MARCH 2016 # 17

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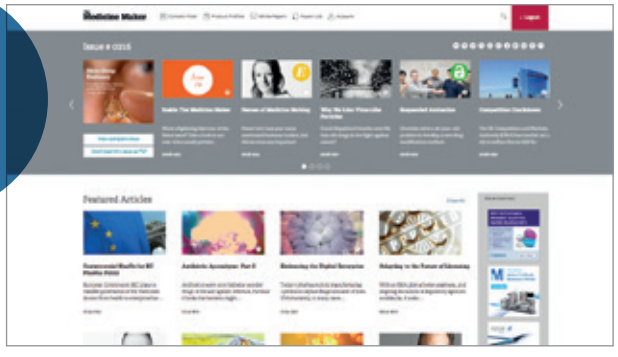



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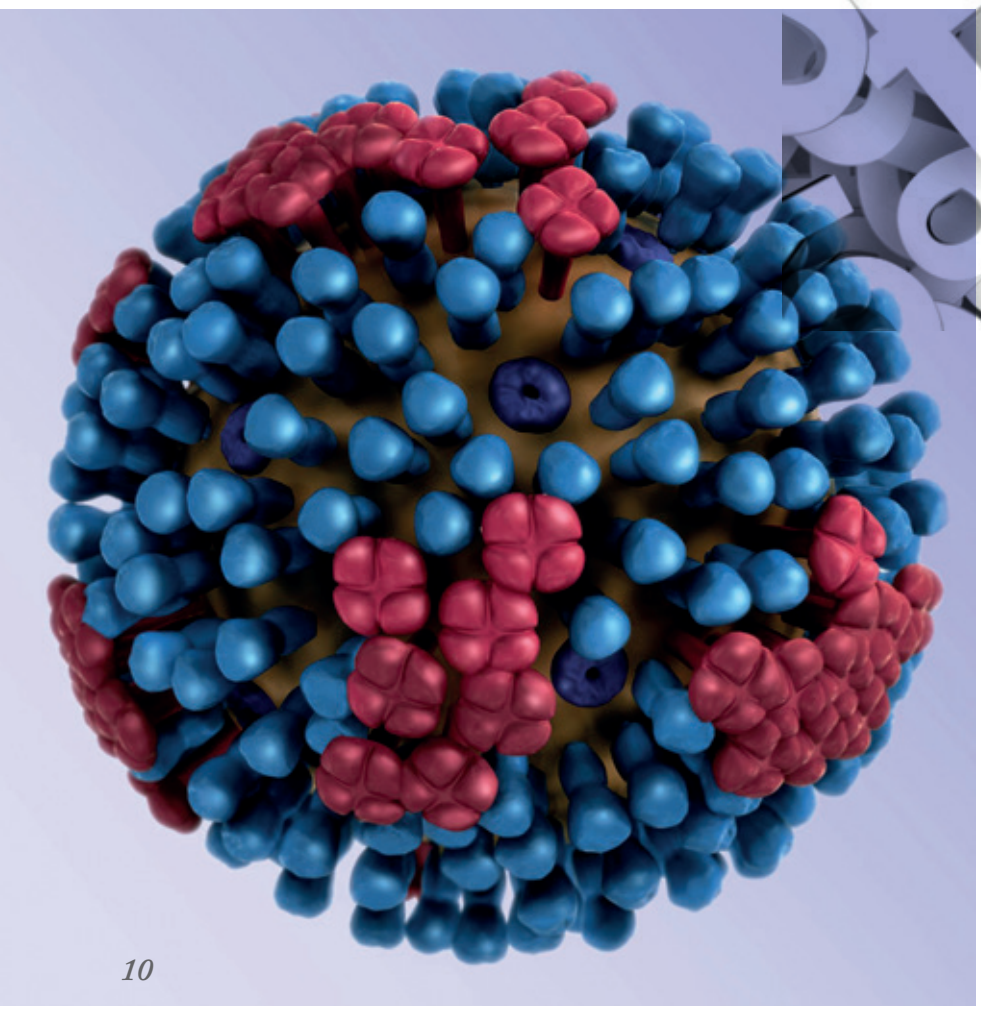

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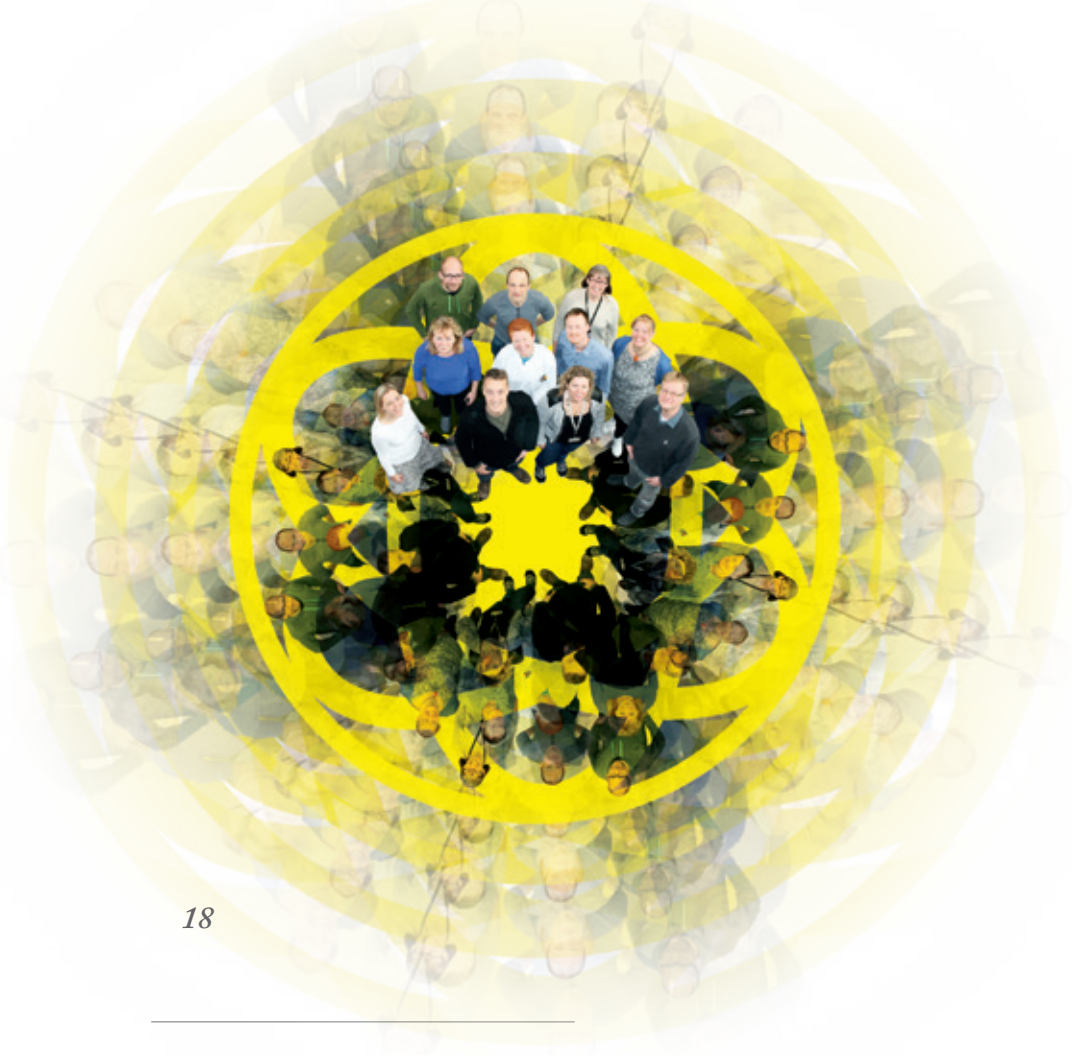
## On The Cover

*LEO Pharma celebrates the potential of open innovation.*



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# The Medicine Maker

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# Open or Closed Innovation?

*Collaboration can be the key to success, but does open innovation truly unlock the right doors?*



"The [pharma] industry is working on everything from human biological targets through to selecting molecules (small or large) to clinical experimentation, animal studies... We're famous as an industry for having agonizingly high attrition rates and yet there are times when you wonder how on earth we managed to pull it off for a single molecule, let alone many."

I've selected that comment from a recent conversation with Stephen Pyke, a statistician at GlaxoSmithKline, because it rings so very true. The development of a new drug is an incredible achievement – and yet, more often than not, the pharma industry receives more criticism about its innovation (or perceived lack of) than it does praise. Drug development today is undoubtedly more difficult than it was decades ago; emphasized perhaps by the common belief that many old medicines, such as aspirin, would not be approved under the latest regulations.

But it's much easier to climb a mountain if you have someone to help you along the way, which is why collaboration is increasingly seen as a winning strategy in pharma. An interesting report on "knowledge exchange" was recently published in the UK (1), showing that 80 percent of UK companies engage regularly with external partners to help them innovate. But the report also showed that many academics do not get involved with commercial activities at all; with just 14 percent of UK researchers engaged – a drop of 8 percent from the previous study (conducted 2008/2009). The report speculates on a number of reasons for the decline – lack of time, and difficulties in attracting commercial partners being two of the main ones.

I believe that the pharma industry needs to ask if it is doing enough to engage academia as true collaborators. Open innovation is a current buzzword with that goal in mind – most big companies operate some kind of open innovation platform – but as Niclas Nilsson, from LEO Pharma, explains on page 18, pharma has an image problem. The result? Even open innovation is sometimes viewed with mistrust. Moreover, open innovation is not well known by all who have something to offer – do academics even know what exactly is available to them? Do they have the time to find out? Perhaps it's time to revisit open innovation initiatives to ask how truly open they are. Such platforms must be thoroughly considered and not simply set up as another 'me too' platform because it is the 'fashionable' thing to do.

**Stephanie Sutton**
*Editor*

*Reference*

1. *National Centre for Universities and Business, "The Changing State of Knowledge Exchange" (February, 2016). http://bit.ly/1QFwgzB*

# 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*

## Vendors Reloaded

**Medicine packaging leaders forming the "Matrix Alliance" will bring improved container and closure systems to market.**

An increasing number of products are being shipped in smaller volumes as pharmaceutical companies see the benefits of highly potent and highly targeted drugs. Effective fill-finish technologies are essential for producing these drugs, alongside containers and closures, but could the technologies be further improved if vendors work together?

Vanrx Pharmasystems, which supplies a variety of aseptic robotic filling systems, has brought a number of vendors together to form the Matrix Alliance. Although naturally competitors, the vendors will collaborate to develop aseptic solutions, consisting of containers, stoppers, caps and nests that work together effectively with new filling machinery.

To expand our knowledge of the Matrix, we asked Greg Speakman from Vanrx Pharmasystems – one of the founders of the Matrix Alliance – to feed us the red pill.

Who and what are the Matrix Alliance?

Everyone involved in the Matrix Alliance is a supplier to pharma companies. Through the Alliance, we can leverage our combined offerings and expertise in aseptic filling (including testing and certification) to help better support the makers of parenteral medicines. Both new drugs and their manufacturing processes are becoming more sophisticated, so we need a new generation of packaging and aseptic supplies.

Collectively, our members make containers (vials, syringes and

cartridges), stoppers, closures and filling machines. The companies on board are ARaymond Life, Daikyo Seiko, Datwyler, Ompi, Schott, Schott Kaisha, Ompi, SiO2 Medical Products, and Vanrx. Each company will provide input on the definition of product sets, their specific components, and their development and testing resources.

### What is the biggest challenge of bringing a new solution to market?

For the vendors, the main challenge is ensuring that components work with the packaging system as a whole; you need a container, stopper and cap. If the container provider simply provides vials to a pharma company, then the pharma company needs to integrate and test the vial with a corresponding stopper and cap. In the Matrix model, the container, stopper and cap providers ensure the products work together and generate test results for the overall solution. The process is much easier for pharma companies – hopefully helping them to get their pharmaceuticals to market faster.

### What specific areas will you be working on?

The Matrix Alliance members will be:

- Testing new pre-sterilized container and nested closure systems for injectable medicines.
- Ensuring the compatibility of components from different members.
- Driving industry awareness of those solutions.

Simply put, the Alliance members will identify 'product sets' – each being a combination of a specific vial, syringe or cartridge, and a corresponding stopper and cap. The components may be produced by one member or by a combination of two or three members.

The task is to ensure that each set of products works well together. And we also need to get this message out to our common customers. I believe the biggest benefit will be the faster exchange of information, which allows us to collectively react more quickly to the needs of pharma companies. For example, I believe that pharma companies will be able to source product sets much more quickly if the suppliers are working together. We can also provide a continuous supply chain of these components at commercial quantities.

### What were the main challenges in setting up the Alliance?

Vendors naturally compete with each other. Our members all bring their own unique knowledge and experience to the collaboration, but some do compete. As well as working together, we all need to build and maintain our own differentiation, innovation, and partnerships. When setting up the alliance, we looked to other industries, such as wireless communication, where standardization on testing and component compatibility enabled new technologies to be adopted more quickly. Once the member companies realized that the alliance wouldn't take away their uniqueness in the market, they saw the benefits and were happy to sign up.

### What are the next steps for the alliance?

Our Alliance members are already working together to test the product sets. The testing includes the compatibility of the different products within a product set and the Container Closure Integrity Testing (CCIT) of the product set. We'll reveal more details about these product sets when they are available. But it's not just about forming new product offerings – we also want the Alliance to act as a forum that provides strategic direction, education, and awareness of new aseptic packaging solutions within the market.

# Fighting Flu with Imitation Antibodies

**Scientists use computationally designed imitation antibodies to fight the flu – and production costs.**

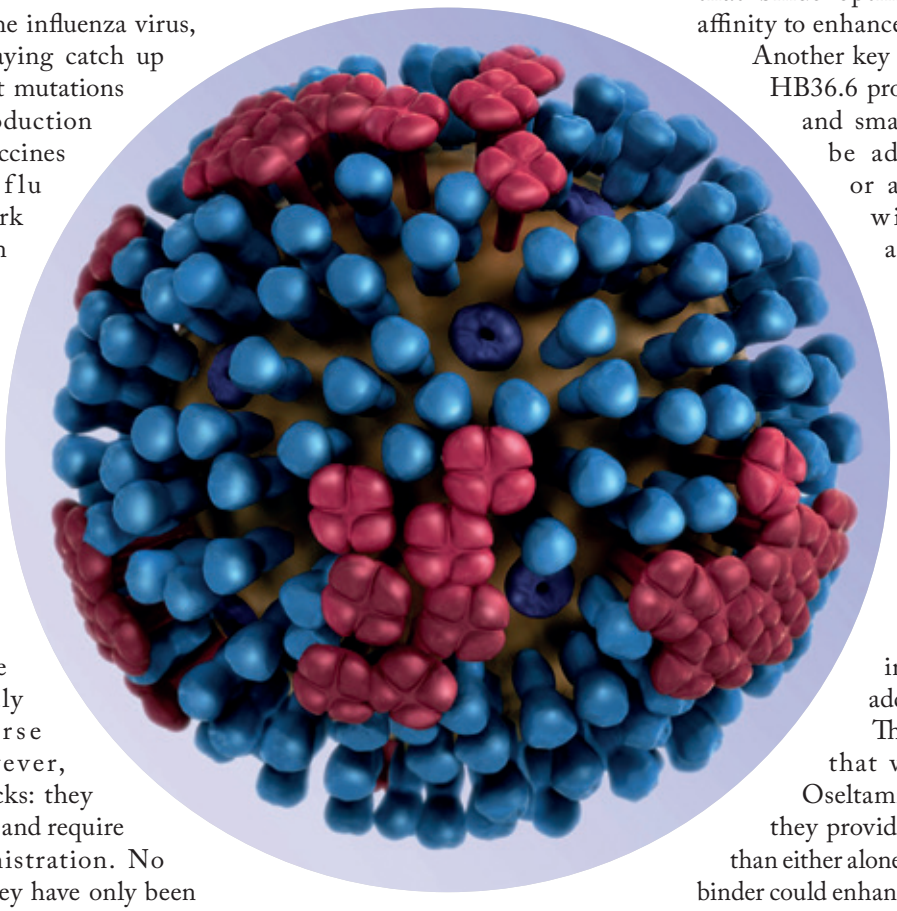
When it comes to the influenza virus, we're constantly playing catch up – the virus' frequent mutations necessitate the production of re-formulated vaccines every year, and flu vaccines don't work well in certain populations, such as the elderly, infants or the immune-compromised.

Not all new antivirals on the market have performed as expected, but scientists believe that monoclonal antibodies (mAbs) could have the potential to broadly neutralize diverse influenzas. However, mAbs have drawbacks: they are costly to produce and require intravenous administration. No wonder then that they have only been developed for severe individual influenza cases within hospital settings.

Now, scientists from the University of Washington want to combine the effectiveness of mAbs with the production costs of antiviral drugs – and are using computationally designed molecules that imitate mAbs to help them in their quest.

