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the Medicine Maker

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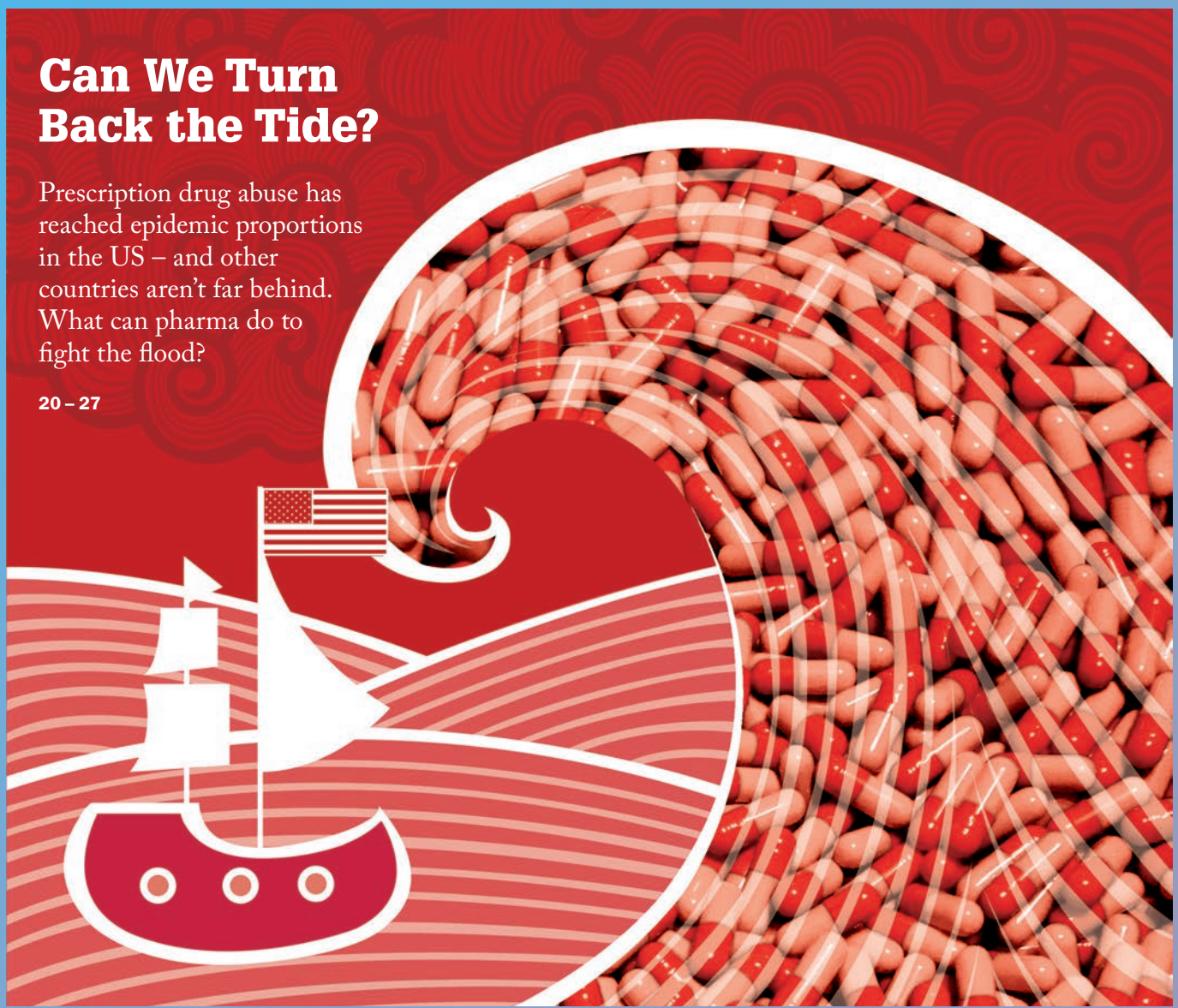

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Online this Month

Tweet Beat

Last month's "The Innovation Game" reported the results of a study from McKinsey, showing poor rates of return from pharmaceutical mergers and acquisitions.

@medicine_maker Jul 13
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Why pharma is looking at outside sources for innovation
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@Kurt_Nielsen Jul 13
@medicine_maker @cha_myoung @McKinsey
Great insights based on the financials! Is the M&A capital efficiency better than ROI of internal R&D?

@cha_myoung Jul 14
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We didn't compare explicitly, but for some companies, wouldn't be surprised if internal R&D was more efficient

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the Medicine Maker *Innovation Awards* 2015

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A Cat and Mouse Game

Following on from this month's feature on prescription drug abuse, we have an exclusive online interview. Drug abusers are finding ways to circumvent first-generation abuse-deterrent measures, meaning that companies must regularly upgrade their delivery systems. Alyn McNaughton, Director of Analytical and Product Development at Capsugel, and Shonagh Walker, Formulation Scientist at Encap Drug Delivery, a division of Capsugel's Dosage Form Solutions, talk us through some of the challenges they face in developing new abuse-deterrent delivery systems.

Read the interview at tmm.txp.to/0715/cat-and-mouse

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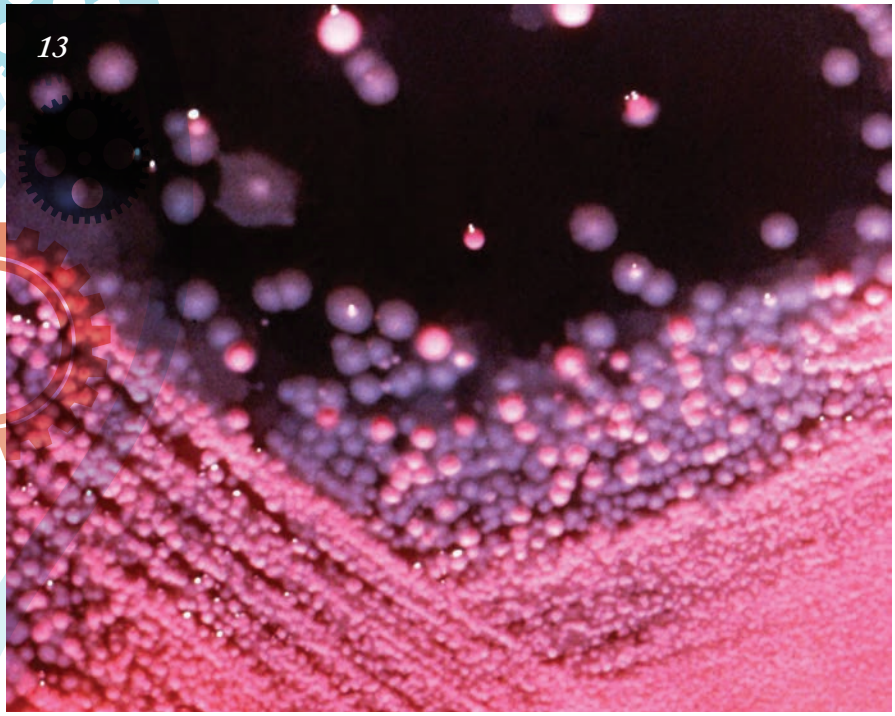

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the **Medicine Maker**

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Editor - Charlotte Barker
charlotte.barker@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Deputy Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com

Associate Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

Associate Editor - Michael Schubert
michael.schubert@texerepublishing.com

Senior Designer - Marc Bird
marc.bird@texerepublishing.com

Junior Designer - Emily Strefford-Johnson
emily.johnson@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

Sales Manager - Helen Conyngham
helen.conyngham@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic and Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic and Audience Associate - Jody Fryett
jody.fryett@texerepublishing.com

Digital Content Manager - David Roberts
david.roberts@texerepublishing.com

Mac Operator Web/Print - Peter Bartley
peter.bartley@texerepublishing.com

Tablet Producer - Abygail Bradley
abygail.bradley@texerepublishing.com

Social Media / Analytics - Ben Holah
ben.holah@texerepublishing.com

Change of address:
tracey.nicholls@texerepublishing.com
Tracey Nicholls, The Medicine Maker, Texere Publishing Limited, Booths Hall, Booths Park, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK
Single copy sales £15 (plus postage, cost available on request tracey.nicholls@texerepublishing.com)

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 752883
sales@texerepublishing.com

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The Epidemic That Cannot Be Ignored

Prescription drug abuse is not just a US problem.

Two epidemics have touched the US in the past year. One highly publicized, the other much less so. Despite the media hysteria, the Ebola outbreak – which killed over 11,000 people, mostly in West Africa – resulted in only 10 cases and two deaths in the US. Compare that with recent figures on what the US Centers for Disease Control and Prevention (CDC) has officially declared an "epidemic of prescription drug abuse": 16,000 deaths each year are caused by overdoses of prescription opioids – just one outcome of over 8 million Americans abusing prescription drugs, as we discover on page 20.

But, you say, "drug use and abuse is not a new phenomenon!" That's certainly true, but the sheer scale of prescription drug abuse – and the resulting fatalities – is shocking. For the areas worst affected by the epidemic, the impact on families and communities has been devastating.

Though the US has been hardest hit, it would be a mistake to think of this as an American problem. Prescription opioids are already amongst the most abused drugs in many countries, and European nonprofit drug policy foundation EURAD reports up to 1.9 million prescription drug addicts in Germany alone.

Abuse-deterrent formulations are one part of the solution. Formulating commonly abused drugs so that they cannot be easily snorted or injected to give an instant hit, or including a substance that induces unpleasant side effects when taken in unhealthy quantities, may deter abuse at an early stage; for example, preventing patients from taking too much prescribed painkiller or steering their children away from experimenting with them. But people are ingenious. Determined addicts quickly overcome these measures or switch drugs. To see a real long-term impact, abuse-deterrent features need to be introduced in all frequently abused drugs – a goal that the FDA is working towards for the most abused opioids.

New classes of drugs that fight pain without the euphoria and physical dependence of opioids would go a long way to solve the problem – but developing such compounds is easier said than done. Until then, a delicate balance must be struck between the right to effective pain relief and the devastation caused by addiction.

Charlotte Barker
Editor

Gaurvika Nayyar & James Herrington

Gaurvika Nayyar is a Healthcare Strategy Consultant, and currently a Program Manager for United States Pharmacopeia's 'Promoting the Quality of Medicines' Program. Prior to joining USP, Gaurvika – who is passionate about using business strategy to transform global health – worked on pharmaceutical access and commercial strategy, corporate social responsibility, emerging markets and health economics programs at organizations such as Janssen Pharmaceuticals, the Bill and Melinda Gates Foundation and Deloitte.

James Herrington has over 30 years of experience in global public health. Since 2014 he has been Professor of the Practice in the Department of Health Behavior and the Executive Director of the Gillings Global Gateway, University of North Carolina, Gillings School of Global Public Health. Before this, he spent 10 years as the Director, Division of International Relations, Fogarty International Center, at the NIH. James is from Oklahoma and a member of the Chickasaw Nation.

Gaurvika and James explain how fake medicines are costing lives on page 18.

Robert Bianchi

Robert Bianchi is the Vice President and Chief of Scientific and Technical Affairs at the Prescription Drug Research Center in Chicago. He retired as the director of the Drug Enforcement Administration (DEA) Special Testing & Research Laboratory in July 2000, after 34 years of Federal service. At the DEA he held a number of increasingly responsible positions as an analytical chemist, laboratory supervisor, headquarters program manager, director of the New York Laboratory and chief of laboratory operations section. He directed studies to evaluate the abuse resistance of several different controlled substances formulations and has participated in developing and implementing Risk Management Action Plans for prescription drugs with high abuse potential.

Robert reviews efforts to thwart prescription drug abuse on page 20.

Mir Imran

Mir's life as an entrepreneur began very early – as a young boy in India he built and sold toys to his classmates. After studying electrical and biomedical engineering at Rutgers University, Mir co-founded a medical company to develop the first implantable defibrillator, and since then has been involved in starting up dozens of healthcare companies. Today, he is the founder and Chairman of InCube Labs, LLC, a research laboratory and business incubator for medical and technology companies. He also serves as director for several life science companies.

Mir tells us why he believes fear is the enemy of entrepreneurship on page 48.

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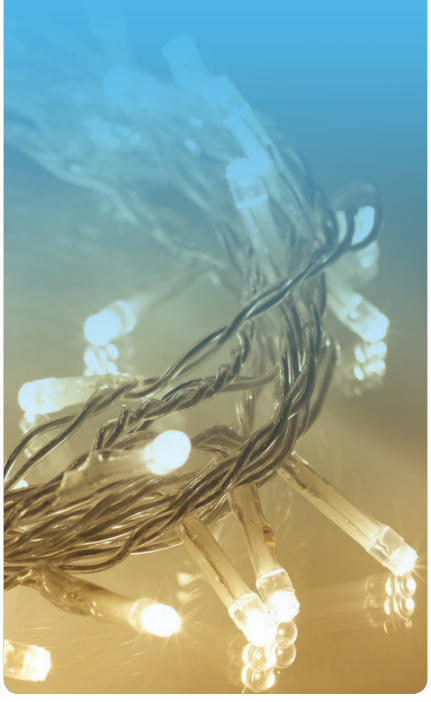

Highly Potent; Highly Targeted

A new mathematical model aims to improve drugs for cancer, viruses and bacteria

Peixuan Guo, Professor of the College of Pharmacy and Director of the University of Kentucky's Nanobiotechnology Center, has antibacterial resistance in his sights. Moreover, he hopes to hit two birds with one stone by improving drug efficacy as well.

