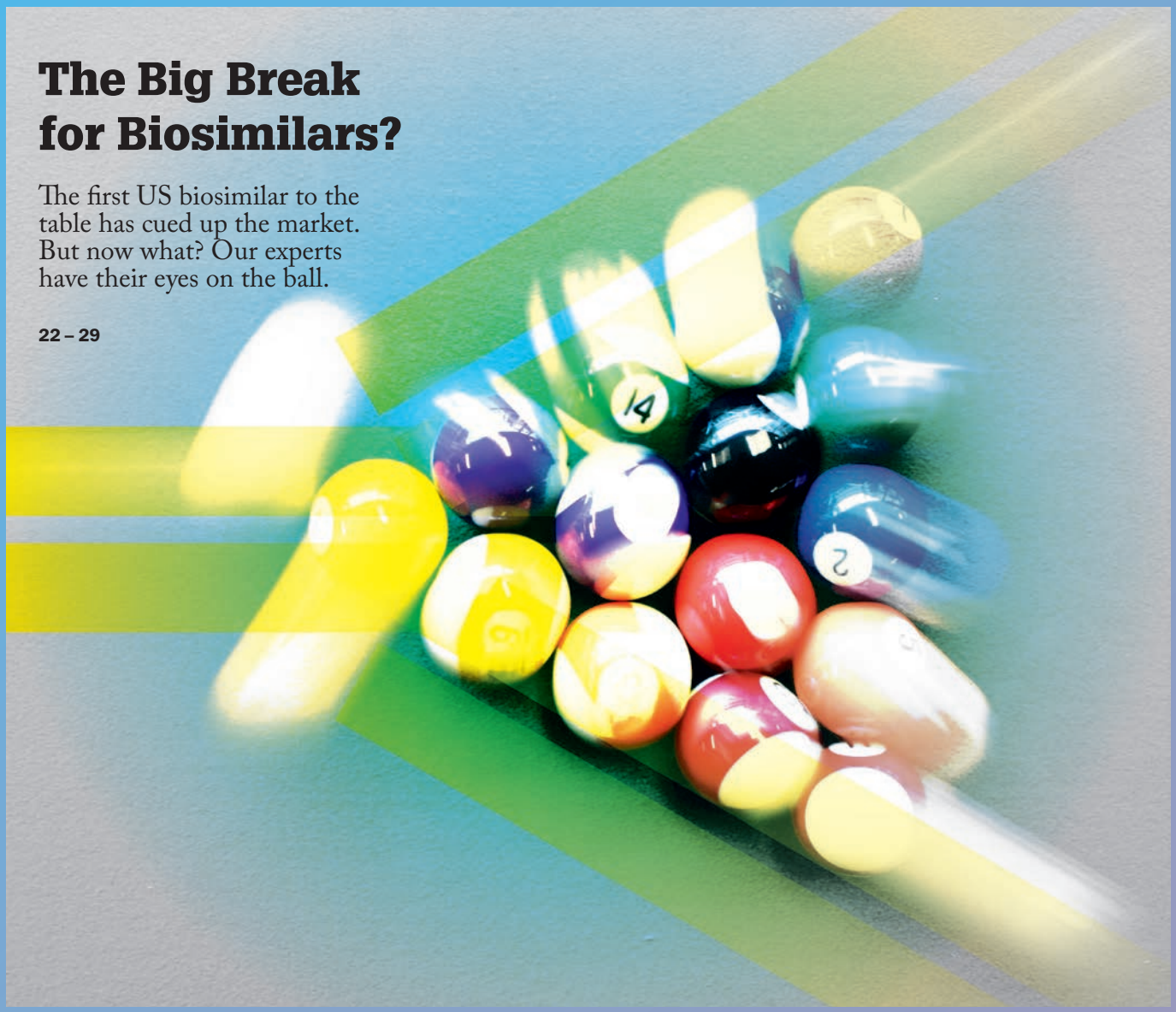
MARCH 2015 # 06

the Medicine Maker

The Big Break for Biosimilars?

The first US biosimilar to the table has cued up the market. But now what? Our experts have their eyes on the ball.



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Online this Month

Bemused By Biosimilars?

We take an in-depth look at biosimilars on page 22, but if you need a 101 in biosimilars and how they compare with generics then this online interview with Professor Begoña Calvo from University of the Basque Country in Spain may just do the trick.

tmm.txp.to/0315/biosimilars-101

Thank you!

Since January you've been nominating the people who you think deserve a place in The Medicine Maker's 2015 Power List. Nominations are now closed and our panel of judges is reviewing the entries. Thank you to everyone who submitted nominations – we look forward to bringing you the full Power List of the 100 most influential people in drug development and manufacturing next month.

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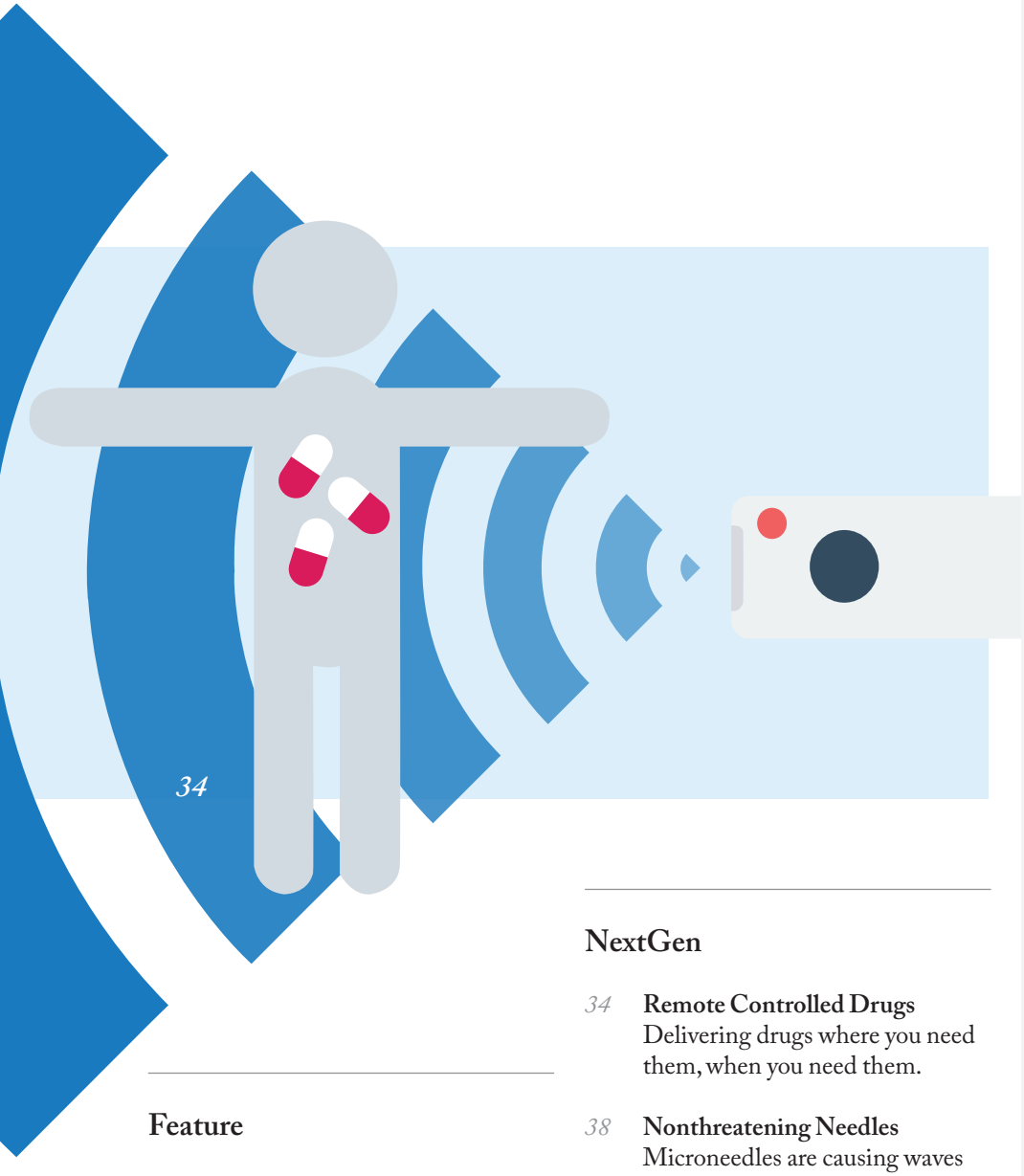

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Practical Innovation

Innovation in pharma isn't synonymous with drug discovery

On page 12, we highlight the pioneering work of scientists from the Max Planck Institutes in Potsdam and Magdeburg, who received the inaugural Humanity in Science Award, supported by our sister magazine The Analytical Scientist. Peter Seeberger and Andreas Seidel-Morgenstern have spent several years developing a new production method to increase the yield of crucial artemesinin-based malaria drugs. The resulting photochemical reactor can transform waste products generated during traditional extraction from the source plant, sweet wormwood, into a range of anti-malarial drugs. The technology required is not overly complex, expensive or bulky – in fact, the apparatus fits into a suitcase, and Seeberger estimates that 400 of these systems would take care of the worldwide production of artemisinin.

