specialized sample preparation techniques and digestion regimes. Metal speciation is also challenging and requires the use of either intricate targeted sample preparation to solubilize only the desired species or chromatographic separation, followed by ICP-MS as an ion detector. The latter approach is becoming more common within inorganic laboratories as techniques such as HPLC-ICP-MS become more affordable and accessible.

Companies will need to implement a control strategy to ensure that their drug products meet the new guidelines, which may range from purely paper-based risk assessments (if manufacturing controls and existing elemental impurity data are sufficient) to analytical screening of complete product portfolios. Where initial risk assessments highlight potential

control issues, targeted analysis of specific products or components may be necessary. Screening involves examining at least 24 elemental impurities at 30 percent PDE in multiple dosage forms with multiple maximum daily doses.

I believe the risk of elemental impurities being present in the majority of final products is generally low because of existing manufacturing and supply chain controls. However, providing sufficient evidence for this within an ICH Q3D risk assessment without the use of screening data can be difficult – especially given the lack of existing elemental impurity data for many product components. In higher risk scenarios – for example where the patient is exposed to exceptionally high doses, or where products contain significant quantities of natural, mined excipients – provision of adequate evidence is even more important. The finalization of ICH Q3D, and the associated implementation of USP <232> and <233>, has been a long drawn out process. Some in the industry have been slow to react to the forthcoming changes and many others still do not understand the guideline's requirements. But we're now over half way through 2017 and the 2018 deadline is looming...

Breathe It In

The potential of inhaled drug delivery goes beyond traditional respiratory medicine.

By Simon Moore, Director of Inhalation Science and Engineering at Envigo, UK.

Historically, inhaled drugs have targeted the main respiratory diseases, namely asthma and chronic obstructive pulmonary disease. Inhaled drug delivery, however, has a number of inherent advantages that can also benefit other therapeutic areas. Compared with oral drugs, for example, inhaled medicines avoid first-pass metabolism and degradation in the GI tract. Inhaled drugs also often require lower dose levels and usually provide faster onset of action (1). And when it comes to comparison with parenterals, inhaled drugs are less intrusive and provide improved stability, especially for proteins and peptides (2).

Despite the benefits, however, the development of inhaled products poses unique challenges; for instance, creating an effective drug formulation requires considerable expertise in particle science. The size of the particle is pivotal for inhalation studies to ensure effective lung deposition. Traditionally, the fine drug particles required have been produced by mechanical micronization, using air jet mills. These particles are then often combined with a lactose carrier to improve drug stability and dose control, depending on the drug type or compound class. More recently, formulation options have expanded thanks to advances in particle engineering techniques and technologies, as well as nanotechnology, which allow for greater control over the size, shape and chemistry of particles.

When planning efficacy and toxicology studies using inhalation technologies (regardless of formulation), dose delivery methodology and the reproducibility of effective dosing are crucial. The main methodologies for drug delivery in non-clinical studies are intratracheal and inhalation dosing. Intratracheal dosing involves anesthesia and intubation, with the drug delivered via bolus through the intubation tube, and is principally used for early screening studies. This method is simple, uses minimal amounts of drug, and the delivered dose is easily quantified. However, it is prone to artefactual toxicological and pharmacological results, and the particle size used in testing often differs from that which will be used non-clinically.

Inhalation dosing, on the other hand, delivers compounds to conscious animals by the clinical route of administration (the lung), removing the risk of intratracheal artefacts. The challenging aspect of this method is the necessity for specialist inhalation technology capabilities and experience. Having the ability to reproducibly control the aerosol during both intra- and inter-exposures is pivotal in ensuring that study integrity is maintained; failure to achieve reproducible control may compromise study endpoints, allowing poorer data interpretation and reducing the scientific impact of the study. At worst, the study may need to be repeated if the aerosol is not controlled effectively.

There is also the inhaler device to consider – another significant development challenge. A proprietary inhaler provides a unique opportunity for extended patent protection; in the US, for example, GlaxoSmithKline's Advair (Seretide) came off patent in 2010, but the Diskus delivery device remained in patent through 2016. An inhaler device must be matched to the patient, easy to use, forgiving of poor technique, and able to provide feedback to the user about dose emission and technique. And though this may sound straightforward, it is challenging to achieve in practice – and without a good inhaler device, a drug is unlikely to be successful.

In my view, although the challenges involved in inhaled drug development are perhaps greater than for other routes of administration, inhaled drugs do offer

benefits to those companies that have the scientific expertise to develop them. The industry is competitive, and companies need to move beyond the traditional methods of drug discovery and development. Switching established products to another delivery format can extend a product's value proposition – and potentially lead to a more effective medicine. Drugs can easily be de-risked early in development by incorporating additional endpoints into initial in vivo studies and by taking advantage of new particle engineering methods. There are still tremendous opportunities to develop new and improved therapies that will have a positive impact on the lives of patients – and there are many drug delivery options, including the inhaled route, and technologies that have yet to be fully explored.

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Science Versus Trump

Proposed cuts to the funding of US scientific agencies will be detrimental to global health – not just the health of Americans.

By Catherine Bollard, President of the International Society for Cellular Therapy, US.

President Donald Trump's budget request for 2018 caused a huge stir in the scientific community because of its potential impact on research. Funding for a number of agencies has been cut, including the National Institutes of Health (NIH). The NIH's proposed 2018 budget is $26.9 billion, down from $34.6 billion in 2017. All eyes will now be on Congress, which ultimately decides what funding agencies receive. It is important to emphasize that although Trump's focus is on the US, his views and policies have a global impact, especially given that a number of US federal agencies support global research. Foreign position scientist programs, involving travel to and from the US, have been incredibly effective in addressing global health issues, such as HIV, malaria and Ebola. When you see budget cuts that could affect these programs, you realize the devastating impact it could have.

Some members of the US public argue that their tax dollars shouldn't be spent on research and trading outside of the US, but it is important to emphasize that global research ultimately helps the US. For example, although the Ebola epidemic mainly affected Guinea, Liberia, and Sierra Leone, it also ended up on America's doorstep and caused a huge panic. The epidemic was brought under control with an international collaborative effort funded from multiple sources, including the US. The funding is also being used to develop a vaccine, which is progressing well so far, and will help many people in future breakouts. Another example is Zika, which has begun to affect the US. Tackling Zika requires global collaboration. Zika cannot be studied effectively without bringing foreign doctors to countries like the US to be trained appropriately – or without sending doctors from the US to Central South America. Yes, American taxpayers' money may be spent on these global initiatives, but ultimately it will still benefit the US. Ebola and Zika are just two examples; there are multiple other diseases that are unlikely to see a cure without global funding.

As an industry, we have made incredible leaps forward in science and medicine. In particular, I believe that cell therapies have come a long way and we are on the verge of a major shift in medical care. Cell therapies, however, do not fit the general pharma business model so the field needs help to reach its full potential. Cell therapies require extensive research and development, and usually involve the manufacturing of a unique product on a per patient basis, which makes it a less attractive therapeutic model for pharma companies. Though some research projects in drug-focused fields may be picked up by the industry if government funding decreases, it isn't likely to happen with cell therapy research given the challenges around commercialization and return on investment.

The US political climate isn't the only one that could impact global health and science – we still don't yet know how Brexit and other changes in UK politics might come into play. I believe that funding global initiatives and collaborative approaches across multiple countries are the way to tackle today's unmet medical needs in areas such as cancer, immune related disorders and neurodegenerative disease. The industry needs to voice its concerns over propositions that could damage scientific progression. The International Society for Cellular Therapy has a presence in the US and internationally, and we are looking for other avenues to affect change. But, for now, uniting the scientific community to educate people about the importance of funding global ventures is highly important.

HEAL THE WORLD

Beyond developing medicines, what is the pharma industry doing to help make the world a better place?

Modern medicine is considered one of humankind's greatest advances, and the pharma industry is undoubtedly responsible for saving countless lives. The industry is also well known for making large profits, but as well as investing money back in R&D, many companies feel the need to give something back to society and global health in other ways – by donating cash, vaccines, or establishing not-for-profit foundations, for example. To celebrate pharma's philanthropic side, we explore just a few of the many positive stories that often go unreported – examples of companies making a difference, as well as making medicines.

DOING IT FOR THE KIDS

When looking to do good, many companies choose to focus on children's health, particularly in developing countries.

By William Aryitey

The emotive issue of child mortality resonates with us all, and some of the statistics from the World Health Organization are shocking. Of the 5.9 million children who died before their fifth birthday in 2015, more than half could have been saved by access to simple, affordable interventions. Donations have their place, but Lisa Bonadonna, Global Head of the GSK-Save the Children Partnership, says that collaboration is one of the most sustainable ways to make a difference – pharma has the resources and manufacturing knowhow, but charitable organizations understand the realities of helping people in need – often in challenging locations and environments. Here, Bonadonna tells the story of how GSK and Save the Children came to work together – and how mouthwash inspired a new medicine for preventing neonatal sepsis.

How did the collaboration begin?

The initiative was kicked off by GSK's former CEO, Sir Andrew Witty. Both Justin Forsyth – the former CEO of Save the Children – and Andrew were looking to take their organizations in a similar direction. Andrew wanted to ensure our medicines were available to whoever needed them, not just high-income or high-resource settings. And Justin knew that if Save the Children wanted to effect a wider gamut of change, he'd have to involve the private sector in some capacity. After Andrew reached out, the pair had a few conversations, culminating in a seminal meeting with the top people at GSK. During that presentation, it was actually Emma Walmsley – the current CEO of GSK – who asked the question, "How do we make this happen?" As of 2013, the partnership officially began.

When Emma started her new role as the CEO earlier this year, one of the things she initially prioritized was sitting down with myself and Kevin Watkins – CEO of Save the Children at the time – to let us know that she was committed to GSK's global health goals and, in particular, the partnerships we had.

How do the two organizations work together?

A pharma company like GSK has the expertise and ability to develop and make high-quality healthcare interventions, but it's organizations like Save the Children that provide the practical information about a medicine's potential use. A really good example of how we work together is the development of the chlorhexidine gel (Umbipro), which is applied to newly cut umbilical cords. The United Nations issued a call for more chlorhexidine treatments to tackle neonatal sepsis – which kills hundreds of thousands of babies every year. Chlorhexidine is a component of our consumer mouthwash, Corsodyl, so we were very familiar with working with this active ingredient. And we thought that perhaps we could develop something to help tackle neonatal sepsis.

Initially, GSK were thinking of a liquid formulation, but this is where the experience of Save the Children came into play – they explained that liquid formulations were difficult to implement in low-resource settings, particularly those where people are living in remote, traditional dwellings. Not only can liquids be more challenging to store, they could also be mistaken for other common treatments. This led to the decision to formulate a gel with a better temperature and humidity stability profile, and a sachet which has little pictograms showing clearly how it should be used. The gel has so far been used on over 15,000 newborns in our partnership program in North-West Kenya, and has helped stop the practice of putting harmful substances like dung or ash on the umbilical cord.

We also work with Save the Children in the middle of the Democratic Republic of Congo – a particularly challenging environment. Initially, there was no cold chain supply to get vaccines safely into remote communities, but one part of our program was to install solar fridges that allow the provision of vaccines to children in areas that otherwise wouldn't receive a single dose. I've personally been to some of these communities; it's very emotional. Thousands of mothers showed up with their babies to

I think that those people who are critical of projects **like our partnership with** Save the Children **need to see the motivation that lies behind it:** saving children's lives."

complete their vaccination course – some of whom travelled for a day or more just to get to the clinic.. Seeing the work we're doing in person really reinforces the fact that we're truly touching lives.

How does this collaboration differ from other initiatives at the company?

GSK has always had a long-standing commitment to global health, from our Albendazole program (to date we have donated seven billion doses) to our 20 percent reinvestment of profits from Africa and Philippine regions into healthcare and training for those regions. Donations are valuable, but collaborations based on a shared value space – like our collaboration with Save the Children – help to establish more sustainable solutions for the longer-term. For example, our Umbipro gel is being made available at a not-for-profit access price and, additionally, GSK is willing to make available information to support local manufacturers willing and able to make the gel themselves.