In contrast to mAbs (which require hybridoma cell production), the computationally designed molecules – depending on size – can be produced at much lower cost in E. Coli or synthesized without cells, according to the researchers.

"We have designed a protein that mimics the binding of a potent broadly neutralizing mAb to the HA protein on the surface of the influenza virus,"



says Deb Fuller, co-author of a recent study claiming that a single dose of the protein (HB36.6) provided superior protection when compared to 10 doses of Oseltamivir (Tamiflu) against H1N1 virus (1).

The team used computer modeling to design the (HB36.6) antiviral drug. "Most antivirals are discovered by screening natural or synthesized compounds for the ability to neutralize the virus in vitro until you get a hit," says Fuller. "Computational design is an elegant and more directed approach that focuses on the key interactions known to disrupt the virus, which means there is potential to do 'one better' than nature by optimizing those interactions, resulting in an antiviral that binds optimally, with greater affinity to enhance potency."

Another key finding was that the HB36.6 protein – unlike mAbs and small peptides – could be administered before or after the infection without engaging a host response. "This suggests that HB36.6 could be developed as a superior approach to protect those who are immune compromised, including the elderly, which make up the majority of deaths from seasonal influenza each year," adds Fuller.

The team also found that when HB36.6 and Oseltamivir were combined, they provided better protection than either alone, suggesting that a flu binder could enhance the effectiveness of flu antivirals currently on the market. *JS*

*Reference*

1. *M.T Koday et al. "A Computationally Designed Hemagglutinin Stem-Binding Protein Provides In Vivo Protection from Influenza Independent of a Host Immune Response", PLoS Pathog. 4, 12, e1005409 (2016). PMID: 26845438.*

# Pharma Thieves

**A new study estimates that 11.6 billion euros' worth of goods are being stolen across Europe each year – but what about pharmaceuticals?**

Estimating the scope of cargo theft has been the subject of a number of studies over the past decade. In 2007, the European Commission found that around 8.2 billion euros' worth of goods are stolen each year during transit through Europe (1). In February 2016, FreightWatch came up with a figure of 11.6 billion euros (2) – nearly US$13 billion – but what proportion of that figure can be attributed to pharmaceuticals?

Daniel Ekwall, Associate Professor at the University of Borås, Sweden, surveyed pharmaceutical companies, asking them about the value of drugs lost in each cargo theft. Ekwall and his colleagues found that pharmaceutical companies are losing €233,750 on average per theft and that firms suffer approximately eight or nine cargo thefts per year. The researchers extrapolated the figure to include the whole industry and combined the findings with those of another paper, reaching a figure of 30.8 million euros (3). Ekwall emphasizes that the figure is only an estimate and that the true value of pharma cargo theft is difficult to quantify.

"We found that Italy was a major hotspot for pharma cargo theft," says Ekwall. "The result from the survey was very clear here – and this actually surprised me. I was expecting more activity closer to the largest cities in Europe, such as London and Paris, because it is a pattern that can be seen in other statistics on cargo thefts in general." Though Ekwall admits more research is needed to explain why Italy is such a hotspot, he suggests that it could be linked to organized crime groups in Italy and their involvement in black markets for pharmaceuticals.

Another worrying trend picked up by the researchers was that violent theft is becoming a more frequent occurrence – with many drivers and terminal workers being threatened and/or assaulted.

"To tackle this problem we need better security and, more importantly, better collaborations between the different stakeholders in this problem," says Ekwall. "This means Law Enforcement Agencies and other Governmental Bodies as well as goods owners, carriers and insurance service providers." Ekwall hopes that as more companies open their loss-books to researchers, better and more accurate descriptions of pharmaceutical theft will emerge. *JS*

*References*

1. *European Parliament, "Organized theft of commercial vehicles and their loads in the European Union", July 2007. www.setpos.eu*
2. *FreightWatch, "Putting a price tag on underreported cargo theft in Europe," February 2016. www.freightwatchintl.com*
3. *D. Ekwall, H. Brüls and D. Wyer, "Theft of pharmaceuticals during transport in Europe," Journal of Transportation Security, 1-16 (2015).*

# A New Administration

**Despite controversies, Robert Califf will finally take the reins at the FDA.**

In a vote of 89-4, US senators have confirmed Robert Califf as the FDA's next commissioner. Califf is a world renowned cardiologist and clinical trials expert who has published over 1200 papers, making him one of the most cited medical authors in the US (1). Prior to joining the FDA, Califf was a Professor of Medicine and Vice Chancellor for clinical and translational research at Duke University. He also served as Director of the Duke Translational Medicine Institute and the Duke Clinical Research Institute – where he led a number of landmark clinical trials in cardiovascular research.

But it's not been a smooth path to the top of the FDA by any means. Califf was nominated for the job by President Obama in September 2015, but concerns were raised about his "close ties" to the pharma industry; Califf has received research grants and consultancy fees from a number of big pharmaceutical companies, leading some to call into question Califf's objectivity and his ability to curb the growing costs of prescription medicines (2). Despite the controversies, Califf's nomination has also received a great deal of support from organizations such as the American Heart Foundation and the New England Journal of Medicine. *JS*

*References*

1. *FDA, "FDA Statement on Senate Confirmation of Dr. Robert M. Califf," (March, 2016). http://1.usa.gov/20VngvF*
2. *T. Howell, "Senate confirms Robert Califf, Obama's pick to lead FDA, despite opioid outcry," Washington Times, (February, 2016). http://bit.ly/1TvwU9a*

## Califf in numbers

### *Credentials*

**135** Number of organizations who have endorsed Califf, including the American Heart Association.

*Years spent with Duke University School of Medicine and the Duke University Medical Center* **33**

**>1200** *Publications in peer reviewed journals*

**13** *Months spent as deputy head of the FDA*

**$320,000,000** Annual research budget of the Duke Clinical Research Institute – which Califf founded and headed up.

### *Industry ties*

**5** *Number of pharma companies who have paid Califf research grants – including Novartis, Johnson & Johnson, Lilly and Merck.*

*Number of companies Califf has equity in* **4**

**$87,500** largest consulting payment received by Califf in 2012 from Johnson & Johnson. 20 percent was a management fee – the rest was for his consultancy, which he donated to charity.

**1951:** Born

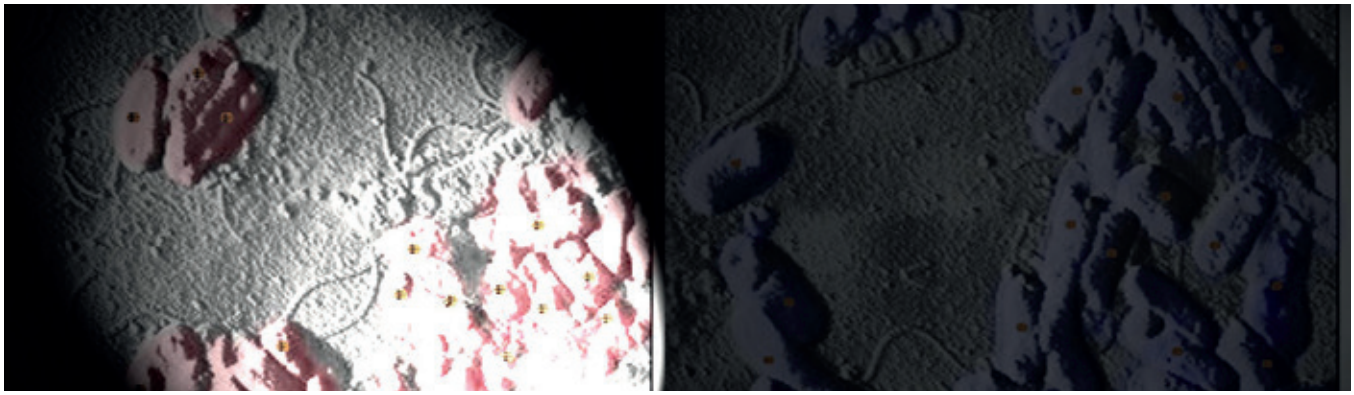
**1978:** Graduated from the Duke University School of Medicine

**1980:** Granted tenure at Duke University

**January 2015:** Appointed Deputy Commissioner of the FDA's Office of Medical Products and Tobacco

**September 2015:** Nominated by President Obama to be FDA Commissioner

**February 2016:** Confirmed as Commissioner by Senate



# Elimination by Illumination

## Could light-activated quantum dots put the "antibiotic apocalypse" on hold?

Are we on the cusp of a grim future in which pan-drug resistant superbugs roam freely, unfazed by antibiotics? With some bacteria having already become resistant to all drugs, some researchers are warning against a coming antibiotic apocalypse... But in the hopes of holding off the dystopia, scientists from the University of Colorado Boulder have used "light-activated nanotherapy" to kill multi-drug resistant bacteria (1).

"During our previous studies, my colleague and I were designing nanoparticles to generate tuneable redox species," says Anushree Chatterjee, Assistant Professor of chemical and biological engineering at Colorado Boulder. "When working on diagnosing disease cells, we realized that drug resistant strains were susceptible to certain redox potentials/species, which led us to design nanoscale semiconductor nanoparticles – or quantum dots – as therapeutics with specificity for bacterial infections, while leaving the mammalian host intact."

Small quantum dots deliver their therapeutic effect by freely diffusing inside bacteria when added in very small concentrations. When the dots are activated with light, they produce redox species that disturb redox homeostasis of the bacteria. "We show that nanomolar concentrations and a weak light source is enough to kill 92 percent of superbugs that are resistant to all clinical antibiotics tested in our lab," says Chatterjee. "Of course, simply increasing the concentration and/or light intensity kills more bacteria, and we have also demonstrated these effects."

Chatterjee hopes the new technique has the potential to open doors for a number of different nanomedicines, and to intensify efforts towards novel therapeutics for superbugs. "Besides therapy, we have also shown that these redox species can easily be tailored to have no effect on light illumination, using similar size, charge and light absorption in another nanoparticle, or show photoproliferative effect in another nanoparticle," says Chatterjee. "These photoproliferative particles can hopefully be used in bioreactors, biofuels and other biotechnological applications that can benefit from improved bacterial growth."

The researchers are currently conducting pre-clinical trials with in-vivo studies in animal models. Chatterjee adds, "As a next step, we hope to be able to secure funding from federal agencies or private donors to pursue this therapy further, and conduct clinical studies and trials to tests the true efficacy and promise of novel light-activated therapy." *JS*


*Reference*

1. *C. Courtney et al. "Photoexcited quantum dots for killing multidrug-resistant bacteria," Nature Materials (2016).*

# 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*

## Breaking Glass

**Glass is the most important primary packaging material for injectable drugs, but the demanding requirements of today's sensitive biologicals mean that we must consider newer, safer alternatives.**

*By Holger Krenz, Senior Applications Scientist, SiO2 Medical Products, Auburn, Alabama, USA.*

Risk mitigation is clearly a big issue for the pharma industry, and companies must go to great lengths to ensure that the necessary tools are in place to manage every potential risk. To this end, we've seen countless innovations across the field to ensure that development activities are well documented, that production processes are validated, and that clinical trials are run efficiently. Additionally, we've seen greater focus on the patient interface, which has spurred the development of patient-friendly drug delivery devices, such as auto-injectors, pre-filled syringes and ancillary systems.

Despite these innovations, one area of drug packaging has remained more or less unchanged for decades – the packaging for parenterals. Container shelf life plays a very important role in ensuring the stability and reliability of the drug product. The traditional material of choice for primary packaging is borosilicate glass. Glass is a natural product with excellent intrinsic properties; it is inert and virtually gas impermeable. Unfortunately, there are also some drawbacks – glass is fragile, difficult to control within the manufacturing process, and its batch-to-batch quality varies due to the natural source of its ingredients.

Today, traditional glass primary packaging must cope with the requirements of a new generation of sensitive biological drugs that do not tolerate any impurities. Typical borosilicate glass comprises 70 to 80 percent pure silicon dioxide; the rest of the composition includes metals, such as boron, aluminum, and sodium. These metals can create problems with the drug formulation, including direct reaction with formulation components that may shift the pH of a biological drug product and trigger the formation of particles. Ion exchange and hydrolysis of the glass can result in glass delamination, which produces particles that may cause contamination. Ions or particles leaching from glass packaging into the drug are also a worry.

The industry is doing the best it can to manage the risk of leaching, but it's a complex science and likely to remain a challenge for some time. In addition, integrating glass pre-filled syringes and cartridges with injection molded mechanical devices, such as auto-injectors, is tricky. The brittle qualities of glass and the manufacturing tolerances used are wider when compared with plastic pre-prefilled primary containers, which affects auto-injector reliability.

Revolutionary thinking is needed to tackle the glass parenteral packaging problem. One solution would be to start from scratch with a new design for a primary packaging system that can cope with all the industry's packaging requirements, as well as being unbreakable and having a glass-like appearance with glass-like barrier properties. Such a design would provide consistent quality for ensuring defined interaction with the drug formulations,

and would be compatible with existing industrial filling lines. Right now, we live in very exciting times as the parenteral packaging industry is undergoing change in both new drug development and primary packaging. New and established manufacturers are entering the market with creative packaging concepts to address special needs coming through pipelines, including polymer syringes and vials that use multilayer plastics with oxygen scavenging materials to simulate glass. Recent product offerings combine polymer science and plasma technology to produce hybrid packaging systems that use high precision injection stretch blow molded manufacturing and clean pharmaceutical grade cyclic olefin polymer (COP) with a plasma-deposited glass-like internal barrier coating.

I believe that it is about time we embraced these kind of innovations in primary packaging; they will help to change the parenteral packaging landscape for the better. They will not only be safer in terms of eliminating problematic leachables, but will also provide better manufacturing tolerances, and offer more reliable performance when combined with other drug delivery systems, such as auto injectors. The end result? Safer medicines and hopefully improved patient compliance.

My concern is that pharma can be a conservative business and reluctant to break from tradition. Whenever a new innovation is seen in formulation or a primary container, it is necessary to understand the regulatory requirements and the potential new failure modes – but if you don't have the courage to embrace new packaging concepts for parenteral drugs, then the risk of failure significantly increases. As an industry, we should be using the most innovative and modern options that have been designed to meet the needs of drugs today.

# Surveying the New World of Drug Delivery

**The drug delivery field may be about to see dramatic shifts in accepted modalities. Nanoparticles, targeted delivery systems and a move from oral to transdermal routes will all play a part in tomorrow's drug delivery landscape.**

*By Karan Verma, Research Analyst at Frost & Sullivan, Pune, India.*

There has been a lot of innovation in drug delivery over the last two or three years, which has translated into significant customer interest in shifting from conventional drug delivery mechanisms to newer ones. We've captured this activity in our reports by analyzing the use of current and next-generation delivery systems. I'm particularly interested in targeted drug delivery for oncology applications, like newer delivery systems that present the drug directly at the tumor site, rather than just letting it swim through circulation until it eventually gets to the tumor.

But there has also been a lot of progress in drug delivery for cardiovascular applications; for example, drug-eluting biodegradable devices that are resorbed within two years. Such advances are interesting because they combine drug and device; drug-loaded stents are a good example, and various drug delivery routes have been adopted to manage indications such as hypertension, ischemic heart disease and coagulation.

The drug delivery sector is also very exciting from an M&A perspective. We've seen some interesting acquisitions over the last two or three years – it's another major reason why the sector interests me.

In our analysis, we have identified a number of key forces that are acting to change the drug delivery landscape. One is the intense interest in targeted drug delivery. Targeted drugs can generate therapeutically effective concentrations in the disease area, with minimal effects on surrounding tissue, which is particularly beneficial for oncology drugs that can have a drastic effect on healthy tissue. Nanoparticles are being designed in such a manner that the drug payload can be safely delivered to the tumor site and specifically released at the site of the disease. In this manner, the drug's bioavailability is greatly enhanced and the procedure to apply multiple drugs at a similar site can be suppressed as it leads to chemoresistance in cancer patients and failure of a high number of cancer therapies.

Another trend is the focus on bioavailability, which is critical for drug efficacy. Additives that enhance the bioavailability of the drug allow it to better perform the intended action. Similarly, mechanisms to improve the solubility and stability of the drug in a biological environment can have a big impact. I also find it very interesting that many of these technologies are also being used outside of human drug delivery; for example, I'm seeing use in animal health and even in the cosmetics industry.

One of the big challenges in the industry is non-compliance with oral drug regimes. Some patients forget to take them, and

others don't like the taste of the drugs. Because of this, we are seeing a shift from the oral route to other routes. In particular, there is a lot of interest in the advantages of drug delivery via the transdermal route (both active and passive forms). This was discussed in this magazine last month (http://tmm.txp.to/0216/patches), but it is worth noting, however, that reformulation for alternative routes can be a big challenge.