Increasing production efficiency using continuous flow processing may not sound like a particularly dramatic innovation, but the potential impact is huge. Malaria is a disease of poverty, killing hundreds of thousands of people (mostly children under 5) every year and placing a huge economic burden on some of the world's poorest regions. At present, the cost of production of artemisinin drugs is higher than the affordable price in sub-Saharan Africa where the disease is most prevalent. Counterfeit drugs consequently flood the market. If the drugs were cheaper, governments and NGOs could invest in other valuable initiatives and the temptation to buy potentially fake drugs on the black market would be reduced.

The award illustrates the fact that innovation is not the sole preserve of scientists concocting the latest breakthrough drug in the research lab. Pharma R&D is picking up again, with the highest number of new drug approvals for years, but it's widely acknowledged that the era of blockbuster drugs is over – the low-hanging fruit is gone. But what about drug development and manufacture?

In its first six months, The Medicine Maker has explored new production methods that could revolutionize both small and large molecule manufacturing; environmental initiatives for 'green' drug production; and innovative drug delivery mechanisms. In this issue, we explore targeted delivery mechanisms that could allow toxic drugs to be administered without side effects (page 34); anyone who has visited a cancer patient undergoing chemotherapy will know what a difference this could make to their lives. Even something simple like a new tablet design could help elderly patients who drop more drugs than they take.

It is widely acknowledged that drug production has lagged behind in the innovation stakes. For creative medicine makers, perhaps the low-hanging fruit is still up for grabs…

Charlotte Barker
Editor

Natalie Privett

Efficiency is something of an obsession for Natalie Privett, whether she is loading the dishwasher in her New York apartment or considering the delivery of health interventions in the developing world. In fact, it was her passion for doing good more effectively and efficiently that led her to pursue her Masters and PhD at Stanford University's department of Management Science and Engineering. Now, as an Assistant Professor of Management and Policy at the Wagner Graduate School of Public Service, her research focuses on operations and supply chain management in the context of global public health, international public service, and nonprofit management.

Natalie summarizes the top ten global supply-chain challenges on page 19.

Lifeng Kang

Lifeng Kang's laboratory focuses on micro-scale technologies for drug delivery and tissue engineering. The potential of the technology is clear – drug carriers can be precisely designed to facilitate the controlled release of drugs into human tissue, while in tissue engineering, Lifeng's team fabricates scaffolds with increased complexity to control the cellular micro-environment and enhance cell–cell, cell–matrix and cell–soluble factor interactions.

On page 38, Lifeng explains how microneedles could have a big impact on drug delivery.

Joshua P. Cohen

Turned off by his family's predilection for the medical profession – following in the footsteps of the family patriarch, all four of his siblings became physicians – Joshua Cohen obtained a degree in economics. "However, as a child growing up I was obviously subconsciously affected by all that health talk around the dinner table, as I specialized in health economics," says Joshua. His research has run the gamut from the ethics of healthcare distribution to personalized medicine to neglected disease drug development.

Joshua is one of six experts helping us to map the biosimilar journey so far on page 22.

Carol Lynch

Carol Lynch is Head of Biopharmaceuticals and Oncology Injectables at Sandoz. In this role, she leads a 2700+ person organization focused on the development, manufacturing and commercialization of biosimilars and oncology injectables. Carol is also responsible for Sandoz's biopharmaceutical contract manufacturing business. "I began my career with Novartis UK in sales and marketing and have since held various roles of increasing responsibility in Global Marketing and Development at Novartis," says Carol.

Sandoz recently won the first biosimilar approval in the US; Carol tells us more on page 10.

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Upfront

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

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way.

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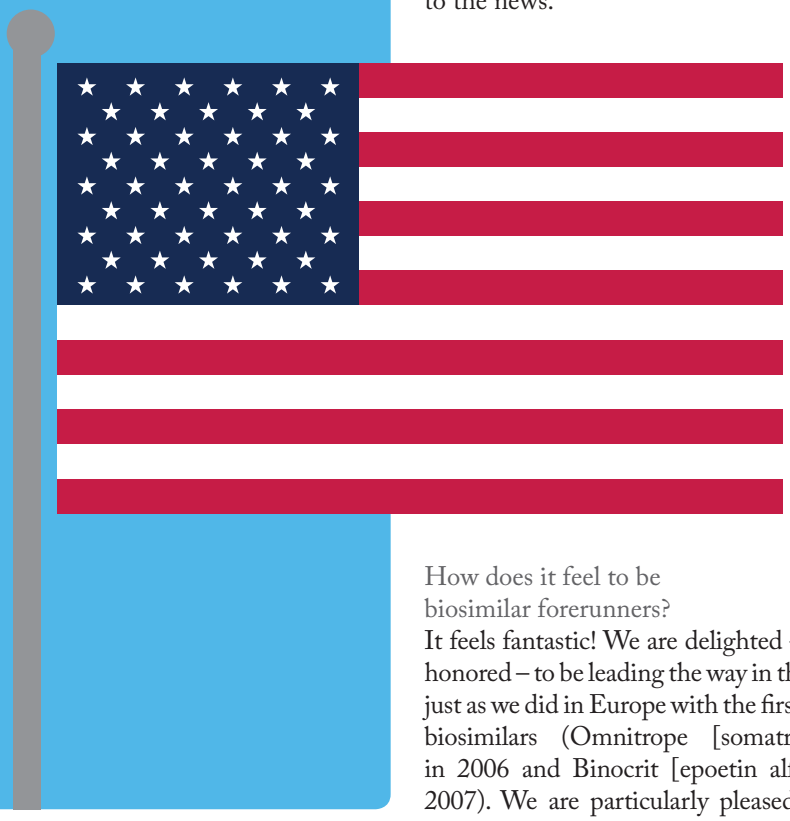


America's Most Wanted: Biosimilars

It's been a long road, but the FDA has finally given the nod to the first official biosimilar in the US

On 6 March 2015, the FDA approved America's first biosimilar – Sandoz's Zarxio (filgrastim-sndz), a biosimilar to Amgen's Neupogen (filgrastim), originally licensed in 1991. Is this the big break biosimilars were looking for in the US market? Read our in-depth analysis on page 22. Here, we catch up with Carol Lynch, Global Head of Biopharmaceuticals & Oncology Injectables at Sandoz, to get her reaction to the news.

How does it feel to be biosimilar forerunners?

It feels fantastic! We are delighted – and honored – to be leading the way in the US just as we did in Europe with the first ever biosimilars (Omnitrope [somatropin] in 2006 and Binocrit [epoetin alfa] in 2007). We are particularly pleased that FDA approved Zarxio for all originator indications. It further reinforces the whole scientific basis of the biosimilar development model, which is about proving similarity to the reference product, rather than 'reinventing the wheel' on safety and efficacy.

But this isn't ultimately about Sandoz and science – it's about improving outcomes for patients, who are now a big step closer to seeing genuine competition in the world's largest biologics market. It's been a long time coming, but there is now a real opportunity to increase overall access to high-quality biologics across the US.

Can you take us through the steps leading up to the approval?

To summarize, lots and lots of detailed hard work over many years! The US biosimilar approval pathway was first signed into law in 2010, five years after the introduction of a regulatory framework for biosimilars in the EU. Since then, there have been two parallel work streams: working with the agency and other stakeholders to support the development of a scientific framework for biosimilar approval under the umbrella of the Biologics Price Competition and Innovation Act, and working directly with the FDA to actually navigate the pathway for the first time with our Zarxio dossier.

It's always difficult to jump in first…

Yes – the chances of failure are greater. With hindsight, the big advantage of going first on this occasion was that we had the opportunity to engage in a meaningful and sustainable dialogue with the agency about the scientific principles of a successful regulatory process, including the best way to leverage the FDA's own substantial experience of evaluating reference product changes over time.

How do you see the US biosimilars market developing?

We believe that customers, physicians and patients in the US will gradually adopt biosimilars. As seen in Europe and in other countries where they are marketed, high-quality biosimilars have increased patient access to important and often life-saving treatments, and have helped generate savings for payers and healthcare systems. Having said that, we do not expect this will be all smooth sailing – after all, this is a new market. Overall, it will be essential to drive public acceptance as this is still a new field in the US.

One of the most immediate issues is the question of non-proprietary names (INNs) for US biosimilars. We still hope that the FDA will follow the tried-and-proven EU approach and assign biosimilars the same INN as their reference products. This approach would ensure scientific consistency, optimize safety and traceability by following the accepted practice of using brand names to identify products, and avoid unnecessary confusion about the nature of biosimilars.

Silent Data

Information from "stalled" drug trials should be published, not tossed aside

Only about one in 10 drugs that enter clinical development will make it past regulators. An analysis from researchers at McGill University has revealed that most trial data for drugs that don't make the grade are never published (1).

The study examined drug trials in three areas – cancer, cardiovascular and neurological diseases – between 2005 and 2009. While 75 percent of clinical trials for approved drugs were published, this falls to 37 percent for drugs that reached Phase III clinical development, but were not approved within 4.5 years.

"We expected to see a lot of nonpublication," says study author Jonathan Kimmelman, "but we were frankly very surprised to discover that so large a fraction of trials for unapproved drugs are never shared with the broader scientific community through publication."