What drew you to your role?

With a PhD in immunology I was all set for a career in R&D, but things ultimately turned out very differently! I started out as a molecular biologist, but I had the good fortune to work in numerous roles in the pharma industry, including clinical trials, medical affairs and commercial. Eventually, I leveraged my academic background and became Vice President and Head of the adult portfolio of vaccines with GSK – a fascinating and rewarding experience. I was in this role when the H1N1 pandemic hit. It was a privilege to be part of the team that handled a global pandemic so very well in terms of delivery – I think the final number was well over 300 million doses of vaccine delivered globally in about six months, which is phenomenal. This experience peaked my interest in public health, so I did a Masters in the London School of Economics and the London School of Hygiene and Tropical Medicine in health policy and financing. As I completed my studies, GSK decided to embark on a partnership with Save the Children – one of the world's leading children's charities – and were looking for someone to manage the collaboration.

How do you feel about those who criticize pharma's charitable endeavors?

At GSK, we have also learned so much from the partnership – particularly in terms of how to solve problems using a low-resource lens. Sometimes you need to step back and come up with a new solution that's actually low-tech and low-resource – often that's the best fit for the situation.

Within GSK, our employees are really motivated by the company's commitment to global health. We have an employee volunteering program called PULSE, which gives employees the opportunity to get to know some of our partner organizations and work with them on a skills-based volunteering basis. The program is oversubscribed every year. We also have cases of people saying they want to join the company, in part due to our partnerships and work with global health (which all underpins GSK's approach to helping the company retain its top ranking in the Access to Medicines Index).

Today, there is a lot of criticism and cynicism towards pharma, and I don't think I can fight it simply by saying "it's not true". All we can do is show the benefits to all those involved, and let the results speak for themselves – and continue to help save 1 million children's lives with the support of all our GSK and Save the Children colleagues worldwide.

MORE THAN PR

The first principal of corporate social responsibility is to improve lives – but goodwill and positivity are infectious.

By James Strachan

Some people view the charitable work of pharma companies as nothing more than a public relations exercise, but Rob Smith, Senior Director of Corporate Social Responsibility and President of Eli Lilly's Lilly Foundation, believes that CSR is about actions, not words.

What is your role at Eli Lilly?

In July this year, I celebrated my 21st anniversary with Lilly. My career started in finance where I had a number of jobs, including working in investor relations, which was a great role to better understand our company, industry, and what shareholders expected of us. I have been in this role, leading CSR and the Lilly Foundation, since 2005. We have worked to make our efforts more global and more strategic, including the philanthropy of the Lilly Foundation. Our areas of focus are global health, strengthening communities, especially our headquarters community of Indianapolis, and employee engagement.

How are you improving global health?

One prominent example has been our work on multidrug-resistant tuberculosis (MDR-TB). In the late 1990s, we began working with Paul Farmer and Partners in Health (PIH) to provide greater access to two older antibiotics, both off patent, for MDR-TB. PIH had independently seen that these two drugs, in combination with other medicines, proved highly effective in treating MDR-TB in a study they conducted. What began as a straightforward donation

program evolved into a comprehensive, multiyear collaboration to improve health outcomes for those suffering with the disease.

A key part of the partnership involved the transfer of manufacturing technology and expertise. The motivation? We knew it would not be good for the global health community to be reliant largely on one high-quality supplier for the two medicines, so we worked to transfer our technical capabilities to a number of companies worldwide – particularly in locations where the disease was most prevalent.

The Lilly MDR-TB Partnership has been a long-term collaboration with nearly 40 partners and combined investment of nearly $200 million since 2003. I am proud to say that this work has led to improved diagnosis and treatment of MDR-TB. Regarding our technology transfer, we learned many lessons during

this process and wanted to share them with others by writing a white paper (http://bit.ly/2f001p1).

Going forward, we will expand our work in global health, especially diabetes and cancer. We will also continue our long-standing work with the International Diabetes Federation on the Life for Child Program. As part of this program, we are donating about 250,000 vials of insulin every year to help around 13,000 children with type 1 diabetes in dozens of countries. We also will build on our long-term partnership with AMPATH in Western Kenya to help with their efforts to improve cancer screenings, diagnosis and care.

You also do a lot of work closer to home in Indianapolis…

That's right. Our corporate headquarters are in Indianapolis, Indiana, USA, along with 25 percent of our workforce, and our largest R&D footprint in the world. We have been involved in helping our home community for over a century and that continues to this day. We view this as the right thing to do, but also good for our business. For example, recruiting and retaining great talent is easier if we are operating in a strong, vibrant community. We have many things happening here in Indianapolis, but our main focus is on expanding access to high-quality education opportunities for children from low-income families. One of the guiding principles behind our philanthropy is that we use our resources and position in the community to rally others to join us. By leveraging resources from both private and public sectors, we can have a greater, more sustainable impact.

For example, we rallied the Indianapolis community to invest more in early childhood education. We committed $2 million from our Foundation, raised another $8 million in the business community, and through communications and advocacy, helped pass a local ordinance investing $20 million in public funds to support this effort. Along with leveraging state investments, we now have a five-year, $50-million program that is supporting 1,600 3-4-year-olds from vulnerable circumstances to attend high-quality pre-kindergarten.

How important is local CSR?

First, this sounds simplistic, but we believe that you cannot be a good global corporate citizen if you are not a leader in your "backyard." Beyond that, working in our home city is a business priority. We are a large firm in a relatively small city and we're competing for talent with organizations in San Francisco, San Diego, Boston, New York, and international locations like London and Hong Kong. Attracting employees is much easier if we're operating in the context of a strong and vibrant community.

We've shown that companies like ours can have a great impact in home communities. Lilly is, generally speaking, held in very high regard in Indianapolis – people trust us and are willing to follow our lead if we want to work on an issue to move our community forward. I think pharma companies can sometimes be treated with skepticism or distrust, but because of our 140-year history in the city, we aren't viewed with that same suspicion. People here know us not as faceless corporate "giants," but as people.

How do you engage employees in CSR?

We have a number of employee engagement programs. For example, our "Connecting Hearts Abroad" program involves

THE PATH TO SUCCESS

With Steve Davis, President and CEO of PATH

PATH has been around for 40 years and is one of the largest non-governmental organizations (NGOs) in the world. PATH works in 70 countries, employs more than 1,600 staff, and focuses on reducing inequity in health by driving innovation to deliver systematic change in global health outcomes. Oftentimes, PATH steps in where market forces are unable to deliver health solutions to the most vulnerable populations, and has five main platforms: vaccines, drugs, diagnostics, devices, and service and system information.

Success stories

- I am particularly proud of the Malaria Vaccine Initiative, which was driven by PATH and GlaxoSmithKline, along with a number of other partners. It resulted in the world's first approved malaria vaccine. We are now conducting pilot studies on how to introduce the vaccine.
- Around 15 years ago, we embarked on a project to tackle meningitis A – a big problem in parts of Africa. We worked with ministers of health, the FDA, and a number of companies to identify a vaccine – with the agreement that the eventual price of the vaccine had to be below 50 cents per dose. We successfully developed a vaccine called MenAfriVac, which was prequalified by the WHO. Around 300 million people have been immunized so far and meningitis A is now on the verge of being eliminated in the "meningitis belt" of Africa. We're now working on getting the vaccine incorporated into various national immunization systems, as well as developing a

sending employees to communities in need around the globe. Since 2011, we've sent almost 1,000 people on two-week volunteer assignments.

The assignments are quite varied; we work with our non-profit partners – including those who are associated with our global health programs – to identify needs requiring specific skills (healthcare, IT, pharmacy, communications, and so on). We then ask Lilly employees to apply for the program and match the projects with the appropriate skillset. In addition to these skill-based placements, there are also a number of general volunteer slots that are available to anyone. It is gratifying that nearly every volunteer who takes part in the program returns saying it was the experience of a lifetime. We also encourage returning volunteers to share their experiences with other staff, or organizations and community groups they might be involved with externally. When you have employees at all levels of the company talking about what they did and what they learned with stakeholders, the reputation of the company can only be enhanced, but in a truly authentic way – as opposed to things that might be more impersonal, like a corporate press release.

What is the key to successful long-term CSR?

Is starts with a commitment to collaboration and then how a company, over time, can deploy a comprehensive set of assets and capabilities in addition to philanthropy. Moreover, while this may sound obvious, it is critical that companies engage with a sense of humility. The challenges we face are complicated and sustainable solutions simply do not reside within one organization. Being open to new ideas and adaptive strategies is absolutely essential.

SMALL TOUCHES, BIG HEART

It doesn't take a big investment to make a difference – sustainable contracts and more subtle efforts can also go a long way to helping others worldwide.

By Stephanie Sutton

In the 1990s, Nik Kotecha founded a pharmaceutical company, which today is based in Loughborough, UK, called Morningside Pharmaceuticals Ltd. Kotecha had always enjoyed giving back and helping others, so one of the aims of the business was to make a difference to the developing world by exporting high-quality medicines.

"In the 1990s, there were few regulations in developing countries and most medicinal products came from the Far East or local manufacturers. These products were competitively priced and affordable for local populations, but they weren't always made to the highest quality standards," explains Kotecha. "We saw a niche for an export business as there was a great need and demand for high quality medicines in developing countries. The UK is well known for its medicines and high standards, and the business model of Morningside Pharmaceuticals Ltd is built around 'Brand UK' and the quality this represents."

Today, the lion's share of Morningside's business lies in the UK market – the company conducts its own R&D and manufacturing, and its portfolio includes Morningside licensed medicines and generics for a range of different medical conditions and diseases affecting both developed

polyvalent version of the vaccine to tackle other strains of meningitis.

- We have helped a Chinese company with their development of a less expensive version of a Japanese encephalitis vaccine, and obtaining WHO prequalification so it can be used to protect people across Asia.
- We have worked with biotech companies and Sanofi to develop a new method to produce semi-synthetic artemisinin – the antimalarial compound derived from the wormwood plant. Supply of artemisinin is dependent on the wormwood crop, which fluctuates drastically in supply and price. The new method is semisynthetic and provides an additional stable source of the drug.
- We have worked with Pfizer, Becton Dickinson (BD) and others to create and roll out an alternative, self-injectable method of delivering the contraceptive drug, Depo-Provera using a simple delivery device, Uniject.
- We have driven a scheme involving an adhesive sticker that changes color when exposed to a certain temperature – indicating that a vaccine has been out of the cold chain and thus cannot be used. It has been rolled out across seven billion units and we estimate the number of lives saved to be in the hundreds of thousands – and the number of dollars saved to be in the millions.
- We have worked with the Zambian government to change the way they tackle malaria by focusing on the 80 percent of non-symptomatic carriers of the parasite. Through this, we have seen a 92 percent reduction in malaria where the program was rolled out in Southern Province of Zambia.

Find out more about Steve in this month's Sitting Down With on page 50.

and developing nations. The company's biggest customer is the UK's National Health Service. Despite this, the company remains committed to the developing world and has contracts with a number of non-governmental organizations, including UNICEF, Doctors Without Borders, the World Health Organization and The Red Cross.

"Working with aid agencies is a personal passion. I have traveled extensively and seen the incredible work these agencies do. At Morningside, we have a department and distribution centre just for aid and we work incredibly hard to make sure agencies get what they need in the necessary timelines," says Kotecha. "It's very important in this business to be responsive. During the Ebola crisis, which developed very rapidly, we supplied more than 10 million examination and surgical gloves and numerous numbers of pallets of medicines – and we had to do so very quickly. When supplying products, it's important to be thorough with the documentation required for export (easily overlooked). Finally, for medicines, there is temperature control and safe storage to consider, which is

a significant challenge in countries that lack infrastructure."