In general, the pace of big pharma innovation in the drug delivery field can be slow, but I think this will change in the next five years, particularly with the advent of nanotechnology – an area we expect to grow significantly in influence in the near future. Nanoparticles have a good drug loading capacity and can be used in various applications (including vaccines) through a number of delivery routes, including oral and nasal. They've been in the news for a while now, and they'll have a growing impact on drug delivery over the next five years – watch out for magnetic nanoparticles, nanotechnology-based cyclodextrines, and fluid crystal nanoparticles...

However, it can be a struggle to demonstrate that a novel system has clinical effectiveness that is equivalent or superior to existing delivery systems – and that's why new technologies may require another 5–10 years before they are widely adopted. Another point is that small and medium companies working in this space lack funding; they need to partner with bigger firms. In fact, many of these small companies develop technology with the sole intention of licensing it to a bigger company.

As with any change, there are challenges, but I'm positive about the future. Why? Because many of the companies and CEOs I've spoken to are themselves more positive about new formulations than existing ones. There have been big changes in the last five years, but there are so many companies working in this drug delivery space now that I think it's going to shift even more quickly in the next five years.

One of the key trends I mentioned was the use of these applications across industries; for example, in cosmetics, formulations such as cyclodextrins and dendrimers are being used in fragrances, nanocrystals are being used in topical creams, and nanoemulsions are being used in nail polish compositions. I think it's very important to note that mechanisms used in drug delivery systems do not necessarily pertain only to medicines. Technology convergence is a key success factor for any industry. In today's world, there is no space for an industry that does not want to converge – and that goes for drug delivery as well.

# The Case for Continuous

**"Batch is best," according to many in the industry, but when cost reductions and greater efficiencies are a priority, continuous processing is becoming increasingly compelling.**

*By Reiner Lemperle, Authorized Officer, Gebr. Lödige Maschinenbau GmbH, Paderborn, Germany.*

The highest standards in quality and safety go hand-in-hand with pharmaceutical production (and rightly so), but this demanding regulatory environment has had one negative consequence; there can be a delay in implementing new technical innovations. This is a recognized problem in the industry and the FDA has tried to counteract this tendency with initiatives like Quality by Design (QbD) – as well as the recent draft guidance on Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base.

One area where I feel that pharma is lagging behind other industries is continuous processing. The automotive industry is perhaps most famous for continuous processing, but batch processing is still very much the norm in pharma – even for very large quantities. Continuous processes have even been viewed with some scepticism from pharma manufacturers because of the perceived regulatory barriers and costs of equipment. In reality, however, regulators are becoming far more receptive to continuous processing. For example, QbD encourages the use of advanced process analytical technologies (PAT) to delve deeper into the know-how of processes. PAT is all about analyzing product quality continuously, in real time, and is an enabler of continuous processing. If you're using PAT then why not go the extra mile and start considering continuous processes?

Traditionally, economic production of large quantities of product has been the main driver for implementing continuous processing (and we all know that pharma manufacturing is expensive, so any cost reductions are a benefit), but there are other advantages too. In my view, continuous processing is compelling even in the case of small production. Here are just some of the benefits:

- Consistent product quality. Once validated, a continuous process should produce products of identical quality every time.
- Production quantities are definable over time. As soon as the requested production quantity is achieved, the process is terminated.
- Smaller machines. As there is less product in the machine at any time compared with a batch process, drums and drives of a smaller size can be selected for the same output.
- Less manual handling. Continuous machines can be integrated in comprehensive units with automatic process control, which makes manual handling redundant and saves money.
- Less cleaning. With batch processing, cleaning can be necessary after each batch. In continuous processes the unit only needs to cleaned after a product change.

I am a big advocate of continuous processing and I enjoy discussing the advantages. But this doesn't mean that batch processing is obsolete. Batch and continuous processes offer individual benefits. The decision as to which process is best in a specific case is contingent on a precise analysis of the task at hand. Implementing continuous processes also involves a number of challenges. The most important point is to fully understand your product's characteristics, such as porosity and flow behavior. You'll also need to define your throughput. In general, continuous machines in the pharmaceutical industry are designed for throughputs from 5 to 500 kg per hour, so they can be used for small quantities or the development of new recipes, as well as high volumes of drugs. Small quantities can be produced within a couple of minutes and large quantities within several hours, days, or weeks, depending on the process.

I believe that continuous processes will be increasingly used in the pharma industry; in recent years, there has been a great improvement in the number of systems and machines available for this purpose. In reality, you don't need anything truly specialized – all continuous machines and units can be used in the pharmaceutical industry, as long as they comply with GMP requirements.

# THE BRIGHT STAR OF OPEN INNOVATION

Pharma companies are notoriously protective of their intellectual property, so it's a big deal to open up and give knowledge away for free. Nevertheless, it is the path that LEO Pharma took with its Open Innovation platform – and they've learnt that, if you give a little away, you can expect much in return.

*By Stephanie Sutton*

The Medicine Maker's inaugural Innovation Awards were published in December 2015 (http://tmm.txp.to/1115/innovation), with the aim of showcasing the technologies that make medicine making possible – and we featured everything from printing units to coaters to drug delivery technologies. The vast majority of entries were from traditional vendors, but we also received a more unconventional entry from LEO Pharma – a multinational pharma company based in Denmark. LEO Pharma is well known for a number of medicines, particularly those focusing on dermatology. But rather than talking about its own medicines, LEO wanted to tell us about a new 'product' for the research community.

In March 2015, LEO launched an Open Innovation platform (http://openinnovation.leo-pharma.com/), asking researchers to join them in discovering new treatments for people with skin conditions. I must confess that, when we launched the Innovation Awards, I did not expect to see a research platform such as this amongst the entries. But the beauty of innovation, of course, is that it does not always take the form that you expect. There was no doubt in the judges' minds that LEO Pharma's platform was truly innovative – and so it took the top spot in the awards. Not only is it completely free, but it also breaks away from some of the traditional legal agreements that are seen in many other 'open' innovation initiatives in the pharma industry. Here, we learn more about how it was set up – and why the decision was made to break the mold and give science away for free. We learn that, by sharing your problems, you are likely to receive far more solutions than you could ever have envisioned alone.

# A STORY OF SHARED SCIENCE AND SOLUTIONS

*As told by Niclas Nilsson*

LEO Pharma's open innovation project didn't come about from someone saying 'let's do open innovation'. Instead, it stemmed from the recognition that we needed to do something different. Back then I hadn't even heard of open innovation….

Curiosity has always been my personal driving force. Good things tend to come from being curious, whereas nothing will happen if you're indifferent. My interest in science was an expression of my curiosity. I started out by focusing on physics, computers and electronic engineering, but then I decided that I wanted to apply it differently. I looked for something that was still scientific, but completely different to engineering and electronics. The answer was biology.

In a way, I had to twist my mind to get into biology, but I ended up with knowledge of molecular genetics, medical sciences, programming, robotics, mathematics and electronics. The combination steered me towards work in drug screening, and it was easy for me to jump into that position because of my interdisciplinary education. In many cases, people still specialize in one field, but interdisciplinary connections are really important for open innovation – and for future innovation. I believe that open innovation models will lead to a big change in how we work. In the past, pharma has just done what pharma does best, which is to be very, very specialized. But that eventually leads to a dead end because it becomes very difficult to do more of something or to do it better. Eventually you have to start doing something different.

I started at LEO in 2004 as a research scientist, later moving up to lead a team on molecular pharmacology. The company was investing a lot of resources in setting up what we call 'disease-relevant' screening. This isn't target-specific because we aren't screening chemicals to find something that works on a single protein target (reductionist approach); instead, we prefer the phenotypic drug discovery approach, which takes biological complexity into consideration. And rather than just focusing on one target, it opens up the opportunity for new and different discoveries.

I thought we could get more out of our investment in drug screening technologies and I decided that the solution was simply to test more molecules. Unfortunately, there are only so many compounds that you can manage in a rather small company, which is why collaborations are so common in pharma. Classical materials transfer agreements (also known as MTA) – where you agree to test a technology partner's compounds – are often preceded by months or even years of negotiations. Given the timeframes, I'm not sure if this approach significantly adds to the discovery pipeline in an optimal manner. My feeling was that we needed to make it simpler to get more new molecules into the system so that we could fully leverage the potential of LEO's proprietary models and assays, which we've invested a lot of time and money on. I believed that we could add throughput to drug discovery processes from external molecules, such as hits, leads, molecular probes, or even candidates.

At the same time, we were starting to become aware as a company that we needed more exposure of our name – which was hammered home when someone from a big pharma company said they'd never heard of us, even though LEO is a more than a hundred years old and employs about 5000 people globally! We suddenly realized that it doesn't matter what you think of yourself – if no one knows about you, then you don't exist – and ultimately it means that no one can work with you. To change that, we had to announce our presence, open up and offer something. So I had two main goals in mind: to increase the throughput in our model systems and to help make others aware of us. Open innovation interested me, but talking about open innovation is much easier than actually implementing it...

Fortunately, I met with a great person called Jonathan Lee from Eli Lilly. He introduced me to Lilly's open innovation platform and I realized then that since other people were doing it, it was possible. After a major re-organization in our drug discovery operations, we made a strategic decision to 'leverage external knowledge', which evolved into a commitment to open innovation. It was new to us as a company – and a big step – but we knew that it must be done. I stepped out of science and began focusing solely on an open innovation platform. My single-minded focus was an absolute must because it was such a huge change – and challenge – for us. That was about two and a half years ago and I've been working on it ever since. Today, I am heading LEO Pharma's open innovation initiatives in R&D.

## Overcoming Catch-22

So, how do you go about setting up an open innovation platform? Once LEO had made the decision to embrace open innovation (with me as the project leader), I had to work out what to do next. LEO specializes in dermatology and we have a large number of approved drugs on the market for patients (on a side note, we helped 48,000,000 patients in 2014). But to aid us with our research efforts, we've also developed a range of very effective, phenotypic disease-relevant in vitro bioassays, which I've already mentioned. So the starting point was offering external collaborators the opportunity to test their compounds using our assays in an open innovation approach. A simple proposition but much easier said than done!

Pictured: Christine Brender Read, Manager In vitro Biology, OI role: Head of Assay operations; Birte Thoke-Jensen, Senior Technician, OI role: Assay development; Martin Stahlhut, Senior Scientist, OI role: Assay development; Peter Hansen, Senior Technician, OI role: Assay development; Jakob Felding, Senior Director, OI role: Head of Skin Research; Mette Skovgaard Bendsen, Principal Technician, OI role: Compound Management; Lone Moess, Senior Technician, OI role: Compound Management; Niclas Nilsson, Head of R&D Open Innovation, OI role: Strategy, design and implementation; Anne Caprani Winkel, Senior Technician, OI role: Data Management; Eva Hansen, Principal Technician, OI role: Assay development and execution; and Peter Scheipers, Senior Scientist, OI role: Science evaluation.

Open innovation is impossible without proper management endorsement, but even that is not enough on its own; open innovation is a big change and you can't push it down people's throats. I needed to do a lot of preaching to convince people of the vision and to create enough stakeholders to help me implement it. Of course, the natural reaction from most people being asked to change is 'why?'. If you've been doing something that works for a hundred years then why change it? It's hard to argue with that, so instead I had to focus on explaining why it was in people's best interests to change by identifying the local benefits of open innovation for each department involved – and removing the obstacles of 'extra work'.

I spent almost the entire first year drumming up support for the project. At times, it felt like I was in a Catch-22 situation – I needed to show people what the end result would look like in order to engage them, but at the same time we needed to work on it before we had a definition of the end result. I persevered, and gradually I built up a practical and concrete picture of what it was we should do. At this stage, not everyone will get it – and you shouldn't expect them too – focus instead on the small percentage that do understand the project and on those who can make all the difference to its success.

## Let it go

Once you have your supporters, you need to address the practicalities, such as how to make open innovation accessible to external partners. In my case, I was asking how I could make it easy for others to

### *Opening Up Big Pharma*

Most Big Pharma companies have established some kind of open innovation platform. Some do not require compound structure to be submitted whereas others do. The rights to generated data can also vary.

- Eli Lilly's open innovation platform is called OIDD (Open Innovation Drug Discovery). OIDD focuses on neglected and tropical diseases, diabetes and oncology. Researchers get access to computational design tools and can submit compounds for screening.
- AstraZeneca/MedImmune's open innovation collaborations span target validation, pathway exploration and translation. The main areas of focus include cardiovascular, respiratory, oncology, inflammation and autoimmune diseases.
- Bayer offers financial support for small molecule drug development via its Grants4Leads initiative. The latest call for submissions is open until the 30 March 2016. The company also has a Grants4Apps initiative that focuses on supporting healthcare startups and developer teams.
- GlaxoSmithKline has established an 'open innovation strategy', which has a particular focus on the developing world. The company is involved in various open innovation activities. For example, in 2010, the company turned its Tres Cantos lab in Spain into an open lab. Projects from universities, not-for-profit partnerships, and other research institutes are chosen on a regular basis. GSK also has an open innovation platform dedicated to innovation in consumer healthcare.

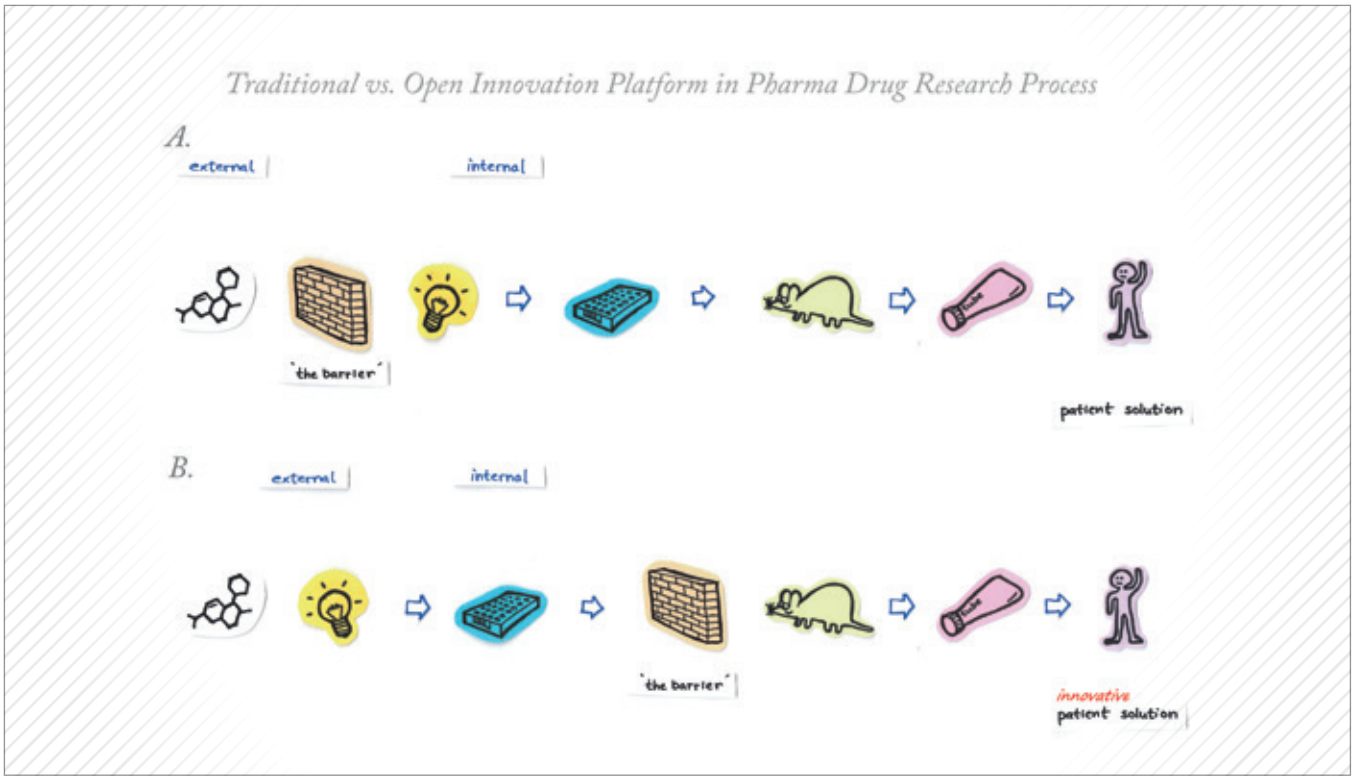



Figure 1. How to go from an idea to patient treatment – the pharmaceutical drug R&D process simplified. A) Traditionally, a barrier exists to protect the confidential R&D tools, which makes it really hard for an external idea, in the form of a molecule, to enter the process. B) Open innovation can be implemented to enable evaluation of external opportunities. The barrier is moved to the right, effectively exposing the early R&D biology tools and allowing external partners access to them.