These 'lost' data could be crucial to speeding up drug development, says Kimmelman. "These trials return all sorts of valuable information – including clues about how we might pursue other drug candidates. Researchers often do not appreciate that this information is vital for drug development and contributes to the evidence base of even validated medical practice. They also do not appreciate that nonpublication violates the ethical contract with subjects who participate in such studies."

Recent years have seen some moves towards greater transparency for clinical data, with GlaxoSmithKline agreeing to make detailed clinical data available to researchers on request, and the EU passing new legislation to make reporting of all drug trials compulsory. "I think there are generalized trends towards greater data transparency in drug development," says Kimmelman. "People know this is a problem, but there is so much farther to go."

Kimmelman would like to see all trial results published in full, regardless of whether the results are disappointing. "Academic medical centers and ethics committees should demand that all trial protocols contain a statement committing to publication of results, regardless of whether they are exciting or conclusive. Public funders, too, can demand that all trials recruiting patients at centers receiving money from them are published." *CB*

Reference

1. *A. Hakala et al., "Accessibility Of Trial Reports For Drugs Stalling In Development: A Systematic Assessment Of Registered Trials", BMJ 350, h1116 (2015).*

Rewarding Humanity

An antimalarial medicine-making project wins the inaugural Humanity in Science Award

In 2014, our sister publication – The Analytical Scientist – launched the Humanity in Science Award in collaboration with Phenomenex. The goal? To identify a breakthrough in analytical science that has truly benefited humanity. Now, the winning project has been revealed: a new, cost-effective production method for antimalarials, developed by Peter H. Seeberger and Andreas Seidel-Morgenstern of the Max-Planck Institutes in Potsdam and Magdeburg, respectively.

By coupling flow chemistry with advanced chromatography methods, Seeberger and Seidel-Morgenstern were able to manufacture artemisinin combination therapies (ACTs – the most effective drugs to treat malaria) from plant waste material, air and light. The new process is currently being implemented in a pilot plant in Vietnam and produces an active pharmaceutical ingredient with a purity of greater than 99.5 percent.

Artemisinin was discovered in the 1970's as a promising antimalarial candidate; unfortunately, its molecular complexity has pretty much thwarted attempts at commercial synthesis. Instead, artemisinin is almost exclusively obtained via extraction from the wormwood plant, which is mainly grown in Vietnam. An unstable supply creates a volatile market and, worse still, up to 50 percent of ACTs in Africa and Asia are counterfeit.

"This recognition of our work by an international jury of leading scientists encourages me to continue our work on translating our scientific breakthrough into a production facility. Thereby, those in need of malaria medications will benefit from better access and lower prices, while the dangers of

Left to right: Rich Whitworth (The Analytical Scientist), Andreas Seidel-Morgenstern (Max-Planck Institute, Magdeburg), Alex Gharagozlow (Phenomenex), Peter H. Seeberger (Max-Planck Institute, Potsdam).

fake medications are reduced," said Seeberger, who is director of the Institute of Colloids and Interfaces. "This process is just one example of the power of continuous processes that will revolutionize the production of life-saving medications in developing countries."

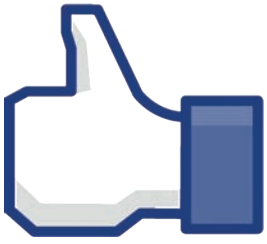
Seidel-Morgenstern, director of the Department of Physical and Chemical Foundation of Process Engineering, continued, "An efficient isolation of a continuously synthesized target component requires the development of advanced separation processes. Considering the reactor effluents generated in Peter's group as pseudo-ternary mixtures (an impurity fraction 1, the target, and an impurity fraction 2), artemisinin and artesunate could be purified with our process using several periodically operated chromatographic columns. The approach can be applied to also solve other challenging separation problems."

Editor of the Analytical Scientist, Rich Whitworth commented, "Though the chemistry and engineering involved in this project are both spectacular and innovative, the impact of the resulting complete process is most spell-binding. Peter highlighted in his acceptance speech that 660,000 people die of malaria each year – and 90 percent of those are children under five. Sadly, it is a disease of poverty – the question is, how can we stand by and do nothing? Peter and Andreas have proven that collaboration and perseverance can provide the ultimate reward – and they are already applying their production philosophy to other global diseases."

Seeberger and Seidel-Morgenstern presented their work at two symposia held at the Pittcon trade show in New Orleans, and received $25,000 in prize money at a gala dinner. We'll be sharing the story behind their work in a future issue of The Medicine Maker. To read more about the winners and runners up, and to keep updated on the 2016 award, visit www.humanityinscienceaward.com. *SS*

Mining Social Media

New technology interprets slang and banter to find out what people really think



Pharma's forays into the brave new world of social media have not always been successful (tmm.txp.to/0214/brave) – but mining social media for information has attracted a lot of attention. But how exactly do you extract meaningful data from online chatter?

"Most systems for extracting adverse drug reactions (ADRs) follow a dictionary-based approach. The main drawback of these systems is that they fail to recognize terms which are not included in the dictionary," wrote Isabel Segura-Bedmar, Ricardo Revert and Paloma Martinezin in a recent paper (1). "In addition, the dictionary-based approach is not able to handle the large number of spelling and grammar errors in social media texts."

To help overcome these issues, the Spanish researchers have developed a system that mines social media and specialized blogs to detect potential ADRs. They have developed a prototype system (2), which uses the framework of Project TrendMiner (a project funded by the European Commission to deliver open-source, real-time methods for mining and summarizing online media) and a linguistic processor based on Daedalus's commercial MeaningCloud technology.

Put simply, the system analyzes comments on social media with natural language processing techniques that can "translate" colloquial descriptions into more structured information. As well as identifying drug names, illnesses and effects, the system registers co-occurrences too; for example, when looking at anti-anxiety drugs, the system can take into account references to the active ingredient, generic name, or commercial brand name, and also pick out references to therapeutic effects and adverse effects.

The researchers envision the technology being used by pharma companies to listen in on what people are saying online about their drugs, or to gather information on suspected ADRs that could be used to supplement existing information sources. *SS*

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Personalized Labels

Just how prevalent is pharmacogenomic information on European drug labels?

Advances in DNA sequencing, and a thirst for biostatistics and bioinformatics… the era of genetics is truly upon us – and increasingly found on our drug labels, with a growing number incorporating pharmacogenomic information (1). According to a group of regulatory experts who recently reviewed the labels of all 517 medicinally products centrally approved in the EU until August 2014, the next challenge is to assess how such information will be used to improve drug therapy and patient outcomes.

"Almost 15 percent of medicine labels examined contained pharmacogenomic information that directly impacts patient treatment. One of the aims of our study was to address how prevalent pharmacogenomics labeling is in Europe at the moment," says Falk Ehmann, lead author of the study and scientific secretariat of the European Medicines Agency's (EMA) Pharmacogenomics Working Party.

Fifteen percent may not sound like a lot, but between 1998 and 2010 there were never more than two new authorized medicines per year that included pharmacogenomic biomarkers. By 2013, there were 10 and the number is growing. But pharmacogenomics brings challenges for all stakeholders, such as translating data from pharmacogenomics studies into clinically relevant and meaningful product information.

"Regulators have the scientific evidence and check that the necessary information is included on a drug label, but this information also has to be used in the right way by healthcare professionals. And that, of course, is another story," adds Ehmann.

Ehmann and his co-authors also looked at where exactly the pharmacogenomics information appears on the drug label, as this clearly has implications for its impact and use. "I think physicians need to be more aware that drug labels may contain a high proportion of genomics in the label. The information needs to be clear and understandable, and we need to ensure that the information is acted upon in practice to really make sure that pharmacogenomics is translated into better patient care," says Ehmann.

Diagnostics are needed to apply pharmacogenomics in the most beneficial way for patients, and as Ehmann points out, there are areas for improvement: "If we have a drug that should only be taken or dosed based on the outcome of a diagnostic test, then the infrastructure has to be there to ensure that you can test correctly. In the US, labels name specific tests that should be used, with consequences on liability. In the EU, centrally approved drug labels do not contain this information guaranteeing that the tests used in practice would have the same performance as those used during clinical trials. I think that a more harmonized approach could improve treatment outcome." Notably, EU legislation on (in-vitro) diagnostic medical devices is currently under review.

In the study, Ehmann and his co-authors write, "Patients' expectations to receive the best individualized or personalized medicine are likely to increase and prescribers need to be trained and reassured on the availability and utility of genomic testing. Payers need to be convinced about the positive cost–benefit ratio of pharmacogenomic-guided healthcare. Affordable companion diagnostics and timely molecular profiling technologies in suitably qualified infrastructures are prerequisites. Current initiatives by the European Commission towards a more harmonized and transparent approach to companion diagnostic regulation will facilitate this trend."

Although challenges lie ahead in the

area of pharmacogenomics, Ehmann says there are positive developments in the pipeline, including at the EMA. Two guidelines on pharmacogenomics during the drug development and the post-authorization phase have recently been drafted, both of which aim to facilitate the integration of pharmacogenomics into drug development and usage for the benefit of patients (2,3). *SS*

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Premature Revelation

FDA scolds company for revealing interim trial results

At the start of March, positive results were disclosed from an interim safety trial of Orexigen Therapeutics' weight-loss pill Contrave that appeared to show that the drug reduced cardiovascular events compared with placebo. The news caused the company's shares to jump by over 50 percent.