Morningside's aid to developing countries is mainly built on business contracts rather than donations. Kotecha says that donations of vaccines and other medicines definitely have a place, but there is also a need for steady business contracts so that agencies can get exactly what they need when they need it. In addition, the company has gotten involved in healthcare summits. In April 2017, Morningside sponsored the East African Healthcare Summit,

THE VALUE OF GIVING BACK

By Stephanie Sutton

"CSR can offer benefits to firms in many ways, including greater attractiveness of the firm to its employees, advertising and improved pricing power with customers, and insurance from activists. My research with Po-Hsuan Hsu at University of Hong Kong has focused on how corporate philanthropy can benefit pharmaceutical innovation," says Fred Bereskin, Assistant Professor of Finance at the Alfred Lerner College of Business & Economics at the University of Delaware. Bereskin's focus is on corporate finance, particularly innovation and corporate governance, and he says that pharmaceutical firms are some of the most generous, in terms of their philanthropy; however, not all companies understand how philanthropy can ultimately benefit innovation and help develop partnerships with outside organizations. For one thing, collaborations with academic and not-for-profit organizations can include licensing deals that result in valuable patents. One common model in big pharma is to establish a research institute; the Center for Advanced Cellular Therapeutics created by Novartis and the University of Pennsylvania in 2012, for example. The center was partly funded by a $20-million grant from Novartis – and demonstrates how a direct donation can benefit innovation (as well as patients in need of cell therapies).

"Corporate philanthropy typically occurs in one of two ways: through direct contributions, or by donations from corporate-sponsored foundations. The most important difference is disclosure – whereas the activities of

> **It's important** to talk about **these types of projects to hopefully inspire others. Initiatives and** costs don't need to be huge."

where ministers of health from countries such as Uganda, Rwanda and Kenya attended to discuss the challenges in the region and where improvements could be made.

Small touches

Pharma companies are well placed to help out with the huge challenges in the developing world, but they are also in an effective position to help out with local communities too. Kotecha says that even small gestures can have a significant impact. For example, earlier this year, the company helped fund a minibus for the UK charity, Age UK. The minibus is used to help reach lonely, elderly people and to take them to community centers where they can socialize. The company is also involved with "Billy's House" in Nottingham, which is run by a charity called CLIC Sargent, which is part of Children with Cancer UK. Nottingham hospital has a ward for pediatric cancer patients and Billy's House is a place where families can stay free of charge. In March 2017, Morningside also funded a new IT system for another UK charity called Inter Care – the system helps the charity track recycled surplus quality medicines and healthcare goods it sends to rural health units in Africa, as well as ensuring that the charity is compliant with UK regulations. More recently, the company made a donation to a Leicester based charity, Healing Little Hearts, which sends teams of medical specialists to perform lifesaving heart surgery in centres situated in India, Africa (Kenya, Tanzania), Mauritius and Malaysia.

"Many pharma companies are doing fantastic work with local charities and the developing world, but it's not always well publicized," says Kotecha. "I feel it is important to talk about these type of projects to hopefully inspire others. Initiatives and costs don't need to be huge. Even a minibus for local elderly people can make a big difference. The minibus we funded helps around 200 elderly people a week."

Like many others in the industry, Kotecha's desire to do good is driven by wanting to help others rather than business goals – but doing good can certainly bring good karma to oneself and a company. Morningside won a UK Queen's Awards for International Trade in 2012, with judges commenting they were impressed with the company "turning its mission statement of providing nations worldwide with affordable and accessible healthcare into a reality". Kotecha also adds that it's surprising how many people choose to join the company because of not only the company's successful work in the UK, but because of its work with NGOs. Kotecha himself has also not gone unnoticed. In November 2016, he was invited to attend a Trade visit to India with the Prime Minister, Theresa May, alongside other captains of industry with the goal of drumming up business to help negotiate a post-Brexit trade deal. Kotecha was also awarded an OBE (Officer of the Order of the British Empire) in 2017 for services to entrepreneurship, innovation in pharmaceutical services and philanthropy.

Kotecha adds, "The main part of our business comes from the UK, so our work with developing nations, the UN and NGOs is a smaller part of the business, but I think it's amazing what we've helped to achieve. The real hard work comes from the volunteers working with NGOs but I'm glad we can help in a small way."

charitable foundations in the US are publicly available in Internal Revenue Service filings, direct giving is not," says Po-Hsuan Hsu, Associate Professor of Finance at University of Hong Kong.

He adds that many companies often resist disclosing their direct-giving activities – perhaps because they are trying to protect certain competitive secrets associated with their partnerships. "Conducting and funding research-related activities in the form of philanthropic programs has a number of advan¬tages over conventional in-house R&D. From the perspective of an NGO that may otherwise be reluctant to develop a collaborative relationship with a for-profit firm, the partnership can be more readily justified under the auspices of philanthropic support," explains Hsu. Traditionally in pharma, low-return or non-core projects can also run the risk of being shut down in company cut backs or facing difficult internal hurdles, but partnering with an NGO can help prevent this from occurring.

Consistent with the restrictions and limitations of foundation giving, Bereskin says that direct giving (and not foundation giving) is often associated with future innovation. "This makes sense when we consider that activities that are ostensibly promoted as direct giving can in fact be driven by the associated benefits to firms' research activities," he adds.

The findings of Bereskin and Hsu show that companies can "do good" while "doing well" for their shareholders. "Indeed, our findings can be seen as persuasive evidence that many activities that take the form of philanthropic giving are also designed to increase corporate sustainability and long-run values through effective collaboration with outside research organizations," says Hsu.

A CAREER OF RESPONSIBILITY – AND COLLABORATION

Most of my career has been spent in international development – liaising with governments, local communities, businesses and foundations, aiming to improve lives and opportunities in communities around the world. And if there's one thing I've learned, it's that collaboration – across sectors, governments, communities and people – is the key to effective social endeavors.

By Shannon Trilli

I believe that corporate responsibility is about the principles and beliefs that guide how a company responds to or engages with broader society. CSR is an opportunity for companies to demonstrate their higher purpose, mission and comprehensive values, and can also foster employee pride and motivation, and provide opportunities to connect meaningfully with stakeholders and customers.

Managing CSR isn't for everyone. Some who love the idea of CSR end up struggling with the part of the job that is often embedded in corporate hierarchy. I certainly never thought I would end up directing CSR for a company in the pharma sector. My original plan was to head to New York and become a lawyer! But what has not changed is my sense that I have a responsibility to give back to my community – both global and local.

The event that changed the course of my career came out of the blue. One of the deans of the University of Texas – where I was studying – asked me to lead a volunteer project aimed at improving local community relations on behalf of the university. The project involved hundreds of students, City of Austin representatives and community members. Through my participation, I realized that I enjoyed – and had a knack for – organizing large, multi-faceted projects, and developing relationships with people and forming teams to get the job done. I have since come to realize that connecting and bringing together different people from different sectors and various walks of life is hugely important for international development, local community-building and CSR. I learned powerful lessons about listening and creating space for those who don't always have a megaphone or voice to speak and take part in social programs.

Instead of law, I chose to study non-profit management at New York University. And I really caught the international development bug during my thesis project – which included developing a strategic plan for a hospital in Mozambique. At the same time, I landed my first CSR role working for The McGraw Hill Companies, where I was able to launch the first "global volunteer day" for the corporation.

After graduating, I decided to join the US Peace Corps. This led me away from the concrete jungle to a village in Bolivia – quite a change! The project involved working with local communities, municipalities and businesses to foster economic development, and gave me an understanding of what it is to be a citizen of another society and community.

After my Peace Corps service closed, another opportunity came my way when an organization called UMCOR (United Methodist Committee on Relief) – whom I had worked with on the Mozambique hospital project – asked me to cultivate and implement a $75-million partnership between the United Nations Foundation, The Global Fund to Fight AIDS, Tuberculosis and Malaria, and

LITTLE AND LARGE

Big Pharma has the resources to impact millions of lives through corporate social responsibility, but charity on a smaller scale also makes a difference.

Doing good on a large scale

- In parts of Africa, negative attitudes towards infertility can have devastating consequences for women. Merck KGaA's More Than a Mother campaign aims to de-stigmatize female infertility, as well as raise awareness about male infertility. The project hopes to achieve this through integration into existing healthcare infrastructure, such as HIV, maternal health and mother and child programs. Merck are also investing in education and training for African embryologists and trying to "build advocacy" by working with policy makers, healthcare providers, fertility experts and the media. The More Than a Mother campaign also involves the "Empowering Berna" project. Berna Amullen is a Ugandan woman who suffered mistreatment, discrimination and violence as a result of her infertility. Merck provided support for Berna to start her own business. The Empowering Berna project helps other women suffering from infertility to set up their own businesses.
- The Sanofi Espoir Corporate Foundation – launched seven years ago – focuses on three areas: childhood cancer, maternal and child mortality, and access to healthcare for the world's poorest populations. The Foundation's three year budget is €15 million and, so far, it has donated

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UMCOR. The aim was to reduce death and illness from malaria as part of a greater maternal and child health strategy in Africa. It was a real eye opener. First, I learned the value of partnership and cooperation, working with ministries of health, non-government organizations, donors, and corporates. And second, the malaria program shaped UMCOR's health sustainability strategy, meaning that not only did we work to fight malaria in Africa directly, but did so by investing in local leadership and health infrastructure, and by building and connecting national teams who led the programs on a country-by-country level. The impact was real – we demonstrated that lives could be spared and improved with our health programs. And I realized that there is no better professional achievement than to prove that you can promote life.

I worked for UMCOR for seven years before deciding, after so many years of travel and intense humanitarian work, that it was time to transition – and it just so happened that a former boss was now head of CSR at S&P Global (SPGI). As part of their re-branding process, the company was launching a new, aligned CSR strategy and they had an opening.

Two years later, Catalent reached out – and I'm now responsible for building up the CSR strategy of a company that went public only three years ago. In addition to more deeply engaging our communities and demonstrating Catalent's commitment to improving health and the environment, I look forward to helping us more meaningfully connect to employees, customers, and stakeholders. It was a thrill to return to the global health sector. Healthcare is such an important sector; companies in this space have unique capabilities to make an incredible difference to people's lives. We will be formally announcing the new CSR strategy very soon, but as a top-line preview, I am hoping to continue what I – and Catalent – have been doing for a long time: promoting better, healthier lives. There will be three areas of activity that will drive our strategy, including supporting local communities and organizations, minimizing our impact on the environment, and leveraging our Pharmaceutical Supply Chain Initiative (PSCI) membership to further develop and execute our environmental strategy.

In many ways, we as a global community and business sector are still grappling with "the basics," as outlined by the ten Principles of the UN Global Compact: human & labor rights, environmental responsibility and corruption. So at a minimum, proactively honoring the principles – and holding suppliers and customers accountable – is what businesses must strive for when fulfilling their leadership role in greater society.

Going beyond the minimum, I think companies in the healthcare space are uniquely placed to solve many social problems, and contribute to decreasing poverty and improving economic and market opportunities by helping people live healthier lives.

Through my time in international development, I've learned that real change is only possible though collaboration – charity and philanthropy alone are never enough to address the systemic, root causes of social ills and poverty that impact us all.

Shannon Trilli is Director of Corporate Social Responsibility at Catalent.

122,000 boxes of drugs and 331,500 doses of vaccines across China, Ecuador, Haiti, India and Macedonia.

- Zuellig Group, an Asia-based pharmaceutical company, donates an average of $2.3 million every year to the Zuellig Family Foundation, which focuses on improving health conditions in rural Filipino communities. It provides training programs for local government health leaders, including mayors and municipal health officers, to strengthen health leadership and improve governance. The program serves 640 municipalities in the Philippines – 42 percent of the country – aided by partnerships with the Philippine health department, the United Nations, and the US government.