<< "I wanted to reduce the time it takes to negotiate a materials transfer agreement." >>

test their chemical assets in our models. In particular, I wanted to reduce the time it takes to negotiate an MTA. But many problems popped up once I started exploring this topic, such as issues relating to disclosure of the science and the biological models we've developed. Disclosure is the key aspect of open innovation, but it is difficult for a traditional pharma company to accept. When you disclose, you open up, and when you open up, you give your competitors access to some of your knowledge – and potentially your intellectual property (IP).

Rather than focusing on the problems, I think it's beneficial to think of what you are trying to accomplish. For example, if you need a drill, the normal approach is to consider the attributes you want – something mobile and sturdy – and design the best drill. But in reality, you actually need what the drill can do for you; for example, making a hole two meters up in a 10-cm thick concrete wall – and that should become the focal point rather than assuming that you need a drill. If you asked someone else to suggest a solution, they may come up with a different tool to a drill. So in order to get access to those different and innovative solutions – e.g., novel molecules, mode-of-actions or targets – you have to disclose the science behind the models you are using and tell people what you are looking for.

For LEO, looking at what we wanted to accomplish helped us to focus on the barriers in a different light. To gain the trust of external collaborators, and to make it easy for them to work with us, full disclosure, openness and maintaining security were key factors – we couldn't debate that and so the question became, what do we need to do internally to make these things happen?

A long negotiation with our legal department ensued. The biggest problem was IP. I had to argue that we could not perform open innovation alone and that we needed to give something away in order to get something back – which is virtually unheard of in pharma. From a return of investment (ROI) perspective, it's pretty hard to argue for open innovation!

Selling the idea internally had to be done step by step. At first, there was reluctance to disclose the secrets of our top biological assays, but now we tell everyone about our assays. It was a huge step, but as a result of that we will get access to innovation that we didn't know existed. Pharma is not always good at innovation. With open innovation, you disclose what you want to achieve and ask if anyone can provide a solution. With our approach, we disclose information concerning our proprietary assays on

psoriasis and eczema (human primary skin cells that we stimulate with cytokines to induce disease phenotype) and tell people how they work. The external researchers get access to our assays, but in return we get someone who says, "Wow! I work in oncology on protein X and I didn't think it was relevant for psoriasis, but now that you say it could have a role I'm going to try it in your assay." It could produce good results, which means that you have someone on the outside offering fresh innovation, which the pharma industry desperately needs. This kind of orthogonal innovation – where you get novel solutions from a field outside your usual sphere of engagement – is an important aspect of innovation, and open innovation might just be able to deliver it.

Disclosure is not the only topic that we had to discuss with the legal team – ownership of the data was another key issue. And we chose to give this up too for the benefit of open innovation. An external partner sends us their compound to test with our assays; we perform the test, create the data and then we give the data back. The external partner now has ownership of the dataset and can use it as they please. We only ask to take it forward if we think it looks interesting – which is something that will always need negotiations.

Since we don't have ownership of the data, our external collaborators can take the data to our competitor if they want. But we have to accept that! Not everyone is comfortable with the approach, but you can make arguments in favor of it. Firstly, we are only giving away early discovery models – systems that only give indications that a particular molecule might be relevant for a given disease. Turning that knowledge into a commercial product is very complex, so really there is little value in what we're giving up from a product perspective. And if a collaborator does decide to go to a competitor, we would know about it, we have seen the data, and it's simply a discussion with a competitor. It's not a real loss for us – the only loss we make is the costs of running the tests on those compounds, which is not particularly significant in the bigger picture. When you break everything down like this, there aren't really any problems – only opportunities.

And in fact, rather than trying to justify open innovation from a ROI perspective, you can talk about the opportunity for cost. What would it cost us if we didn't have the opportunity to test this molecule? It would have gone to the competitor of course, without our knowledge.

We've also dispensed with the requirement for the external partner to disclose the chemical structure of their compound. This is for our benefit too – we don't want people sending us information on chemical structures and then claiming in the future that we stole their invention – we still want to be able to work on our own chemical structures, even if someone accidently sent something similar in to us. We only ask for an arbitrary name of the compound and the molecular weight, so that we can perform technical quality control. Our legal team deserve a lot of praise because of the major changes that were made to the legal

## *Investigating Inflammation and Dermatology*

LEO Pharma has a number of disease-relevant in vitro bioassays to help identify compounds that may have potential in inflammation and dermatology. But the exact assays used in the company's Open Innovation initiative may vary – and are also under constant development.

*Psoriatic inflammation in human keratinocytes*
Primary human keratinocytes are stimulated using a psoriasis-specific cytokine cocktail that induces an inflammatory response measured as an increase in IL-8 secretion. Test compounds are tested for the ability to inhibit this inflammatory response.

*Eczematous inflammation in human keratinocytes*
Primary human keratinocytes are stimulated using an eczema-specific cytokine cocktail that induces an inflammatory response measured as an increase in CCL5 secretion. Test compounds are tested for the ability to inhibit this inflammatory response.

*Human PBMC release of TNF-alpha*
This 'classic' inflammatory assay uses primary human peripheral blood mononuclear cells (PBMC) activated by lipopolysaccharides (LPS). The compounds are tested for the ability to inhibit LPS-induced TNF-alpha release.

*IL17 release from human PBMC*
Primary human PBMC are stimulated with CD3 and CD28 to release IL-17 and IFN-g. Cell viability is also measured to determine potential cytotoxicity. This assay is currently under development, but will be available for open innovation soon.

framework to accommodate all of this. We wouldn't have been able to reach our goal without the legal team sharing our vision.

### Breaking business barriers

No one uses an open door, if they don't know that it exists. Once we had the plan for LEO's Open Innovation platform we had to make sure people knew about it. We've got a web portal, but perhaps one of the main barriers in getting the research community to engage with open innovation is the way the term has been somewhat misused. Most 'open innovation' platforms demand compound structures or other IP information that subsequently binds you to the pharma partner. Big pharma has a really bad reputation – we are the big, bad wolf and the public opinion seems to be that if we can steal anything, we will. Many of the researchers I've spoken to tend to feel that there is always a 'but' with a big pharma open innovation initiative, so not requiring compound information is a great way to create trust. And not asking for compound information also protects your own assets, so it's win-win.

We've made it as easy as possible to get involved with our platform – all someone has to do is to download the PDF from the portal website (it's a simplified legal framework document that is about protecting the external partner rather than us. I encourage you all to have a read). The collaborator signs the contract, writes down the compound and company name, and sends it in. We then countersign it and send it back, together with glass vials for the partner to transfer their compounds. The glass vials are marked with bar codes from our internal data management system – and they enter our processes just as our own internal compounds would. Within about eight weeks or so, we send a PDF report back to the partner. The report basically says, "Here is your data. You may use it in any way you like."

Occasionally, we may say that we are interested in discussing the compound further and suggest exploring a more formal collaboration, which is when we proceed to legal agreements and negotiations. But the point of open innovation is to make it really easy to try something at the early stages and to make it scientific. So, in our initiative, at first there are no business barriers or restraints, which allows our external collaborators to focus on the basic science. And if we overlap, then we can talk business.

### Innovating for patients

Our Open Innovation platform launched in March 2015 – so this feature marks our one-year anniversary! We haven't been advertising the platform a great deal yet and there are still some tweaks to be made, but so far it's been a great success. We've had around 15 open innovation partners (a mix of universities and companies) in the last year, and we've tested around 150 compounds. Three of those were interesting… and one of our open innovation partners works with targets that we didn't even know existed, so through open innovation we now have access to compounds that target new molecules and proteins. That example really demonstrates the success of the approach. And the real beauty is that the process is very scalable. We have the capacity to test many more compounds than we did during the past year – we deliberately kept a low profile during 2015 to give us room to make adjustments as we went along. But 2016 will be more about how we ensure that the Open Innovation platform evolves into an established, smoothly operating process.

We are very lucky as a company. LEO is a foundational company, so we don't have any shareholders and we don't have to report to

or give any money back to our owners. Perhaps that is why we could do things differently. I can only imagine what it must be like trying to explain the benefits of giving away something for free to shareholders! But there are huge benefits in learning to let go. I'd like to see more genuine open innovation projects in the industry, as it would help everyone in the pharma ecosystem.

The end goal for any pharma company should be to help patients. I think this can be forgotten at times. All pharma companies claim to be patient-centric, but for some this just means having photos of patients on the wall; that's not what being patient-centric is. Our CEO clearly states that if we find new treatments for patients, then business will follow; in other words, it's about adapting to patient needs. I think this is very significant and it has changed how the company works. We are being patient-centric by admitting that we don't have the best solution internally, but that someone else may have it – and so we have constructed an interface to help us to find new solutions by asking others to join us and collaborate on finding new ways to help patients.

Another exciting project that I am working on involves trying to engage patients in open innovation – the next step in developing the open platform. We are trying to create a community that can drive the science forward more effectively; an open source and open science community that will include industry, academia, biology, chemistry, patients and more. We actually have ten anthropology students in Copenhagen looking into what it would take to engage patients in open innovation drug discovery research. And here we come back to the importance of being interdisciplinary, which is how I began this article. These students are getting patients to rate their treatment needs and to translate those needs into drug research properties, which may help us to find new molecules. Open innovation is not just about inviting universities and biotechs to bring us new molecules; it will also allow us to request molecules with particular properties that reflect what patients want – and that really is patient-centric.

Instead of innovating themselves, many large companies are buying pipelines. But what happens when there is nothing left to buy? I believe that pharma will increasingly need to rely on innovation from external partners – and we need interfaces that tap into external innovation. If it's open then it is more appealing and inviting. And though it may sound bold, if pharma companies fail to adopt open innovation then one day they will surely suffocate. If you want to set up an open innovation project, I recommend that you learn to give a little – and you will gain a lot!

I really believe that what we have done will make a big difference for the pharma industry, for patients and the whole scientific community. Science is all about doing things together; building on someone else's results and standing on someone else's shoulders – that's how we can reach higher levels together. Apart from anything else, open disclosure and open science prevents people and corporations from needlessly repeating work and making the same mistakes all over again.

It's a new way of working – and pharma needs to realize that it doesn't have to mean anarchy, altruism or philanthropy. There is a sustainable business model and open innovation isn't really that difficult or strange. It's really simple; you just allow other people to work on your problems and share your desires and dreams.

*Niclas Nilsson is Head of R&D Open Innovation at LEO Pharma A/S, Denmark.*

Other relevant personnel (not pictured in the article) were also involved in the Open Innovation project: Mikkel Svoldgaard Gadsboell, Director R&D Legal, OI role: Legal counsel and contracts; Tine Skak-Nielsen, Senior Principal Scientist, OI role: Assay development; Peter Bredekjaer Nielsen, Student Assistant, OI role: Operations; Lene Torp-Milojevic, Technician, OI role: Assay execution; Birgitte Davidsen, Senior Technician, OI role: Assay execution; Kathrine Abell, Senior Manager, OI role: Head of explorative biology; Lena Mårtensson, Senior Director, OI role: Business and Partnerships; and Thorsten Thormann, Vice President, OI role: Head of Research.

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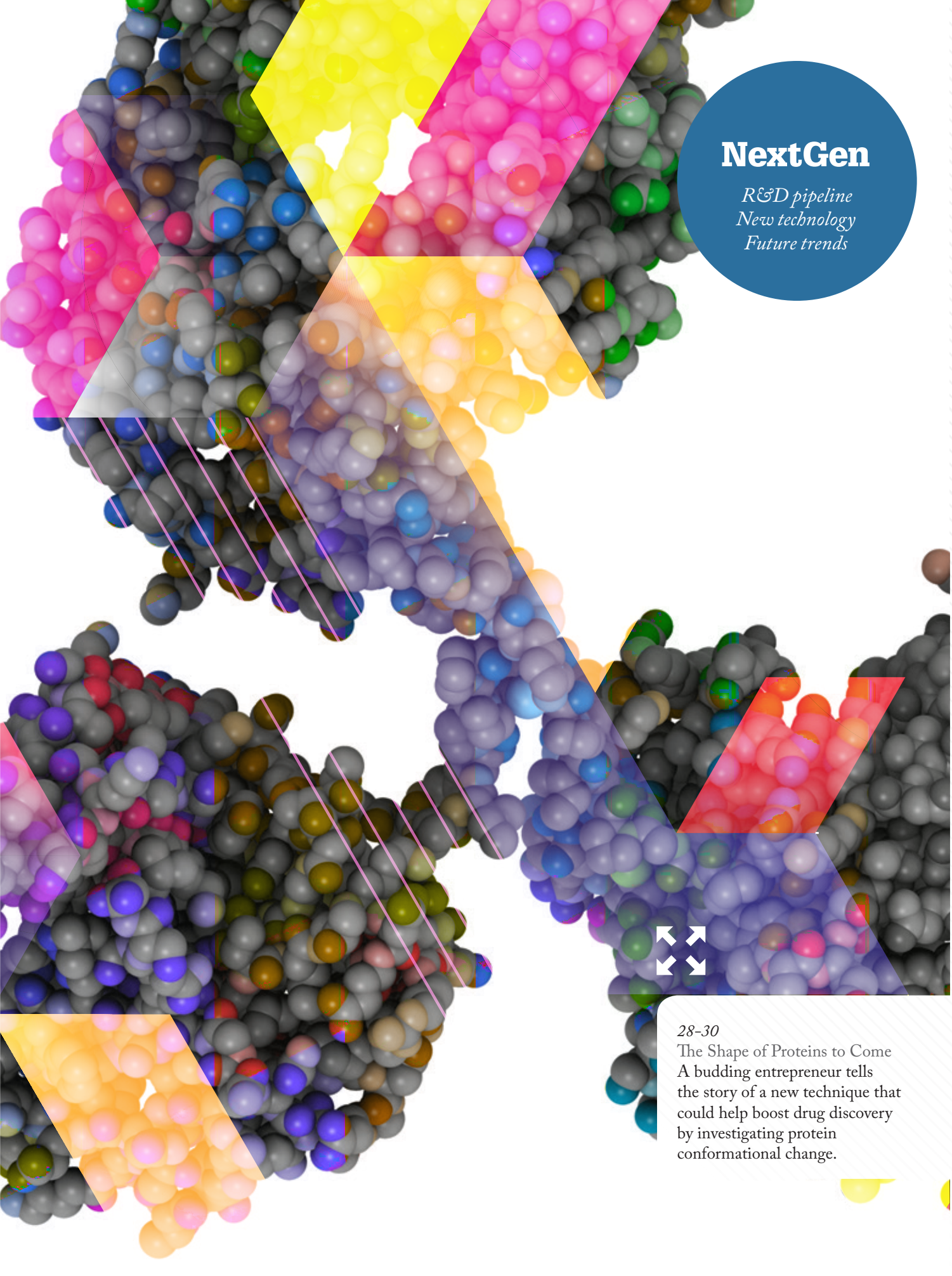
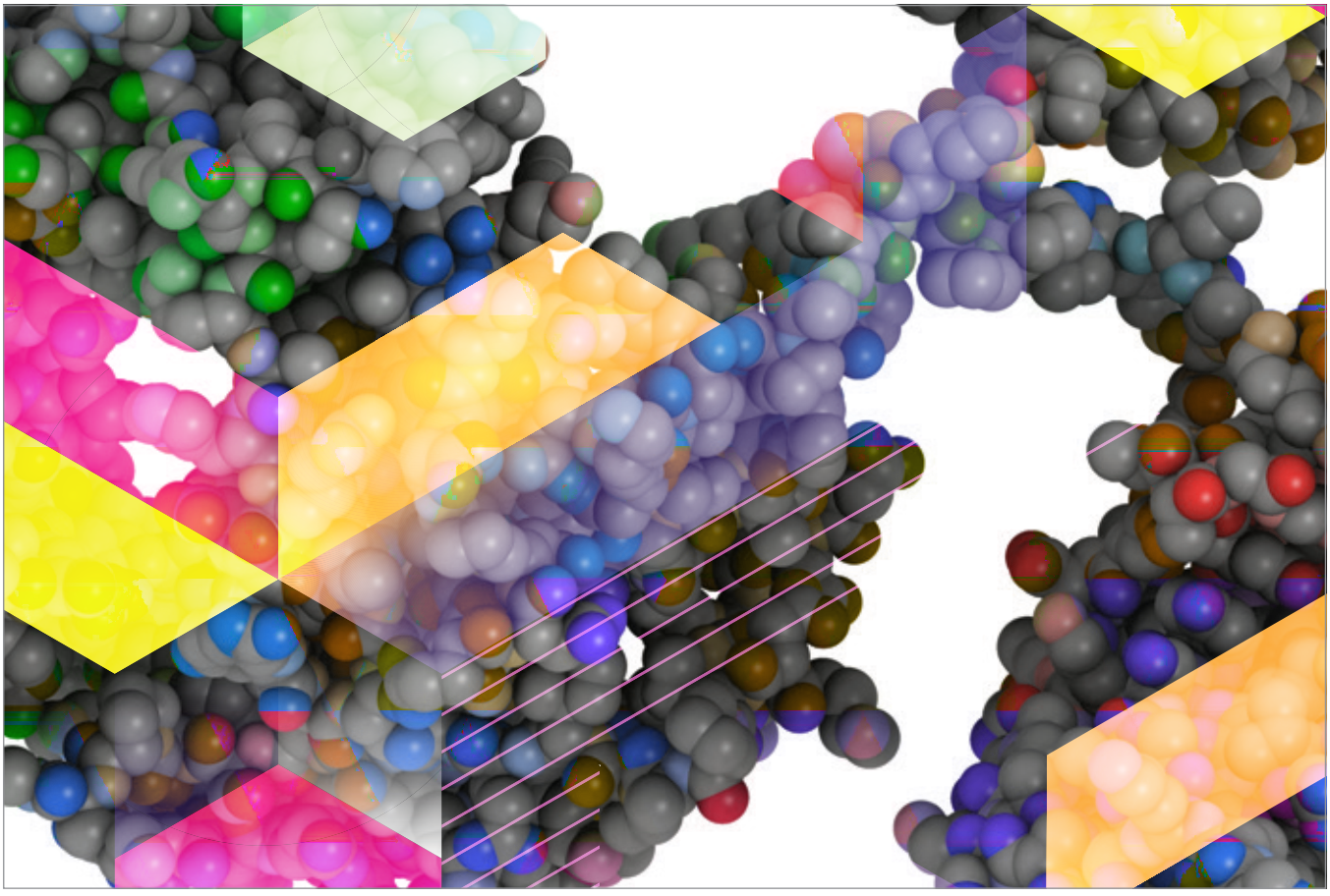


# NextGen

*R&D pipeline*
*New technology*
*Future trends*



# The Shape of Proteins to Come

**A new technique allows scientists to see conformational changes caused by ligand binding in real time, opening up new screening options for drug discovery.**

*By Charlotte Barker*

Protein conformational changes play a key role in signaling (after all, changes in shape cause changes in function); however, it has been difficult to study those changes in real time. Crystallography, dual polarization interferometry, and binding assays have all been used, but inherent limitations have curtailed widespread use. Now, with a new technique based on the optical principle of second harmonic generation (SHG), biophysics start-up Biodesy hopes to put conformational data in the hands of scientists around the world. Investors currently include pharma giants Pfizer and Roche – and Biodesy's first commercial system launched in January 2016.