Guo and his colleagues have developed a method to target the multi-subunit complexes that viruses, bacteria and cancer need to function – and it could help develop more highly potent (and targeted) drugs.

The new approach has taken more than a decade to reach fruition but, in a nutshell, the team studied the relationship between the stoichiometry of a target component and inhibition efficiency, and developed a mathematical model that elucidates the potency of drug inhibition. Guo explains, "I found that virion assembly inhibition depends on the stoichiometry of the components. The unusual efficiency of inhibin primed me to investigate the mechanism of inhibition. It took more than 10 years to develop a mathematical model including Yan Hui Triangle and binomial distribution to elucidate the mechanism of inhibin. We found that the high efficiency of inhibin is due to K = 1; that is, binding of a drug to any one of the multiple subunit machines at any one of the locations will inactivate the entire biological machine or the complex."

He compares it to a chain of Christmas lights on a serial circuit; breaking a single bulb stops the entire system, which inspired him to design a mathematical model to clarify the mechanism of this kind of potency. "Developing drugs by targeting vital components with high stoichiometry would lead to new drugs with higher potency, and I expect that the method will have broad applications for drug development in many biological systems," says Guo. "Using this method is relatively simple. The drug developer can simply check published literature and find the multi-subunit machine as a drug target. The key, which is also the most challenging part of the entire project, is to identify a multi-subunit machine or functional complex with a structure or sequence that are unique to the pathogen species or different to its counterpart in normal cells to build-in selectivity."

The inhibition data for the mathematical model are based on a bacterial virus that is not pathogenic, but Guo will continue the study through collaborations. Indeed, Guo indicated that biological systems contain a wide variety of functional complexes composed of multiple subunits. For example, AAA+ hexamerics are essential for, amongst other processes, DNA replication and repair, viral genome packaging, nuclear pore transport, and transport of drugs. "Finding a unique or mutant AAA+ hexameric complex in certain cancer cells is one way to go. If such a target was found, it would be an ideal substrate for highly effective anticancer drug development," he says.

"I hope this work will help all medicine makers develop better drugs in the future." *SS*

Reference

1. *D. Shu et al., "New Approach to Develop Ultra-High Inhibitory Drug Using the Power Function of the Stoichiometry of the Targeted Nanomachine or Biocomplex," Nanomedicine 10 (12), 1881-1897 (2015).*

Green Light for Malaria Vaccine.

After 28 years of R&D at GSK, the world has its first malaria vaccine

In July, GlaxoSmithKline's Mosquirix received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Health. The positive news – and world first – follows nearly 30 years of research and development; the candidate was proposed by GSK scientists in 1987.

The vaccine will be used in sub-Saharan Africa and is cleared for use in children aged 6 weeks to 17 months, with clinical trials showing that it should help offer protection from malaria for at least three years (1). The Phase III trial involved more than 16,000 young children and was conducted by 13 research centers in eight African countries.

But what happens after the three years are up? According to the PATH Malaria Vaccine Initiative, which partnered with GSK to develop the vaccine, a "considerable" amount of work is being done that could, one day, lead to implementation in different age groups (2). In other words, the new vaccine could just be the starting point.

The vaccine itself is not 100 percent effective. Trial data show that over the first 18 months, following three doses of the vaccine, malaria cases were reduced by around half in children aged 5–17 months at the time of first vaccination, and by 27 percent in infants aged 6–12 weeks. At the study's end, four doses of the vaccine reduced malaria cases by 39 percent over four years of follow-up in children, and by 27 percent over three years of follow-up in infants. But given that more than 660,000 people die from malaria each year, 90 percent of whom are children under five (3), the vaccine will likely save thousands of lives.

Mosquirix is also known as RTS,S, which relates to the science behind the vaccine. The active substance is a recombinant antigen expressed in Saccharomyces cerevisiae, coded RTS,S (4). The RTS,S antigen consists of two proteins (RTS and S) that spontaneously assemble into mixed polymeric particulate structures intracellularly. The vaccine uses a proprietary AS01 adjuvant system that consists of a liquid suspension of liposomes with two immunostimulant components: 3'-O-desacyl-4'-monophosphoryl lipid A (MPL) and Quillaja saponaria 21 (QS21).

When designing the vaccine, researchers targeted the free sporozoite and intra-hepatic stages of the Plasmodium falciparum parasites. The aim was to induce circulating antibodies that reduce the load of sporozoites reaching the liver, as well as to stimulate T-cell responses that promote the destruction of infected liver cells and impede further intracellular parasite development.

There are still hurdles to clear before Mosquirix will be made widely available. One of the next steps will be for two independent advisory groups from the World Health Organization (WHO) to review the data for the vaccine and make policy recommendations (potentially by the end of this year) on how it could be used alongside other malaria-prevention tools, assuming national regulatory authorities in sub-Saharan Africa approve it. GSK will also be submitting an application to the WHO for pre-qualification of Mosquirix, which would help inform vaccine-purchasing decisions. The WHO policy recommendations and pre-qualification are both required by Gavi, the Vaccine Alliance, before the vaccine can be introduced into immunization programs supported by UNICEF.

GSK has announced Mosquirix will

be sold at a not-for-profit price; the aim is for the price to cover the cost of manufacturing plus a return of around five percent, which will be reinvested into research and development for second-generation malaria vaccines. *SS*

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2. *PATH MVI, "PATH Malaria Vaccine Initiative Welcomes Positive Opinion by European Regulators on GSK's Mosquirix (RTS,S)," (July 2015). www.malariavaccine.org*
3. *Rich Whitworth, "Questioning Our Values," The Analytical Scientist (March, 2015). theanalyticalscientist.com/*
4. *WHO, "RTS,S/AS01 Candidate Malaria Vaccine Summary for the SAGE Meeting," (October 2009). www.who.int*

Riddle Me This, Biosimilar

The first US biosimilar – Zarxio from Sandoz – has been cleared for market. But the judges say it wasn't an easy decision

After much back and forth and legal wrangling, the first US biosimilar – Sandoz's Zarxio (a biosimilar of Amgen's Neupogen) – is set to launch in early September. A ruling from the US Court of Appeals for the Federal Circuit stated that biosimilar manufacturers must wait 180 days to launch a product after receiving FDA approval – March 6, 2015 for Zarxio. Will there be additional chapters in the saga? Ask Amgen…

The case, which began in October 2014, has been closely watched; after all, many thought it would set a precedent for future biosimilar launches. The Federal Circuit admitted that it has been a difficult case, demanding that it "unravel the riddle, solve the mystery, and comprehend the enigma" of the US Biologics Price Competition and Innovation Act (BPCIA) (1).

Interpretation of the BPCIA lies at the heart of the argument. For example, the BPCIA states that manufacturers must give 180 days' notice of their intent to launch a biosimilar, but there are differing opinions as to exactly what that means. In March, the US District Court for North California dismissed Amgen's claim that the notice could only be given after FDA approval (rather than before), since this would effectively turn the notice into an "automatic 180-day bar against marketing". But in a two-to-one decision in July, the Federal Circuit agreed with Amgen that notice should be given after approval.

Not every aspect of the case went in Amgen's favor. Another point of contention between Amgen and Sandoz was the sharing of information regarding the biosimilar application (the so-called "patent dance"). Amgen argued that the BPCIA required Sandoz to provide information to Amgen about the application so that the company could check for patent infringement, but the Federal Circuit agreed with Sandoz that this was optional.

The judiciary process was certainly not clear cut; three judges were involved in the case, two of whom dissented in part. Indeed, the final ruling stated that decisions had to be made from a "series of imperfect choices". *SS*

Reference

1. *United States Court of Appeals for the Federal Circuit, Amgen Inc., Vs Sandoz Inc (July, 2015). www.cafc.uscourts.gov*

(Anti)Bacterial Factory

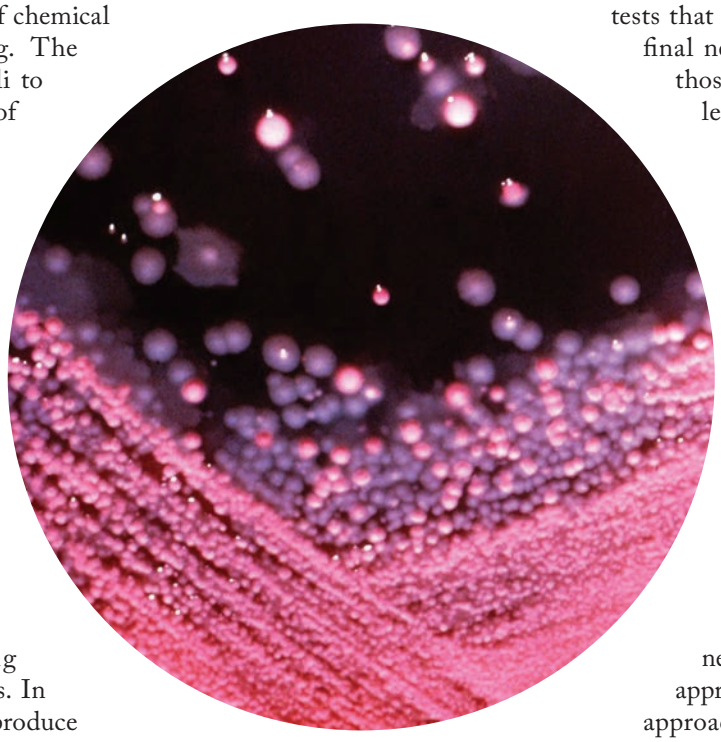
Engineered E. coli colonies could be trump cards in the war against drug resistance

Antibiotic resistance has been described as one of the most significant threats facing patient safety. Could E. coli lend a helping hand in the fight? Yes, according to a research team at the University at Buffalo led by Blaine Pfeifer, associate professor of chemical and biological engineering. The team has engineered E. coli to synthesize 42 new forms of the antibiotic erythromycin – three of which have been shown to be effective against bacteria resistant to the version of erythromycin currently used in clinics. And the E. coli factory could be used to produce even more variations. We spoke with Pfeifer to find out more.

How did the work begin?

I was interested in making natural products more accessible by developing alternative production routes. In this case, we were able to produce the antibiotic erythromycin through a heterologous host system and then use the engineering tools of the new platform to produce analogs of the original compound. Production through E. coli provides a maximum operating space that few other production routes can offer.

We look at this as one contribution to the emerging theme of solutions to the antibiotic-resistance crisis. As opposed to ongoing efforts to discover completely new antibiotic compounds, our approach leverages the engineering capabilities of the E. coli platform and the pathway complexity of erythromycin to significantly alter the chemical diversity of an established antibiotic. In other words, our system allows us to engage in a game of molecular chess – a battle between the mechanisms bacteria use to thwart antibiotics and the engineering capabilities we have to produce new compounds.



How does the platform work?

Here, I have to credit the first author of this work, Guojian Zhang (1). He designed 16 pathways for a sugar molecule attached to erythromycin, as a way to systematically vary the molecular content of this moiety. We knew that without glycosylation, the compound does not have any antibiotic activity, so we thought this would be a good place to vary molecular structure and observe new bioactivity. The engineering tools of the E. coli system enabled this design to move quickly, and to our surprise and satisfaction, we were able to generate over 42 new erythromycin compounds due to the variety of steps in the overall pathway. Even more gratifyingly, we observed new bioactivity.

Have you started thinking about scale up?

There is still a series of experiments and tests that must be completed before a final new drug is available. But if those are successful, this system lends itself well to process development given the properties of the E. coli host – a workhorse in the biotech industry.

The analogs produced here are really just a small sub-set of those possible. So, one future direction is to further test the analog-producing limit for the platform we have at hand. There's also the goal of pushing current and future analogs through the clinical tests needed to result in a new FDA-approved antibiotic. Finally, the approach outlined here could, in theory, be applied to numerous other current antibiotics to produce novel analogs capable of overcoming bacterial resistance.

Reference

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Biomimetic Protection of Biomolecules

Porous shells – inspired by sea urchins – help defend biomacromolecules from the outside world

Vaccines and other biomedicines can easily be denatured or decomposed by unforgiving conditions. But does nature already have the answer for protecting at-risk biological material? Well, many organisms collect and process minerals to fabricate tissues that serve structural or functional purposes, and Australian scientists believe that the process of biominerialization can be used to protect biomolecules. Starting out with some preliminary experiments, researchers from Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) added proteins to an aqueous solution containing the chemicals needed to produce synthetic porous shells (1).

"Firstly, we investigated the chemical reaction to determine the best 'biomineralization' conditions for the production of the porous shells. It was surprising to see that biomacromolecules were acting like micro-reactors, bringing ligands and cations (the precursors of the porous shell) together. The conditions were enough to trigger the formation of a tri-dimensional porous hybrid network, also called a metal-organic framework. Next, we investigated the generality of the method, and discovered that the vast majority of biomolecules were triggering the formation of shells within a few minutes," says Paolo Falcaro, a researcher in material engineering at CSIRO.

Subsequently, the team studied the properties of the protected system by exposing the encapsulated biomolecules to extreme conditions such as boiling organic solvents and high temperatures. The result? The shells prevented deformation and decomposition that would almost certainly result in loss of bioactivity. In addition to the potential ability to preserve and deliver proteins, antibodies, vaccines, DNA and enzymes, Falcaro believes that the method could open up a new world of applications for biomolecules in chemical processing and biostorage.