But the announcement also caused more than a ripple at the FDA, who are "very disappointed by Orexigen's actions." Ironically, it also further highlights the more typical problem on the other side of the coin: not publishing negative results (see "Silent Data" on page 11).

"In order to protect the integrity of an ongoing trial, preserving confidentiality of the interim results is essential. Disclosure of such results could negatively impact the conduct of the remaining portion of the trial by contributing to unanticipated changes in recruitment and/or retention, treatment administration, other aspects of study conduct, or loss of objectivity in safety event reporting," said the FDA in a statement.

Orexigen was required to perform the safety study regarding potential cardiovascular events by the FDA as a condition for its approval of Contrave back in September. The disclosure came about because Orexigen had applied for a patent based on the interim results and relating to Contrave's potential to reduce cardiovascular events; certain information from the study was required for the filing, which has now been made public.

Even before the study data was leaked, the FDA said that it had already determined that the trial (LIGHT) was not robust enough to satisfy safety requirements. "The FDA required Orexigen to complete a second cardiovascular outcomes trial and that requirement remains in effect," said the agency.

However, what has been seen cannot be unseen and the FDA admits that it is "reassured" by the interim data. It has encouraged the company to complete the study since it could provide complementary or supportive information. How feasible that is now that trial participants have seen the data remains to be seen. An article in Forbes provides the analogy of trying to get toothpaste back into the tube... (1).

In the meantime, the FDA reminds people not to get carried away. "FDA considers these preliminary data far too unreliable to conclude anything further about the cardiovascular safety of Contrave. Furthermore, these data should not be interpreted to suggest that Contrave reduces the risk for cardiovascular events." *SS*

Reference

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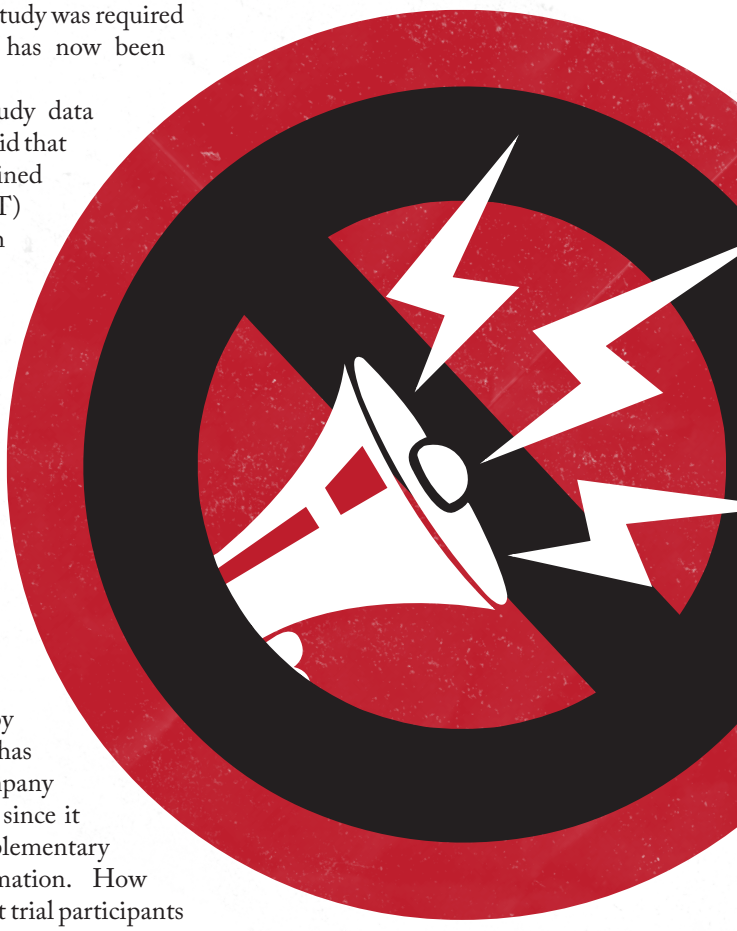

Funding Dementia Discovery

$100 million pledged to kick start investment in new research

Dementia breakthroughs are firmly on the agenda in the UK after the government and J. P. Morgan announced a $100-million Dementia Discovery Fund to help finance new drugs. The Fund is being backed by Alzheimer's Research UK and a number of pharmaceutical companies including Biogen, GlaxoSmithKline (GSK), Johnson & Johnson, Lilly and Pfizer, who have all committed "in principle" to invest in the project.

Medicines in clinical development for dementia and other neurodegenerative diseases have a 95 percent chance of failure – double the failure rate seen in other areas of research. Only three new dementia treatment drugs have been approved in the past 15 years.

"The rise of dementia is fast becoming one of the world's greatest health threats," said Patrick Vallance, GSK's President of Pharmaceutical R&D, in a recent press release. "This Fund is a really smart way of bringing together great minds and communally increasing our understanding of dementia. It's also a good way of sharing the financial risk associated with conducting drug discovery research in this field."

The investment is being structured as a typical venture capitalist fund, but is apparently the first to focus solely on dementia research. Promising early-stage research programs to invest in will be scoured from across the globe, with a scientific advisory board of representatives from each of the partner organizations providing input during the selection process. Any proceeds from the eventual license or sale of programs will be returned to the Fund and its investors.

In a blog post, Lilly's global brand development leader for Alzheimer's disease added, "When Lilly scientists began researching Alzheimer's disease more than 26 years ago, I imagine they expected we would have made more progress by 2015. As a field, we have made progress, and continue to do so today. But now is the time to take our learnings across the finish line to confront one of the largest global health challenges in developed and developing nations alike."

The Fund was announced by the UK's health secretary, Jeremy Hunt, at the World Health Organization's First Ministerial Conference on Global Action Against Dementia. *SS*

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In My View

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

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

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Small Pharma

Legislation on pediatric medicines is sowing the seeds for a better future, but we must maintain momentum if children are to get the best possible care.

By Helen Sammons, Clinical Associate Professor, Faculty of Medicine & Health Sciences, University of Nottingham, UK.

In 2007, new legislation compelled drugmakers to test new products in pediatric populations – a big step forward for children. Doctors should never again be put in the position of having no information on whether a new medicine is safe or effective for younger patients. Unfortunately, there is a catch. The vast majority of drugs being prescribed for children are not new – they are old drugs often used off label.

Off label doesn't always mean no evidence – take amoxicillin. Until recently, the label for amoxicillin meant that most children under the age of 10 were being treated off label. In the UK at least, it was common use and we had precise guidelines on dosages. The risks for children in this instance were very small.

However, there are other medicines, much more rarely used in children, where very little information exists. In those cases, we base the off-label doses on anecdotal evidence or on the theory of a group of experienced clinicians. But with no pharmacokinetic studies, we often make an educated guess at best. For medicines like salbutamol, when used intravenously in acute asthma, there is a large variation in practice in terms of speed of administration and exact dosage. Given that the drug is typically given to very sick children, it raises some concerns.

Dosage is not the only issue. We also need formulations that are appropriate for all age groups. A lot of medicines don't have a palatable oral formulation, so it can be a real challenge to get a child to take them. Or we have a tablet for adults but a child's dose is a tenth of that, so we're having to dissolve the tablet, dilute it and then take a tenth of the dose out. A small error in this process could have serious consequences.

Historically, drug companies have (understandably) shied away from pediatric trials. Carrying out clinical trials in children is challenging and by their nature all clinical trials carry some level of risk. However, research and evidence-based practice should now be considered part of everyday care, especially in children. The pediatric population is one of the very few where consent is not given by the person taking part in the study, so issues of assent and consent do require careful handling. Older children are encouraged to participate in decision-making but definitive advice is difficult since there is such a wide range in children's ability to understand risk. Even adults often find it hard to conceptualize a 1-in-1000 risk versus a 1-in-100,000 risk, so finding ways to clearly communicate risk to children is vital.

There are practical issues too – something that both industry and academic researchers sometimes fail to consider. I sit on an ethics committee for pediatric studies and some of the proposals we receive have clearly been copied word for word from the adult protocol. That might include taking 10 blood samples in the first 24 hours, which could be very distressing and potentially harmful to young children. Though it may make trials more expensive, there are ways around this – for example taking research samples only when clinical samples are

"Pediatricians are in a better position than ever before when it comes to medicines hitting the market."

being taken, scavenging samples from clinical practice and using a cannula for repeated samples. Computer modeling can be used to pull together samples from many different children, so that each child only has to give a few.

Spurred on by the 2007 legislation, the pharma industry has made big steps forward in planning and conducting pediatric studies for new drugs. I believe pediatricians are in a better position than ever before when it comes to medicines hitting the market today. But while the same legislation also provided a number of incentives to develop off-patent drugs for pediatric indications, only one drug has come though this pathway so far. It's evident that the current incentives are not capturing pharma's interest, and need to be reviewed. There are a number of pediatric and neonatal academic networks conducting studies on off-patent drugs, but we need all stakeholders, including pharma, on board if we're to keep the momentum going for children's medicines.

The real proof of progress comes down to a simple question: if your child comes into hospital today, how likely are they to be given an unlicensed or off-label medicine? Unless we can update older drug product labels with solid pediatric trial data, the answer will remain "likely".

Supplying Health to the Whole World

New and improved drugs are released every year to tackle global health needs – and many pharma companies have initiatives to supply those drugs to the developing world. Unfortunately, efforts are wasted without proper supply chain management. Here, we prioritize the top ten challenges.