The technique involves labeling the protein of interest with proprietary dyes and tethering them to a lipid bilayer surface (Figure 1). A femtosecond laser is applied, causing the dyes to generate second harmonic light. The intensity of the signal correlates with the position of the label relative to the surface, and hence the magnitude and direction of the conformational change can be calculated.

## A new angle

Biodesy founder and CSO Josh Salafsky has always been fascinated by the intersection of physics and biology. "I liked the idea of bridging those two worlds, and applying physical tools and ideas to biological systems," he says.

A few months into his post doc at Columbia University, sitting in a lab meeting, he was struck by an intriguing idea. "I realized that there was the possibility of labeling a biomolecule so that you could detect it by SHG. It was an analogous idea to fluorescence, or any other label-dependent detection modality,

but it just so happened that no-one had really thought to do it with SHG."

SHG has been used to study the organization of molecules in inorganic compounds, but not typically for biological molecules. Convinced that SHG held promise for studying structural biology, Salafsky started working on the technology full-time. The discovery that SHG could be used to detect conformational change (and with very high sensitivity) soon followed and, with encouragement from colleagues at Columbia, became the main focus.

"SHG has a number of properties that make it almost tailor-made for looking at protein structure – and for doing high-throughput drug discovery experiments," says Salafsky. "In particular, SHG is much more sensitive to Ångström-level movements of a label caused by structural change than other common techniques like fluorescence. And SHG can be measured easily in real time in a physiological environment, unlike other high-resolution techniques like crystallography."

The first iterations of the technology did not quite match up to the automated, high-throughput machines demanded by the pharma industry, however. "The rudiments of that first setup are actually still found in the marketed product – the Biodesy Delta – but it lacked the high-throughput capabilities and sensitivity that we have now," says Salafsky.

One of the first prototypes took up residence in Salafsky's garage, generating data for several published papers (photo right). It was while working with this original garage setup that Salafsky had a breakthrough moment. "I was doing some experiments on integrins provided by Timothy Springer at Harvard. I applied a control peptide: no change. Then I added a peptide that stimulates conformational change, just one amino acid different than the control peptide, and I saw a change in the signal. That was the moment I knew that I was seeing conformational change caused by ligand binding. I felt that this could be used in so many different ways for drug discovery and basic research. And I knew how easy the process was because I was doing it in my garage! I knew I had something."

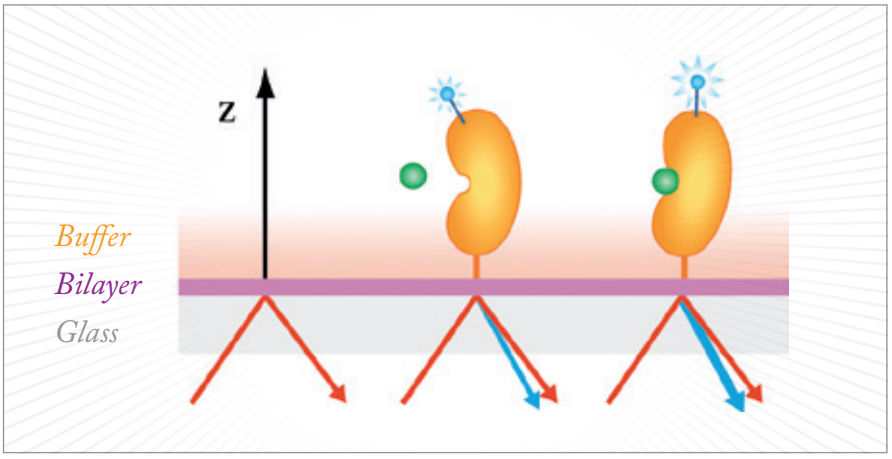



Figure 1. Ligand binding triggers a conformational change that brings the label towards the surface normal, increasing signal (blue light). Conversely, movement of the label away from the normal results in a reduced signal.

*"I felt that this could be used in many different ways for drug discovery and basic research. And I knew how easy the process was because I was doing it in my garage!"*

Joshua Salafsky

An early prototype in Joshua Salafsky's garage

## The birth of Biodesy

In 2013, Biodesy was ready for the next step. Formerly entrepreneur-in-residence at GE Healthcare, Greg Yap met Salafsky during early financing discussions, and was immediately drawn to the concept. "It was the combination of the potential for something really game-changing, together with a near-term opportunity to make a difference in drug discovery," says Yap. "My whole career has been based at the intersection of biology and business. I am always looking to translate discoveries into impact, to help move medicine forward, and Biodesy has the opportunity to do just that."

Yap joined the company as CEO and co-founder, and helped Biodesy secure an initial $15 million investment to commercialize the technology. The name Biodesy (pronounced bi-odyssey) was inspired by the scientific field of geodesy. "Geodesy is the study of the

## The Journey So Far

*2000*
Initial concept to label biomolecules to detect them by SHG

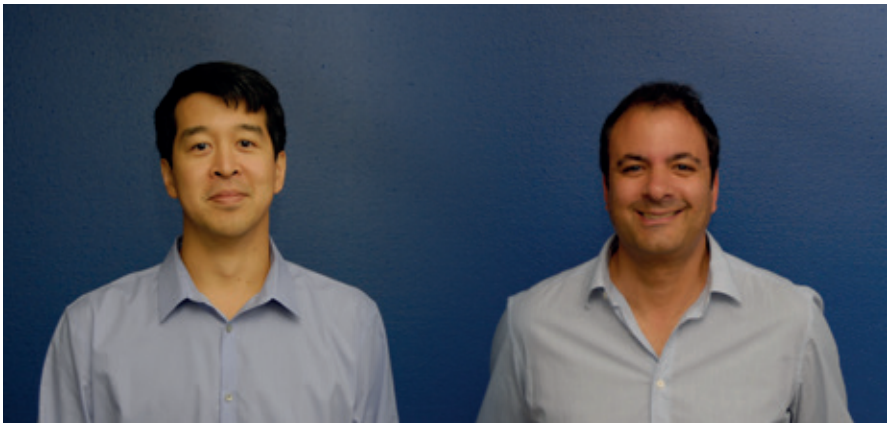
*2002*
Initial concept to use SHG to detect conformational change in biomolecules

*October 2013*
Biodesy, Inc. founded; Series A funding raised

*January 2014*
Biodesy Delta product development started

*December 2015*
20th pharmaceutical customer signed

*January 2016*
Biodesy Delta launched; Series B funding raised



Biodesy

Left: Greg Yap, co-founder and CEO of Biodesy. Right: Joshua Salafsky, inventor of the technology, and co-founder and CSO of Biodesy.

shape of planets, and Biodesy stands for the study of the shape of biological molecules," explains Salafsky.

Prior to the product launch, the company has been offering the technology as a service, and their clients include seven of the top 10 pharma companies. "Now we're in the process of migrating those customers over to using the product," says Yap. "Our goal was always to get instruments into customers' hands, so that they could do experiments in their own labs."

The same properties that made the Biodesy prototype simple enough to run in a garage, now make the final product easy to use in the lab, according to Salafsky. "You don't have to know anything about SHG to run a Biodesy Delta. Someone can learn to use it in a day – and they don't need to be a PhD scientist."

There has been lots of interest in the technique, says Yap: "Pharmaceutical companies are keen to use the technology for high-throughput screening, to identify new hits, to characterize and differentiate those hits, and to understand the mechanism of action in the discovery pipeline. There has also been a tremendous amount of interest from basic researchers. Nearly every researcher is studying an interaction of some kind but relatively few of them get access to structural information at the moment, because of the expense, time and expertise required."

An application the team hadn't initially considered – but which pharma customers were keen to explore – was screening for allosteric compounds, which bind outside the active site. "These are sites that are often not seen in crystal structures, which only provide a static snapshot. By screening proteins in solution you're in a good position to identify binding sites that might open only fleetingly," says Salafsky, "With any totally new technology, it is often customers who figure out some of the most interesting applications. And as we get the technology into customers' hands, the applications are expanding."

"Drug discoverers have never been able to screen based on the conformational change induced by a ligand or inhibitor," adds Yap, "So that's something very exciting to pharmaceutical and academic scientists alike."

### An ongoing odyssey

The team continues to work on improving and expanding the system. Long-term, the technology has the potential to develop into a quantitative structural method, measuring angular change in the protein to model protein structures and structural motion in real time.

Launching the product onto the market is just the start, says Yap. "The company is a testament to Josh's talent and perseverance. Not just in having the original insight, but sticking with it through all of the work to make it practical. It's a tremendous journey, and we're only just getting started."

So what advice does Salafsky have for other budding scientist–entrepreneurs? "Do what you love, because you'll need that drive to keep you going; it is a lot of hard work and uncertainty for a long time. But most of all, never sacrifice the quality of the science," concludes Salafsky.

*Charlotte Barker is the Editor of The Translational Scientist (www.thetranslationalscientist.com), a sister publication to The Medicine Maker. This article was first published in The Translational Scientist.*

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Waseem Asghar

# Meet the Winner

## Waseem Asghar

Waseem Asghar, Assistant Professor at the Departments of Computer Engineering & Electrical Engineering, Computer Science, and Biological Sciences, Florida Atlantic University, USA, has been chosen as the winner of the 2016 Humanity in Science Award for "development of a new paper and flexible material-based diagnostic biosensing platform that could be used to remotely detect and determine treatment options for HIV, E-coli, Staphylococcus aureas and other bacteria."

Waseem will be presented with a humble prize of $25,000 during an all-expenses paid trip to Analytica 2016 in Munich, and his work will feature in an upcoming issue of The Analytical Scientist.

## Could it be you in 2017?

Analytical science has been at the heart of many scientific breakthroughs that have helped to improve people's lives worldwide. And yet analytical scientists rarely receive fanfare for their humble but life-changing work. The Humanity in Science Award was launched to recognize and reward analytical scientists who are changing lives for the better.

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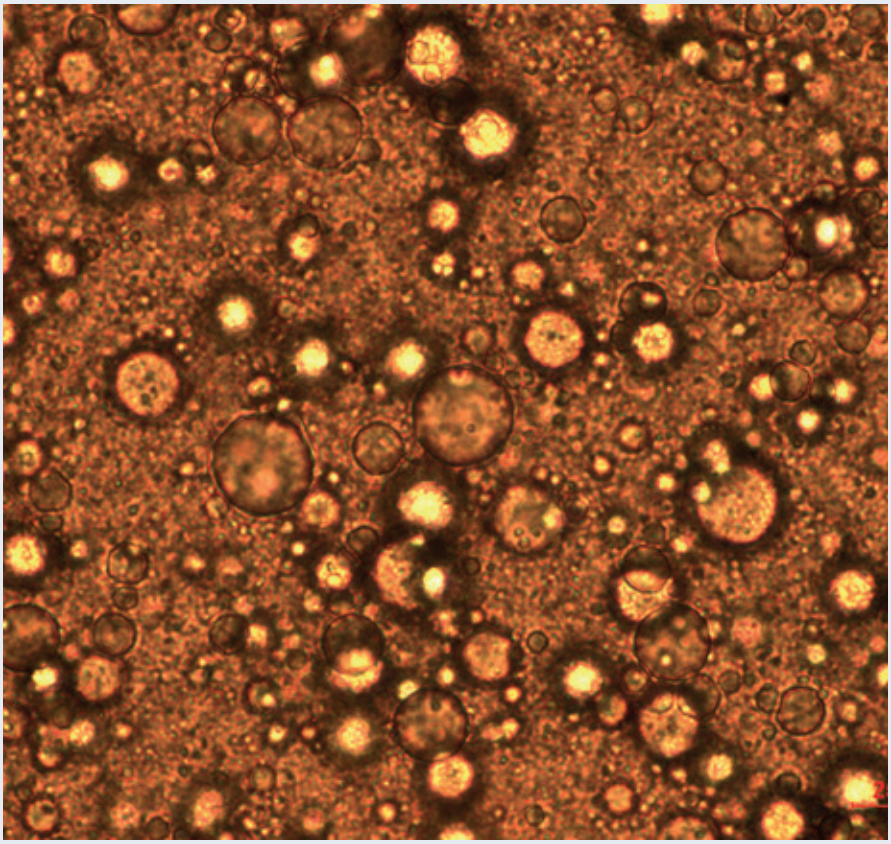
# Micro-Formulating for Dermal Drug Delivery

**Industry is beginning to appreciate how formulation microstructure makes a fundamental contribution to dermal drug delivery – and this new understanding emphasizes the key role of excipients.**



Norman Richardson's career has taken him from cancer research to BASF's Skin Delivery group. His experience as a customer, he argues, makes him a better vendor. Richardson's clients include Lakshmi Raghavan (CEO of Solaris Pharma Corporation) and Padam Bansal (Senior VP R&D of Amneal Pharmaceuticals) – both based in New Jersey, USA. Bansal focuses on Amneal's topical drug delivery pipeline, while Raghavan, who started out in physics, is now hooked by dermal drug delivery.

All three are fascinated by the challenges of dermal drug delivery, but the skin is a complex organ, and its structure and role present specific problems for formulation teams. Perhaps a better understanding of the complex 3D structures found in semi-solid formulations will help drug developers cross this barrier.

## Barriers to entry

Raghavan reminds us of the amazing role of our skin; "It's a thin, 15 micron layer that regulates the temperature of your body, stops you drying out, and keeps out foreign bodies – it's extraordinary." However, such properties also present a fundamental problem for pharma: the skin keeps out drugs – very effectively. A great variety of formulations have been developed to overcome this obstacle, such as ointments, gels, creams, lotions, spray on products, films, and patches, for example, but they all must address the same four challenges:

i. effective transfer of product from its container to the appropriate skin surface in a way that is acceptable in terms of appearance, odor and touch.
ii. pervasion of API through the dense, protein- and lipid-rich skin layer known as the stratum corneum.
iii. avoidance of product-induced irritation or inflammation.
iv. delivery of API to the correct anatomical compartment, whether local or systemic.

According to Richardson, understanding how excipients can address these challenges can determine success in dermal drug delivery. Raghavan expands, "Hydrophilic molecules can't easily penetrate the stratum corneum – but hydrophobic molecules are blocked by the underlying dermis. So your product needs to have a balance of hydrophilic and lipophilic properties, which excipients can help achieve," he says.

"To get systemic uptake," adds Bansal, "you may need penetration enhancers to help carry the drug through the skin. If you don't use a penetration enhancer, then you may be forced to apply the drug over a greater surface area. But at the same time you need to avoid unwanted binding of API to other excipients, as this could inhibit absorption."