"It was fascinating learning that useful natural biomacromolecules were acting like a living entity, bringing together chemicals and generating a self-protective crystalline porous shell," says Falcaro. "Interestingly, the shell is porous and allows small molecules to diffuse through it. The shell can be dissolved on demand by adding a weakly acid solution."

How is the shell made? Easy, says Falcaro – akin to preparing instant coffee. The addition of two chemicals (Zn^{2+} ions and 2-methylimidazole) to an aqueous solution that contains the biomolecules is enough to promote the formation of the protective porous shells.

At the moment, the shells can be prepared only with certain organic ligands and metal ions. "From the chemistry perspective, we are currently investigating other ligands in order to tailor the pore size and topology. From the biochemistry perspective, we are trying to predict the 'biomineralization' efficiency of proteins with different hydrophobic/hydrophilic domains and surface charge," says Falcaro. "We are also investigating the efficacy of the shell for different biological systems." *SS*

Reference

1. *K. Liang et al., "Biomimetic Mineralization of Metal-Organic Frameworks as Protective Coatings for Biomacromolecules," Nature Communications (2015), doi: 10.1038/ncomms8240.*

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A Blast From Potions Past

Are ancient texts hiding the answer to antibiotic resistance?

By Christina Lee, School of English, University of Nottingham, UK.

Some view science as a relatively modern invention, but scientific knowledge and ingenuity go back thousands of years, even if the language used to describe phenomena sound ridiculous to modern sensibilities. As an example, in medieval times diseases were thought to be transmitted by dragons. It sounds outrageous, but it means that there was at least an understanding that some diseases are airborne.

I want to share a fascinating research project that stems from studies in arts and humanities rather than science. Subjects that fall under the umbrella of arts and humanities are sometimes perceived to have less practical value, but there is potential for these subjects to make a difference in many ways. They should not be dismissed or forgotten. Let us consider the problem of antibiotic resistance. Pharmaceutical companies are urgently seeking an answer, but have they thought to look in the past?

I recently became involved in a pilot study where I am working alongside microbiologists to test Anglo-Saxon recipes for antibacterial effectiveness. My colleagues and I didn't really set out with any intention of making an important medical discovery; we simply found it fascinating.

I study history, particularly Anglo-Saxon England and the Viking world. One day, a colleague asked me about Anglo-Saxon antibiotics; after all, infections have been around forever. Because we had a wider network of people around us who were interested in infectious disease we decided to test an old remedy to see if it had any antibiotic effects. We turned to Bald's Leechbook – an old English medical text that contains various recipes (some of which sound insane) passed on from various sources, including the Romans – and decided to test a remedy for styes – eye infections caused by Staphylococcus aureus.

And so off we went to recreate the recipe as authentically as possible, with ingredients such as garlic, wine and bile from a cow's gall bladder. The recipe had very precise steps; to start, we had to pound it and strain it through a clean cloth (not pleasant!). Not just any cloth, either – Bald's Leechbook is often quite specific about what textiles to use. It sounds crazy until you consider that wool, for example, has compounds such as lanolin, which affect different chemical reactions. We also had to use a brass vessel, leave the mixture to stand for nine days, and so on… There were many steps and we followed as best as we could. The finishing touch? Applying the ointment with a feather. It was an entertaining exercise, but when we applied the ointment to cultures of MRSA bacteria, I didn't think it would work.

But I wouldn't be writing this following a failure. Sure enough, it killed the bacteria. We were astonished and did a few other experiments; none of the ingredients worked separately, but together the outcome was always the same, resulting in up to 99 percent of the bacteria being killed. So we decided to try it on mice, with the help of a bacteria expert in Texas. The recipe still worked. Our collaborator was stunned!

Our university press officer thought it was intriguing too so she thought we should put out a press release. Soon after that, it seemed that the entire world was interested. The story went viral – we were

receiving hundreds of emails every day from newspapers, as well as patients demanding that we hand the recipe over. Nothing can prepare you for that kind of attention!

We've written a research paper on the work, which is due out soon. And now we're looking further into the research to see if there is more potential there. Of course, this is extremely early work and we have no idea if it can be transferred to humans.

It is amazing to think that somewhere in Europe all those years ago someone wrote down this knowledge. Which begs the question, where will the spark of inspiration for the next antibiotic or blockbuster medicine come from? Future scientists? Scientists of the past? Or maybe from academics studying arts and humanities? We're certainly looking forward to testing more recipes from Bald's Leechbook…

Multimodal Spectroscopy: Production Workhorse

Manufacturing is getting smarter; only a cross-discipline approach will ensure the success of tomorrow's processes.

By Rudolf Kessler, Professor of Chemistry at Reutlingen University and Head of a Steinbeis Technology Transfer Center, Germany.

The European Commission's smart manufacturing vision "Manufuture for 2020" and the US FDA PAT/QbD-platform (Process Analytical Technology, Quality by Design) are both helping to increase interest in the concept of intelligent manufacturing. It is a transdisciplinary technology where process chemists, process engineers, chemometricians and many other technologists must work together. In short, the holistic process analysis component will be the bedrock that supports the production of smart materials in smart factories! Indeed, process analytics by spectroscopy can improve understanding of how the process operates, and can be used to determine potential targets for process improvement by removing waste and increasing efficiency (1).

I have no doubt that optical spectroscopy – together with chemometrics – will play an important role in transforming industry from reactive to proactive production. Because spectroscopic techniques can detect morphological (from scatter) and chemical features (from absorption) simultaneously, the complete fundamental functionality of a compound is inherent in every spectrum.

However, we must recognize that sensitivity, selectivity and robustness of each individual technology, in combination with the wavelength range used, has limitations because of the structure of the measured species and the optical configuration selected. Furthermore, in any application, a key issue is finding the causal link between the measured spectral features and the final target quality. I believe multivariate data analysis of big data will be a key technology in the future. Proper process analysis means understanding the causal relation between measurement and response, and with spectral imaging, the spatial distribution in the x-, y- and, possibly, z-direction may also be of interest (1).

Many of you will know that ultraviolet- and visible (UV/Vis) spectroscopy is a highly sensitive technique for electronic transitions, while mid infrared (MIR) spectroscopy is specific for vibrational transitions. However, we also know that near infrared (NIR) spectroscopy is less sensitive than MIR due to lower cross sections of higher order vibrational transition probabilities. Clearly, the major advantage with NIR is that even at higher concentrations no sample preparation (for example, dilution) is necessary, but I think it is important to emphasize that both NIR and MIR spectroscopy are highly sensitive to water absorption. And in recent years, Raman spectroscopy has developed into a highly sensitive and versatile technique, proving to be a very good process-monitoring tool, especially in aqueous systems such as those found in biotechnology.

Currently, NIR- and Raman-spectroscopy are the workhorses in PAT applications, and multimodal spectroscopy will be the all-in-one sensor of the future. Samples containing phase boundaries that display simultaneous and superimposed wavelength dependent absorption and scattering effects cannot be characterized by a single measurement. Here, multimodal spectroscopy will come to the fore because of its ability to deal with combinations of measurements in different wavelength regions or in different optical set ups (for example, transmission and reflection).

In the future, special emphasis will be given to measuring not only the chemical entities but also their lateral distribution in an object. Spectral imaging (also known as chemical imaging) is an emerging field for a wide range of applications; for example, finding biomarkers in a tissue or controlling and qualifying pharmaceutical tablets or food. In addition, push broom imaging (line scanning) technology

will allow multiplexing, thus reaction tomography or measurements in micro-reactor systems will be possible.

Therefore, I am very confident that process analysis, together with spectroscopy and intelligent data analysis, will play a more important role in modern manufacturing and processing. The German government's "Industry 4.0" concept describes the future of industrial automation as being arbitrarily modifiable and expandable (flexible), able to connect different components from multiple producers, enabling those components to perform tasks related to a context independently (self-organizational), with an emphasis on ease of use (user-oriented). Spectroscopy – particularly the workhorse techniques of vibrational spectroscopy – will be an important set of tools to realize this concept (2).

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Fake Medicine, Genuine Risk

How can we fight the global pandemic of falsified and substandard medicines?

By Gaurvika Nayyar, Global Health Consultant, San Diego, CA, USA and Jim Herrington, Executive Director, Gillings Global Gateway, University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC, USA.

In April 2015, the American Journal of Tropical Medicine and Hygiene (AJTMH) published over a dozen papers, alerting the world that falsified and substandard medicines risk the lives of up to four billion people (1). The supplement – "The pandemic of falsified medicines: laboratory and field innovations and policy perspectives" – presented 17 scientific articles that offered data and recommendations on developing a coordinated and effective response. Falsified and substandard medicines are a recognized problem on virtually all continents, and so can certainly be considered a pandemic. Moreover, the increasing global scientific awareness of the problem is evident by the number of articles on "fake drugs" cited in PubMed, which has increased ten-fold over the last 50 years (Figure available online) (3). Furthermore, government, public, company and surveillance reports of poor-quality medicines have been increasing in volume; however, it is likely just the tip of the iceberg – many cases still go un-, under-, or mis-reported (4). And poor-quality medicines are not just limited to anti-infective medications for developing countries, developed countries are also affected. Of course, there is debate on the extent and size of the problem, but 'murder by medicine' continues to be profitable (by some estimates a $75 billion criminal enterprise) with only minimal punishable consequences in many countries (5).

For a prime example of how we are losing a decade of public health progress to drug resistance, consider antimalarial medication. Timely access to quality antimalarials is the difference between life and death in pediatric populations in endemic countries. Recent surveys show a third of poor-quality antimalarials in Southeast Asia are falsified and an equal proportion of antimalarials in sub-Saharan Africa are substandard (6). Another paper estimates that in 2013 alone, approximately 122,350 deaths in children under five years of age in 39 sub-Saharan African countries were associated with exposure to poor-quality antimalarials (7). Over the last decade, the progress in malaria control and elimination are truly unprecedented, but past experiences have shown that reductions in malaria incidence are difficult to sustain (8). Poor-quality antimalarials can encourage drug resistance by exposing parasites to sub-therapeutic levels of drug, and fake medicines allow resistant strains to spread unchecked even when medicines are provided. Indeed, poor-quality medicines are putting millions of dollars of investment to control and eliminate malaria at risk.

The locus of any epidemic response is the diagnostic or detection tools that can reliably identify the problem and its extent. In the AJTMH supplement we showcase new and promising technologies ranging from paper cards to field assays that can detect falsified and substandard medicines. However, the need to cross compare and test these technologies for validity and then scale them up for widespread application has never been more pressing. The persistent barrier of limited funding for field evaluations of such technologies is being addressed by organizations like the United States Pharmacopeial Convention (USP), who have been pioneers in launching field evaluations of select technologies (9). Unfortunately, the bulk of data on the prevalence of poor-quality medicines is convenience sampled, fragmented and collected using different measures, and thus does not represent the true extent of the problem.

There is no silver bullet to curb the

pandemic of poor-quality medicines, but we need to focus on three main areas: i) develop and compare accurate and affordable technologies to identify high-quality medicines at all levels of distribution; ii) use a top down and bottom up response with an international convention and national legislation to ensure production and distribution of quality assured medicines, thus protecting patients from perpetrators; and iii) set standards for data collection and testing, coordinate surveillance, and strengthen regulatory systems.

Poor-quality medicines injure and kill the most vulnerable of patients, lead to distrust in the healthcare system, promote drug resistance, and threaten decades of progress in global public health. To tackle the problem, we need to combine political willpower with industry engagement.

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Addiction by Prescription

Prescription drug abuse has already reached epidemic proportions in the US – and other countries look set to follow the dangerous trend. What can drug makers do to help stem the tide?

By Robert Bianchi

Here in the US, prescription drug abuse is sweeping the nation. In 2012, an estimated 2.4 million Americans used prescription drugs non-medically for the first time within the past year, which averages to approximately 6,700 new users per day, according to the National Survey on Drug Use and Health. Prescription drug abuse is the non-medical use of a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited.

In 2013, an estimated 24.6 million or 9.4 percent of the American population aged 12 or older were illicit drug users. Marijuana remains the most commonly used illicit drug with 19.8 million users (more than heroin and cocaine combined). Non-medical use of prescription drugs is the second largest category of abused drugs at 6.5 million users or 2.5 percent of the population. The Centers for Disease Control and prevention classified this phenomenon as an epidemic.

The classes of prescription drugs most commonly abused are opioid pain relievers, such as Vicodin or OxyContin; stimulants for treating attention deficit hyperactivity disorder (ADHD), such as Adderall, Concerta, or Ritalin; and central nervous system (CNS) depressants for relieving anxiety, such as Valium or Xanax.

Prescription opioid pain medications such as oxycodone and hydrocodone can have effects similar to heroin when taken in doses or in ways other than prescribed, and research now suggests that abuse of these drugs may actually 'open the door' to heroin abuse. There were 22,767 drug-related overdose deaths in 2013; 71.3 percent involved opioids. Gil Kerlikowske, the former national drug czar, said that the current culture of writing narcotic prescriptions for moderate pain, which began about a decade ago, must be changed and that doctors need to be retrained. The US makes up only 4.6 percent of the world's population, but consumes 80 percent of its opioids – and 99 percent of the world's hydrocodone, the opiate in Vicodin.

Nearly half of young people who inject heroin reported abusing prescription opioids before starting to use heroin, according to three recent studies (1). Some individuals reported taking up heroin because it is cheaper and easier to obtain than prescription opioids. Many of these young people also report that crushing prescription opioid pills to snort or inject the powder provided their initiation into these methods of drug administration.