Doing good on a smaller scale

- Divas Pharmaceutical Company, based in India, donated 50 motorcycles to the Visakhapatnam traffic police in Andhra Pradesh, India.
- Vectura, a pharma company based in the UK, organized a sponsored bicycle ride between their two UK offices in Chippenham and Cambridge – around 150 miles. The ride raised money for Asthma UK, which provides support for around five million people.
- Tobinco Pharmaceuticals Limited, and its Samuel Amo Tobbin Foundation, donated two incubators to the St Paul's hospital in Akatsi, Ghana. The aim is to reduce the number of deaths due to premature birth at the hospital.
- • Thea Pharmaceuticals, an ophthalmic pharma company based in the UK, spent a day gardening for Blind Veterans UK. The company raised money for the charity, and it's Surgical and Medical teams planted a natural, woodland garden.

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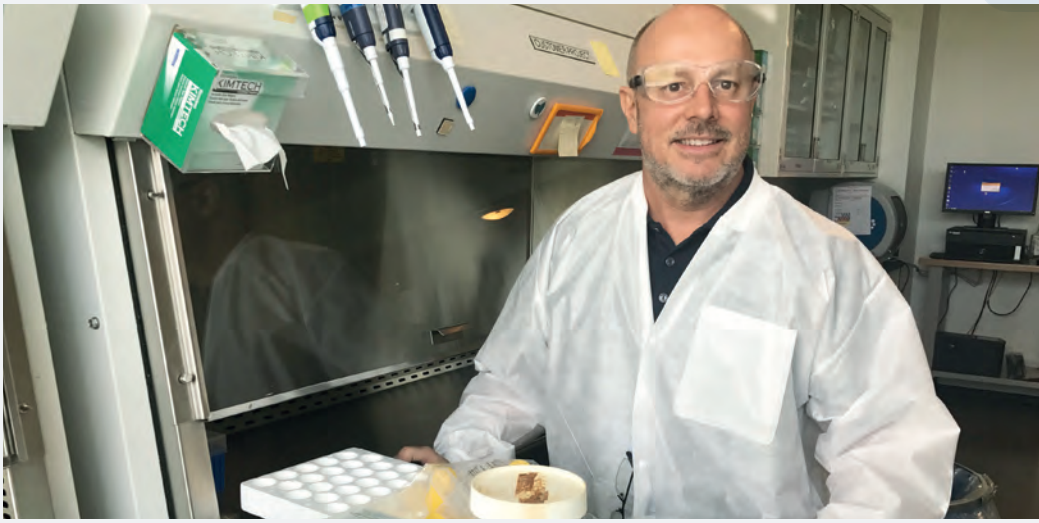
Finding That Special Source

Bioprocesses are highly complex – and we are only now starting to fully understand the impact of cell culture media on the critical quality attributes of bio therapeutics. Here, we trace the supply chain back to raw materials and learn how fundamental research is driving advances in cell culture media.



By Kevin Kayser, Senior R&D Director at Merck KGaA, MO, USA.

I joined Sigma-Aldrich (now Merck KGaA) in 2002 as an R&D manager in molecular biology product development, before moving into cell culture media in 2006 and then through several roles to my current position. Looking back, it's amazing to see how far the field has come in just 15 years.

When I entered the cell culture media space, monoclonal antibody titers were around a gram per liter or less; today, we see titers as high as 10–12 g/L range. Redesign of cell lines, cell culture media and advances in bioprocessing technology have both been crucial to this huge boost in productivity. In 2006, the industry was still using serum for many processes. Since then, we've progressed from formulas using non-defined complex components, i.e. full serum, to reduced serum amounts, to a variety of plant-derived hydrolysates, to the use of formulas with much more chemically defined ingredients.

Perhaps the biggest change is our approach to fed-batch processes, both in terms of media and feed design. In the early days, the cell culture media had most of the components needed for cell growth; today, the "basics" are included, and the rest of the components are fed into the process on a regimented basis, providing the nutrients the cells need, and, crucially, when they need them. In essence, we are now able to direct the cells to protein production rather than just increasing cell density – a common goal of the past, when the theory was more cells equal more protein. That's really not the case, and so we've had to learn how to drive specific productivity of individual cells, which is not always an easy task, especially when put into the context of secreting a high amount of a recombinant therapeutic protein that is not a natural part of the cells' architecture! To succeed, we, as an industry, have needed to increase fundamental knowledge of the biochemistry of the cell lines used.

Critical raw material quality

Modern cell culture media are typically made up of anything between 50 to 80 components (although some commercialized therapeutics are grown in cell culture media comprising over 100 components). Each component comes from a particular source – and they also come with a particular "risk". All cell culture media manufacturers must consider those risks, as well as the potential of those risks being passed onto customers. There are two risks which perhaps concern drug producers:

i. Viruses. Is there any chance of inadvertently introducing an adventitious agent into a process? Some may recall the Vesivirus 2117 contamination incident at Genzyme's Allston Massachusetts plant in 2009 – resulting in millions of dollars in lost revenue from delays to Cerezyme and Fabrazyme production and, more importantly, interruption to the supply of life-saving medicines to patients.
ii. Process variability. Individual raw materials originate from diverse sources – mining, complex chemical synthetic routes, and so on – and each one, put simply, must be what we think it is; for example, sodium chloride should consist of sodium chloride and only sodium chloride. Invariably, however, impurities or manufacturing intermediates creep into play. These impurities and/or manufacturing intermediates can have an effect on cell culture and can be a source of process variability.

In the past, the industry never really understood much about the variability of impurities or the biological significance. Over the last four or five years, companies have started to more fully understand the implications of lot-to-lot variability, impurity profiles, and any trace elements that may be present. Some of those trace elements can have a strong impact on CHO-cell

enzymes; copper at ppb levels, for example, can activate enzymes that actually alter the critical quality attributes of the resulting therapeutic (1). Consider a pharmaceutical company that is trying to match a certain quality profile filed in its IND material; the company could be hindered by the process variability introduced by trace level copper in a raw material. Likewise, consider a biosimilar developer trying to match an originator profile. In both cases, reducing process variability is essential, which necessitates fully characterized starting materials.

Controlling variability

There is a multiplicity of raw material vendors (including Merck KGaA – although in fact, we are one of our own biggest suppliers when it comes to our cell culture media business). For any cell culture media manufacturer, establishing a robust supply chain is absolutely key. Such supply chains can only be built with time and trust. The credibility of individual suppliers stems from good and effective validation and quality systems, especially in terms of change notification (after all, a seemingly small process change at the start can have big consequences in the final application). A robust supply chain often necessitates multiple suppliers of qualified materials to maintain continuity.

But, importantly, if there is variability, we need to be able to measure it – and understand the potential impact. Going back to my copper example: for one client, trace level concentrations of copper may actually be beneficial by providing the right level of glycosylation. For another client, the glycosylation profile may be affected detrimentally. What does this mean? Firstly, we recognize how essential it is to accurately report copper levels. Secondly, universal specifications are only useful as a starting point. Customers may have some idea of how copper affects their process, but we often have to work side-by-side with them to develop a custom solution.

"For any cell culture media manufacturer, establishing a robust supply chain is absolutely key."

Room for research

Back in 2009, we put together a research and development team dedicated to raw materials, which focuses on the biological and analytical characterization of all the compounds used in our cell culture media. The team strives to answer some pretty fundamental questions about those compounds. Why does a particular compound need to be there – or, in other words, what is its biological function? In bioprocessing, we're essentially taking cells out of their native environment and forcing them into a new role in therapeutic drug production – so there's a lot of opportunity to remove components that we no longer need. Perhaps selenium is simply there because "we've always done it that way!" (You can actually learn something about the taxonomy of media design simply from where people went to grad school...) The team is also investigating the levels of impurities from lot-to-lot and from vendor-to-vendor – as well as the biological impact of those different levels of impurities.

When it comes to understanding the impact of cell culture media, we shouldn't be passing the responsibility onto our clients – we believe that we, as a supplier, must drive that research. And our R&D team allows us to become raw material masters! Once we started digging, we realized that to answer many of our questions we have to run the full gamut of research – everything from high-level science, such as the fundamental nutritional biochemistry of CHO cells, to more routine work, such as looking at the variability in the manufacturing process for salt, for example.

A dynamic approach

Cell culture media has blossomed from the seemingly simple to the almost infinitely complex. And getting it right – at least for us – demands a multifaceted approach – or, in other words, the involvement of several areas: scientific research and development, quality, supply chain management, operations, and more. If we find something in R&D that may have some sort of impact – copper, for example – we need to set in motion a chain of events that spreads throughout the entire organization. It's not all about cool science – it has to be translated into both the quality and manufacturing organizations to become fully realized.

Our focus on R&D has also allowed us to optimize our own raw materials and additives for use in upstream processes, which gives us a unique advantage; for example, our EMPROVE® product portfolio offers a high level of quality that, in turn, can feed back into our cell culture media business. The result? Improved resource efficiency for both us and our clients. Notably, products bearing the EMPROVE® trademark also come with comprehensive regulatory documentation, which can contribute to quality when clients file registration dossiers.

Right now, we're working in an ever-evolving field, where new scientific knowledge about raw materials and their impact can be dynamically applied to improved products or better process understanding (both of which help our customers reach their own goals, whether that be improved quality or increased yields to drive down costs) – and that's very exciting.

Reference

1. *IH Yuk et al., "Effects of copper on CHO cells: cellular requirements and product quality considerations", Biotechnol. Prog., 31, 226-238 (2015).*

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Being (Bio)Better

Why stop at biosimilar when improvements can be made? Biobetters can be challenging to develop, but offer dual rewards: more effective medicines for patients and valuable intellectual property for the developer.

By Darrell Sleep

Biological drugs have undoubtedly revolutionized treatment (and the pharma industry), but there is a downside – cost. The complex manufacturing processes and quality control required to develop safe and effective biopharma medicines tend to result in expensive final products, causing problems for cash-strapped healthcare systems (and negative media coverage for the industry). Less costly – but therapeutically equivalent – versions of approved biologics are therefore in high demand. This is why biosimilars are well established in Europe, and are making inroads into the US market. But given the highly competitive biosimilar space, many companies are seeking an edge – striving for biobetters.

A biobetter addresses the same target as an existing biopharmaceutical (and usually through the same mode of action), but aims to provide an improvement; for example, by enhancing safety, efficacy, or tolerability, or by offering a better dosing regimen. "Better" can be achieved by making structural changes to the original biologic (through chemical modification, amino acid alteration or protein fusion) or by opting for an improved formulation method, amongst other options.

The biobetter pathway

One well-known and clinically proven route towards a biobetter is to increase the size of the original biologic to above the kidney filtration limit by chemically attaching polyethylene glycol (PEG). PEGylation can be achieved by random conjugation to exposed chemical attachment sites on the protein surface or via site-specific conjugation to pre-existing or mutationally introduced attachment sites. PEGylation has a long history of use for G-CSF, erythropoietin, interferon-α and interferon-β, but achieving a homogenous product can be challenging. The resultant PEGylated product can have reduced bioactivity and, a nondegradable polymer, PEG can also accumulate in the body, leading to renal tubular vacuolation, amongst other issues.

A size increase can also be achieved by boosting the O- or N-linked glycosylation status of the biologic. Like site-specific conjugation of PEG, the introduction or creation of an N-linked glycosylation attachment site (N_1X_2Ser/Thr_3, avoiding a proline at X_2) by genetic modification at a suitable site within the biologic can enhance a drug's half-life, while minimizing the negative impact on potency. To date, this approach has only been successfully applied to erythropoietins and, unlike PEGylation, it also limits the production to mammalian cell culture.

Non-covalent association of the drug to a well-known, large endogenous circulating plasma protein, such as albumin, is yet another approach. The ability of albumin to bind to fatty acids has been specifically exploited in the development of insulin detemir, a myristoylated insulin analogue with the (14-carbon saturated) fatty acid chemically attached to a specific lysine. Insulin degludec is an ultra-long acting insulin with palmitic diacid (a 16-carbon saturated fatty acid) attached to the same lysine; the longer fatty acid side chain further prolongs the plasma half-life of insulin degludec.