With all these hurdles, it is perhaps not

*"Microstructure affects product properties such as rheology, viscosity and spreadability, and therefore influences product efficacy."*

surprising that after decades of research, only ~25 transdermally-delivered drugs are on the market. But this could change. Richardson says, "Formulation design, not least attention to formulation microstructure, will help overcome these delivery challenges."

## Micro construction

But what exactly is formulation microstructure? "The ingredients of a topical formulation, such as polymer, medium, and API, interact in various ways to form a structural relationship," says Raghavan. "Ideally, this structure should hold the drug in a stable and homogeneous state. Microstructure features include aspects such as the droplet sizes in an emulsion, the size distribution of the API particles, and the homogeneity of API dispersion in the formulation."

Interest in microstructure is as much pragmatic as academic – Bansal points out that microstructure affects product properties such as rheology, viscosity and spreadability, and therefore influences product efficacy. Raghavan concurs, adding that the rate of drug release is also affected by microstructure. Richardson provides evidence for the practical importance of understanding microstructure from his experience with a topical anti-inflammatory that had developed batch-to-batch stability issues. "The first thing I did was to look under the microscope. I immediately saw that the API crystals in the unstable formulation were significantly smaller, suggesting the API dissolution rate was higher and oxidation/degradation more rapid. The solution was to increase crystal size. You wouldn't have worked that out without paying attention to microstructure."

But how easy is it to modulate formulation microstructure? Richardson is clear; the choice of excipients is key – but to make an informed choice, you must do your homework; namely detailed studies (using tools like microscopy and differential scanning calorimetry) to show how excipient selection can influence the microstructure of semi-solid formulations, and to provide a firm understanding of how the resulting microstructure affects formulation performance. "We've used microstructure studies to identify critical aspects of PEG mixtures, such as the ratio of solid to liquid PEG that gives best stability," Richardson says. "With that knowledge, we can make intelligent decisions about the optimal mixture of high and low molecular weight PEGs, and the best process parameters."

"We found that the viscosity and spreadability of a PEG-based ointment were fine in low volume batches but unsatisfactory after scale-up," Bansal adds. "The viscosity changes were caused by altered mixing and heating parameters at larger scale, and microstructure studies showed that by keeping the heating step below a certain temperature, the desired product attributes were preserved."

Raghavan agrees. "The exact form of the microstructure can be affected by the formulation process – the temperature at which you mix the ingredients and the cooling rate, for example. If you cool it too fast, the viscosity drops from say 100,000 to 30-40,000; but by cooling it slowly you can preserve the microstructure."

Microstructure is certainly a hot topic – there was standing-room only at Richardson's recent seminar at the American Association of Pharmaceutical Sciences event held in Orland, Florida, last year. The interest reflects a broad acceptance that the performance and functionality of semi-solid formulations is driven not only by the individual ingredients in the formulation, but also by the complex structures that form when these ingredients are mixed together. "The excipients assemble into physical structures, and these structures drive product functionality – they are as important as the API," says Richardson.

And that is why Bansal – and others like him – turn to experts for advice. "In topical drug products, excipients are critical for API delivery. That's why we work closely with our suppliers and manufacturers, so we know what's going to happen if we subject an excipient to higher temperatures or longer mixing times," he says.

The new appreciation of microstructure is also influencing regulatory oversight. "Regulators increasingly request information about the localization or state of the API in the microstructure, such as its crystalline form, aggregation, and homogeneity," Richardson says. "Addressing these questions requires microscopy and rheology, both of which are routinely employed by my colleagues and I."

"Put simply," concludes Raghavan, "it's clear that microstructure studies are an essential development tool that can help prevent successive failed formulations."

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# Best Practice

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# Not Spoiling the (Biopharma) Broth

## Can sophisticated (spectroscopic) sensors streamline bioprocess monitoring to better meet FDA standards?

*By Dörte Solle, Philipp Biechele, Christoph Busse and Thomas Scheper*

The ability to measure all process variables is of great importance in the field of bioprocess monitoring, control, documentation and approval. In 2002, the FDA launched a new initiative to promote innovation of process analytical technologies within the pharmaceutical industry. The aim? To create processes that generate products of ensured quality. How? By using effective and suitable sensor systems for measuring quality-related process variables.

Process analytical technology (PAT) has been part of biotechnology, biopharma production, and the food industry for some years, with some of the sensor technologies used for bioprocess monitoring well established and reliable. And yet, despite newer systems being available for bioprocess monitoring, many are still not commonly used – most likely because the implementation of new sensor systems into already approved processes would lead to a time-intensive and expensive re-approval of the process.

### Three's a charm

Most bioprocesses are three-phase systems; the cells are dispersed as a solid phase in a liquid medium phase, which is aerated by a gas phase (1 – please note that all references can be found in the online version of this article: http://tmm.txp.to/0316/solle). The interactions among these three phases are complex, and there are several types of variables to consider among these three phases: physical (for example, pressure, temperature), chemical (for example, pH, $pO_2$, nutrients, and metabolites) and biological (for example, biomass concentration, cell morphology). Monitoring and control of physical variables are common during bioprocesses, with chemical variables like pH and $pO_2$ also being established. For nutrients, metabolites and the biological components, however, sensors are either not established or are not available.

Biological components often react very sensitively to environmental changes, sometimes resulting in adverse effects on activity or reproducibility of the process. Detailed analysis and monitoring of the three phases – combined with deep process knowledge – is therefore necessary to control and optimize cultivation processes for high product concentration and quality, as well as for documentation purposes.

*"The most important variable in bioprocesses is the biomass – the solid phase in the complex, three-phase system."*

At present, most variables are monitored off-line by sample taking or by at-line HPLC. Off-line sensors are possible, but less desirable because of infrequent sampling and long response times; without closely following important process dynamics, efficient control of the process is not possible (2). In-line or in-situ sensors are essential in bioprocesses so that the actual state of the bioreactor can be controlled and monitored at all times. However, developing sensors suitable for bioprocesses is a complicated challenge, because sensors interfaced directly with a bioreactor must be robust enough for the harsh condition of sterilization, and must not be affected by fouling or by interference with the medium. Subsequently, not all analytical tools from the laboratory are suitable for in-line monitoring of bioprocesses in an industrial environment.

### State-of-the-art tech

In bioprocesses, changes in the concentrations of several gases, especially oxygen and carbon dioxide, provide information about cell growth, metabolism, and productivity, and can be monitored by off-gas analytics – very common in bacterial and yeast cultivations.

The concentrations of dissolved gases, including oxygen and carbon dioxide, as well as various nutrients, metabolites and products, need to be monitored in the liquid phase. Classical electro-chemical sensors can be used for pH, $pCO_2$ and $pO_2$ measurements in steel bioreactors, using standard ports. For disposable bioreactors, optical chemosensor systems – also called optodes – can be used for those variables. Optodes are based on the interaction of a matrix-embedded indicator and the analyte (3) and can be pre-sterilized within the disposable containers by γ-radiation and can be connected to optical fibers via transparent materials, such as glass. Such optical chemosensors are used to monitor chemical variables, but for nutrients and other biological variables, spectroscopic measurement is recommended. Common spectroscopic methods for bioprocess monitoring are focused on the spectral range from UV to MIR, including fluorescence and Raman spectroscopy. Various bioprocess variables can be measured in different spectral ranges (4–16) (see Figure 1).

There are several advantages to using

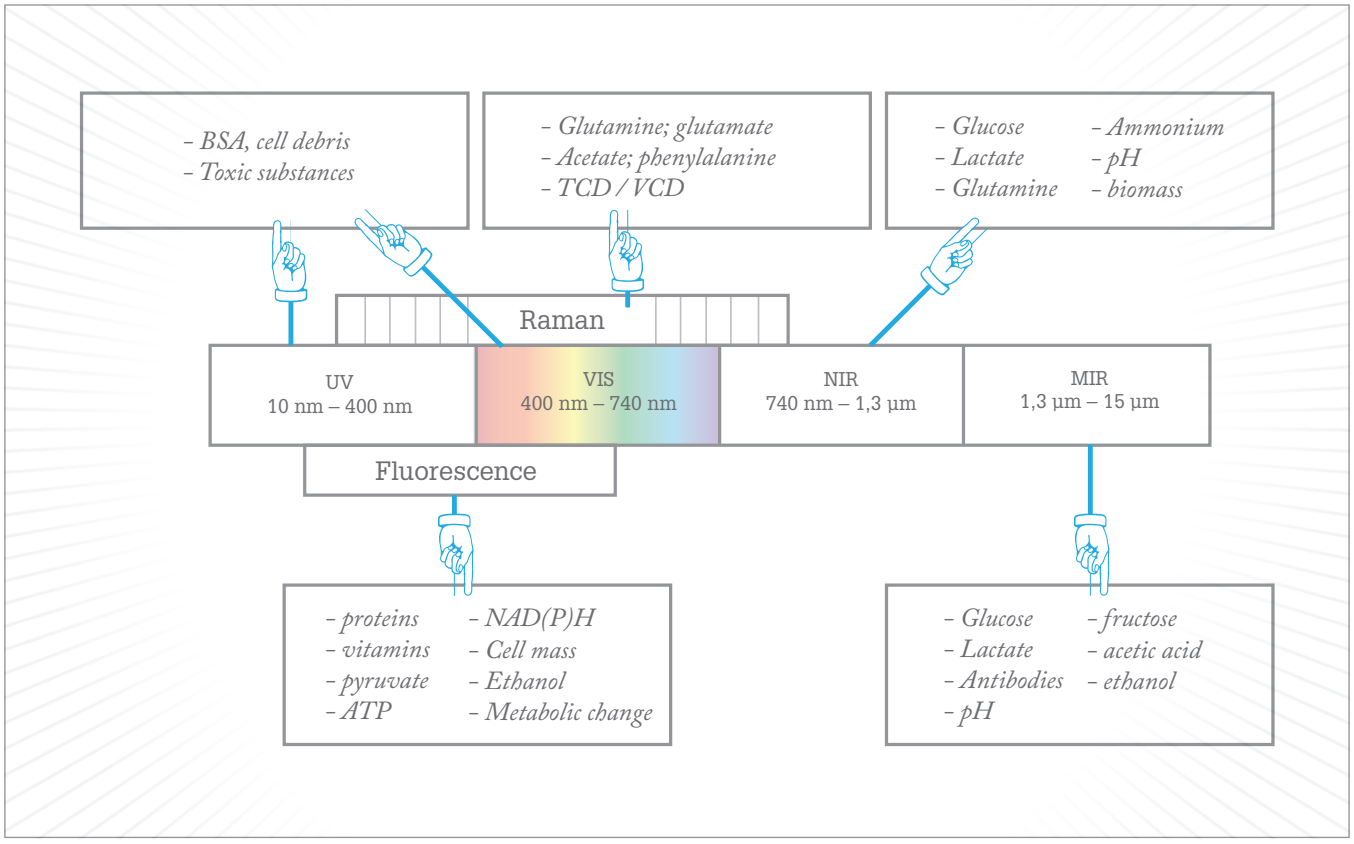



Figure 1: Spectral range for bioprocess monitoring with accessible variables.

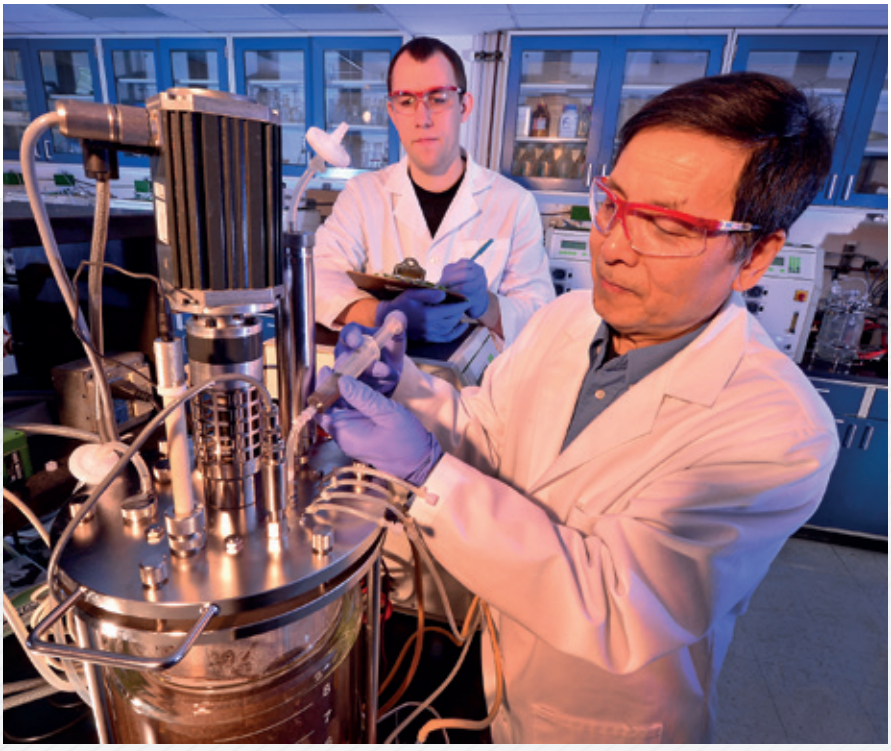
spectroscopic sensors. No sampling is needed (except for calibration), there is no interaction between the sensor and analytes, and several different process variables can be determined simultaneously. However, chemometric data analysis is required for spectroscopic bioprocess monitoring to extract relevant process information.

The most important variable in bioprocesses is the biomass – the solid phase in the complex, three-phase system. The biomass can be characterized by its concentration or by its metabolic activity, and different analytical methods exist to determine both of these. The measurement of the optical density (OD) by turbidity is one of the most frequently applied technologies for biomass monitoring, but impedance measurements can also provide metabolic information about culture condition. And through so-called in situ microscopy (ISM) – microscopy directly in a bioreactor – it is possible to acquire pictures of the suspended organisms and to analyze the cell concentration, cell size, cell distribution, and morphology automatically by image-processing algorithms (42).

In addition to the biomass, the concentration of viable, metabolically active cells is of special interest in bioprocesses because they are the only ones able to grow and produce the desired product. The determination of bioactivity is possible by certain sensors; for example, turbidity probes allow inferences about cell size and morphology, impedance sensors can be used for the observation of lipid storage in yeast (43), and image analysis by ISM systems makes information on cell size and morphology accessible. However, special systems have been developed specifically to analyze the metabolic activity of cells. The oxygen uptake rate (OUR) is a robust indicator of the determination of cellular activity, and as one of the fundamental physiological characteristics of aerobic culture growth, it has been used frequently for the optimization of bioprocesses (44–46).

## Getting on-line

Several sensor technologies provide an enormous amount of data, especially when spectra are generated via in-line sensors at high frequency. The data must be correlated to important process variables, like substrate concentration, or to the actual process status in a calibration



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## From UV to MIR: the biomass monitoring spectrum

Infrared spectroscopy includes spectral areas of near infrared (NIR, 740 nm to 1300 nm) and mid-infrared (MIR, up to 15000 nm). In general, IR light excites different vibrational modes of molecules. Each organic and inorganic compound has a special spectral IR signature from these vibrations. IR spectroscopy offers very fast, robust and sensitive multi-analyte information from the culture broth of bioprocesses. It is a non-invasive process analytical technology, applied in-line by direct beam or optical fiber.

MIR radiation excites fundamental rotational vibrations of functional groups from organic compounds. Molecules such as glucose, lactate, fructose, acetic acid, ammonia, and even antibodies (17) have a characteristic absorption spectrum which can be used to identify single components in bioprocesses quantitative, sensitive, and specific.

A high degree of water absorption appears in MIR spectra. However, in-line measurement in aqueous solutions is possible using appropriate fiber optic probes that incorporate attenuated total reflection (ATR) technology and Fourier transformation (18–20). The measurement principle of ATR probes results in a very short (only few µm) path length and cells cannot be detected because they are too large to enter the measuring zone.

NIR spectroscopy is also based on different vibrational modes, overtone and combination vibrations after excitation. Important targets are the O-H, C-H and N-H bonds. The NIR range is thus suitable for monitoring of substrates such as glucose and lactate, biomass, and the products of a bioprocess (17, 21). As a result of the lower energy of the NIR and the resulting overtone vibrations, the bands are much broader, often overlapping, and not as specific as in MIR spectroscopy (20). Thus, NIR spectroscopy has a more qualitative character, compared to the more precise and quantitative MIR spectroscopy. NIR spectroscopy offers a more global view to a bioprocess, e.g. by batch trajectory (22).

Due to its higher robustness, NIR spectroscopy is better applied for monitoring industrial production processes. MIR spectroscopy is well suited for process development and optimization due to its multiplexing technology and the fact that fragile ATR fibers are used.