The causes

Several issues are contributing to the rise in prescription drug abuse in the US:

Direct-to-consumer advertising

The public has been conditioned by the media and the pharmaceutical industry to believe that there is a pill available to cure every ailment. "Direct-to-consumer advertising of drugs has been legal in the US since 1985, but only really took off in 1997 when the FDA eased up on a rule obliging

companies to offer a detailed list of side-effects in their infomercials. Since then the industry has poured billions of dollars into this form of promotion. The only other country in the world that allows direct-to-consumer drug ads is New Zealand (2). To date, there is a paucity of quantitative data on prescription drug misuse in New Zealand (3,4). However, New Zealanders as a population have some of the higher drug-use rates in the developed world, evidenced in the 2007/2008 New Zealand Alcohol and Drug Use Survey, which reports that one in six (16.6%) New Zealanders aged 16–64 years had used drugs recreationally in the past year (5). But the misuse of prescription drugs for their psychoactive effects is an international problem.

Perceived safety

Many believe that prescription drugs are safe to use non-medically because they are FDA approved, prescribed by a doctor and friends or relatives use the medication safely. What many people fail to recognize is that prescription drugs are effective in relieving pain or treating ailments when used properly under a doctor's supervision.

Prescribing practices

The number of prescriptions for some medications has increased dramatically since the early 1990s. Opioid prescriptions have increased from 76 million in 1991 to 210 million in 2010. Stimulant prescriptions have increased from 4 million in 1991 to 45 million in 2010 (6). Unintentional overdose deaths involving opioid pain relievers have quadrupled since 1999. Over 970,000 prescribers wrote 259 million prescriptions for painkillers in 2012 (7).

Easy access

Unused prescriptions are frequently retained for future use in the family medicine cabinet, making them readily accessible for abuse. Most prescription drug abusers obtain their first experience free from friends or the family medicine cabinet. Drugs with high potential for abuse should be stored in a secure location and properly disposed of when no longer needed.

Information availability

Internet sites provide a wealth of knowledge on the manufacture and use of mind-altering substances. For example, websites like www.Erowid.com, www.Bluelight/ru.org and www.Drugs-forum.com offer personal experiences, information and support for addicts. The information age provides easy access to information that was previously only available through clandestine sources. Today, anybody with a smart phone or tablet has access to previously forbidden information. Because readers can learn how others abuse drugs they may feel they can do the same experiments safely.

Doctor shopping

Doctor shopping is a common practice where drug abusers visit several doctors in an attempt to obtain multiple prescriptions. The abusers frequently have their prescriptions filled at different pharmacies to avoid detection.

The antidote

Federal and state governments have initiated numerous plans to reverse the trend of increasing prescription drug abuse by engaging importers, manufacturers, distributors, pharmacies, physicians and patients. Anyone who manufactures, distributes, dispenses, imports, or exports any controlled substance or who proposes to do so must obtain a DEA registration unless exempted by law (8).

In particular, the federal government is:

- Tracking prescription drug overdose trends to better understand the epidemic.
- Encouraging the development of abuse-deterrent opioid formulations and products that treat abuse and overdose
- Educating health care providers and the public about

Dependence Versus Addiction

Physical dependence occurs because of normal adaptations to chronic exposure to a drug and is not the same as addiction. Addiction, which can include physical dependence, is distinguished by compulsive drug seeking and use despite sometimes devastating consequences.

Someone who is physically dependent on a medication will experience withdrawal symptoms when use of the drug is abruptly reduced or stopped. These symptoms can be mild or severe (depending on the drug) and can usually be managed medically or avoided by using a slow drug taper.

Dependence is often accompanied by tolerance, or the need to take higher doses of a medication to get the same effect. When tolerance occurs, it can be difficult for a physician to evaluate whether a patient is developing a drug problem, or has a real medical need for higher doses to control their symptoms. For this reason, physicians need to be vigilant and attentive to their patients' symptoms and level of functioning to treat them appropriately.

prescription drug abuse and overdose.
- Requiring that manufacturers of extended-release and long-acting opioids make educational programs available to prescribers about the risks and benefits of opioid therapy, choosing patients appropriately, managing and monitoring patients, and counseling patients on the safe use of these drugs.
- Using opioid labeling as a tool to inform prescribers and patients about the approved uses of these medications.
- Developing, evaluating and promoting programs and policies shown to prevent prescription drug abuse and overdose, while making sure patients have access to safe, effective pain treatment.

Many states have instituted prescription drug monitoring programs (PDMP). A PDMP allows authorized users (including licensed healthcare prescribers eligible to prescribe controlled substances, pharmacists authorized to dispense controlled substances, law enforcement, and regulatory boards) to access patient controlled substance history information. The PDMP is committed to assisting in the reduction of pharmaceutical drug diversion without affecting legitimate medical practice or patient care. Currently, 49 states have PDMPs, which have been very effective in reducing prescription drug abuse. However, until a national database is developed, abusers will take advantage of the ability to visit neighboring states to do their doctor shopping.

Drug Enforcement Administration

The mission of DEA's Office of Diversion Control (www.deadiversion.usdoj.gov) is to prevent, detect, and investigate the diversion of controlled pharmaceuticals and listed chemicals from legitimate sources while ensuring an adequate and uninterrupted supply for legitimate medical, commercial, and scientific needs.

"DEA is committed to reducing the destruction brought on by the trafficking and abuse of prescription drugs through aggressive criminal enforcement, robust administrative oversight, and strong relationships with other law enforcement agencies, the public, and the medical community," said DEA Special Agent in Charge Keith Brown. "The doctors and pharmacists arrested are nothing more than drug traffickers who prey on the addiction of others while abandoning the Hippocratic Oath adhered to faithfully by thousands of doctors and pharmacists each day across this country."

In 2005, DEA initiated a special operation (Distributor Initiative Program) to enforce provisions of the Controlled Substances Act requiring registrants authorized to distribute controlled substances to prevent diversion by designing and operating a system to identify suspicious orders and report them to DEA. The law defines suspicious orders as "orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency"(9).

Americans can now take expired, unneeded, or unwanted prescription drugs to one of over 5,200 collection sites across the country free of charge and anonymous, no questions asked. Since its first National Take Back Day in September of 2010, DEA has collected more than 4.1 million lbs (over 2,100 tons) of prescription drugs throughout all 50 states, the District of Columbia, and several other US territories.

Abuse-resistant formulations

Opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties. Most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse – swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It simply means that the risk of abuse is lower than it would be without such properties. Because opioid products must be able to deliver the opioid to the patient, there may always be some abuse of these products.

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product.

As a general framework, abuse-deterrent formulations have been categorized by the FDA as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse (e.g., reformulated OxyContin).
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be

Holding Back the Tide

The not-for-profit Center for Lawful Access and Abuse Deterrence (CLAAD) was formed in 2008 by Michael C. Barnes, the current executive director and former counsel to the White House Office of National Drug Control Policy. CLAAD and its coalition work with policy makers, law enforcement and patient advocacy organizations to reduce prescription drug abuse and optimize patient access to care, and abuse-deterrence is a central aspect of that mission. We speak with Kyle Simon, Director of Policy and Advocacy, to find out more.

Why is prescription drug abuse such a big problem in the US?

Several factors have led to what the Centers for Disease Control and Prevention (CDC) has identified as a prescription drug abuse epidemic. Over-supply of opioid pain medications, lack of knowledge around how to treat pain that led to overprescribing and subsequent substance use disorders, criminals who caused the proliferation of pill mills and overdose-related events, and doctor shopping by people with substance use disorders all led us to where we are today.

What can drug companies do to tackle prescription drug abuse?

Researching, developing, and bringing to market medications that are less rewarding to divert, misuse, or abuse is a good start. Abuse-deterrent formulations (ADFs) are not a silver bullet, but by making medications harder to crush and snort or melt and inject, we can save lives and stem the epidemic. Additionally, companies must work with all sectors of society to educate the public that prescription drugs can be life-saving and help people lead healthy productive lives when used appropriately, but can be life-threatening when abused.

What evidence is there that ADFs are effective in reducing misuse?

A recent report by the manufacturer of reformulated oxycodone showed a reduction of about 20 percent in the number of prescriptions and overdose-related events. However, it's important to re-state that ADFs are not a solution in themselves, just one part of a comprehensive approach to reducing prescription drug abuse – particularly for first-time opioid users who are not purposely seeking to misuse or abuse a medication.

What can be done to improve the poor uptake of ADFs?

The FDA recently finalized guidance for manufacturers of branded opioids that will serve as a road map for how to obtain ADF labeling. The same must be done for generic manufacturers so that commonly abused controlled substances can be made safer and brought to market. The delay in finalizing the guidance and lack of clarity by policy makers regarding exclusivity on the market still serve as obstacles, but we are seeing more products being developed.

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sequestered and released only upon manipulation of the product. For example, a drug product can be formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted (e.g., Talwin Nx, Suboxone, Embeda).

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted (e.g., Oxecta oxycodone/niacin).
4. *Delivery System (including use of depot injectable formulations and implants)* – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs* – The properties of a new molecular entity or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the CNS, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act. (e.g., Vyvanse amphetamine).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.

7. *Novel approaches* – anything new that is not captured in the previous categories.

There are approximately 30 abuse-deterrent formulations currently under consideration for approval by the FDA. Used correctly, they do seem to have an impact. The most widely recognized opioid associated with the prescription drug epidemic is OxyContin, which was initially approved by FDA in 1995, with the reformulated version approved in 2010. The selection of OxyContin as a primary drug of abuse decreased from 35.6 percent of respondents before the release of the abuse-deterrent formulation to just 12.8 percent 21 months later (10). In April 2013 the FDA approved updated labeling for Purdue Pharma L.P.'s reformulated OxyContin (oxycodone hydrochloride controlled-release) tablets. The new labeling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting).

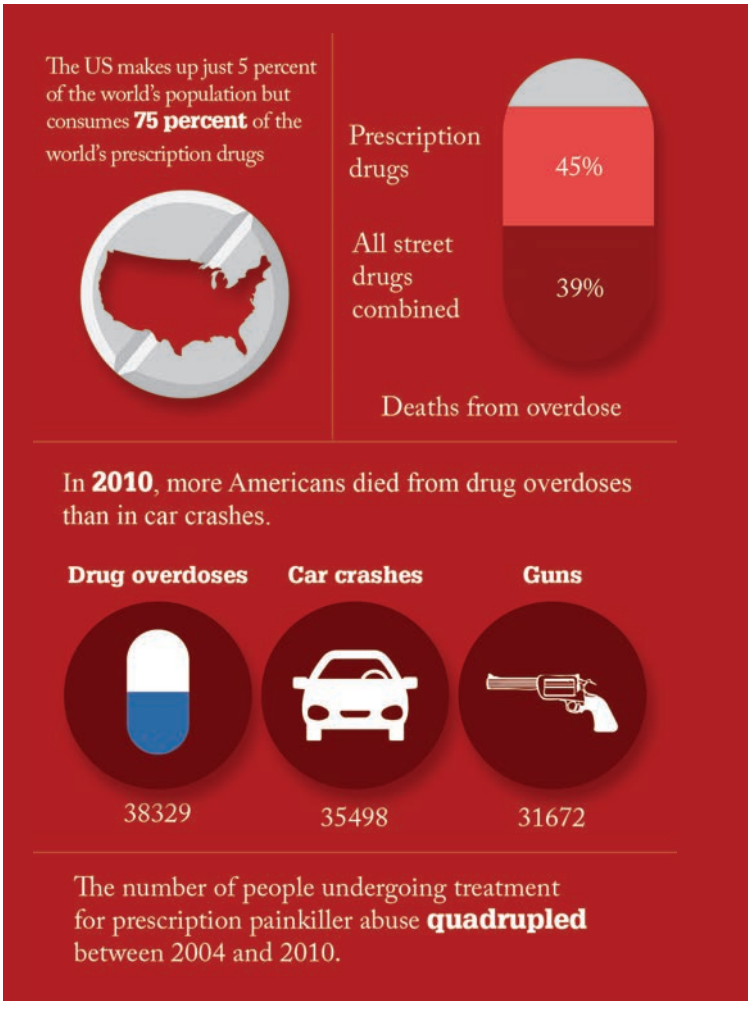
The FDA approved Zohydro ER in October 2013, indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It was the first hydrocodone formulation that did not contain acetaminophen, unlike many immediate-release hydrocodone products, with the aim of reducing the risk for potential liver toxicity due to overexposure of acetaminophen. However, the FDA approval of Zohydro ER came against the advice of its own advisory committee, which expressed concerns about the potential for abuse. Since then, the drug has been at the center of ongoing controversy, with consumer groups and attorneys general of numerous states asking the FDA to reverse its approval of the drug, and bills introduced in the House and Senate to keep it off the market.

A major criticism of Zohydro ER has been that it was not available in abuse-resistant formulation. In September 2014, a coalition of more than 15 consumer groups and medical experts fighting the opioid epidemic called for new leadership at the FDA, charging that the agency's opioid policies are exacerbating the nation's epidemic of opioid addiction and overdose deaths. In October 2014, drug maker Zogenix announced submission of a supplemental New Drug Application for a modified formulation of Zohydro ER designed to have abuse-deterrent properties. The new formulation uses BeadTek, which, the company notes, "incorporates well-known pharmaceutical excipients that immediately form a viscous gel when crushed and dissolved in liquids or solvents."