Following the same principle, liraglutide is a glucagon-like peptide 1 (GLP-1) (7-37) analogue with a palmitoylated Lys 26 and arginine substituted for Lys 37. A new acylated, long acting GLP-1 analogue with a half-life that enables once-weekly dosing – semaglutide – was developed by substituting Ala 8 with alpha-aminobutyric acid to reduce degradation by the protease dipeptidyl peptidase-4 (DPP-4), while Lys 26 is modified with stearic diacid.

A number of biosimilars have been created by adding fatty acids, additional carbohydrate chains or chemical polymers, but advances in protein fusion technology are really revolutionizing the field. Like PEGylation, protein fusion aims to increase the hydrodynamic radius to reduce elimination via kidney filtration. Synthetic peptides with large hydrodynamic radii can be used; for example, random peptides composed of the amino acids Ala, Glu, Gly, Pro, Ser and Thr (XTEN), a glycine rich homo-amino acid polymer (HAPylation), or a Pro, Ala, Ser polymer (PASylation). Alternatively, the drug can be fused to a protein with an intrinsically long circulatory half-life, such as albumin, transferrin, or the Fc portion of IgG. Albumin and IgG have the longest circulatory half-life of any plasma protein (approximately three weeks) because of their additional interaction with the FcRn receptor.

Albumin advantage

The path you choose to develop your biobetter will depend on the biologic you are working with. Out of all the approaches available, many companies are focusing on albumin, which has been used in a number of biobetter products already. For example, paclitaxel is a hydrophobic chemotherapeutic drug, which binds to circulating albumin in the bloodstream and is transported around the body. Because of its low aqueous solubility, paclitaxel can be formulated in a blend of solvents, and diluted in bags before patient administration. However, the solvent cocktail has been associated with significant side effects including

hypersensitivity reactions, nephrotoxicity and neurotoxicity – all of which must be managed separately by the administrating clinicians. In response, an alternative albumin-based formulation was developed. Abraxane (marketed by Celgene) is an albumin-bound biobetter formulation of paclitaxel, which is composed of water soluble ~130 nm albumin-paclitaxel nanoparticles – and so avoids the need for solvents. After injection, the albumin nanoparticles dissociate and the paclitaxel circulates associated with albumin. Abraxane is approved for the treatment of breast, pancreatic, and non-small cell lung cancer, and is currently in clinical development for the treatment of melanoma, bladder and ovarian cancers.

Albumin is widely distributed throughout the human body and can bind a range of ligands, including metal ions, hormones, bilirubin, hemin, as well as a range of hydrophobic molecules. For drug developers, including biobetter developers, there are a number of factors that make albumin intriguing. Albumin is highly stable and soluble – and, as noted earlier, it has a half-life of three weeks (a combination of its size and interactions with cell-surface proteins and the neonatal Fc receptor, which mediates a salvage mechanism that rescues albumin from degradation). Small angle X-ray diffraction studies have shown that, in free solution, albumin molecules repel each other, which is perhaps why albumin also reduces drug aggregation (1).

Albumin can be covalently attached to the drug by chemical conjugation, but genetic fusion is an alternative strategy (2), which has been exploited by GlaxoSmithKline and CSL Behring with GLP-1 (Tanzeum/Eperzan) and Factor IX (Idelvion), respectively. Tanzeum/Eperzan is an approved once-weekly Type 2 diabetes treatment, while Idelvion is the first approved hemophilia treatment to offer up to 14-day dosing intervals. The extended circulatory half-life significantly reduces the burden on the patient and, in the case of Idelvion, has allowed prophylactic treatment for adults and children that can help prevent bleeding while relieving the

"For drug developers, including biobetter developers, there are a number of factors that make albumin intriguing."

"Development of biobetters also represents a cost-effective life cycle management strategy."

stress of frequent treatment from the patient and their family.

There is also evidence that albumin fusions are less immunogenic than half-life extension strategies based on PEGylation – a very important point given that anti-drug antibodies (ADA) can impact drug efficacy and drug clearance, or cross-react with related proteins. Over 20 percent of patients who receive PEGylated IFN developed ADA, compared with less than 1 percent who received an albumin-IFN fusion (3). Similarly, ADA were generated in 0.9 percent of those receiving PEGylated G-CSF, but in only 0.5 percent of patients receiving an albumin G-CSF fusion (4).

Scientists have further characterized the mechanism by which FcRn rescues albumin from intracellular degradation to increase its circulatory half-life (5). In particular, teams have identified variants of albumin with differing affinities for FcRn. These variants have correspondingly different serum half-lives, which means it should be possible to give a drug a longer or shorter half-life based on need. Reducing the half-life, for example, may be useful in cases where extended drug exposure is associated with adverse reactions.

Developing better medicine

With drug development costs continuing to rise – and with many patients missing out on new medicines because of cost barriers – it is imperative that the industry considers alternatives. Since biosimilars and biobetters are based on existing drugs, they are relatively low risk; the biological target for therapeutic intervention has already been validated. The approved drug will also have the required potency, an acceptable dosing size, interval, and route of administration, as well as the necessarily acceptable toxicological, side-effect and adverse reaction profiles. In addition, the required in vitro and in vivo model systems, along with the necessary clinical biomarkers and end points, will have been developed, validated and accepted during the clinical phases and at the approval stage. What does that mean? It allows developers to reduce R&D set-up costs and de-risk the clinical development by "borrowing" from an existing knowledge bank.

Given that biobetters are considered to be new chemical entities, marketing approval requires a new data package (quality, efficacy and safety), and more work than developing a biosimilar, which may leave you wondering why you should invest. Apart from the chance of

bringing better medicines to patients, there are business advantages to consider. For example, the higher barriers to entry in the biobetters field automatically limit the number of competing products – and biobetter improvements can offer commercial advantages in the marketplace; biosimilars can only compete on cost. The drive to develop a biobetter arises from the known suboptimal performance of the original drug (for example, in vitro or in vivo chemical or structural instability, product heterogeneity, immunogenicity, or a suboptimal formulation in terms of handling before or during administration to the patient).

To date, biobetter developers have focused their attention on developing new products with improved formulations, greater in vitro or in vivo stability and longer circulatory half-lives. In the future, the largely untapped potential of biobetters to deliver enhanced drug performance by increasing the drug delivered to the desired anatomical location or target tissue at the desired quantities, while reducing off-target toxicity and adverse events, will be more widely explored.

By improving on the characteristics of an original drug, aspects of each biobetter are highly likely to be patentable, creating opportunities for intellectual property. Development of biobetters also represents a cost-effective life cycle management strategy; if the originator becomes the biobetter developer, it can extend market exclusivity and provide the means to compete in a crowded product field through performance differentiation.

Darrell Sleep is Chief Scientific Officer at Albumedix, Denmark.

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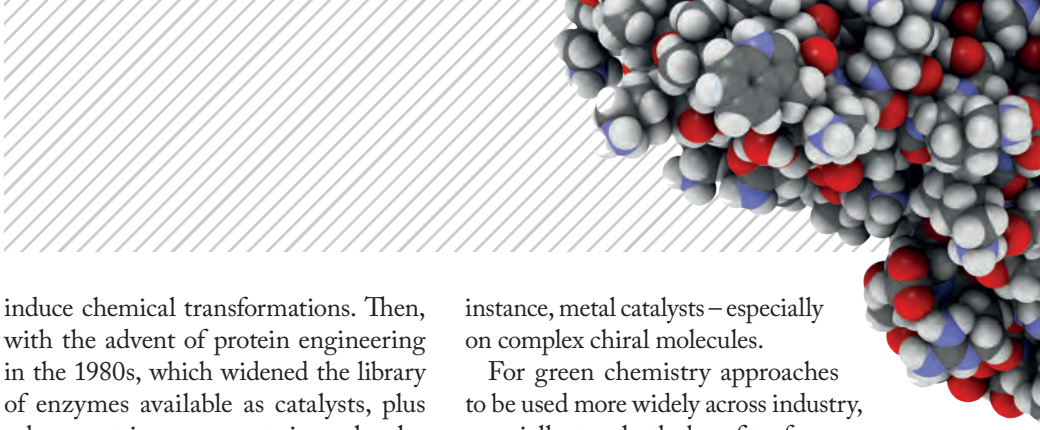


Catalyzing Success

Biocatalysis can bring many benefits to drug synthesis, but can enzyme immobilization enhance the process further?

By James Strachan and Stephanie Sutton

Biocatalysis – the use of natural substances (usually enzymes) to speed up chemical reactions – has roots stretching all the way back to ancient Mesopotamia, where it was used for the manufacture of food and drink. Somewhat more recently, the pharma industry has become interested in using enzymes to catalyze drug synthesis reactions to eliminate the need for high temperatures and polluting solvents. The snag for pharma companies is that unless enzymes are immobilized, they cannot be reused, which is crucial for economic viability. But if they are immobilized, they tend to lack stability – which is also key. How can this conundrum be addressed?

Stéphane Corgié founded Zymtronix in 2013 after finding a way to immobilize enzymes without sacrificing stability or productivity. The company is in its early stages, but Corgié has set his sights on revolutionizing pharma manufacturing, drug discovery, and agriculture. We find out more from Corgié.

What's the history and presence of biocatalysis in the pharma industry?

Biocatalysis involves using natural substances to speed up chemical reactions. It underpins some of the oldest and most important production processes, including the production of wine and cheese. It was at the beginning of the last century – thanks to experiments carried out by Ludwig Rosenthaler in the early 1990s – when scientists recognized that biological components could be used to induce chemical transformations. Then, with the advent of protein engineering in the 1980s, which widened the library of enzymes available as catalysts, plus subsequent improvements in molecular biology, scientists began to see the potential of using enzymes to enhance drug production. Biocatalysts have high selectivity and tend to require milder reaction conditions, which leads to a number of advantages in chemical production, including greater yields and lower costs. Biocatalysis started to be used on an industrial scale in 2002 when DSM used engineered lipases in the production process for diltiazem. With the rapid development of protein engineering since, several classes of enzymes have now evolved for use in drug production.

The biggest drawbacks of biocatalysis are the time and complexities involved in designing an adequate biocatalyst – although this is improving as the industry gains more experience and designs new tools to evolve enzymes. When you use the right enzymes, biocatalysis allows you to collapse several synthetic steps into one. Enzymes are also reusable, biodegradable and are Generally Regarded as Safe (GRAS). In addition to the lowered environmental footprint because of the reduced need for solvents and toxic chemicals, the reactions typically work at room temperature, so require less energy.

What we've seen so far in the pharma industry is, by and large, cost savings and process improvement driving the development of enzymes for manufacturing. At the end of the day, enzymes are proteins and are expensive, so cost saving needs to be consequential to trigger the adaption of enzymes as a new manufacturing method. However, many companies are beginning to realize that using numerous solvents and industrial chemocatalysts is quite expensive, even compared with the proteins used in biocatalysis. Moreover, biological catalysts are much faster and more selective than, for instance, metal catalysts – especially on complex chiral molecules.

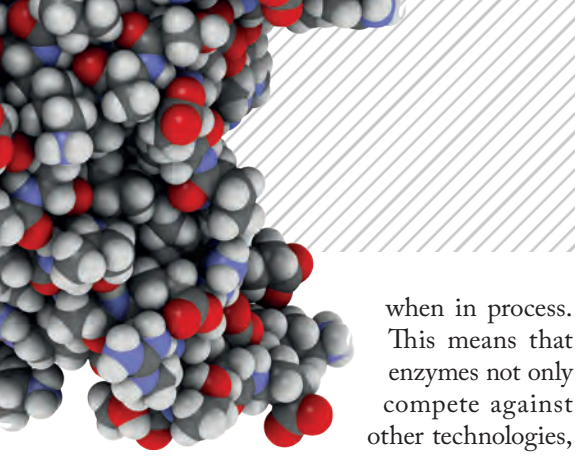
For green chemistry approaches to be used more widely across industry, especially at scale, the benefits of enzymes need to be demonstrated in terms of both speed and cost – and that's already started with some big companies, such as Pfizer and Merck.