By Natalie Privett, Assistant Professor of Management and Policy, Robert F. Wagner Graduate School of Public Service, New York University, USA.

Medical research and development continues to make progress, turning once impossible goals into achievable possibilities. Yet global health success continues to elude us, resulting in an ever-widening gap between objectives and on-the-ground realities. It's a gap that cannot be filled by pharmaceutical R&D alone. In many cases, the technology, medicine and treatments exist to improve global health, just not in the right place at the right time. And that's where effective supply chain management comes in.

To better understand the challenges of global health pharmaceutical delivery (GHPD) supply chains, we undertook interviews and surveys of professionals working in the field. By examining the results of our research, we were able to identify and prioritize the top ten issues in GHPD supply chains:

1. Lack of coordination. The current system of health delivery is siloed, fragmented, and ultimately uncoordinated. Such fissures follow NGO/public/private designation, product types, projects, and funding entities. This complexity makes management and distribution difficult.
2. Inventory management. In GHPD supply chains, this is a complex challenge, especially considering the lack of information and unique contextual challenges. More specifically, such issues involve inventory inaccuracies, quantification, uninformed push systems, inventory allocation, product availability management, and appropriate IT systems.
3. Demand information. The absent and/or aggregated nature of demand information creates serious consequences in procurement and management decisions. There is rarely access to any consumption data and, in fact, most stages of in-country supply chains only know demand in terms of their received orders.
4. Human resource (HR) dependency. HR limitations are increasingly recognized as a key bottleneck in developing countries. The lack of qualified personnel and appropriate training leads to high workloads and low performance while leaving key duties unattended. In fact, there are often insufficient trained staff to perform even basic supply chain

duties. Logistics-specific positions are rare, instead medical personnel are often responsible for making supply chain calculations and decisions.

5. Order management. Problems in order management (planning, ordering, and follow-up) are heavily linked to a lack of reliable demand information and shipment visibility, and are only exacerbated by long lead times. It is generally unknown if there is enough product in the system or at the central medical stores. Consequently, ordering and planning are based on assumptions and experience.
6. Shortage avoidance. There are a few principal strategies employed to avoid and react to shortages; namely frequent ordering, frequent replenishment, large buffer stocks, and expensive emergency ordering.
7. Expiration. A major source of product wastage at every stage of in-country supply chains, expiration comes with significant consequences, including financial losses, safe disposal efforts, and lack of stock elsewhere. Causes include medicine selection, forecasting, demand quantification, procurement, warehouse management, inventory management, employee training, and use. It is not uncommon to find expired medicines being used unknowingly to fulfill an order.
8. Warehouse management. Many issues center on poor storage conditions, organization, procedures, capacity, and shared space management, which in turn stem from the lack of proper equipment, electricity, and training. Such poor organization can often lead to issues with capacity, inventory policy adherence, discrepancies, and control.
9. Temperature control. Another major cause of wastage is temperature failure of pharmaceutical products from exposure to hot or freezing temperatures in transport and/or storage, resulting in large monetary loss and high risk to patients. Throughout the supply chain, temperature deviation most typically occurs during in-transit delays or at the lowest supply chain levels, due to inadequate oversight.
10. Shipment visibility. Once a shipment leaves the manufacturer, it is increasingly difficult to track and trace in the supply chain. Shipments typically become invisible before ever reaching their final destination. Accordingly, it is often unknown if products make it to intermediate warehouses, health facilities, or final recipients. Similarly, recipients typically have no information on when an order will arrive.

Clearly, there are some major obstacles to overcome. So where should we begin? In analyzing these top ten GHPD supply chain issues, it quickly becomes clear that four issues drive the entire list: lack of coordination, insufficient demand information, shipment visibility and, most notably, development of human resources (including expertise, training, and personnel capacity). These are the issues we need to tackle first if we are to get medicines to those who need them and allow everyone to benefit from breakthroughs in pharma R&D.

Kicking Batch Habits

The industry has been dipping its toe into the water of continuous manufacturing for years. Are we finally ready to dive in?

By Richard Fazackerley, Technical Director, Finished Dose, Aesica Formulation Development, Nottingham, UK.

Many facilities across the world are still strongly wedded to a batch process philosophy. To be fair, it has served the industry well, especially as it suited current technology. Most of the operating principles for key equipment have not fundamentally changed since their original inception, despite additional features and PC controllers.

Historically, there has been reluctance to change the model – if increased capacity was required, you simply made more or larger batches. But this philosophy has led to a significant amount of work in progress and required forward cover in the supply chain to avoid the risk of stock out. Indeed, the industry been a laggard in moving away from familiar processes and technologies. An absence of economic drivers and perceived regulatory barriers

"Change is most definitely in the wind."

has added to the disinterest in change. Moreover, many companies have such large estates of legacy technology that changing was seen as an extremely challenging task.

However, in recent years pharma has seen a marked shift away from the old culture of risk aversion and is calling out for more efficient economic models. Gone are the days of "if it ain't broke, don't fix it." Change is most definitely in the wind and we're starting to see a move away from traditional attitudes and towards the new reality of continuous manufacturing. The principles of continuous manufacturing have been around for decades but it is only now that the technology has come of age that many larger companies are starting to adopt them. Many of the perceived external barriers have gone. There is a positive regulatory environment, with agencies supporting the adoption of this new disruptive technology. Plus, the technology itself has now reached a point where it is both available and commercially viable.

The global pressures of the 21st Century will not relent. Quality and compliance will remain an important focus for all manufacturing industries, but performance will be the key to ongoing survival in light of ever-increasing cost pressures from payers. Maximizing efficiency is essential in today's world as margins erode, R&D productivity struggles, and payers challenge each new product introduction.

Personalized medicine will result in more targeted products, resulting in lower demand for individual drugs and undermining the current system of batch processing and supply chain practices across the industry. It's clear that continuous manufacturing is much better positioned to meet today's – and tomorrow's – demands.

Another area where traditional batch processing falls down is the ability to develop new products as quickly and efficiently as possible, particularly in the earlier stages of development where there are potential constraints on API supply and a high risk of failure. Continuous manufacturing allows companies to develop and explore the process with minimal amounts of API using a combination of small-scale, advanced process control systems and integrated process analytical technology. In other words, you get as much information as possible for as small an API investment as possible, as quickly as possible.

"It's clear that continuous manufacturing is much better positioned to meet today's – and tomorrow's – demands."

With all of these benefits, it's no wonder there is so much activity around continuous manufacturing from both pharmaceutical companies and equipment suppliers – and not just for development and manufacturing. Continuous manufacturing technology offers a way to fundamentally change supply chain models by moving away from a large fixed asset base to a more mobile capability where the factory can be moved to where the demand is.

We are on the cusp of a revolution – are you ready?


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The Big Break for Biosimilars?

The first US biosimilar has been pocketed and the game is on. We bring six experts to the table to discuss the impact on industry dynamics.

By Stephanie Sutton

Back in April 2006, the first biosimilar in the European Union received marketing authorization – Omnitrope, developed by Sandoz as a biosimilar to Pfizer's Genotropin (somatropin). At the time, there was no sign of a biosimilars pathway in the US, but everyone anticipated that such products would eventually jump the Atlantic. 'Eventually' was nearly nine years later when on March 6, 2015, the FDA officially approved the first US biosimilar – Zarxio (filgrastim-sndz) from Sandoz (1), which is approved for the same indications as Amgen's Neupogen (filgrastim). Is the US biosimilars market now open for business and ready to start churning out a whole raft of new products? That really depends on who you speak to...

"There is probably one question that many will be asking – particularly those unfamiliar with US law: why has it taken so long for the US to open its doors to biosimilars?"

There's no doubt that Zarxio is a major milestone for biosimilars, but while some groups are hailing it as a triumph, others have highlighted their concerns (see "Mixed Reactions"), particularly as the FDA has not yet issued guidance on some aspects of biosimilars, including interchangeability and naming. Nor has it finalized other drafts of biosimilar guidance. Sandoz also has a number of hurdles to overcome before Zarxio becomes available on the US market. Firstly, there's that lawsuit from Amgen to deal with.

"As per requirements in the US Biologics Price Competition and Innovation Act of 2009 (BPCIA), biosimilar developers must provide originator companies with six months' notice before launching," explains Duncan Emerton, who runs The Biosimilarz Blog (www.biosimilarz.com) and is senior director, syndicated insights & analysis, at FirstWord. "Sandoz argues that it has provided this notice, but Amgen says that notice can only be given on the day of FDA approval. Amgen and Sandoz are currently locked in litigation related to this issue, and Sandoz has committed not to launch until April 10, 2015, or a decision by the court, whichever is earlier."

The court ruled in Sandoz's favor on March 19, but Amgen says it will appeal. We won't go into the finer points of the so-called 'patent dance' here (read more at tmm.txp.to/0314/patent-dance) – suffice to say, the path ahead is by no means clear.

Late to the table

There is probably one question that many will be asking – particularly those unfamiliar with US law: why has it taken so long for the US to open its doors to biosimilars? Our timeline shows that the US is well behind Europe, Japan, South Korea and other countries, and in fact, the whole process has taken so long that there is a misconception that some biosimilars are already available.