Pre-market studies

In April 2015 the FDA issued non-binding Industry Guidance: "Abuse-Deterrent Opioids – Evaluation and Labeling" (11). The guidance explains the FDA's current thinking about the studies that should be conducted to demonstrate that a formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

Studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous and include the appropriateness of positive controls and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study. There are three areas of pre-market studies:



Smart Students Engineer a Solution

In response to the growing epidemic of prescription drug abuse, mechanical engineering students at John Hopkins University have developed a high-tech pill dispenser that is highly tamper resistant, personalized to the patient and can be opened only by a pharmacist. The device so impressed their mentors that they have applied for NIH funding to develop the prototype further. We spoke with Megan Carney, who developed the device along with her teammates.

What was your initial reaction to the project brief?
I was really excited at the possibility of creating a tamper-resistant pill dispenser because I thought it was a very interesting application of mechanical engineering. Drug abuse is a huge problem and designing something that could reduce the number of deaths from overdoses was very motivating.

Tell us about the device
The device is personalized to the patient only, secure and resistant to many household tools (hammer, drill, screwdriver), easy-to-use, and compact while also holding a month's supply of pills. The device requires the patient to scan his or her fingerprint. The correct fingerprint activates the spring-loaded cartridge and rotating mechanisms to dispense the prescribed number of pills.

How difficult was it to come up with a feasible design?
We went through many rounds of designing and prototyping and then settled on a version of our final design around the winter of 2014 (halfway through the class). Once we had a rough outline of the design, we improved upon it by focusing on different components and testing them individually and then combining them and testing them as a cohesive system.

What was the most exciting part of the project?
I really enjoyed testing our device and seeing its results. A great moment was when a fellow student attempted to break into the device and couldn't, despite many attempts and using a variety of household tools. That's when we knew the device was really secure!

1. *Laboratory-based in vitro manipulation and extraction studies* (Category 1). The goal of these studies should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. The resulting information should be used when designing Category 2 and Category 3 studies.
2. *Pharmacokinetic studies* (Category 2). The goal of these studies should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration.
3. *Clinical abuse potential studies* (Category 3). In addition to their use by FDA, clinical studies of abuse potential are important for assessing the impact of potentially abuse-deterrent properties. The preferred design is a randomized, double-blind, placebo-controlled and positive-controlled crossover study. These studies are generally conducted in a drug-experienced, recreational user population.

Currently, data on the impact of an abuse-deterrent product on drug abuse in the US population are limited, and thus the optimal data sources, study variables, design features, analytical techniques, and outcomes of interest of post-market epidemiologic studies are not fully established.

What can pharma do?

The pharmaceutical industry has spent billions of dollars developing abuse-resistant delivery systems for prescription drugs that have a high potential for abuse. This is a market-driven industry and companies engage in research if there is an economic benefit in producing abuse-deterrent drugs. It is not likely that the industry will continue to conduct expensive research needed to produce truly abuse-deterrent forms of controlled substances, unless incentives are offered. The FDA has approved abuse-deterrent labeling for several products that have demonstrated that their formulation is more difficult to abuse than currently available drugs. However, an area of concern that has not been addressed by the pharmaceutical industry is oral abuse by simply taking multiple dosage units. Should an abuser take more than the recommended dosage they will achieve the desired euphoric effect. This form of abuse does not require any time-consuming manipulation or extraction that may require equipment or chemicals.

In July 2012, the FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting (ER/LA) opioids approved for moderate to severe, persistent pain that requires treatment for an extended period

(12). The REMS introduces new safety measures to ensure that the benefits of a drug or biological product outweigh its risks, while ensuring access to needed medications for patients in pain.

"Misprescribing, misuse, and abuse of extended-release and long-acting opioids are a critical and growing public health challenge," said former FDA Commissioner Margaret A. Hamburg. "The FDA's goal with this REMS approval is to ensure that health care professionals are educated on how to safely prescribe opioids and that patients know how to safely use these drugs."

Under the new REMS, companies will be required to make education programs available to prescribers based on an FDA Blueprint. The REMS also will require companies to make available FDA-approved patient education materials on the safe use of these drugs. The companies will be required to perform periodic assessments of the implementation of the REMS and the success of the program in meeting its goals. The FDA will review these assessments and may require additional elements to achieve the goals of the program.

Training for prescribers

Based on an FDA Blueprint, developed with input from stakeholders, educational programs for prescribers of ER/ LA opioids will include information on weighing the risks and benefits of opioid therapy, choosing patients appropriately, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, and addiction, and general and specific drug information for ER/LA opioid analgesics.

Updated medication guide and patient counseling document

These materials contain consumer-friendly information on the safe use, storage and disposal of ER/ LA opioid analgesics. Included are instructions to consult one's physician or other prescribing health care professional before changing doses; signs of potential overdose and emergency contact instructions; and specific advice on safe storage to prevent accidental exposure to family members and household visitors.

Assessment/auditing

Companies will be expected to achieve certain FDA-established goals for the percentage of prescribers of ER/ LA opioids who complete the training, as well as assess prescribers' understanding of important risk information over time. The assessments also cover whether the REMS is adversely affecting patient access to necessary pain medications, which manufacturers must report to FDA as part of periodic required assessments.

Modern medicine has provided a vast array of therapies to cure disease, ease suffering and pain, improve quality of life, and save lives. However, as with many new scientific discoveries and new uses for existing compounds, the potential for diversion, abuse, morbidity, and mortality are significant. Prescription drug misuse and abuse is a major public health and safety crisis. We must take urgent action to ensure the appropriate balance between the benefits and the risks. No one agency, system or profession is solely responsible for this undertaking; we must address the issue as partners in public health and safety (13).

The ultimate solution to prescription opioid abuse would be the development of a new entity that relieves pain without addictive or euphoric properties. Patients will have access to necessary pain medications without the risk of addiction and abusers will have no incentive to seek euphoria from such a new entity.

Robert Bianchi is Vice President and Chief of Scientific and Technical Affairs for the Prescription Drug Research Center, Chicago, IL, USA.

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Holistic Bioanalytics in the Clinic

Lawrence (Larry) Lesko is a bioanalytical veteran with many years of academic and FDA experience under his belt. Now, as director of the University of Florida's Center for Pharmacometrics and Systems Pharmacology, Larry uses metabolomics to discover biomarkers of drug toxicity.

Larry became a chemist (and the first scientist in the family) at the age of seven with a Christmas gift that fired a growing interest in magic rocks, rockets and (by today's standards) dangerous chemical reactions. At high school, Larry's lifelong interest in pharmaceuticals began with a part-time job at the local pharmacy, where he was tasked with drug compounding, learning about solutions and precipitation as he went – essentially, a continuation of his childhood chemistry set experience...

So, when did the serious academic learning begin?

I applied for – and received – a five-year scholarship at Temple University's School of Pharmacy from the Pennsylvania state senator. My dad was a former coal miner and my mum worked in a factory, so it really was the only option for me to get ahead. Pharmacy school seemed to be the natural choice – and I enjoyed it, but I realized that I wouldn't actually have the opportunity to practice much science if I continued down that path. In particular, I had become very interested in the scientific process of drug development. I recognized I needed an advanced degree to get into that field, so went back to graduate school and did summer internships at a couple of pharmaceutical companies. I worked at Roche in New Jersey and Wyeth Laboratories in Philadelphia and got exposed to many aspects of pharmaceutical development – including mass spectrometry and other analytical methodologies.

And so you chose to go into industry after your PhD?

Actually, after weighing up my options, I decided to go into academia. I interviewed for a position at Texas Southern University, which was looking to improve pharmacy graduation rates. They offered me an intellectual challenge (or opportunity) that I couldn't resist, and they asked me to start a graduate research program, which sealed the deal. I succeeded in both areas – and set up an analytical laboratory – before moving up to the University of Maryland in Baltimore to become director of the Pfeiffer Clinical Pharmacokinetics Research Laboratory and an associate professor of pharmacy. A couple of years later, I found myself the director of what was essentially a fully-loaded analytical service laboratory.

Was there a common theme driving your many career moves?

Looking back, I was passionate about building successful entities – whether an analytical lab or a graduate program. My next move was to the University of Massachusetts Medical Center (director of its Clinical Pharmacokinetics Laboratory) and then onto a company called PharmaKinetics Laboratories, where I was vice-president of the Analytical Laboratory Services Division. We did contract work for the pharmaceutical industry and I headed up bioanalytical method development and validation – and that's where I really got into mass spectrometry. In the contract world, you're always competing with other laboratories, so you have to stay at the cutting edge in terms of sensitivity. I hired a mass spectrometer specialist to run the mass spec lab and develop assays. It really was the analytical big time! We ran three shifts of analytical chemists – a real 24/7 analytical factory – to maintain the high throughput needed for industry customers.

And then you spent nearly 20 years at the FDA...

That's right. I knew a couple of well-known leaders in the FDA – Carl Peck (Director of CDER) and Roger Williams (Director of the Office of Generic Drugs – OGD), and they invited me to take up a new position, developing a new research program in cOGD. I joined the FDA in 1992 as director of research at OGD down in Rockville, Maryland. The position required a very broad-based view of analytics; the research revolved around finding new clinical and analytical methodologies to show bioequivalence of generic products in challenging areas (topical creams or inhalable medicines, for example). In 1995, the FDA opened the Office of Clinical Pharmacology and Biopharmaceutics – and I was asked to become the director and build the office from the ground up. We started with 20 people and I left in 2011 when we had nearly 180.

What were your main highlights at the FDA?

We developed guidance for industry on bioanalytical method development and validation, which is the state of the art today. Another highlight was getting involved with personalized medicine in 2002. I was asked to look at approved drugs and determine in which cases genomics could be introduced into the label. We updated the labels of around

15 important drugs in that nine-year period. Perhaps more revolutionary was the Voluntary Genomics Data Submission Program that we started. We felt that the pharmaceutical industry was not sharing the work they were doing in pharmacogenomics with the FDA – so we created a "safe harbor." Companies could submit data for advice rather than for review, preparing them (and us) for the future. We received around 100 voluntary submissions, which got our internal staff up the learning curve very quickly. Often, there is a perception that regulatory agencies are followers and unlikely to adopt new science readily – I really wanted to change that perception and enable the FDA to lead the field.

You were also involved in the Critical Path Initiative.

Correct. One of the goals was to introduce innovations into drug development. One of the innovations I led was model-based drug development, which used quantitative methodologies, bioinformatics and in silico studies to design and model clinical trials and reduce the regulatory burden for pharma companies. We started the Division of Pharmacometrics in 2008, which was responsible for assessing companies' modeling and simulation data.

How did you end up back in academia?

Well, that story is relevant to my current use of mass spectrometry. In 2010, I got interested in innovations related to drug safety – a paradigm that hadn't shifted in about 40 years. Safety evaluations tended to be retrospective; that is, companies put a drug through a clinical trial or introduced it into the marketplace, and only then recognized an adverse event. I wondered, why do we react rather than predict? A question that led to my interest in integrated systems biology. I started the Mechanistic Drug Safety Program at FDA, which used software and analytical methodologies to investigate drug–adverse event pairs. For example, if you took a drug and had a skin reaction, we would use bioinformatics approaches to

"Looking back, I was passionate about building successful entities – whether an analytical lab or a graduate program."

track the event back to a drug mechanism. Therefore, we could explain adverse events and use the information gained to predict potential adverse events for new drugs. The program is now used in the review of new drug applications (NDAs) for safety. Anyway, I moved to the University of Florida in 2011 and became the director of the Center for Pharmacometrics and Systems Pharmacology.

I wanted to continue my work on drug safety, so we purchased two Agilent LC-MS systems. One was a triple quadrupole MS (the Agilent 6460 QQQ) for targeted metabolomics to enable the study of biomarkers at the cellular level and use them as a signature of a drug–toxic event relationship. And we needed the second system – a time-of-flight MS (the Agilent 6550 LC qTOF) – for global metabolomics to identify new biomarkers of drug toxicity.

Yusuke Tanigawara at Keio University in Tokyo was studying the metabolomics of anti-cancer drugs from a therapeutic mechanisms perspective; I spent a week in his laboratory and was very impressed by his LC-MS instrumentation. And next door to us is the Sanford-Burnham Medical Research Institute – I also gained some recommendations from the scientists there on which models I should be looking at to match my needs; sensitivity is a huge driver for us, and given my long history of managing analytical labs, I also wanted efficiency – and that means robust instrumentation with little-to-no downtime. Notably, the Agilent systems are pretty kind to new users, and it was relatively easy to transfer assays from the literature. More importantly, the Agilent support team was always on hand should the need arise.

Can you share specific projects your working on?

Right now there are two main projects. One is a study of drug-induced kidney damage; can the metabolome act as a "reporter" of toxicity ahead of a clinical laboratory test for serum creatinine (which only highlights a problem after 50 percent of the damage has already occurred)? If we can predict renal damage earlier, we can change the drug or drug dosage or introduce extra fluids and improve the patient's future quality of life. It's really an important unmet medical need. We've started out with a serious candidate that causes toxicity – the chemotherapy drug, cisplatin – which has an adverse event rate for renal damage as high as 35 percent for cancer patients in intensive care (around 7-10 percent for other patients). That's a lot of people with kidney damage. We obviously want to move onto other nephrotoxic drugs as the project moves forward; one of the interesting research questions is whether or not the metabolomic signature for cisplatin is drug specific or applicable to other drugs that can cause kidney damage.