What are the challenges of working with biocatalysts at an industrial scale?

An effective enzyme catalyst doesn't necessarily make a good process. Although enzymes are more efficient than traditional chemocatalysis, they can be difficult to use in industrial conditions – they are proteins after all. The main challenge is making sure that the performance and cost at scale are significantly lower than what would be achieved with regular chemistries and catalysts.

Timing is also everything. Once the decision has been made to push a molecule to market, pharma companies must be able to quickly demonstrate, optimize and implement production of the molecule, and understand how to maximize production

"The biggest drawbacks of biocatalysis are the time and complexities involved in designing an adequate biocatalyst."



when in process. This means that enzymes not only compete against other technologies, but also against time – every day your product is not on the market, you are losing money. If it takes years to develop the right enzymes and the right process versus adopting classic chemistry solutions, then companies will always choose the latter. With current biomolecular tools, enzymes can now be evolved fast enough to stand a chance against other chemistries. I hope that my company can help speed things along by providing the next step. We are giving enzymes an extra boost at the start with a toolbox that quickly finds the best parameters to achieve peak performance.

What's the story behind Zymtronix?

I started out investigating the use of enzymes for high-value chemicals from plant feedstocks at Cornell University. At the time in the US, there were a number of programs aimed at converting biomass into fuels, but I was interested in doing other things with biomass. There are many different chemical fractions in plants, with the one used for biofuel production having the lowest commercial value. Other fractions contain the building blocks for higher value chemicals. One example is lignin. Maximizing the use of biomass and going after these molecules makes economic sense, but lignin is a very stable plant polymer and very difficult to degrade – only some species of fungi have the enzyme system to do so. Our goal was to develop a new biocatalytic approach to enable commercial use of these enzymes. Immobilizing the enzymes to make them reusable was a first step; we developed materials that trap these enzymes and started to assay them. We discovered that we were also increasing their potential upon immobilization and making them less prone to inhibition at the same time, which is the main problem when using these enzymes in such applications. Finally, we were able to depolymerize lignin into small aromatic molecules using our immobilized and stabilized peroxidase enzymes. We then started to look at what our technology platform could do for other enzymes, as well as boosting performance upon immobilization.

What's different about your immobilization technology?

Enzyme immobilization (the process by which enzymes are physically or

chemically coupled on a material to make them insoluble so that they can be easily separated from solution), allows the reuse of biocatalysts, and thus reduces the cost of goods. There are different approaches to immobilizing enzymes, including adsorption, cross-linking, and molecular entrapment; however, the main drawbacks of these methods is that they result in the loss of activity of a percentage of the enzymes – the drop in enzyme activity can be anything between 10 to 90 percent. Clearly, when you buy one kilo of enzymes you don't want only 10 percent to be active.

Our approach is different. We let our material build itself around the enzymes so that they can be perfectly fitted. We implemented a process to find the optimal way to immobilize and prevent loss of activity. We started with peroxidase and once we immobilized the enzymes we saw a dramatic and unexpected jump in activity. We observed similar behavior with other oxidative enzymes – and that became the basis of Zymtronix! To prove the technology worked, we purchased some enzymes from other families that were already being used in pharma process chemistry and immobilized them. Although we did not see a jump in activity in all the cases, we were able to maintain full activity. On top of this, the materials we use are highly magnetic so the enzymes can be easily captured.

After patenting the technology, we had to figure out what to do with it. Various industries use biocatalysis, but we were initially drawn to pharma because many of the active ingredients are chiral, and so very well suited to enzymes (which are also chiral molecules). Our goal is to offer a universal, high-performance yet flexible solution to fit in with clients' process needs. Demonstrating the stability of the materials is key when dealing with pharma companies, so we have collaborated with a team of chemical engineers at Rutgers University for third party validation. We are focusing on those oxidations that can solve many problems in the pharma industry – and other industries more broadly. In particular, we're focusing on hydroxylation – and we think we can make a big difference.

How else are you using immobilized enzymes?

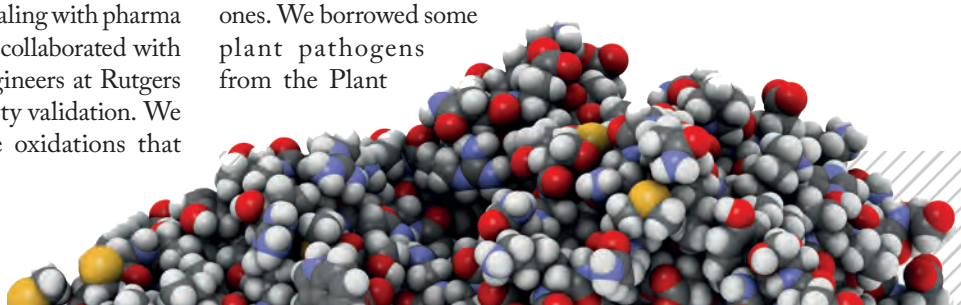
Our bodies transform and eliminate dangerous or foreign chemical compounds – including drugs – using a battery of enzymes. The resulting metabolites can be more active and potentially more toxic than the drug itself. Regulatory agencies and drug innovators use an array of in-vitro tests to make sure drugs are safe before starting clinical trials and marketing them; however, one of the bottlenecks is producing and screening the metabolites that our bodies produce. We are developing high-throughput metabolism assays using immobilized and stabilized human metabolic enzymes. A better understanding of the enzymes involved in drug metabolism could be a game changer in drug development as it would enable more accurate predictions of toxicity and risks.

Outside of pharma (but perhaps interesting for readers anyway), we are also working within the agricultural industry to offer a cleansing solution based on stabilized biocidal and fungicidal enzymes. Few people are aware that, although many vegetables are grown in the US, the seeds are often imported. Plant pathogens can travel on the seeds from production plants in other countries and during stringent border sanitary inspection, many seeds are destroyed. We are developing a solution that could sanitize whole batches of seeds by killing a broad range of bacteria and fungi without affecting the viability of the seeds – especially sensitive ones. We borrowed some plant pathogens from the Plant Science department at Cornell to test our theory and, fortunately, our experimental formulation worked the first time around! Since then, we have been developing our formulations in vitro against a broad array of fungi and bacteria to show that they are compatible with other active ingredients and, importantly, don't harm the seeds.

"A better understanding of the enzymes involved in drug metabolism could be a game changer."

What's next for the company?

So far, most of the enzyme processes that we have addressed have been fairly rudimentary; one enzyme, one reaction. But I want Zymtronix to become a new way of thinking about enzymes in processes! We have recently demonstrated that entire systems of enzymes, including co-factor recycling, can be quickly optimized and scaled-up with the added benefit of being reusable. In essence, we are trying to open new doors to synthetic biochemistry with increasingly more complex and elegant processes – by using enzymes the way biological systems do. Imagine the ability to engineer entire pathways within stable materials that can be reused without having to compromise with the constraints of living things. For me, that is next wave biocatalysis.



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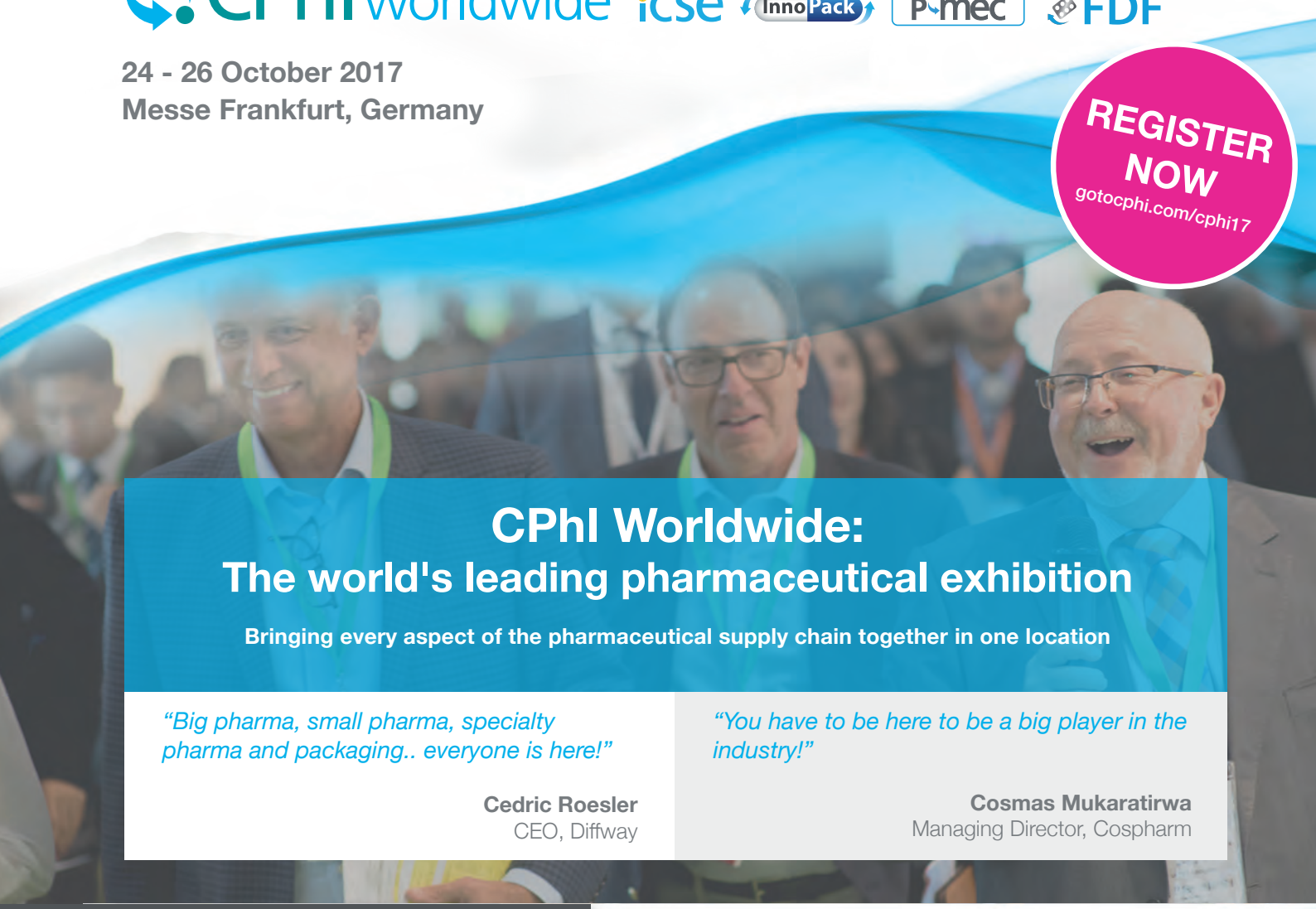