UV/Vis spectroscopy uses ultraviolet and visible light (10–740 nm) to excite electrons of molecules, the observable transitions taking place at unsaturated bonds, such as in aromatics (11). A variety of analytes, substrates, metabolites, and products can be determined with UV/Vis spectroscopy, which has high sensitivity, and high resolution spectrophotometers can be compact, inexpensive, and robust, making these instruments interesting for industrial process applications (21). However, UV/Vis spectroscopy does not currently play a major role in bioprocess monitoring (23) despite the use of CCDs or photodiode arrays making UV/Vis spectroscopy even more attractive.

Using fluorescence spectroscopy, many important molecules for bioprocesses can be monitored and controlled, including proteins with aromatic amino acids (tryptophan), NAD(P)H (biomass), ATP, pyruvate, vitamins, pyridoxines, coenzymes, and flavins (12, 21, 24–27). Each fluorescence-active compound has a specific pair of excitation and emission wavelengths. Simultaneous measurement of several different fluorophores in the culture broth is possible by 2-D fluorescence spectroscopy (13, 24, 28–31).

Raman spectroscopy is another form of vibrational spectroscopy. It is based on shifted wavelength scattering of molecules, after excitation by monochromatic light, usually produced by adjustable lasers (32). Several analytes, including glucose, lactate, acetate, formate, glutamine, and glutamate, can be measured (1, 15, 21, 33–37). The use of Raman spectroscopy is limited by the strong fluorescence activity of several biological molecules in the culture broth (34). The fluorescence signals overlay the Raman bands. To avoid fluorescence, low energy lasers can be used, but then heating effects can occur (21, 24, 38).

model. Afterwards, the model can be used to predict the variables or the process status from on-line spectroscopic data. For these correlations, multivariate data analysis must be applied because the relevant information is distributed over the entire data set and cannot be found in a subset of a spectrum nor in only one spectrum (47, 48). Such chemometric methods are used to provide interpretable information from the enormous amount of spectroscopic data of a bioprocess.

Data pre-processing is a sensitive and powerful tool for spectroscopic data (49), with the method of choice depending upon the spectral data. After data pre-processing, multivariate data analyses are performed to extract qualitative or quantitative process information from the spectral data. Many established applications are based on principal component analysis (PCA), which assesses the main components of spectral variance induced by changes during the process. With PCA, a classification of raw materials, batches, or the process status is possible (50).

All of these qualitative methods can be used to monitor a bioprocess as defined by PAT (51), and high process reproducibility and product safety can be provided by this type of process supervision (52). A process target line, or trajectory, can be identified out of similar ideal process runs (53–56), with different measurements, multivariate spectroscopic data, or univariate classical process data being pooled to generate a holistic view of the bioprocess (57).

In contrast to those qualitative methods, quantitative models are needed to describe correlations between single analytes and spectral data. Using PLS, the values of different variables can be predicted from a spectroscopic measurement by chemometric models (58, 59). For a PLS calibration, representative process data are needed – including both spectral data and the corresponding reference values. The data need to be distributed over the entire process, describing the variance inside a single process run as well as different process runs. Both variabilities need to be considered for calibration, in order to calculate a reliable PLS model with satisfying prediction quality to unknown process data (60–63). The process of model construction is sensitive and extensive, but based on this, broad on-line monitoring in terms of the PAT is possible (64–68).

Novel optical sensors are of course among the major developments in bioprocess monitoring, with spectroscopy increasingly being used for determining variables in-line in the liquid phase – and having strong advantages despite the significant requirement for calibration and data treatment via chemometric tools.

## Part of the (bio)reactor

If we are to meet the special requirements of these modern single-use reactor systems, we need a new sensor philosophy. Conventional sensors were mostly built as reusable devices for long-term operation, but cannot be inserted directly into single-use bioreactors. In comparison to reusable devices, the lifetimes of such single-use sensors can be shorter, but still must be long enough for long-term, continuous production processes. Furthermore, these sensors must be cheap (owing to their single-use nature), small, and modular (21, 28).

Optical sensors and semiconductor devices (for example, ISFETs) are well suited for such purposes (69). Sensor patches or other measurement systems can be connected with reusable external equipment; therefore, the material of disposable reactor systems must be permeable to the sensor signal; for example, glass windows are a common way of transmitting optical signals from the inner space of the reactor to connected external devices, such as optical fibers and detectors. The observable trend of modern bioprocessing toward single use, disposable systems will help to promote the development of new sensor systems or adapter systems that enable the connection of "classical" sensors to disposable reactors.

## Quality first

The FDA specifies that "quality cannot be tested into products; it should be built-in or should be by design". "Built-in" bioprocess quality is enabled by combining process analysis, process knowledge, and process modeling, with tools like multivariate data analysis, bioprocess modeling, Design of Experiments (DoE), and new sensor technologies to reach defined quality goals and to document the process. The process information generated can provide deeper process knowledge for the safe handling of all quality-related variables; the ability to monitor and control critical process parameters (CPP) is the path towards holistic control. The upshot? Quality can be ensured during all manufacturing steps and makes real-time release of products feasible via process validation.

Optical and spectroscopic sensors meet these requirements, as well as offering the possibility to monitor various compounds simultaneously. The downside is that these sensors require complex data handling via chemometric models to derive valid process information. The variety of such sensors described in research is huge, and transfer to broader applications in industrial biotechnology in the near future seems likely. If the biopharmaceutical industry is committed to a total process overview and the ongoing improvement of processes by on-line monitoring (ultimately aiming to meet the goals of the PAT initiative), modern sensors must be embraced – and further development is inevitable.

*Dörte Solle, Philipp Biechele, Christoph Busse, and Thomas Scheper are all based at the Institute of Technical Chemistry, Leibniz University, Hannover, Germany.*

# Fumigation of the Future

**A choice of fumigants are available for fumigating microbiological safety cabinets and high-level containment rooms. One substance that is still used in the industry is formaldehyde, but given that formaldehyde is toxic, carcinogenic and corrosive, you'd be better looking for alternatives.**

*By Andrew Ramage*

Before joining Cherwell Laboratories, I worked in the pharmaceutical sector for well over fifteen years. In that time I spent nearly six years in aseptic manufacturing and nine years as a quality control microbiologist. Those were at two different companies, but there was a common factor – both used formaldehyde as their fumigant of choice.

Formaldehyde has been used as a fumigant in laboratories since the 19th century, with one article I came across about formaldehyde dating back to 1897 (1). Older readers will remember the permanganate-formalin method of generating formaldehyde gas – this was used until fairly recently and is referenced in an article from 1913 in a review of formaldehyde fumigation (2). The health implications were recognized even then, so it is amazing to think this particular method was used for so long. Indeed, until very recently, I was still performing formaldehyde fumigations (although not using permanganate I hasten to add!).

Towards the end of my time at my previous employers, I began looking at alternatives to formaldehyde and I came up with a rational argument that I think worked well, especially when there were many members of staff set against changing the tried and tested formaldehyde fumigations. In fact, my interview at Cherwell involved a short presentation about fumigation. And now I'd like to share that rational here.

For those unfamiliar as to why rooms and equipment are fumigated; it provides an effective means of destroying micro-organisms, both in the air and on the surface, particularly when looking to destroy spore forming micro-organisms. The method of delivery depends on the chemical used and is detailed later in this article. In a nutshell, a vapor of the chemical is produced so all surfaces in the room come into contact with that chemical, therefore destroying or irreversibly inactivating any viable organisms and spores. The action is not immediate, so there has to be a certain length of contact time, which is dependent on the fumigant used. At the end of the process, the fumigant

*"There will be those of you reading this that still use formaldehyde to fumigate – and perhaps would never consider anything else."*

is removed; either by the room or equipment's ventilation system, or by releasing a neutralizing agent.

### Why formaldehyde?

There will be those of you reading this that still use formaldehyde to fumigate – and perhaps would never consider anything else. And then there will be those of you who have never used formaldehyde and are wondering why it's still being used. There are two basic benefits to using formaldehyde: efficacy and cost. Formaldehyde kills pretty much all known microorganisms, which is especially important when you need to fumigate high-containment level areas. And when it comes to cost, let's be honest, the cost of formaldehyde and a boiler is dirt cheap. Here in the UK, a 2.5-L bottle of formaldehyde can cost less than £20 (less than 25 Euros or $28) and a small boiler (although many people still use electric frying pans) is also cheap. The fumigation process is also repeatable and reliable – and it's been used for years. If you are still using formaldehyde – and I know plenty of companies that still are – there is the obvious question of why should you change?

Well, apart from the smell and the stinging eyes when you get a whiff, and the fact that formaldehyde is a sensitizer that can cause allergic reactions, do remember that it is also identified as a class 1 carcinogen (3) by the World Health Organization's International Agency for Research on Cancer and is highly toxic. And then there is the paraformaldehyde residue that remains post fumigation – frequently stuck hard to the surface. I hated cleaning up after formaldehyde fumigations; it takes a long time to clean and can also remain in your room's HEPA filters for a considerable time afterwards, which can mean a long down time for your facility – definitely not the way to go in today's competitive industry (the less downtime the better). In short, formaldeyhde is toxic, carncinogenic and corrosive. I believe that's a good enough reason for any company to consider changing their fumigation process. Its use is not standard practice in all countries, but it's still fairly common in Europe, particularly for small companies. In the medium to long term, however, there is a reasonable possibility that you won't be able to use formaldehyde for fumigations at all in Europe, even if you wanted to.

### The fumes of change

Within Europe, formaldehyde is currently registered as a biocide as per article 95 of the Biocide Products Regulations (4). It is costly for chemical manufacturers to register formaldehyde as a biocide and as fewer companies use formaldehyde, it will eventually no longer be cost effective to produce formaldehyde for that purpose; therefore, fewer companies will bother registering it. There are also some countries in the EU that want formaldehyde removed from the list completely because of its potential hazards. If that happens, it will be difficult to justify the use of

## Formaldehyde Facts

- Formaldehyde was accidentally produced by Alexander Mikhailovich Butlerov in 1859; it was more formally discovered in 1868 by August Wilhelm von Hofmann.
- Formaldehyde is still commonly used by pharma companies in various countries. It has intrinsic anti-bacterial and preservative properties – and is also cheap.
- As well as being used for fumigation, formaldehyde is also used to manufacture certain viral and bacterial vaccines, and has other applications in medicine and healthcare too.
- When using formaldehyde, the highest risk to health is when it is inhaled; it is generally only considered dangerous to those who routinely use it as part of their jobs.
- In the European Union, formaldehyde is banned from use in certain applications (preservatives for liquid-cooling and processing systems, slimicides, metalworking-fluid preservatives, and antifouling products) under the Biocidal Products Directive.
- In the US, formaldehyde used to be well used, but is seen as not acceptable today. In 2011, the US National Toxicology Program (NTP) declared today formaldehyde causes cancer in humans.
- Formaldehyde is not just used by the pharma industry – it's also used in the construction, automotive and furniture industries.

| *Fumigation System* | *Pros* | *Cons* |
|---|---|---|
| *Vaporized Hydrogen Peroxide* | - Fast acting<br>- Non toxic residue<br>- (water) Sporicidal<br>- Fast dispersal<br>- Odorless | - Poor efficacy with mycobacterium |
| *Chlorine Dioxide* | - Excellent efficacy against all organisms<br>- Reproducible results<br>- Non-carcinogenic | - Corrosive over time<br>- Broken down by UV light |
| *Ozone* | - Very fast acting<br>- Rapid dispersal | - Requires neutralization and aeration<br>- Leaves acetic acid odor<br>- Lower efficacy when challenged with high doses of pathogen |

Table 1. Alternatives to formaldehyde.

formaldehyde as a biocide at all.

Another reason as to why formaldehyde's use for fumigation may be limited are due to the EU's REACH (Regulation, Evaluation, Authorization and restriction of Chemicals) regulation – which was discussed in a recent issue of The Medicine Maker (http://tmm.txp.to/0116/reach). There may come a point in the future under REACH when the disposal of formaldehyde will be even more strictly regulated; most likely the release of formaldehyde into the air or into sewerage will be banned. At this point the use of formaldehyde in fumigations will become extremely problematic, to put it mildly.

Admittedly, you can neutralize formaldehyde by passing air through carbon granules or by boiling off ammonia, but do you really want to be handling large volumes of ammonia, or having to arrange for the disposal of carbon granules saturated with formaldehyde? In both cases you will have to prove that you have completely removed the formaldehyde from the air in that cabinet or room. In the case of neutralization with ammonia, you also have to ensure the ammonia has dispersed, which could add to the already lengthy downtime that formaldehyde fumigation requires. And remember, ammonia is classified as both an irritant and corrosive, so it may not be appropriate for use in your facility.

I'm not going to commit to a timeframe as to when any of this may happen. However, if you're using formaldehyde (wherever you are) then I recommend you read up on your respective regulations and to be prepared for change. It would also be prudent to have a plan in place to validate an alternative system sooner rather than later. Obviously,

*"I cannot sugar coat the fact that alternative systems can be considerably more expensive than formaldehyde."*

the EU regulations I've mentioned only apply to Europe. For those of you in the US or other areas, I'm not an expert and I'm not qualified to comment on other geographies so I encourage you to check your country's own regulations to find out if you can or can't use formaldehyde – and even if you can, it doesn't change the fact that it's a carcinogen.

### What's the alternative?

Before I go through the alternatives to formaldehyde, it's important to point out that what you choose depends on what the purpose of the fumigation is. There will be two main reasons for fumigation: to lower the bio burden in that area, such as in a cleanroom; or to destroy known pathogens due to a spillage or post maintenance shutdown in high-containment level facilities. I cannot sugar coat the fact that alternative systems can be considerably more expensive than formaldehyde – the greatest expense will be the setup cost if you are doing the fumigation in-house, which will be the case if you fumigate on a regular basis. If you fumigate on a less regular basis, it could well be worth considering the use of a contractor to do the work for you.

The following is a brief outline of each alternative technology; the details of each one are separate articles on their own. Your current options are hydrogen peroxide, chlorine dioxide and ozone, which have all been tested for efficacy against a range

of pathogens by the Health and Safety Laboratory (4).

The best established of these alternatives is hydrogen peroxide and there are two main types: dry and wet. The dry version is better known as vaporized hydrogen peroxide (VHP). The mode of action requires the concentration of VHP to be maintained below the condensation point. The wet version spreads a layer of hydrogen peroxide onto exposed surfaces. Chlorine dioxide and ozone are true gas systems, as both are gaseous at room temperature.

As previously mentioned, the fumigation method needs to be appropriate to the work performed at your facility. All methods come with their pros and cons, and some claim greater efficacy than others (see Table 1). Some may be more corrosive and some will have limited penetration. Hydrogen peroxide, for instance, has limited efficacy against certain pathogens. Since the quoted study (5), there are now hydrogen peroxide based disinfectants with additional chemicals to make them more efficacious. These include the addition of peracetic acid or silver cations, which claim enhanced efficacy for different reasons.

Whichever method of fumigation you choose, do make sure that it is validated to the standard you require, whether against a particular pathogen, or by reducing the bio burden in that area by a specified amount. The method needs to be repeatable and reliable. Do also consider the cost and efficiency of the chosen system, not just the setup costs, but the down time of your facility as a result of the fumigation process too. The shorter the fumigation process, the sooner your facility will be back in action.

*Andrew Ramage is Microbiology Product Specialist at Cherwell Laboratories, UK.*

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# The Numbers Game

**Statisticians are vital in the pharma industry, but rarely do they receive public fanfare for their work. The Award for Statistical Excellence in the Pharmaceutical Industry aims to change the status quo.**

The winners of the 2015 Statistical Excellence in the Pharmaceutical Industry Award. Nicky Best (right) led the team at GlaxoSmithKline, which has implemented a process that has turned beliefs about the chances of success into formal prior distributions. Pfizer's Katrina Gore (left) was nominated for the prize for her contribution to the development of the Assay Capability Tool (ACT), designed to guide the development of drug discovery assays and to address issues of robustness and reproducibility in research.

If you have a love of mathematics then a career in pharma, at first glance, may not seem like a dream job, but dig deeper and you'll find that effective pharmaceutical development is built on maths – particularly statistics. Stephen Pyke has a degree in mathematics and first decided to go into the actuary business, before quickly deciding that it was the wrong choice. After returning to university to complete a Masters in statistics, he gradually became interested in biology and pharmaceuticals. Today, Pyke is Senior Vice President of Clinical Projects and Quantitative Sciences at GlaxoSmithKline, UK, but he is also Vice President for Professional Affairs at the Royal Statistical Society (RSS). At the latter, he helps thrust statisticians into the limelight with the Award for Statistical Excellence in the Pharmaceutical Industry, a prize jointly sponsored by the RSS and the Statisticians in the Pharmaceutical Industry (PSI) group. So, are pharmaceutical statisticians finally getting the recognition they deserve?

You don't have a science degree. How did you become interested in pharma?