The other project is focused on a rare and serious skin disease called Stevens-Johnson syndrome (SJS), which affects about one in 10,000 people (but has a much higher rate in Asian populations). A common drug that causes it is acetaminophen (or paracetamol) and we wanted to figure out the mechanism behind it. I'm happy to report that we have uncovered the pharmacological mechanism and also how to reduce its risk by using a protective agent. We're writing that up for publication at the moment.

How do you see your research ultimately being applied?

The end game is to employ integrated models that use biomarkers from metabolomics and so-called patient co-variates (like age, race, sex) to inform clinical decisions. For example, in the case of cisplatin, we might look at changes in a metabolomic profile based on 25–50 biomarkers and use that information to offer clinical options; for example, reducing the dose by half (since the patient still needs the drug) or minimizing toxicity by giving a concomitant medication that would block toxicity-causing pathways.

"The end game is to employ integrated models that use biomarkers from metabolomics and so-called patient co-variates (like age, race, sex) to inform clinical decisions."

Your work on metabolomics appears more applied than most...

If you look at the broader world of metabolomics, it's very technology focused. A great deal of emphasis gets placed on the minutia of the analytical methods – and there's nothing wrong with that; it's important to drive the technical aspects of the field forward. It's a very similar scenario in personalized medicine, where half a conference can be devoted to next-gen sequencing and other technology. But the people at the technology end are not often clinically oriented. In many ways, I would say that technology has raced ahead of application in all the omics. We have the technology we need – let's put it to good use. As a clinical professor, I want to convert information from these new tools into valuable knowledge that can have a positive clinical impact – something I am very passionate about.

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34–38
Is Biopharma Ready to Say Goodbye to Batches?
Continuous manufacturing has been the norm in the automobile industry for over 100 years, but biopharma has been slow to let go of traditional batch processes.

Is Biopharma Ready to Say Goodbye to Batches?

Very few biologics are made using continuous processing equipment like bioreactors. Clearly, the biopharmaceutical industry has a long way to go before it's ready to embrace (potentially) superior manufacturing models. Why?

By Ronald Rader and Eric Langer

Biopharmaceuticals are perhaps the most complex of all high-tech products, yet the most fundamental aspects of their manufacture have remained unchanged for decades. Most other modern industries have adopted continuous manufacturing (1), exemplified by the automobile assembly lines Henry Ford introduced over 100 years ago, petroleum refineries and newer steel mills, which run non-stop. In contrast, nearly all biopharmaceutical product manufacturing still involves batch processes.

Mature industries have long figured out how to adopt continuous manufacturing because it is more efficient and cost-effective. Continuous processing can, when done well, manufacture the same product using much smaller-scale equipment and fewer people. For example, consider a steel mill that heats, melts, refines ore and pours the metal into molds, with each component process done on a very large scale as a single batch – it might process 100 tons at a time with one batch per week, producing 5,000 tons/year. Now compare that with a mill with the same manufacturing capacity, but operating continuously – if two tons are processed every two hours, it would produce 8,500 tons/year. Moreover, the in-process materials need not be moved into and out of storage, meaning that labor needs are lower and more evenly spread.

The same holds true for biologics manufacturing, where a continuous process at smaller scale not only saves resources, space and labor, but also allows better process monitoring and control – in an industry where this aspect is vitally important. And if something does go wrong with continuous processing, only the affected material need be collected and discarded, rather than an entire batch.

Old/new technology

Continuous bioprocessing (CPB) is not new, and a few commercial products have been manufactured using perfusion technologies for several decades. For example, adherent fiber-based bioreactors have been in common use for monoclonal antibody (mAb) manufacturing using fused-cell hybridomas since the 1980s, before recombinant mAb manufacture became dominant.

But these technologies took a back seat to batch bioprocessing for a variety of reasons. One is that continuous processing can require more sophisticated operations. In our annual report on biomanufacturing, we asked 238 bioprocessing professionals about issues concerning perfusion versus batch-fed processes. Of the 19 areas evaluated, the Top 3, where a majority of respondents reported perfusion as presenting more concerns (versus fed-batch) included:

1. *Process operational complexity:* Complexity introduces elements of risk that in a biopharma situation can create very costly, sometimes disastrous operator errors. The simpler, the better, in most cases.
2. *Process development control challenges*: Optimizing bioprocessing is an ongoing project, and if a batch process at small-scale is tweaked, a clear outcome can be observed and extrapolated to improvements at larger scale. In continuous bioprocessing, controlling all the parameters is sometimes more challenging.
3. *Contamination risks:* Risks of contamination of a process is a major industry concern. Worries about how those risks may affect a CBP facility put this high up on the list of potential concerns.

Though many of the perceived problems with perfusion have already been improved, there appears to be continued resistance to adoption of new processes. Perceptions and attitudes regarding perfusion will likely change for the better in coming years, as more bioprocessing professionals develop hands-on experience with perfusion operation and its advantages.

In classic batch method manufacturing, antibodies are commonly manufactured using bioreactors and other vessels holding more than 10,000 liters, with process preparation (cleaning, sterilization) and processing taking three weeks or more. In contrast, using a 500-liter perfusion bioreactor (where spent, product-containing culture media is continuously removed at same rate that fresh media is added) and continuous chromatography equipment for purification, the same or likely more product can be produced in the same overall time – as there is far less of the down-time associated with batch processing.

Comparative studies at largest mammalian scales, such as blockbuster mAb manufacture in fixed stainless steel facilities, continue to show improved cost–benefit ratio using fed-batch, with perfusion more cost-effective at up to 500 kg/year capacity. However, building a batch facility could cost more than $120 million, while the much smaller CBP facility could cost $25–35 million. Operating expenses will be comparable or lower for the continuous facility. This is

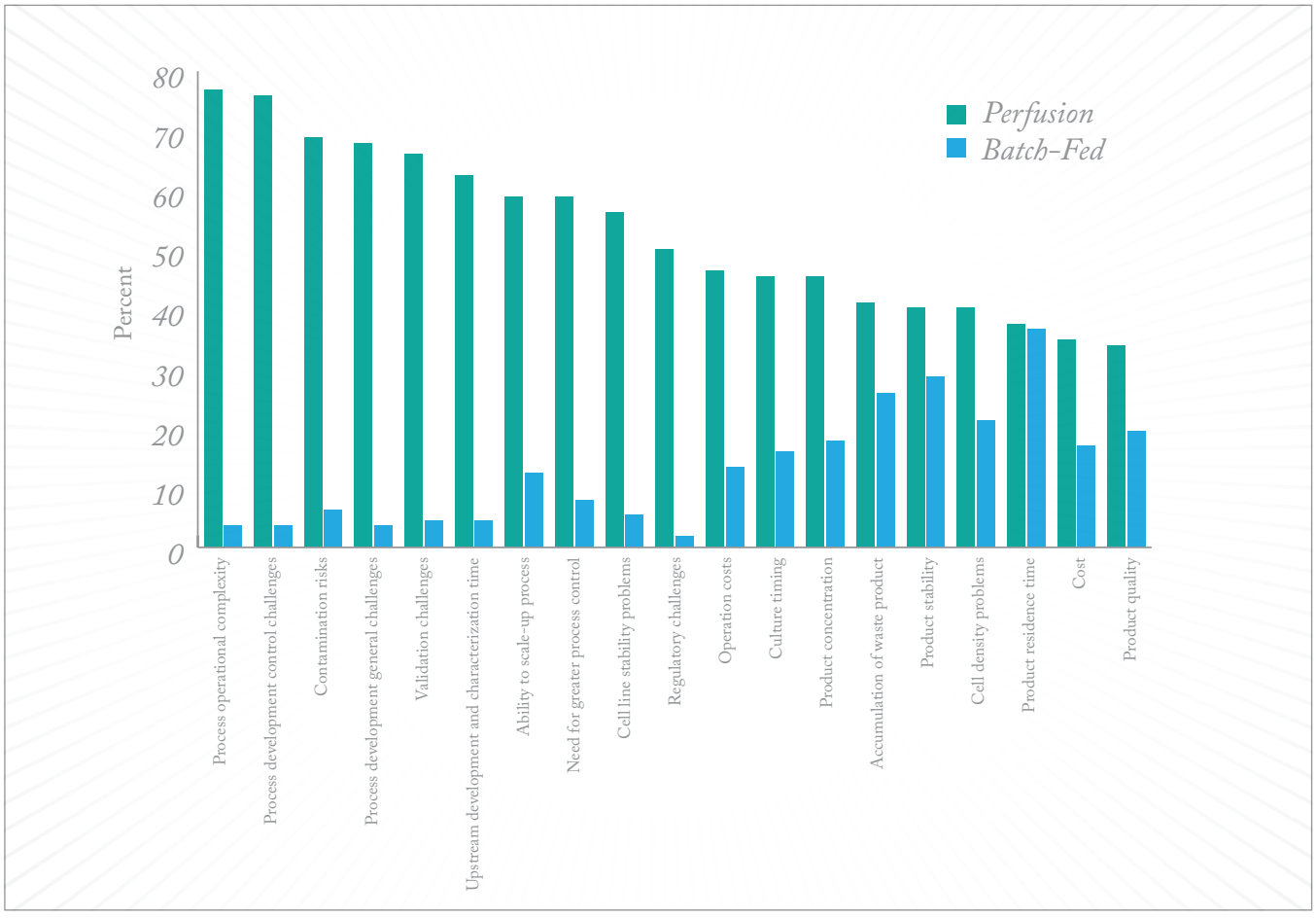

Figure 1. Comparison of perfusion versus batch-fed bioprocessing concerns.
Source: 12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, www.bioplanassociates.com/12th

because a continuous operating facility will tend to be be smaller, and operated with higher productivity (more production over time), compared with a batch bioprocessing facility making the same product.

State of play

Adoption of basic changes in industrial manufacturing methods takes decades – it took over 50 years for continuous steel casting to dominate that industry. And the bioprocessing industry, with its regulated operations, is even more conservative. For example, it has taken well over 10 years for single-use systems using disposable plastic equipment to be introduced at small-scale operations, and it will require at least another decade before these processes are substantially adopted for large commercial-scale biopharmaceutical manufacturing. In the biopharmaceutical industry, adoption of CBP has so far been restricted to a few unit processes being implemented at a minority of facilities. By far, the CBP currently most recognized involves smaller perfusion bioreactors operating continuously for much longer periods of time. Currently, about a dozen, less than 10 percent, of biopharmaceuticals are manufactured using perfusion bioreactors.

The issues restricting adoption of CBP involve the 'complexity' concerns and prejudices noted above, but there are also some significant engineering, design, and integration problems to be overcome. Other major challenges include the need to cost-effectively implement CBP at commercial scales while meeting rigorous regulatory requirements for product quality, predictability and control. The difficulties are surmountable using current technology, but there is a lack of practical know-how and concerns over the availability of cost-effective and specialized equipment usable at larger scales.

"A continuous process at a smaller scale not only saves resources, space and labor, but also allows better process monitoring and control."

CBP has also not been adopted for purification and other downstream processing operations, especially at commercial scale. There are many variations of CBP for downstream

operations in development, but they have not yet made the big-time. Some, such as simulated moving bed (SMB) and periodic countercurrent (PCC) chromatography are projected to be 20–30 percent less costly compared with current methods. But even that isn't enough to motivate the industry to quickly adopt an alternative.

"As technologies advance, more suppliers will develop relevant equipment, and more end-users will implement their own approaches."

Regulatory agencies, particularly the EMA and FDA, are often cited as holding back CBP adoption. But these agencies have generally been very open to CBP. From a regulatory perspective (as with the engineering aspects), the difficulty revolves around overcoming industry inertia that favors the incumbent process, simply because it's easier to get a clunky, more expensive manufacturing operation through the onerous regulatory process than it is to introduce a robust novel bioprocess. So although CBP can make better products, at smaller-scale, and offer superior quality compared with conventional fed-batch manufacturing, adoption will take time. Aspects as simple as how to define a 'batch' have long been cited as hurdles. And although regulatory agencies are increasingly familiar and competent in these areas, few biomanufacturers want to be the guinea pigs in a regulatory test case, when they can simply select a tried (tired) and trusted manufacturing strategy.

An eye on the horizon

Today, existing bioprocesses are typically upgraded to CBP in isolated process steps; for example, fed-batch bioreactors are adapted for perfusion with the addition of devices such as the ATF (alternating tangential flow) system perfusion pumps from Repligen. However, for new drugs, process lines and facilities, CBP will use more broadly integrated technologies that encompass multiple process steps.

Process control and automation is a very important component – and great advantage – of smaller-scale continuous processing. Moreover, statistical methods, such as Process Analytical Technology and Quality by Design (QbD), intended improve and document processes are more amenable to application to continuous versus intermittent batch processes.

By essentially simplifying process and product quality control, CBP can reduce out-of-spec excursions and intra-lot variability.