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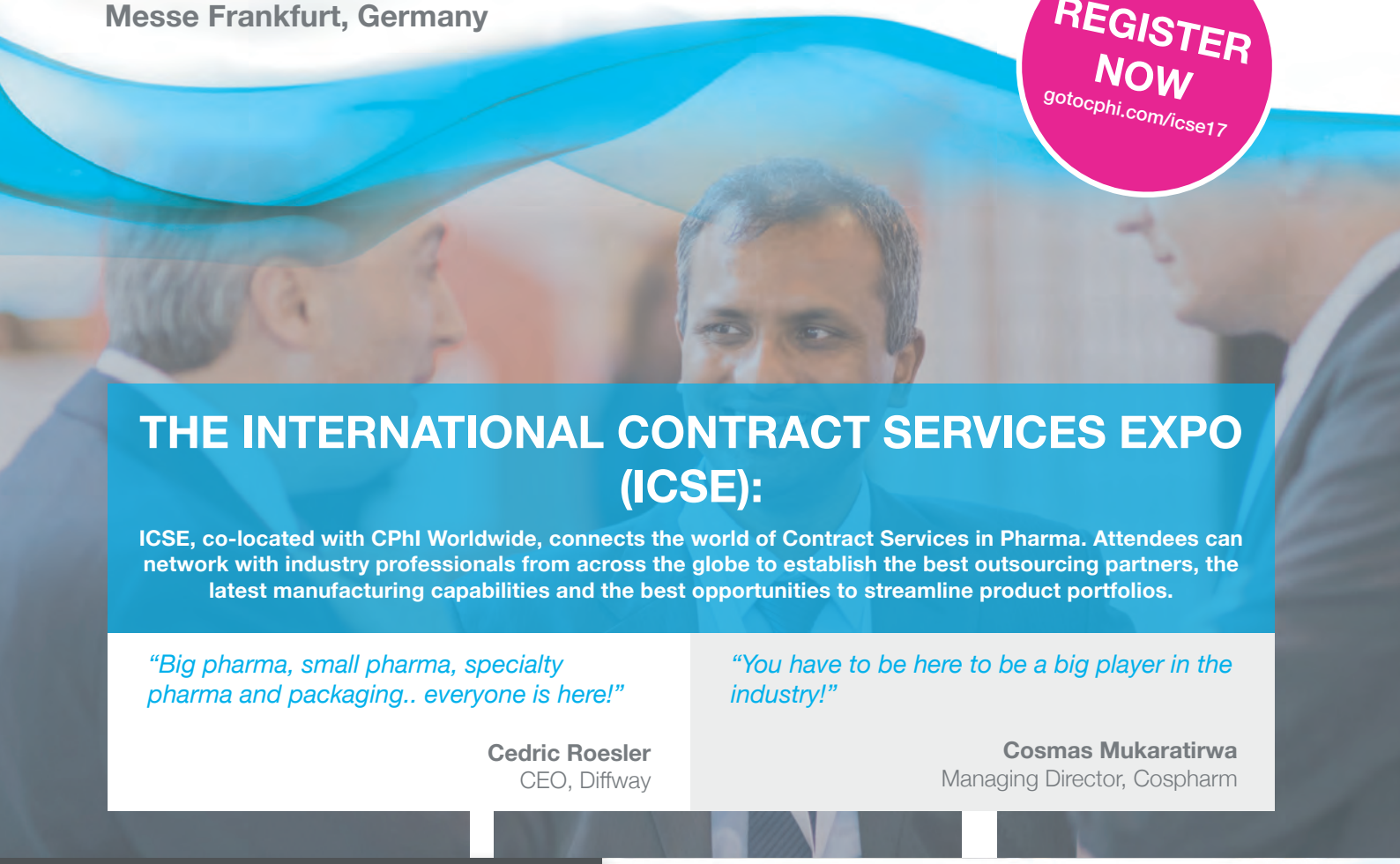

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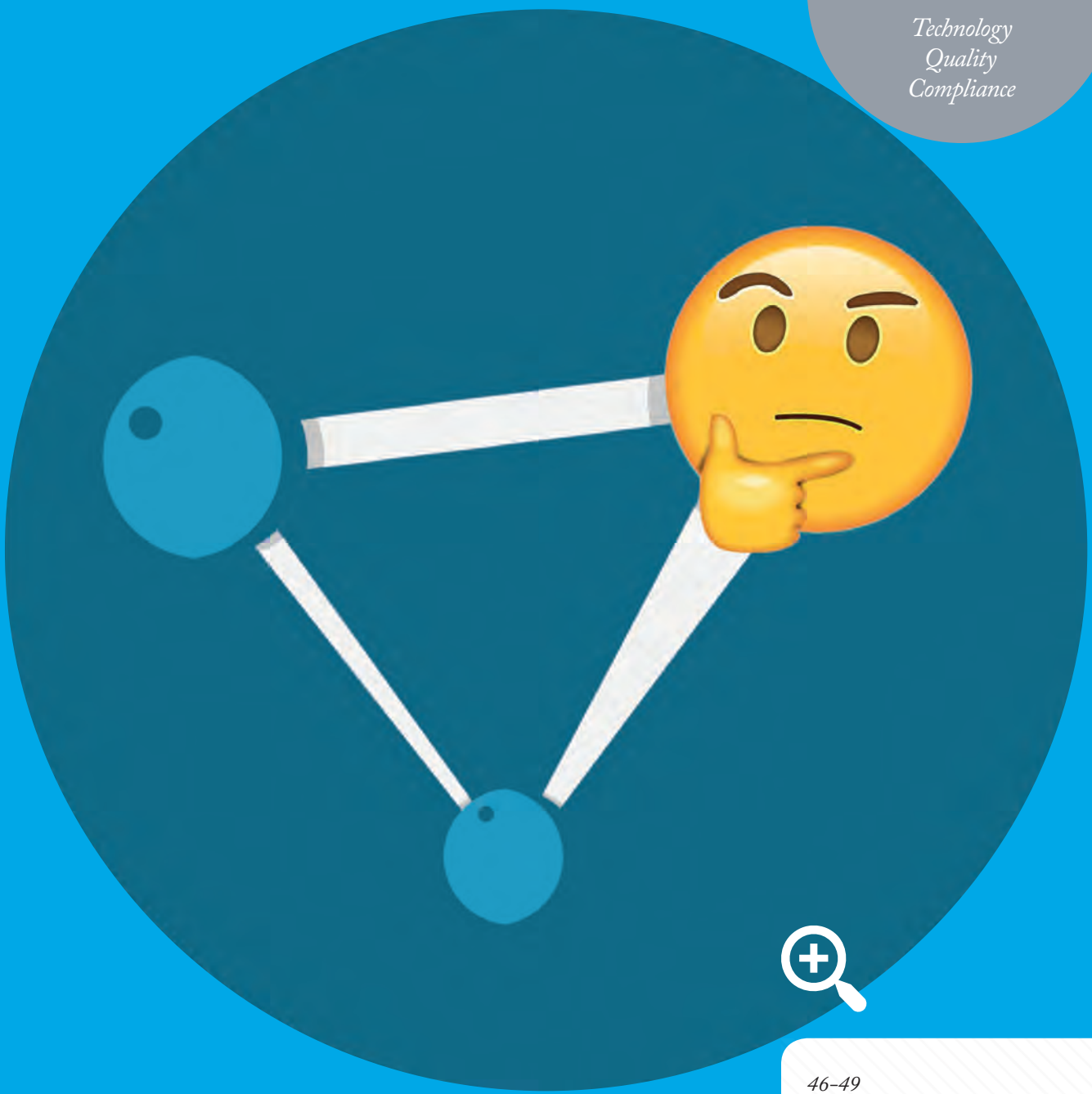

Let the Molecule Decide

Formulation techniques and technologies can easily become more habit than science, but a single technology does not work for all compounds. Each new drug is unique and deserves a fresh approach to formulation.

By Stephen Tindal and Ronak Savla

Every molecule – large and small – has a structure that drives its physicochemical and biopharmaceutical characteristics – and its potential as an active ingredient. The smoothest path to market lies in understanding your molecule's characteristics and applying strategies to overcome any deficiencies as early as possible. With sound expertise and judgment, physicochemical properties, such as the molecule's solubility, permeability, and stability, can be evaluated at the early stages of development – and from there, you can make decisions about the best formulation approach and what the molecule needs to help it become a commercial success.

Of all the decisions made at the early preclinical stages of oral drug development, there are two that are perhaps the most fundamental. The first is to select the nature of the potential API and its form (salt and polymorph), which requires proper physical characterization and optimization of the API manufacturing process. The second is to select an appropriate drug delivery system, with improved solubility and bioavailability usually being key criteria.

Decisions, decisions

Given that most molecules in development are poorly soluble, companies often choose to use a solubility enhancing technology, but which technology is best? Knowledge in the field is growing constantly and today there are many solutions available to help overcome solubility and bioavailability issues. Since each molecule is unique, the challenge is to collect sufficient information in the very early stages of development to support decision making, without consuming precious time and often limited API.

In an ideal world, data are always conclusive, and – if delays are to be avoided – available when a decision is needed. For example, it is not typical for the final API manufacturing process to be established and scaled up prior to drug delivery system selection. It is therefore necessary to consider the fact that future API changes could impact the drug delivery system. In the real world, data tend only to be collected in response to specific requests and may not be available – or may be inconclusive. Because of the sheer number of decisions required to bring a drug product to market, there are frequent occasions where data are not available or where resource or time consuming errors delay programs. In early development, API is typically scarce so it is important to minimize the number of tests as much as possible (without jeopardizing data integrity). If this is done effectively, the most common reasons for drug development attrition (poor pharmacokinetics, toxicity, and poor efficacy) can usually be addressed at the outset.

There is a tendency for formulators to favor a particular drug delivery technology that they have experience with and to pair it with almost every molecule they work with – but no technology is a panacea. A better way of approaching drug development is to pay close attention to the physicochemical data and what it is telling us about the molecule, and to approach formulation selection with an open mind. What is really best for the molecule? What will help it to reach its full potential? We need to let the unique attributes of the molecule dictate our decision, rather than simply choosing the same path that has worked before. Just because something has worked once does not mean it will work well again.

"The challenge is to collect sufficient information in the very early stages of development to support decision making."

Knowledge is power

The starting point for an early formulation project is an API-sparing, cost-effective screening program to determine and quantify the most common parameters that affect the drug molecule's behavior both in-vivo and in the final dosage form, such as purity, solubility, stability, hygroscopicity, melting point, particle size, and excipient compatibility. During these tests, it is important to look for evidence of potential issues and to recommend the collection of more comprehensive data where warranted (for example, from a second lot of the same API). Building a drug molecule's profile helps to determine the development strategies that are feasible, those that are not feasible, and those that are essential.

Two of the most important pieces of information typically collected for each API are its ability to dissolve when dosed to a patient and its ability to permeate across the gut wall into the blood – these data are used in both the biopharmaceutics classification system (BCS) and the developability classification system (DCS). Only a small proportion – less than 10

percent – of molecules in the development pipeline are thought to have both adequate solubility (dose-solubility ratio> 500 ml) and permeability (> 1 x 10^{-4} cm/sec) to achieve good (>90 percent) bioavailability (1). Solubility can be addressed during both API form selection and drug delivery technology selection. During API development, solubility and stability can be improved by chemical modification or by optimizing the physical form of a drug molecule's salt and polymorphic form (including co-crystals). In addition to changing from one polymorphic form to another, solubility can also change for a single form when only purity changes. Early on in development, there may be multiple molecule candidates to choose from. As traditional methods to detect and generate salt forms, co-crystals, and polymorphs demand significant time and API, you have to make a difficult choice: do you proceed without the data or do you complete some of the evaluation with novel methods, such as material-sparing, high-throughput screening (HTS) techniques and in silico screening? Though HTS has greatly increased its ability to cover a larger number of samples in recent years, care must be used in the interpretation of such small-scale experiments. With any in silico or high throughput screening, there is always a concern that the model can only be truly validated once a full data set is compiled.

If the selected API candidate has poor solubility, stability or purity, and is easily ionizable, salt forms may be used to improve one or more of these properties. There are numerous pharmaceutically acceptable salts (hydrochlorides, tartrates, succinates, acetates, and so on) that can be chosen, but a salt form may not be a viable option for drugs that lack an easily ionizable function group. In these cases, co-crystallization could be used to improve chemical stability, hygroscopicity, solubility, dissolution rate, and bioavailability. Co-crystals are non-ionic supramolecular complexes between the drug molecule and a co-former. There are a number of established co-formers that can provide a starting point for a screening campaign.