"Prior to this approval, we had a couple of products on the US market that are considered biosimilars by many analysts. But, they weren't approved in accordance with a formal biosimilars pathway," says Joshua Cohen, research associate professor at Tufts Center for the Study of Drug Development. As an example, Emerton adds, "Many people actually believe that Novartis's Extavia (interferon-beta-1b), a treatment for multiple sclerosis, is a biosimilar of Bayer's Betaseron. Betaseron and Extavia are just different brand names for the same active ingredient, interferon-beta-1b. Moreover, Extavia wasn't approved via the US's 351(k) biosimilar pathway. It's not a biosimilar."

"There are a couple of reasons why the US is behind Europe," explains Mari Serebrov, an analyst with Thomson Reuters and author of the report, 'Biosimilars: A Global Perspective of a New Market: Opportunities, Threats and Critical Strategies 2014' (2). "Many of the biologics targeted for biosimilars in the EU had longer patent protection in the US. Also, US laws are different. The FDA didn't have the authority to develop a biosimilars pathway at all until 2010 when congress passed the BPCIA. Before then, the FDA couldn't do anything. And once it was passed the FDA had to work out how to take this legal statute and turn it into a pathway."

Alex Waldron, vice president of commercial operations at EPIRUS Biopharmaceuticals, which focuses on the development and commercialization of biosimilar monoclonal antibodies (mAbs), adds, "Based on legislation that had to be overcome in the US, there were always going to be particular problems. I think nine years was probably a little bit longer than a lot of people were thinking it would take. Everyone is just breathing a collective sigh of relief on the fact that there is now a clearer path of acceptance for these products to make it into the US market."

And now the first approval is in, it is almost certain that others will follow. Cohen expects to see other biosimilars being approved through the US's 351(k) biosimilar pathway in due time. Other biosimilars are already under review. "Many consider Zarxio and biosimilars of Neulasta (pegfilgrastim) to be relatively easy cases," he says. "There is a lot of clinical experience with these products overseas (so fewer safety and efficacy concerns) and physicians will be more familiar with

them. But I think that some other biosimilars, such as mAbs, will face more of an uphill battle."

MAbs are far larger and more molecularly complex than other biological medicines and their clinical properties can be affected by many different factors. Assessing similarity between a biosimilar mAb and its reference product is challenging, but not impossible as biosimilar mAbs have now been approved in the EU and in other countries. Since the US biosimilar pathway is in its early days, it remains to be seen whether FDA regulators will warm to the complexities of biosimilar mAbs. So far, only one biosimilar mAb has been filed with FDA for approval – Celltrion's Remsima (infliximab), which is a biosimilar of Johnson & Johnson and Merck & Co's Remicade. Remsima has already been approved in the EU, Japan and Canada, and was due for an FDA advisory committee review in March, but this has been delayed "due to information requests pending with the sponsor of the application" (3).

Global state of play

The first official regulatory framework for biosimilars was created by the European Medicines Agency (EMA) in 2005 with the publication of CHMP/437/04 – an overarching guideline defining the key principles of developing a biosimilar. Generally speaking, the biosimilar concept is applicable to any biological medicine that can be thoroughly characterized. Originally, applicants had to conduct studies to demonstrate that their biosimilar was similar in terms of quality, safety and efficacy to a reference medicine authorized in the European Economic Area (EEA). However, in October 2014 the guideline was revised to introduce the possibility of comparing a biosimilar with a reference product approved outside of the EEA, although it must have been approved by a regulatory authority with "similar rigorous scientific and regulatory standards to those of EMA" (4).

The revision comes into force on April 30, 2015, and also includes other amendments regarding the terminology, principles, and requirements for the posology, route of administration and formulation of biosimilars, based on the experience accumulated since 2005. Biosimilars were also covered in previous legislations (Directive 2001/83/EC and Directive 2004/27/EC), and further quality, clinical and product-class specific guidelines have also been introduced in subsequent years.

The evolution of regulatory guidance – and the fact that it has been revised so recently – illustrates the youth of the biosimilar market. Nevertheless, biosimilars already have an impressive reach across the globe, with many countries having established some form of regulatory pathway, although like Europe many have also added additional guidelines or made amendments over the years.

Timeline

2004 – EMA begins forming world's first official biosimilar pathway

April 2006 – EMA authorizes its first biosimilars

August 2007 – EMA authorizes its first biosimilar epoetin

August 2008 – Malaysia introduces biosimilar pathway

September 2008 – EMA authorizes its first biosimilar filgrastim

March 2009 – Japan forms biosimilar pathway

June 2009 – Japan approves its first biosimilar

July 2009 – South Korea introduces biosimilar pathway

March 2010 – BPCI Act passed in US

March 2010 – Canada introduces biosimilar pathway

September 2010 – Australia introduces its first official biosimilar

July 2012 – World's first biosimilar mAb approved in South Korea

September 2012 – India introduces official biosimilar path

June 2013 – EMA authorizes its first biosimilar mAbs

July 2014 – FDA accepts first biosimilar application

September 2014 – World's first biosimilar insulin authorized by EMA

March 2015 – First US biosimilar approved

Mixed Reactions

Here's what major organizations in the US had to say about the approval.

Pharmaceutical Research and Manufacturers of America (PhRMA):
"PhRMA supports a science-based, transparent implementation of the BPCIA biosimilars pathway. In order to meet these goals, we urge the FDA to promptly issue appropriate guidances on key outstanding issues including establishing interchangeability, labeling, and naming of biosimilars products, and to finalize outstanding guidances." (7)

Biotechnology Industry Organization (BIO):
"It is unfortunate that the lack of publicly available naming guidance resulted in FDA's assignment of a 'placeholder' name for the approved biosimilar. We continue to urge the Administration to issue guidance promptly on this crucial matter, as well as on other biosimilar-related issues." (8)

Alliance for Safe Biologic Medicines
"We are particularly encouraged by the FDA's recognition that a biosimilar is a different medication, distinct from its reference product, and that the distinguishable name given to this first biosimilar (filgrastim-sndz) allows healthcare providers to clearly differentiate it from the innovator medicine… One area of concern, however, is in the labeling of Zarxio – the labeling of Zarxio does not state that it is not interchangeable with its reference product, what data were supplied to earn approval is not specified, nor whether or not the product was studied in all the indications for which it was approved." (9)

American Autoimmune Related Diseases Association
"On behalf of the 50 million Americans living with autoimmune disease (AD), AARDA is concerned that the FDA has approved the first US biosimilar drug without first having published any final standards. The FDA has yet to issue final guidance on a range of issues that will impact patient safety, including interchangeability, naming and indication extrapolation." (10)

"Europe obviously leads the way and has served as a role model for many other countries – mainly because it was the first one out there, plus it's well thought out," says Serebrov. "Some countries, like Australia, have adopted the EU model wholesale – when Europe gets a new guideline, Australia adopts it. Other countries take pieces of the European model and tweak it for their market, such as Japan. Once the US model comes out, I think we may see some followers there too. The US can't follow the European model completely because there are specific criteria that the FDA has to include."

One of the newest countries to introduce guidelines for biosimilars is China. Draft guidelines were released in November 2014 and finalized in March 2015 (5). Previously, the country had been approving copies for years without similarity studies. "A lot of people are excited about what's going to happen in China. A lot of biologics haven't been able to get a foothold in the country because of price. With a true Chinese biosimilar pathway, the industry is expecting a higher standard and also waiting anxiously to see what will happen in terms of exclusivity and patent protection," says Serebrov. "Brazil is another country of great interest. And some EU and US companies are trying to increase access in Africa and the Middle East through the promise of biologics at affordable prices." Realizing 'global health' is a major benefit of clear biosimilar guidance, and many companies have recognized the potential of new markets. Serebrov adds, "Companies are making innovations in manufacturing processes and development to really lower the price of biosimilars. It's exciting that we might finally be able to share the hope of these drugs with a larger percentage of people."

India is another market to watch. "There is potential for huge growth in India," says Waldron. "One of the reasons EPIRUS launched into the Indian market is because there are relatively low usage levels of biologics, primarily due to the fact that India is a private-pay market. Take rituximab; I believe that when Dr Reddy's introduced Reditux [a non-comparable biologic of rituximab], it increased the use of rituximab by somewhere between six- and ten-fold over a 5–8 year period. The reason Reditux was able to substantially grow the Indian market was largely driven by its much lower price point – patients who could not have afforded Roche's Mabthera now had access to treatment."

As a non-comparable biologic of rituximab, Reditux is not a biosimilar. It was approved in India in 2007 on the basis of a 17-patient open-label study and was not compared to Mabthera. Before India introduced its biosimilars pathway in 2012, several copies of innovator biologics were approved on a case-by-case basis. A number of products have now passed through India's official biosimilars pathway, although it is difficult to know if all of these were developed in accordance with the pathway's standards since many will have been in development long before 2012 (2).

Top Six Biosimilar Misconceptions

... according to Duncan Emerton

1. Biosimilars aren't as safe as the reference products
2. The quality of biosimilar products is lower compared to the reference products
3. Biosimilar companies aren't able to undercut branded biopharma companies on price
4. Biosimilar companies don't have the capacity to make enough product
5. Biologics are too complex to copy
6. Products approved without head-to-head comparison with the reference product, including non-clinical and clinical studies, are biosimilars

Gain more insight from Duncan in the Biosimilar Index: Tracking the Biosimilar Development Landscape (11).