I'll be honest – I wasn't that interested in biology at school! But I ended up getting a job at the Medical Research Council in North London where I worked in the laboratory of mathematical biology – and the application of mathematical models to biological systems intrigued me. I worked in a really nice group led by Tom Kirkwood, who later went on to work in the area of gerontology; today, he's the Associate Dean for Ageing at Newcastle University's Faculty of Medical Sciences. After that, I got the chance to work at the London School of Hygiene and Tropical Medicine, where I focused on clinical trials, epidemiology, and public health. I was able to work with Simon Thompson (my boss at the time) and Stewart Pocock, who are both very well known in the field of medical statistics. I loved my time there, but I was also gradually getting interested in the pharma industry – and eventually I took the plunge. The rest is history... It's certainly a great industry to work in. People come into the pharma industry for all sorts of reasons, but I think there are very few of us who don't get a sort of warm glow about the end result – treating and preventing disease, or at least mediating the symptoms. It makes you feel really good about your work and its impact.

And the complexity makes it really interesting. The industry is working on everything from human biological targets, through to selecting molecules (small or large), to clinical experimentation, animal studies... and then, when you get into the clinic, there

*"Statistical techniques have been used to develop predictive modeling systems that have transformed the efficiency of the pharma industry."*

are even more questions to answer. We're famous as an industry for having agonizingly high attrition rates and yet there are times when you wonder how on earth we managed to pull it off for a single molecule, let alone many. But of course the key is collaboration – collaboration across different disciplines, and amongst industry and academia.

How important are statisticians in the pharma industry?

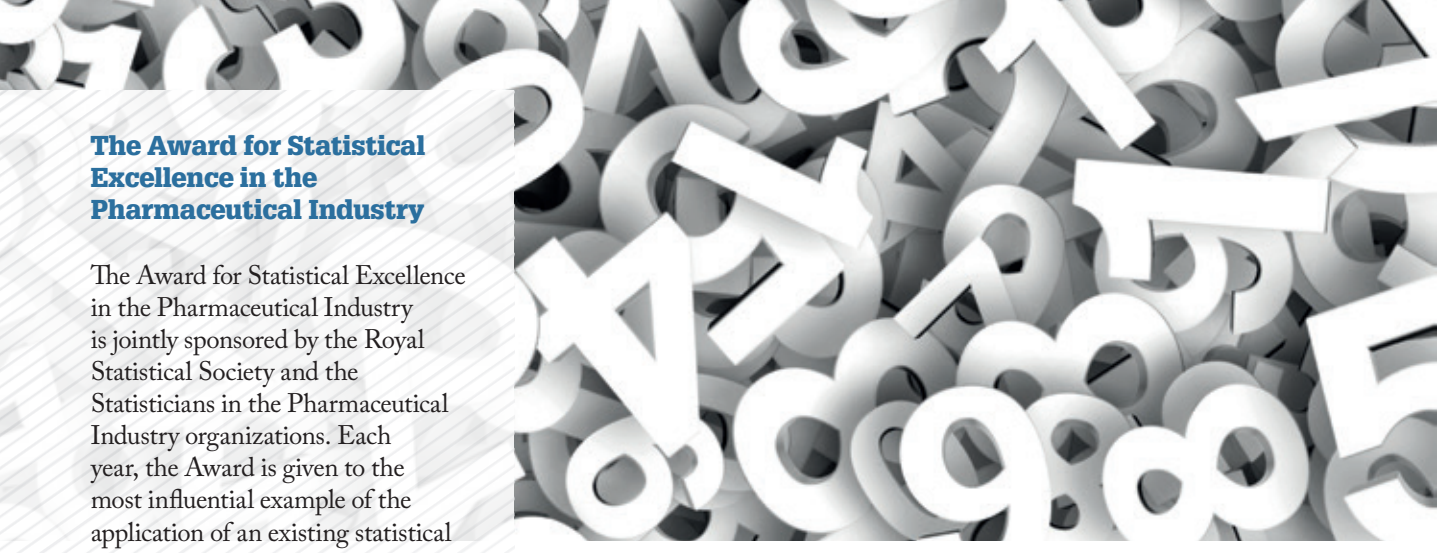
Designing and analyzing clinical trials is a fundamental activity of pharma, and we statisticians are essential to that activity. In fact, the basis of clinical trial design is randomization, which is a statistical concept used to randomly allocate patients in a trial so as to enable fair comparison. But statistical expertise is needed far beyond clinical trial design; the pharma industry is based on the generation of data (and it generates buckets of it), and statistics is about understanding data. To truly understand data, you need a statistician.

Statistics can also forecast the future and process the past. Indeed, statistical techniques have been used to develop predictive modeling systems that have transformed the efficiency of the pharma industry. Predictive models allow us to deduce that, if a drug has the expected mechanism of action, then we should see certain outcomes. Comparing statistically predicted results with actual results can give you a degree of comfort (or a clear warning) about a drug before huge sums of money are spent.

Generating a medicine is a complex process that involves thousands of people, and often it's the people involved at the end of the process who get the glory – the tremendously valuable role played by statisticians is sometimes forgotten. 'Unsung heroes' is a phrase we often use – so I think that the Award for Statistical Excellence in the Pharmaceutical Industry is a nice way to give credit to at least some of these people and the fantastic statistical techniques they develop.

How did you get involved with the award?

The Statistical Excellence in the Pharmaceutical Industry Award is jointly sponsored by the RSS and the PSI organizations. I joined the RSS when I was at university, but now I'm at a stage in my career where I want to give something back, so I got involved with the RSS Professional Affairs committee, which is responsible for certifying statisticians as being professionally competent. It also organizes various events and activities for professional fellows and, in particular, it supports members who work for organizations that are not primarily statistical in terms of their activities, such as the pharma industry. In fact, pharma-employed statisticians have a significant presence in the UK and many of them are RSS or PSI members. With that background, there was a sense in the RSS and PSI that we should be sponsoring an award to celebrate what's best about statistics in the pharma industry. We were



## The Award for Statistical Excellence in the Pharmaceutical Industry

The Award for Statistical Excellence in the Pharmaceutical Industry is jointly sponsored by the Royal Statistical Society and the Statisticians in the Pharmaceutical Industry organizations. Each year, the Award is given to the most influential example of the application of an existing statistical practice, or the implementation of an innovative statistical practice, in the pharmaceutical industry. Although the organizations are based in the UK, they have members globally and international nominations for the award are welcome.

*The deadline for nominations for the 2016 award is midnight on March 31, 2016. Award winners will be notified by the end of April 2016.*
*Questions about the awards should be sent to pharmastatsaward@rss.org.uk and more information is available at http://bit.ly/1oMW3Qh*

Previous winners include:

- Craig Mallinckrodt (2014, Eli Lilly & Company) for his book, Preventing and Treating Missing Data in Longitudinal Clinical Trials.
- Björn Bornkamp (2013, Novartis) for 'Developing efficient statistical methodology and software for model-based design and analysis of Phase II dose-finding studies under model uncertainty'.
- Harry Southworth (2012, AstraZeneca) for 'Producing a method of evaluating clinical laboratory safety data using extreme value modelling'.
- Phil Woodward (2011, Pfizer) for 'A portfolio-wide implementation of a Bayesian framework for early clinical development within a major pharmaceutical company'.

giving out other awards for journalism and for statistics work emanating from government bodies and non-government organizations, so an award for statistics in pharma was an obvious gap. The Award was born about eight years ago and has been an annual event ever since.

The reaction from industry has been very positive. And personally I think that it's great for us statisticians to be able to celebrate our field. Statistics are well respected in the pharma industry, but it's one thing to respect them and another to love them. When I was at Pfizer, I nominated one of the early winners of the award, and it was great to be involved in that way. Last year, the prize was jointly awarded to teams from Pfizer and from GlaxoSmithKline, and I know that everyone involved was delighted about that. I'm a huge supporter of the award and I'm encouraging teams from my organization to put their nominations in. I hope others will too! The deadline for the 2016 award is fast approaching but there's always 2017, if you think you're running out of time.

### What does it take to win the award?

Nominators are asked to complete a form that describes the nature of the work they're putting forward. The work is then evaluated by a small committee, made up of representatives from PSI and RSS. What we're looking for is evidence of impact. As lovely as it is to have done a really thoughtful, clever piece of work, it counts for rather less if it's just published and forgotten about. We want to see evidence that it has an application in the real world. Ideally, we want independent commentary from others – not statisticians per se – indicating that the work has made a difference; that's the hallmark of a winner.

*"As lovely as it is to have done a really thoughtful, clever piece of work, it counts for rather less if it's just published and forgotten about."*

One of the winners from last year used a Bayesian approach to determine the likelihood of clinical trial success. Their system permits the incorporation of various soft and hard information – for example, literature data, pre-existing evidence relating to similar APIs, clinical judgements as to whether a drug would work in the way that the developer anticipates, effects of other treatments previously evaluated in the target population – that can be combined objectively and transparently to provide a level of assurance;

ultimately providing information that is of practical use to the people who make the critical investment decisions. The judges' view was that this method was also beginning to make a difference in terms of the way government bodies evaluated those investments.

Another recent winner was a checklist tool to help people design statistically meaningful and reproducible preclinical experiments. It's intended to support scientists who don't necessarily have a statistician at their elbow all the time. This is not to say that scientists don't think about the issues of reproducibility and statistical power, but they're not usually experts in these issues. This entry got the prize because it was rolled out as a kind of kit, bundled with education and training, and was being broadly adopted for an organization-wide impact. That's exactly what we were looking for.

### Industry evolves rapidly; will it continue to need statisticians?

Undoubtedly! Actually, I believe there is increasing recognition of the need for more trained statisticians to meet future recruitment requirements. A recent report from the UK's Association of the British Pharmaceutical Industry on skill gaps in the pharma industry identified lack of statistical expertise as one of the biggest needs. The shortfall in statisticians for pharma is exacerbated by the current emphasis on big data and digital devices. The explosion of data associated with these devices, and our massively increased ability to access and integrate the data, are of very limited value if we can't analyze and make sense of it all. And for big data you probably need not just statistical skills, but also some facility with informatics, computer science and mathematics. It's hard to find people with that mixture of skills, and that's another gap in the pharma skill base.

Nevertheless, universities are starting to recognize the need – there's now an abundance of courses and research aimed at dealing with big data. Pharma may have influenced that to some degree; many companies, including GSK, interact with leading universities by sponsoring PhD students and post-doctoral fellows. Pharma's connections with academia are getting stronger all the time, including in the field of statistics. But pharma won't be the only industry wanting those skills, and I'm sure that we'll be in a fierce battle to recruit the very best.

# Catapulted to the Top

**Sitting Down With... Keith Thompson,**
CEO of the Cell and Gene Therapy Catapult, UK.

How did you get interested in manufacturing?

I've always been more interested in molecules than whole organisms – and I've also always had a bit of an engineering instinct; I was one of those children who liked to dismantle things to see how they worked, much to my parents' frustration! My academic research career began with monoclonal antibodies, right at the start when their full potential was still being investigated, and I soon got a job to set up a monoclonal antibody laboratory in GD Searle in High Wycombe (UK). As monoclonals became more popular, I was introduced to large-scale manufacturing – and the engineer in me was fascinated by all the stainless steel kit. I then decided that I wanted to move out of straightforward research and get into manufacturing. Over the years I grew various businesses to become global players in biological manufacturing before being approached by the Scottish Blood Transfusion Service, which wanted to modernize the service.

And what prompted your change in focus to cell and gene therapies?

The blood transfusion services have been taking blood out of one person, processing it, testing it, and then giving it to another person for years. I was also involved in other transplants, such as pancreatic islets, which can change patients' lives. It's similar to cells and regenerative medicine when you think about it. When I heard about the new Cell Therapy Catapult that Innovate UK, the UK's innovation agency, wanted to establish to bridge the gap between invention and commercialization, I knew that I wanted to lead it, so I immersed myself in the process to establish it. I was delighted to be offered the chief executive officer position in 2012.

How did you find the move from commercial biotech manufacturing to national associations?

When I first left the biotech industry for the blood transfusion service, it was like landing on planet Zog... There were so many business practices I just didn't understand – but I also learnt that, ultimately, the differences are what you make them.

When you're in business, you measure where you're going financially. But in the public sector, finances are much more static. You aren't bringing in nearly as much new money, so you have to be a good steward of what you have. At the same time, you also have to motivate people around your organization's mission – so it all comes back to leadership. You have to be clear about why you're there and what you're doing; that's what makes people really respond.

What advances would you like to see in the area of cell therapies?

What we're really looking for in autologous cell therapies is an increase in process automation over the next five years to help reduce variability. Right now, cell therapy is sometimes unfairly called a "craft industry" so our goal is to standardize processes. Ultimately, we want to put the factory in the hospital – not a miniature version of a factory, but rather a fully functional 'factory in a box' that's about the size of a couple of big refrigerators. When the automation is good enough to do that, I think it will be the most disruptive thing to happen to cell therapy – and the companies that embrace it will be the ones that have the most success.

What are your hopes for the future of the Catapult?

I've set myself the long-term goal of growing the cell and gene therapy industry to reach an annual value of around £10 billion in the UK – a number that is based on my experience of monoclonals; when I started there was no value – and now there are sales in excess of £50 billion globally, growing at seven percent per annum. I think this goal is eminently achievable. Right now, there are several licensed advance therapy medicinal products in Europe, and I expect that number to increase quite rapidly over the next few years. We've already seen over 500 companies established globally, with the UK being home to some 16 percent of those companies (an increase of about 40 percent since we started). In fact, I personally know of six that have been formed in the last year alone!

I really want the UK to be the go-to place to make and market advanced therapies. I think the Catapult has a lot of first-mover advantage; our £55-million manufacturing center in Stevenage should be fully functional in 2017, and will play a key role in embedding the long-term manufacture and supply chains into the UK.

What are your proudest achievements at the Catapult?

We've gone from an idea on a piece of paper to being recognized as one of the most prominent cell and gene therapy organizations in the world – all within three years. I'm really proud of that, and I just hope I can keep the momentum going.

In our industry, things take time to develop – but it's in my nature to push things to go as fast as possible. I don't want to spend six months dealing with a data package or a year analyzing the results; I want to get the information and get moving. Why? Because I want companies to form and I want people to work in this terrific field. And most of all, I want patients to benefit from new treatments.

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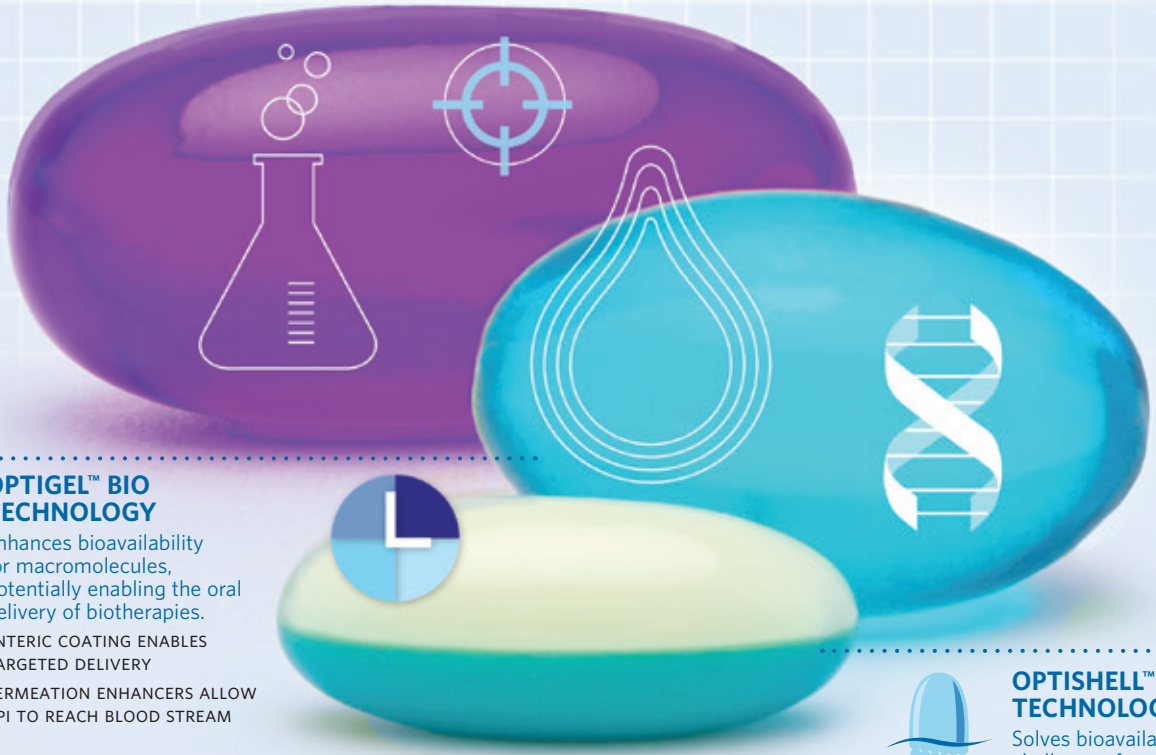

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