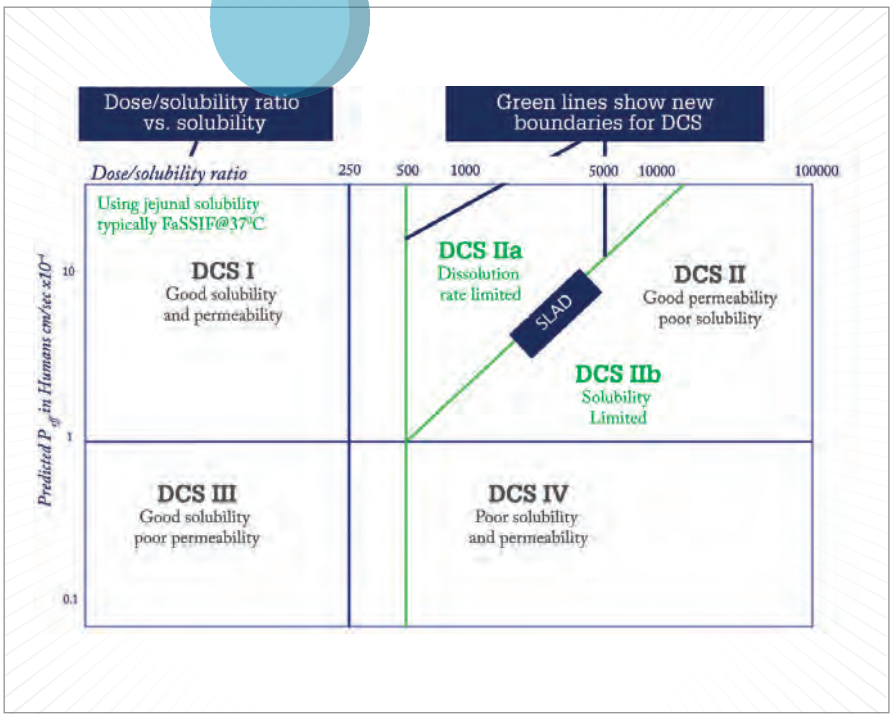

Figure 1. A molecule's position on the DSC plot can help guide the formulator in terms of which drug delivery technologies are most likely to produce a successful product.

Regardless of whether the molecule is a pure form, salt, or co-crystal, the US FDA and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) require identification and characterization of all polymorph crystal forms. Polymorphs are crystals with the same chemical composition, but possess different lattice structures and/or different molecular conformations. Polymorphs have different physicochemical properties and will behave differently (think of carbon as both graphite and diamond). Although a polymorph may have higher solubility, it is likely metastable and will typically convert to the more thermodynamically stable (and less soluble) form over a short time. It is crucial to ensure that the best polymorph is selected and formed every time during manufacture – and that it remains stable during storage.

Finding a formulation

Once you have your API information in hand, the next step is to determine the optimal drug delivery technology. DCS is an effective starting point (2) and takes its cue from the molecule itself. The molecule is classified based on its dose-solubility ratio and effective permeability – and its position on the DCS plot (Figure 1) will help guide the formulator in terms of which drug delivery technologies are most likely to produce a successful oral product. Like every other data set, DCS classification needs to be updated as more information is gathered, and as confidence in the data increases.

The position in the DCS grid determines the optimal starting point for formulation options. Those in Class I (good solubility and permeability) have a relatively straightforward development path where a solution, suspension, tablet

From Small Acorns...

It would not be unreasonable to expect that every pharmaceutical company has a process for drug development that includes experienced, educated people who are familiar with a wide range of technologies, but this is not always the case. Each company has subtly different goals, skillsets, capabilities and experiences built across the molecules and technologies they have worked with – and some will be better than others, according to a natural distribution. In particular, small companies, which usually have the advantage of being able to make fast decisions, tend not to have access to a large pool of talent, and often cannot afford all of the instruments and equipment that are found in big pharma formulation laboratories. In addition, big companies usually have several molecules in their pipeline and part of their strategy allows for a certain level of attrition, whereas a small company's entire future may depend on the success of one asset. It is more important for them to be thorough in early development to reduce the risks of failure in later development stages – a number of common issues, such as poor pharmacokinetics or toxicity, can all be predicted in early development with the right tests.

The pharma industry is fortunate to have a flourishing and well-established contract manufacturing field. If a company doesn't have enough formulation experience or knowledge in house, then there are several contract manufacturers to choose from – some of whom have deep experience gained from formulating hundreds of molecules using different techniques and technologies. With limited amounts of APIs, it is possible to screen API forms and drug delivery technologies together using a combination of in silico screening, high-throughput screening, and parallel technology evaluation. Traditional drug development has relied on selecting a technology early on, at a time when paucity of data may preclude the best selection.

A growing number of drug molecules rest in the pipelines of small companies and they are important players in the pharma field. The industry needs to support these smaller companies by developing accessible outsourcing platforms designed to collect the most relevant data and to gain insight into each molecule's challenges. Overall, this will result in more molecules reaching the market and a wider selection of options for patients.

"The position in the DCS grid determines the optimal starting point for formulation options."

or capsule will work; the choice will hinge on what is likely to be most acceptable to patients and/or the most cost effective – and whether there are any other factors that would prevent the use of a particular technology. Nearly 70 percent of drug molecules in development fall into Class II (good permeability, but poor solubility) and require a solubility enhancing formulation. Class III molecules (good solubility, but poor permeability) are likely to be amenable to suitably designed tablets or capsules, but may require permeation enhancement. Those in Class IV (poor solubility and permeability) may be acceptable in a formulation that includes solubility and/or permeability enhancing technology, providing the target bioavailability is realistic (not 100 percent). What to do with molecules that are deep in Class IV territory? Perhaps it's better to go back to the candidate API selection or to employ a prodrug strategy.

One of the benefits of DCS classification over BCS classification is that the former splits Class II drug molecules into two sub categories: in DCS IIa, the solubility limited bioavailability results from a limited dissolution rate rather than the actual solubility itself, while in IIb the full dose is not expected to dissolve before exiting the small intestine – the strategy for creating a suitable dosage form differs between the two. And the boundary between the two subdivisions is based upon the solubility limited absorbable dose (SLAD), below which all the dose could dissolve and above which the fraction dissolved will diminish with increasing dose.

This important subdivision of DCS is useful in guiding the formulator to the right type of drug delivery technology. For Class IIa, simple particle size reduction or solutions are a great fit. For class IIb, a lipid-based solution or amorphous solid dispersion might be more suitable. If the molecule falls in IIb close to the SLAD boundary, then co-micronization (with the addition of a suitable surfactant) may be successful.

With a promising range of formulation options in hand, the next step is to evaluate

their behavior in pharmacokinetic tests in animals to confirm which performs best under more stringent, in vivo conditions. The data will support the decision on whether to progress to first-in-human Phase I clinical trials, or whether further refinement of the formulation will be required to produce acceptable bioavailability in the clinic.

The final say

The title of this article is "Let the Molecule Decide", but of course it is not the molecule itself that actively chooses its formulation route – the studies and decisions are made by expert scientists from a range of disciplines who have the ability to separate opinion from fact, and to determine confidence in and the reliability of those facts. When we use the phrase "let the molecule decide," what we really mean is that we should eliminate the subjective and increase the reliability of data. Doing so will help us to rapidly and effectively get to a point where both the molecule's nature and its likely in vivo performance are well understood.

Whether it will ever be possible to make these predictions accurately in every case is an ongoing debate. What is certainly true is that scientists are only human and not every development program presents a single clear obvious path and can be conducted with the ideal amount of time and resources. Scientists come from a broad range of disciplines; may or may not have specific qualifications; may or may not be skilled in the analysis of data; and may develop an unintended bias for a particular approach based on familiarity, which can result in molecules being paired with an unsuitable delivery technology. Scientists need to be creative and they need to be able to understand what the data for a given molecule are really "saying". Ultimately, scientists will make their choices, but it is the molecule that will have the final say when it comes to whether or not it can improve patients' lives.

Stephen Tindal is Director of Science & Technology, and Ronak Savla is Scientific Affairs Manager, both at Catalent Pharma Solutions, New Jersey, USA.

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Taking the Transformative PATH

Sitting Down With... Steve Davis,
President and CEO of PATH,
and lecturer, Social Innovation,
at Stanford University, California, USA.

Tell us the story of your career…

My career has taken some interesting twists and turns but in my head they've all woven together. I started out as a Religion major at Princeton University, before doing an MA in Chinese Studies and then going to Law School. I've worked as a lecturer in China and the US, human rights lawyer in Geneva, and IP strategist for Bill Gates' digital media company, Interactive Home Systems (later Corbis) – where I eventually became the sole CEO.

But I have always been passionate about social activism and innovation – sitting on a number of boards in the social sector and being part of several non-profits' startup and growth. After leaving Corbis, I became director of social innovation at McKinsey.

How did you join PATH?

Before being recruited to run PATH, I had served on the organization's board as a private sector leader and worked for a year running PATH's India office at the request of the previous CEO – so it was a great fit.

I couldn't imagine another organization that brings together so many of the different things I care about passionately. Figuring out how to push new approaches to deliver social change is something I love, and PATH is a leader in this. Plus, you get to work on a global scale. I'm driven by the fact that the work we do can potentially impact millions of lives for the better. It's exciting to be a key partner in some of the global conversations about how to actually eradicate disease and prevent pandemics. I think there's a new way to operate as an international non-governmental organization and we're figuring out new business models that will allow us to be even more global in our approach. I see PATH becoming a 21st century innovation enterprise that crosses the social, private and public sectors.

What are the biggest challenges facing global health?

There are some problems that just outrage me. How is it that so many women are dying of cervical cancer when we already know how to prevent and treat it? The HPV vaccine will miss a couple of generations so we also need to focus on how to screen and treat as many women as possible.

There's also an enormous – and growing – burden around non-clinical diseases. We've learned that diseases such as diabetes and stroke aren't just problems for the affluent – there are reams of evidence showing that they disproportionately affect the poor in both developed and developing countries. Prevention is a major problem, but so is treatment: how can you work on hypertension programs in countries like Kenya, where more than half of people have never had their blood pressure taken? There are some interesting low-cost treatment models out there but they aren't being deployed globally. This is a major problem for global health right now: we have the necessary tools to solve many global health problems, but we don't know how to scale them up. This is one of the things I talk about at Stanford as lecturer on Social Innovation – and I think multisector partnerships will be key to figuring out solutions.

How do you approach facing challenges?

In the kind of work I've chosen to do – be it working on the bleeding edge of new technology or as a social and gay activist – it can often seem like the odds are insurmountable. I've faced a number of very different challenges over the years. But whether dealing with the deaths of friends as a result of the New York AIDS epidemic in the 1980s, the world changing overnight after the burst of the Dot Com Bubble, or adjusting to a new political climate (that is increasingly hostile to foreign aid and science), I always hope to have a strategy to fall back on. I believe that if you buckle down and make sure you're thinking through the chess board very carefully, sound strategy can get you through most challenges.

I also strongly believe people are generally good and committed to progress. There are exceptions, of course, but I think it's important to have this fundamental belief – be it in the form of religious faith or secular optimism. It seems to me that author and cognitive scientist Stephen Pinker's theories are correct; we are making enormous progress. I always say follow the trend-lines, not the headlines.

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What changes are needed in the pharma industry to benefit global health?

I think we need to see more multisector partnerships involving pharma and technology companies. I'd also like to see more personnel exchange between different sectors – working in industry is very different to working in the public sector or the non-profit sector and vice versa, and it's important for each side to appreciate those differences. Of course, a big challenge for the pharma industry over the next decade will be working out a pricing model that isn't detrimental to the poor or to industry. I believe that innovative financing mechanisms, such as priority review vouchers in the US, will become increasingly important in this regard.

Finally, there tends to be something of a trickle down model in the pharma and biotech industry, where poorer communities are an afterthought of the target population. I would love to see more companies working to develop therapies with vulnerable communities in mind from the very beginning.

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