Similar... but different

Many companies are jumping onto the biosimilars bandwagon, but hold on Charlie Bucket – it's no golden ticket. Biosimilars are inherently complex and tiny changes in development can have major implications. As a result, they remain expensive and time-consuming to develop.

"Small-molecule generics are in some ways a bit of a photocopying exercise. Biosimilars are much more difficult. You have to go through exhaustive cell-line characterization, pharmacokinetic work and a clinical study," says Waldron. "When bringing an innovator molecule to market, drugs are powered to hit a predesignated endpoint in the Phase III clinical trial. Hitting that endpoint is extremely difficult – the challenge for biosimilars is that not only do you have to hit the same clinical Phase III primary endpoints, but you must also show 'similar' results to the innovator in terms of pharmacokinetics and pharmacodynamics. Some regulations allow for slight improvements in some areas but if you are too much better then you become a biobetter, which leads to more regulatory hurdles. And obviously you can't do worse because then you would be clinically ineffective!"

To date, just 21 biosimilars have been approved in Europe (although two have now been withdrawn) – seven of these have been approved since 2013, including the first mAb biosimilars – Hospira's Inflectra and Celltrion's Remsima (both biosimilars of infliximab). Other biosimilars are also under review by the EMA at the moment. But Cohen says, "Biosimilars in Europe have not really gained the traction some had anticipated. Some physicians are reluctant to prescribe a product that is "similar" and "not the same" – there are issues with awareness and familiarity among providers and patients, and a (false) perception that biosimilars might not be as safe."

Emerton adds, "The biggest challenge for biosimilars is creating the right economic environment, so that all of the key stakeholders involved in prescribing, using and paying for biosimilars are incentivized to use them."

Biosimilars do not offer the same cost savings as generics. Typically, biosimilars offer price reductions of 20 to 30 percent depending on the market, whereas generics can offer 70 to 90 percent. "In some markets, biosimilars are much cheaper but in others they can be almost the same price as an innovator's drug. Some innovators have also dropped their prices to match the biosimilar. With this model, you have a biosimilar that is new to the market, having to build a brand, recoup the cost of development, and competing head to head with a well-known innovator that's been in the market for years," says Serebrov.

Although that's potentially bad news for new companies launching biosimilars and looking for greater market share, there is an upside for patients: lower priced drugs. Competition means that innovators can't just arbitrarily raise the price every year.

"Biosimilars are targeting the blockbuster biologics – the cash cows," says Serebrov, "and this is bringing prices down and expanding use of biological medicines to countries and patients that previously couldn't afford them."

The American game

Although the US is late to the biosimilars party, it does have one advantage: it has been able to benefit from all the lessons learned over the past nine years. Emerton, however, believes that growth in the US will still be slow initially. "More in-market clinical data has been generated in markets outside of the US and I believe that other markets are more open to the biosimilars

Race to the Top

By Erwin A. Blackstone and Joseph P. Fuhr Jr.

Economics is based on incentives. People and businesses respond to incentives and when it comes to biosimilars, the incentives seem to be aligning for considerable competition. Although each individual biologic market is unique, some general characteristics exist concerning biosimilar markets. Many billion-dollar biologics are losing or will soon lose patent protection – and the impending opening of the US market, the largest biologic market, will provide additional incentives for biosimilar entry. Furthermore, the fact that biosimilars are often developed by large pharma companies that can withstand the uncertainty and competitive pressures of the market will ensure a competitive race to the top (or bottom).

On the other hand, biosimilar entry entails substantial risk. R&D costs are high and incurred long before the product is marketed. There are also manufacturing, promotional, legal and regulatory costs. In Europe, biosimilars have had modest (or mixed) success because there has been little financial incentive for stakeholders to opt for lower priced biosimilar products. The German government, however, has an incentive system that encourages the use of biosimilars, which has increased uptake. Interestingly, the EU generic market is not as strong as the US, so it's difficult to predict outcomes. Financial incentives, particularly through pricing, will determine the development of the biosimilar market. In any event, the high price of biologics means that pricing pressures are likely to become stronger.

It also is important to note that the primary policy objective of biosimilars is to increase consumer welfare. Thus, the market share of biosimilars is not a fully informative metric. The relevant welfare benchmark is not the price of the biosimilar relative to the originator, but the comparison price before competition.

Whatever happens, patients should be the final winners, with lower prices and greater access to lifesaving drugs.

Erwin A. Blackstone is professor of economics at Temple University. Joseph P. Fuhr Jr. is professor of economics at Widener University.

concept. That's not to say that the US won't get there eventually, but at the moment I don't see physicians embracing biosimilars in the US," he says. "Payers, however, are a different story. I'm currently writing a report on US payer perceptions and views on biosimilars, and what's come across quite strongly is that payers can't wait to get their hands on biosimilars. They see them as a much-needed safety valve that they can use to ease the pressure in other areas of the health system."

Meanwhile, Serebrov thinks that the US market may actually open up a lot faster. Although no guidance has yet been issued by FDA on the matter, she believes that interchangeability will accelerate market acceptance. To be approved as an interchangeable in the US, the FDA has said a biosimilar must be able to demonstrate the same clinical effect in any given patient. Biosimilars not approved as interchangeables would have to be specifically prescribed by name. Some US states have already enacted biosimilar substitution legislation that will allow pharmacies to automatically substitute an FDA-approved interchangeable for a prescribed innovator.

"If automatic substitution is allowed, we could see faster uptake and biosimilar manufacturers wouldn't have to promote and market those products that are approved as interchangeables," says Serebrov. "Automatic is the key word here; there are other countries that allow substitution at the beginning of treatment but once the patient starts on a treatment they tend not to be switched to another version, whether it is innovative or not. In the US – although we don't have the guidance yet – I think that we could potentially have a more interchangeable system where a patient can be switched back and forth more easily between an interchangeable and the innovator."

But with interchangeability comes concerns. What happens when there is more than one interchangeable on the market for a given reference product? "There are concerns about how realistic interchangeability is. Will your biosimilar truly be interchangeable with the competition? Or will you have to do switching trials with every single one of them on the market? We won't know until the FDA guidance comes out," says Serebrov.

"Payers will likely place biosimilars in lower cost-sharing tiers on the formulary to try to boost their use and reap cost savings. They may sign rebate deals with biosimilar manufacturers that aim to increase their market share, but ultimately, payers will want to have therapeutic interchangeability established, not just biosimilarity. This will be a major challenge, as therapeutic interchangeability is harder to establish than biosimilarity," adds Cohen.

The naming of biosimilars is a hot topic in the US, with pharmacovigilance issues raising particular concerns, as explored in a previous issue of The Medicine Maker (6). "Should a biosimilar have the same International Nonproprietary Name (INN) as the reference product?" asks Emerton. "In the case of Zarxio, the FDA

has given it the temporary INN of 'filgrastim-sndz'. By going with this temporary naming convention, the FDA has created some confusion and raised the specter that distinguishable names for all biosimilars will become the norm in the US. As I see it, this is a victory for the originator companies, which have lobbied against the use of identical INNs for biosimilars. It remains to be seen if the FDA allows interchangeable biosimilars to have the same INN as the brand, so as to facilitate substitution. Much uncertainty still remains."

The naming issue isn't limited to the US. "In Japan, they name biosimilars Biosimilar 1, Biosimilar 2 and Biosimilar 3. And yet there could be two products marketed as Biosimilar 1. For instance, partners Fuji Pharma and Mochida Pharmaceutical each market Filgrastim Biosimilar 1, while partners Nippon Kayaku and Teva Pharma each market Filgrastim Biosimilar 2. I don't know how that will play out in the long term!" says Serebrov.

Waldron also highlights another hurdle for biosimilar medicine makers. "I think that one of the biggest challenges for biosimilar manufacturers looking to break into the US is the legal landscape in terms of intellectual property. It's fantastic to have large companies like Sandoz and Celltrion blazing a trail because they will be a solid bellwether for how the patent situation is going to evolve," he says. "In the US, the major patent is well publicized, but there is no mechanism at this point to firmly establish all patents associated with biologics. I expect to see pop-up or surprise patents coming up last minute to challenge some of these molecules coming in."

Similarity breeds contempt?

Much will be learned about the potential future of US biosimilars in the coming months as Sandoz and Amgen settle their arguments and Zarxio enters the market. "Who will be the market leaders in the long run – large or small companies?" asks Serebrov. "Sandoz is the pioneer and has the largest share of the global biosimilars market but then you also have Hospira and Teva. And then there's Celltrion with its biosimilar mAbs. There are so many other companies that are close to launching their first biosimilar. Some of them are pharma giants and some are start-ups, and they're all following different models so it will be interesting to see which ones are still there ten years from now. We're also seeing a lot of contract manufacturing companies jumping into the space. In emerging markets, where they haven't previously had a market for biologics, they're looking to biosimilars to jumpstart the industry; Brazil, Russia, and South Korea are all getting government help because biosimilars are seen as a big driver for the economy."