It's not all plain sailing. Early adopters of CBP for marketed drugs may encounter issues that reflect the immaturity of the technology in our field; equipment is not always specifically designed for the increased rigors of long-term continuous use, and depending on the application, stainless steel may be preferable to single-use equipment. Indeed, for some very large-scale biopharmaceutical manufacturing, it may end up being more cost-effective to use large dedicated fixed stainless steel systems operating in batch mode. A big question is: is there a future for large-scale biopharmaceutical manufacturing anyway? (see "Precision Biomanufacturing" on page 42)

Some biomanufacturers have become leaders in CPB implementation, including Genzyme and Bayer; both have a great deal of experience in using perfusion for commercial product manufacture. Amgen recently opened an integrated $200 million CBP manufacturing facility in Singapore. Hemispherx Biopharma makes a cell cultured immune modulator that has allowed an 80 percent reduction in related staff. Other companies using perfusion-based CBP include Roche, Johnson & Johnson, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Samsung, Biogen, Novartis and BioMarin, among others. As technologies advance, more suppliers will develop relevant equipment, and more end-users will implement their own approaches. As the industry gains experience and regulators become more comfortable, widespread CBP adoption seems inevitable.

Ronald A. Rader is senior research director and Eric S. Langer is president and managing partner at BioPlan Associates, Inc, Rockville, Maryland, USA.

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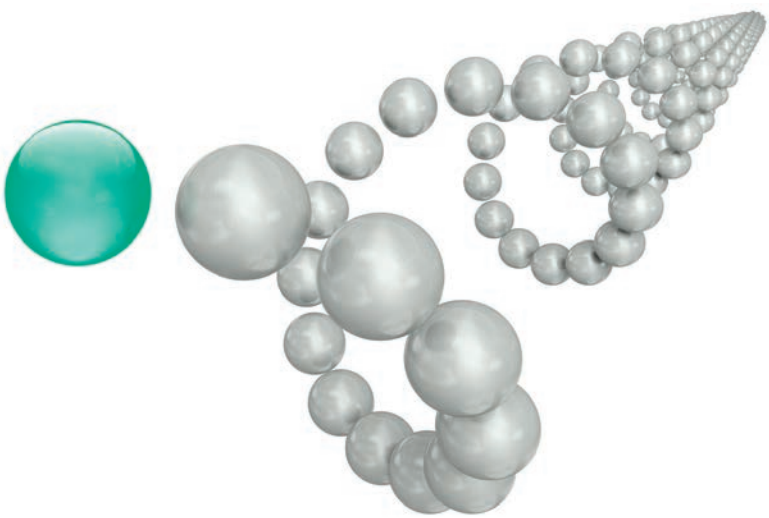

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Decision Support

Suzanne Farid is Professor of Bioprocess Systems Engineering and Co-Director of the ESPSRC Center for Innovative Manufacturing in Emergent Macromolecule Therapies hosted by the Department of Biochemical Engineering at University College London. Farid and her team have developed a range of software tools to help biopharma companies make decisions on the best manufacturing processes, including whether to make the switch to continuous.

Why hasn't biopharma fully embraced continuous bioprocessing?

Traditionally, continuous processing in the biotech sector has been viewed as more complex to operate and with a higher risk of failure. With the introduction of more robust technology options for upstream and downstream processing, we have seen a resurgence of interest. Yet obstacles to adoption still exist. When we ran a roundtable discussion at a recent conference on this topic (2), several participants mentioned issues such as the lack of reliable scale-down tools for continuous processes and the need for better online process analytical technology, control and hardware reliability than is currently available. Furthermore, companies working with stable antibodies may not have the same incentives as those working with labile products, where continuous processing can be a necessity.

How can decision-support tools help?

Decisional tools such as those developed at UCL Biochemical Engineering can act as a testbed to perform in silico evaluations of the technical, financial and risk implications of continuous technologies across a range of scenarios. The cost of experimentation to explore all the options is prohibitive and hence decision-support tools are vital for new technologies to be examined inexpensively, thus saving time and helping to prioritize R&D efforts.

How have you have applied decisional tools?

We have developed and applied decisional tools to examine the bioprocess economics of continuous processing and answer topical questions (3-5) such as: How well do continuous perfusion steps need to perform to compete with the traditional fed-batch processes? Does continuous chromatography offer cost savings for clinical manufacture? How does the business case for integrated continuous bioprocessing change from early-phase manufacture to commercial multi-product manufacture?

On the upstream front, we illustrated how the choice of fed-batch versus spin-filter and ATF perfusion culture depends on the scale of production, failure rate and cell density increase achievable. ATF perfusion processes were predicted to be more competitive for single-product commercial antibody facilities if the cell density increase was above a critical threshold (three-fold higher in this case) and the process economics savings were considered more important than operational feasibility. In contrast, the tool predicted limited use of spin-filter systems in industrial scale processes since they would struggle to compete on economic, environmental, operational and robustness fronts at most cell culture titres and production scales.

Turning to downstream, our integrated techno–economic evaluation of whole bioprocesses that utilise continuous chromatography for product capture predicted that such processes have the ability to offer significant direct cost savings in early clinical phase material generation; this can have a large impact considering the high clinical attrition rates.

"With more robust technology options for upstream and downstream processing, we have seen a resurgence of interest."

Looking at integrated continuous bioprocessing, our analysis predicted that an integrated continuous strategy (ATF perfusion, continuous capture, continuous polishing) is cost-effective for early-phase production and small/medium-sized companies. However, the ranking of strategies switches for commercial production and large companies to the hybrid strategy with fed-batch culture, continuous capture and batch polishing since this avoids the need for multiple parallel trains with the scale-limited perfusion systems. Further considerations that could alter those conclusions include factoring in the cost of development when adopting continuous processing.

the Medicine Maker

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01 South Korea's generic market is projected to grow on average 5% per year between 2013 – 2018 to a staggering $23.84 Bln.

02 South Korea closely ranks after China and India as the third "best outsourcing destination" in Asia.[1]

03 Korea Drug Development Fund (KDDF) will promote the development of the Korean biotechnology sector in the Asia Pacific region aiming to produce 10 new treatments by 2019.

04 Investment in R&D and related facilities is very active and establishment of plants according to the international standards is increasing.

[1] The changing dynamics of pharma outsourcing in Asia, PwC.

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42–45
Precision Biomanufacturing
How can biopharmaceutical manufacturing adapt to the demands of personalized medicine?

Precision Biomanufacturing

Personalized medicine looks set to transform the biopharmaceutical landscape, and will demand significant changes in production methods. The demand for large-scale batch processes will decline – so what is the alternative? The UK's new National Biologics Manufacturing Center is on a mission to answer that very question.

By Jonathan Robinson

As recently as 2009, the UK had the second strongest pharmaceutical industry in the world, but in recent years we have seen the sector falter. The UK is falling behind – fewer new drugs are being discovered here and drug manufacturing is drifting overseas. The UK government recognizes the value of the country's significant expertise within the life sciences sector and wants to make sure we retain our leading position. To that end, a raft of government initiatives are being implemented to support UK life sciences companies and encourage them to develop and manufacture innovative new therapies within the UK. This includes the National Biologics Manufacturing Centre (NBMC), the Precision Medicine Catapult, the Cell Therapy Catapult and the Medicines Technology Catapult.

The Center for Process Innovation (CPI) is part of the UK's High Value Manufacturing Catapult. We help to bring new technologies from universities and small companies into the market by providing the expertise, facilities and funding needed for successful translation. For example, we receive funding from the Advanced Manufacturing Supply Chain Initiative, as part of a consortium with big biopharma firms and a number of small companies with interesting technology. The aim is to streamline the development process for biologics by identifying unsuitable drug candidates earlier in the process. By allowing candidates to 'fail early', we hope to avoid abandoning candidates in Phase II or III clinical trials because they cannot

be manufactured efficiently or aren't compatible with the delivery device.

Making it personal

CPI recently opened the £38 million ($59 million) National Biologics Manufacturing Center (NBMC), with six key goals (see Table 1 on page 45). In addition to optimizing current processes by introducing new techniques and technology, we are looking ahead to see what the next 20 or even 50 years might bring. Specifically, we want to address the increasing trend towards personalized medicine – therapies tailored to sub-populations, or even individual patients. With the advent of fast and efficient DNA sequencing, we are identifying increasing numbers of genetic subtypes of diseases. Breast cancer is a good example; treatment tailored to the hormone receptor and HER2 status of breast tumors is already well established, and as gene sequencing technology has advanced, more and more markers are being discovered.

As personalized or precision medicine becomes more prominent, it will start to challenge longstanding industry supply chain models. We will not be mass-producing these drugs to treat thousands of patients. Instead, patients will be tested for specific genetic or molecular markers and prescribed a drug to match their individual biological characteristics, which means more patient cohorts and smaller quantities of better tailored drugs. For the bioprocessing supply chain, this is a radical change. The large-scale batch processes of today will no longer meet society's needs.

"As personalized or precision medicine becomes more prominent, it will start to challenge longstanding industry supply chain models."

Miniaturized medicine

If personalized medicine takes off in the way we expect it to, what will be the impact on supply chains and what technologies will we need? Can we miniaturize production so that instead of scaling up, we can scale out? We hope to answer these questions with our Factory of the Future project, to understand how to manufacture smaller, more diverse materials by scaling down processes and making it easier to switch production between different products.

One solution is for biologics manufacturing to go mobile. Traditional bioprocessing is divided into separate unit operations (chromatography, filtration, and so on) but in the factory of the future I anticipate we will integrate many steps into single small-scale units that can be moved to the patient. By containing the process within a single piece of equipment you remove the need to work in vast clean rooms and make it possible to work anywhere.

Such small-scale integrated machines could produce medicines in a hospital

"We need to analyze the product as it's produced, and so a major focus for CPI is on-line analytics for real-time measurement and control."

or pharmacy setting to match the individual patient's needs. Plus, mobile manufacturing units can be quickly added or repurposed to create a modular facility with much greater flexibility. Single use components are already well established in the industry and could be incorporated into the manufacturing unit to make it easy to switch production from one drug to another, improve flexibility and bypass costly clean-down steps.

On-line analytics

Analytics are another area where we expect the factory of the future to look very different to today's facilities. Currently, analysis is typically conducted off-line – not ideal if you want to manufacture the product quickly on a small scale. Instead, we need to analyze the product as it's produced, and so a major focus for CPI is on-line analytics for real-time measurement and control.

CPI is agnostic – we must consider all available technology that can help us achieve our goal. We encourage different manufacturing sectors to share ideas and technology, and we may find that the technology we need is already in use elsewhere. For example, the diagnostics industry already uses small microfluidic devices at point-of-care to

Drivers	*Products*	*Costs*
	Increasing diversity of product type	Increasing burden of healthcare cost
Themes	Developing and Integrating New and Improved Process Technologies for manufacture of Biologics	
	Develop and Demonstrate Rapid and Robust Approaches to Process Development using the latest high throughput technologies	
	Improved Technologies for rapid Formulation studies, developing and de-risking Fill & Finish technologies	
	Developing and Integrating New and Improved Analytical Technologies, including online measurement technologies	
	Train and Develop Workforce to match industry demand	
	Biologics Factory of the Future, determining how to manufacture the personalised medicines of the future	
Outcome	Increase in UK Biopharmaceutical Development and Manufacture	

Table 1. CPI Biologics Strategy.

measure analytes in samples. It is likely that elements of that technology could be applied for small-scale biologics production and analysis. In fact, a lot of the analytical technology needed is already in use in laboratories, and we are looking at how they can be brought online and incorporated into a discrete unit.

The road less travelled

Small-scale, disposable versions of current technologies, like bioreactors and chromatography columns, will certainly help get us started, but we also need some seriously fresh thinking. To fill the gap between what is currently available and what is needed, we are reaching out to innovative researchers at universities and small companies. For example, there is a lot of interest in small-scale continuous manufacturing technology and we are kicking off various projects to help bring that to market. Running continuous processes at a smaller scale is particularly challenging and raises a lot of questions – the role of CPI is to answer those technological questions to help the industry move forward.

The Factory of the Future project already has a healthy and growing consortium; the next step is to agree the goals with our partners so that we can start planning what we need to deliver and how we will test new technology. As with any innovation in the pharmaceutical industry, the biggest challenge is changing the current mindset. The industry is understandably cautious about moving away from tried and tested (and regulator-approved) technology. After all, shepherding a new product to market can be risky enough without adding new production methods and technology. However, doubters must see the benefit of taking the road less travelled – especially if they want to be at the forefront of personalized medicine, as current production methods are simply not suitable. The high cost of existing biologics has already caused controversy, and if we are to start producing drugs on a smaller scale, it's imperative that the costs of production are decreased. Flexible, small-scale, high-throughput technology can help drive down the cost of developing biologics – and that can only make them more accessible.

Jonathan Robinson is Head of Business Development for Biologics at the Centre for Process Innovation (CPI), Wilton, UK.

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About the Biopharmaceutical Market in Ireland

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48–49
Fighting Fear -
The Entrepreneur's Enemy
What's the secret to being a successful entrepreneur like Mir Imran? Be fearless but not reckless.

Fighting Fear – the Entrepreneur's Enemy

The true path to success as an entrepreneur is the ability to spot high impact problems – and to be fearless in the pursuit of great solutions.

How often have you heard someone say "I thought of this 10 years ago" when they see a new product on the market? Assuming they really did think of it 10 years ago, then why didn't they do it? According to Mir Imran, an entrepreneur and venture capitalist, what holds most people back in any entrepreneurial endeavor is fear. How do you get the funds? What if it doesn't work? There are many hurdles on the road to building companies, and one must navigate those carefully to be successful.

Over his career of more than 35 years, Imran has been involved in more than two dozen start-up healthcare and medical companies. In this interview, he gives his insights into what makes a successful entrepreneur.

What's the key to success as an entrepreneur?

In any endeavor, fearlessness is crucial. It is important to recognize the difference between fearlessness and recklessness. Recklessness comes from arrogance, but fearlessness comes from confidence in your abilities and a well thought out approach. When I began my career in my twenties, I had many fears. But as I matured and gained more experience, I learned to understand and overcome my fears, and as a result, I had more confidence in my abilities.

How did your entrepreneurial adventure begin?

My background is in engineering, mechanical science and medicine. I started my career in the late 1970s when I co-founded a medical company to develop the first implantable defibrillator. Today, defibrillators are routinely used in cardiology for the treatment of arrhythmia, and the technology has been implanted in a couple of million people worldwide.

Since then, I've started around two dozen companies, mostly in different chronic disease areas. About 15 of my companies have been acquired by large corporations. Most of my colleagues started one or two companies, made some money, and then started playing golf or became venture capitalists. I find golf incredibly boring…

So you are still working on start-ups?

Right. I am fascinated by innovation. How does innovation work? How does creativity work? I've read a whole host of books on the subject – you'll find thousands if you search for them, but none of them teach you how to innovate. Most books talk about how people innovated in the past, or they discuss the character and personality traits of innovators. But most innovators are not introspective, and don't spend much time trying to figure out how they innovate – they are just so happy they did. And most innovators have just one or two big ideas in their life.

I was intrigued by this process, and I thought if I could do it once then why couldn't I keep doing it? And so I did. I now have more than 400 patents in the US and around 1500 worldwide. For example, I do much of my best work through my R&D lab and incubator, InCube Labs, where we pursue major unmet medical needs. One of InCube's portfolio companies is Rani Therapeutics, where we are working on an oral method for delivering biologics, which is something of a holy grail in pharma development. Going after these big problems is what motivates me.

What inspired you to tackle this challenge?

The spark of inspiration came to me about five years ago during a conversation with an executive at a large pharmaceutical company, who told me about an oral biotherapeutic company that they had invested in that had just shut down. I'm always interested in failure – failure indicates unsolved problems – so I asked what had happened. He told me that over the last 40 years there have been hundreds of attempts made at solving the problems associated with delivering biologics orally. Although a few groups have achieved some minor successes, most have failed, and the advances made haven't really led to practical approaches.

After that conversation I started to think more about the topic. If all attempts so far have failed, it's obviously a really juicy problem – meaning that the solution could have a profound impact on the market and most importantly, for patients. With that in mind, I started working to understand the problem more deeply and came up with a completely new approach for solving it.

What progress have you made in the search for this 'holy grail'?

I'd already done a fair amount of work in the gastrointestinal (GI) tract area with other research projects, so I knew the biology and physiology. I came to the conclusion that biologics can only be delivered by injection. But I also knew that intestines do not have pain receptors, unlike the skin; you can poke needles into your intestines all day long and you won't feel a thing. I imagined an orally-administered pill that would travel into the intestine and then inject

the drug. The patient would be oblivious to the process, gaining the benefit of an injected drug without the pain associated with needles.

It's not as easy as it sounds and there were many challenges. First of all, we had to make the capsule pass through the stomach intact, so we developed a pH-sensitive protein that preserved the pill. In the intestine, the pH begins to rise and the outer shell dissolves.

The next challenge was figuring out how to inject the drug. Rather than a traditional metal needle, we made micro-needles out of sugar. The drug is inside the needle in solid form, and the needles are fully inserted into the intestinal wall.

For any injection, you need a force. We created a small polymer balloon that inflates itself using carbon dioxide that's produced by an internal chemical reaction. The two chemicals are allowed to mix together to initiate the self-inflating reaction once the outer shell dissolves. As the balloon inflates, it pushes the needles into the intestinal wall. Because the intestinal wall is designed for absorption of nutrients, it is highly vascularised so when the sugar needle is inserted it dissolves in less than a minute. Once the needles are injected, the balloon collapses, the CO_2 is absorbed in the tissue and the patient passes out the balloon, which by now has the consistency of a tomato skin.

The concept is simple but it's taken us years to figure out all the details. We have done hundreds of pre-clinical experiments with excellent results. We're now in discussion with several big companies and recently announced an initial collaboration with Novartis to begin feasibility studies. As for commercial manufacturing, we've been paying a lot of attention to the scalability of the design from the outset; we've already set up a small pilot line as a starting point.

Not all projects are a success; how do you cope with failure?

While I have had many successes, I have certainly not been immune to failure. But those failures never devastate me. I try to understand and learn from them. I believe that failures can make you a better problem solver, innovator and entrepreneur.

"Failures can make you a better problem solver, innovator and entrepreneur."

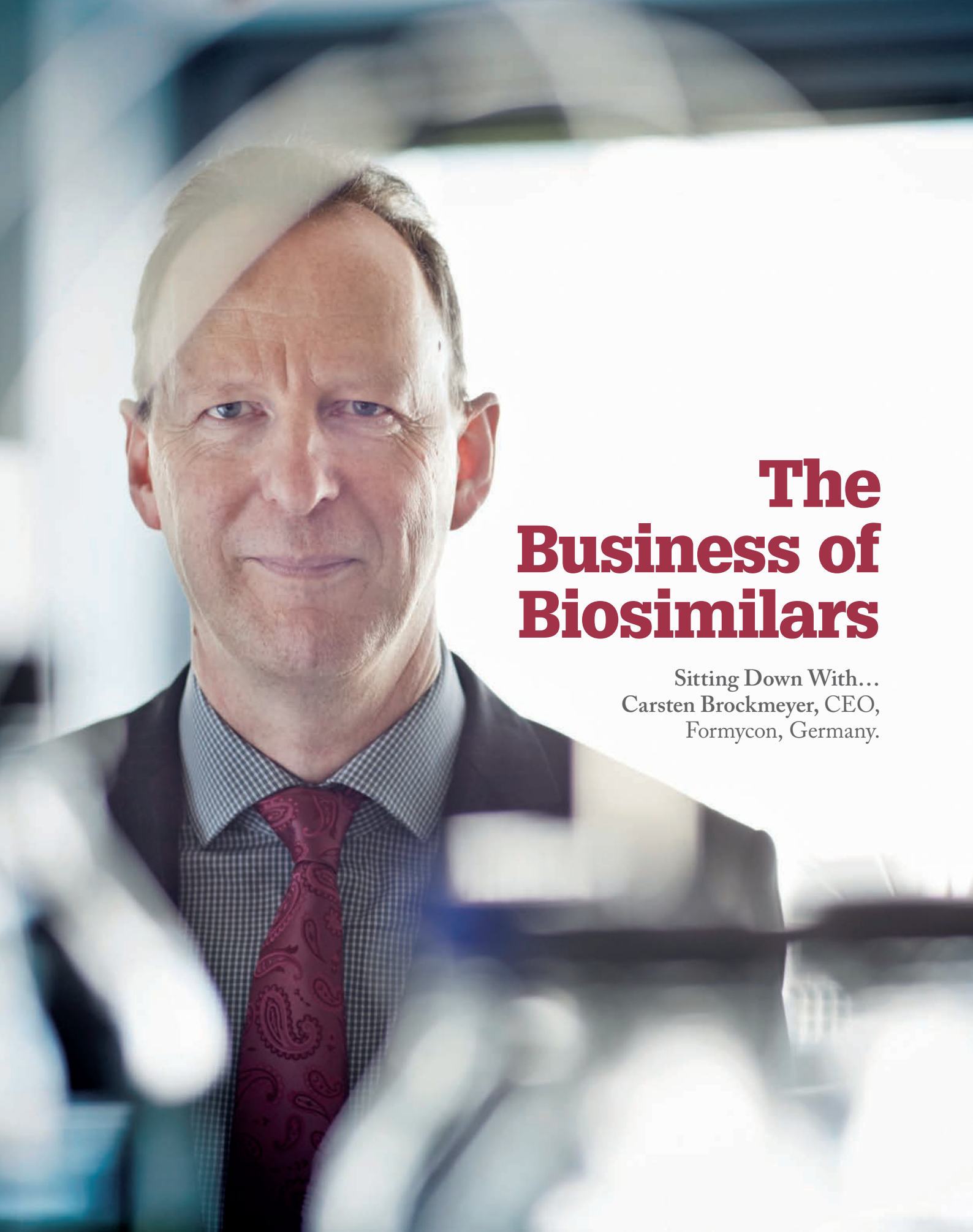
In science, research projects typically fail at the exploratory phase – and that happens before we form companies. That said, companies clearly still fail. The trick is to learn valuable lessons from any failure. In my early days, after four or five successful companies, I had a failure. I had set up a biomaterials company; the business model was to out-license the materials we were creating to other companies. After a couple of years, I realized that medical device companies were not as open to licensing fees, and that it was a horrible business model. There was nothing wrong with the materials we had created and we actually used them later ourselves, but the business model was flawed and not scalable. I shut the company down, and learnt a very valuable lesson about business model choice.

Another failure I experienced was in the early 1990s, when I came across a material with really interesting shape-memory/super-elastic properties. I was so enamored by the technology that I decided to set up a company. I talked to a cardiologist about developing an electrically steerable guide wire. The cardiologist said it was an amazing idea, so I went ahead with the start up.

A few years later, I had developed a product and went back to a larger group of cardiologists. They asked me, "Why on earth have you created this product? We already have guide wires that will allow us to navigate the vascular anatomy." In fact, they weren't interested in complicated electrical steering. It was a real wakeup call. I shut down the project but I actually did make the company a success. Most importantly, it was probably the best lesson I've learned in my entire career: don't fall in love with a technology – focus on the problem. In other words, don't start with a technology and then look for a problem to solve; instead, start with the problem – take the time to understand it inside and out – and then let the problem tell you how it wants to be solved.

Any final words of advice for would-be entrepreneurs?

As I tell many aspiring entrepreneurs, you must select your problems carefully. You must make sure they are worthy of being solved. Is a new solution really needed? Will the new solution be an incremental or substantial improvement over existing solutions? And as you develop the solution, you need to keep asking what attributes of the solution make it worthy of commercialization. If you can tackle these points, you'll have the makings of a successful company.



The Business of Biosimilars

Sitting Down With…
Carsten Brockmeyer, CEO,
Formycon, Germany.

What drew you into the pharma industry from academia?

I'm a biologist by training and have a strong background in human biology, immunology and oncology, so most of my work was close to the clinic. At around the same time, the first monoclonal antibodies were making their way into the clinic, but we had very limited capabilities in academia to produce them. When I had the chance to join Baxter it was a great opportunity for me to help to develop and manufacture products that could have a big impact.

How did you get into biosimilars?

Back in the 1990s, biotechnology didn't exist for generic companies. People said it would be impossible to develop a copy of an existing biotech product because – as the popular phrase goes – the process is the product. It was assumed that you would have to repeat everything from scratch, and submit a full new Biologics License Application (BLA).

But by working in the innovator industry I had learned how to demonstrate comparability for biotechnology products; when we transferred our processes between sites, or changed the cell line used, we needed to demonstrate the comparability of our monoclonal antibodies without having to repeat all of the pre-clinical and clinical studies. And that gave me a head start when it came to developing the world's first glycoprotein biosimilar, Epoetin alfa at Hexal AG.

What was your approach?

The first challenge was to get a clear target specification. For a small molecule, you could simply consult a pharmacological monograph, but there were no detailed monographs for biologics, so we had to confirm the specifications of the originator. We sequenced the originators and established analytical methods to give us a blueprint. It was a completely new approach.

You clearly have a pioneering spirit – is that why you set up your own company?

Starting my own business was something I had always envisaged doing, but I saw a real opportunity when President Obama signed the Affordable Care Act in 2010; suddenly, a regulatory pathway for biosimilars was on the horizon in the US. So I left Sandoz to make my dream come true and establish my own consulting company, Brockmeyer Biopharma, to help companies with biosimilars strategies.

"If you really love what you're doing, sharing expertise is very satisfying."

What's the secret to being a successful consultant?

My company's success was partly based on my previous scientific achievements and track record, but the fact that I really enjoy connecting with people and sharing knowledge was also key. Some people feel that they give away too much of their know-how for free if they speak at congresses, or run workshops, but I think differently; it's a great opportunity to connect with other people and, if you really love what you're doing, sharing expertise is very satisfying.

But then the opportunity at Formycon came along?

That's right. I gave a one-day workshop on biosimilars to Formycon, and at the end of the day, Nicolas Combé (now Formycon's CFO) asked if I would be interested in leading the company on its way into the biosimilar field. It was a tough decision, but I couldn't resist the opportunity.

What has been your biggest challenge as CEO?

Convincing investors in Germany and Europe to support biosimilar development back when the term wasn't really known was tough. Today, biosimilars are very attractive to the investment community. I believe we are now one of the best-financed independent biosimilar developers in the world.

What are the main challenges facing biopharma?

Medical needs are changing as the global population ages, with autoimmune disease, diabetes and cancer becoming more and more prevalent. Biologics are very powerful in treating some of these conditions, but the cost can be a big problem. Even in developed countries, access to biologics is limited because of the high price, and the majority of patients in less developed countries, where 85 percent of people live, have no access to biologics at all. The WHO recently added several monoclonal antibodies to its list of 'essential medicines', so it needs fixing.

I am not against patent protection, but only competition will drive innovation. Competition results in cheaper biologics, which gives more people access. As a company we need to be profitable, but we also need to make the world a better place by broadening access to essential medicines.

If you could go back in time and speak to your younger self, what would you say?

Love what you're doing. I think that's the most important thing in life: do what you enjoy doing and share that with others.

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