Waldron agrees that smaller companies are in with a fighting chance. "Large biotechs and pharma companies are looking to leverage their legacy of producing drugs. They're looking to put their giant global key into the lock of biosimilars and assume that it's going to work in exactly the same way that it's worked with every other biologic that they have brought to market. For biosimilars to become really profitable – and to get them to market quickly – you have to use today's technologies and you have to be flexible and able to approach each region on a market-by-market basis. Smaller, newer companies don't have a legacy, which means that they are always looking forward at new, innovative business models, never backwards."

But no matter the size, all companies looking for a piece of the biosimilars pie must be prepared for the long haul. Uptake in Europe shows that growth can be slow, and even if the US does embrace biosimilars, it's still very early days. Sererbov says, "Companies won't be able to grab a huge market share within a year or two. And there's a lot of educating to be done to tell patients what a biosimilar is and why it's safe."

It's not just the companies making biosimilars who will have to adapt as the market expands – Serebrov believes that the rise of biosimilars may be a shot in the arm for innovator companies too: "This will really push innovators to do more serious innovation, not just a tweak for a longer acting drug – they will truly strive for innovation. And that's a challenge for the biosimilars producers, who will need to find new ways to prove why you should buy their product. Does anyone want to take yesterday's drug when there is something new out there?"

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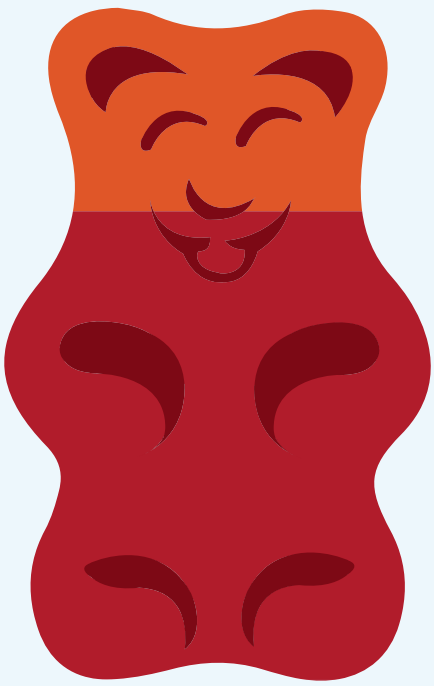
A Sweet Revolution

Glycan analysis poses major challenges for the biopharma industry; how can new technology lighten the load?

About 70 percent of preclinical and clinical candidate biopharmaceuticals are glycoproteins, with carbohydrate structures attached to amino acids in the protein. These glycan groups can have a huge impact on safety and efficacy, so accurate and efficient analysis of glycans is crucial.

In this two-part series, we'll be talking to the scientists who are applying cutting-edge analytical science to unravel the complex role of glycans in biotherapeutics.



Glycoproteins make up 70% of candidate biopharmaceuticals

Pick 'n' Mix Glycobiology

Jonathan Bones, Principal Investigator at Ireland's National Institute for Bioprocessing Research and Training (NIBRT), uses the latest technology to help biopharma overcome challenges in glycan analysis. Here, he shares his work and divulges how using several complementary techniques is the key to (sweet) success.

What's the mission of NIBRT?

At NIBRT, we work in close collaboration with industry partners to solve some of the key problems they face. The mix of fundamental science and real-world problems makes this a very stimulating environment; we're applying the latest analytical science to as many aspects of bioprocessing as we can. My lab has a major focus on glycan analysis.

Why is glycan analysis so important for the biopharma industry?

It's a regulatory requirement to provide detailed characterization of the glycan structures attached to therapeutic proteins; glycans can modify both the efficacy and safety of the molecule. For example, glycans present in the Fc region of a monoclonal antibody can modulate the interactions with Fc receptors in the immune system, which affects efficacy. In terms of safety, when proteins are expressed in non-human systems, such as CHO cells, you run the risk of non-human epitopes on glycan groups, which could elicit an immune reaction in the patient.

New technology allows us to make informed choices throughout the bioprocess, from selecting a cell line, to process testing, to the final product.

How are glycans analyzed?

A typical approach would be to detach the sugars from the protein and attach a fluorescent tag, then use high-performance liquid chromatography (HPLC)/ultra-HPLC or capillary electrophoresis (CE) to separate the fragments by size and polarity. Once you've separated the glycans, you usually want to characterize their structure. One method is exoglycosidase digestion, which uses enzymes to break down the sugars in a very specific and sequential manner. By looking at what you have removed and what remains, you can fit the puzzle pieces together to work out the structure. The other key technology is mass spectrometry (MS), typically used in combination with LC or CE to give you the full picture.

You make it sound relatively straightforward…

Not exactly! One of the biggest challenges is the complexity of glycans. The sequence of a protein is linear – you can visualize it as a string of beads – and we can use enzymes to break apart the beads for analysis in a predictable manner. Glycans, far from being linear, are complex branched molecules with multiple points of connection – more like LEGO® blocks than beads. That adds huge complexity because we not only have to identify the sequence of monosaccharides that makes up the glycan, but also their position and linkage orientation.

Glycan analysis for monoclonal antibodies is hard enough, but when you start looking at the larger therapeutic proteins like interferons, recombinant hormones or erythropoietins, it's a whole new ball game, with large, complex branching glycans and modifications with inorganic substituents or sialic acids. To unravel this complexity, you need not just one analytical technique but a range of complementary, orthogonal techniques to confirm that what you found with the first technique is what's truly there.

How are you helping to overcome these challenges?

Right now, we're doing exciting work on new technology for quantitative and full structural characterization of glycans in biotherapeutics. We're starting to adopt advanced technologies from proteomics – we're robbing the proteomics toolbox and making it our own!

Over the past five years there has been a lot of progress in quantitative analysis of glycans, with new tandem mass tags and isotope labels being developed. Currently, most analyses rely on relative results – so it's sometimes hard to be sure whether seeing the same-sized peak on a chromatogram indicates exactly the same glycan profile. We are looking at new, stable isotope differential labeling methods, in which two independent samples are labeled separately, then run together (multiplexed) through the same LC-MS analysis. Such an approach allows us to minimize the technical variation and identify genuine changes in the molecules.

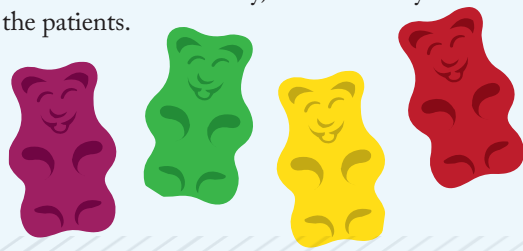
What technological advances have had big impacts on your work?

In recent years, new analytical technology has made it easier to generate the information we need. High-resolution accurate MS has really helped us to nail down structures and characterize modifications with confidence. We also do a lot of MS/MS work, using negative-ion MS to both sequence the glycan and provide additional structural and positional information. Ion mobility MS is another technology we are exploring as an add-on to LC separations – it provides another level of selectivity.

What makes glycan analysis such an exciting area?

The complexity in glycobiology gives you a lot of scope as a researcher, plus new technology and methods become available all the time. My background was in small molecules, but when an opportunity came up to work with Professor Pauline Rudd here at NIBRT, and subsequently Barry Karger at the Barnett Institute, Northeastern University in Boston, I couldn't resist taking on a new analytical challenge.

The most satisfying aspect is seeing the science we do coming to fruition – working with the team here to translate research concepts into actual solutions that benefit the industry, and ultimately the patients.



Instrumental Sugar Rush

With Ken Cook

In the past, it's been difficult to measure and analyze glycans – carbohydrates in general have weak polarity, do not easily stick to common column types and are difficult to detect after separation. But times have changed. More effective columns, advanced mass spectrometers, and new fluorescent reagents have made glycan analysis faster and easier. This, in turn, has generated ever-increasing interest in this field, and new advances for biopharmaceutical companies.

Safety is the top concern for all drug manufacturers. It's crucial that anti-self glycans are not inadvertently included in glycoprotein therapies, or they could potentially kill rather than cure. Glycans also play an important role in efficacy and can act as highly effective biomarkers. For example, changes in the complex glycan structure of serum glycoproteins can be used to detect heavy drinking – something that patients often lie about.

So how can new technology help harness this potential? First, the ease of analysis has improved greatly. The first really effective columns for glycans were all amide hydrophilic interaction liquid chromatography (HILIC) columns, which can only separate by size and heterogeneity. Now, we've brought out two new columns that can also separate different charge states. These are particularly suitable for complex glycans, such as those found in serum proteins, which can have up to six charge states.

Monoclonal antibodies typically have much simpler glycan groups, and with the high-resolution mass spectrometers that have come out in the last couple of years, such as Thermo Scientific™ Orbitrap™-based instruments, we are now able to analyze the whole antibody at once, including any glycan groups. A single analysis obviously offers a big time-saving compared with the traditional method of deglycosylating the protein, separating out the carbohydrate, adding fluorescent labels and then carrying out liquid chromatography, often coupled with mass spectrometry (LC-MS).

Of course, getting good data from chromatography or mass spectrometry is only helpful if you can interpret it. In recent years, there has been a lot of work done on bioinformatics, both by universities and vendors, and there are now several software packages (including SimGlycan® from PREMIER Biosoft) available that can accurately identify the glycan structure from the results of an analysis.

In combination, these new techniques and technologies are allowing biopharma companies to characterize glycans with more accuracy and in more detail than ever before.

Ken Cook is EU Bio-Separations Manager at Thermo Fisher Scientific.

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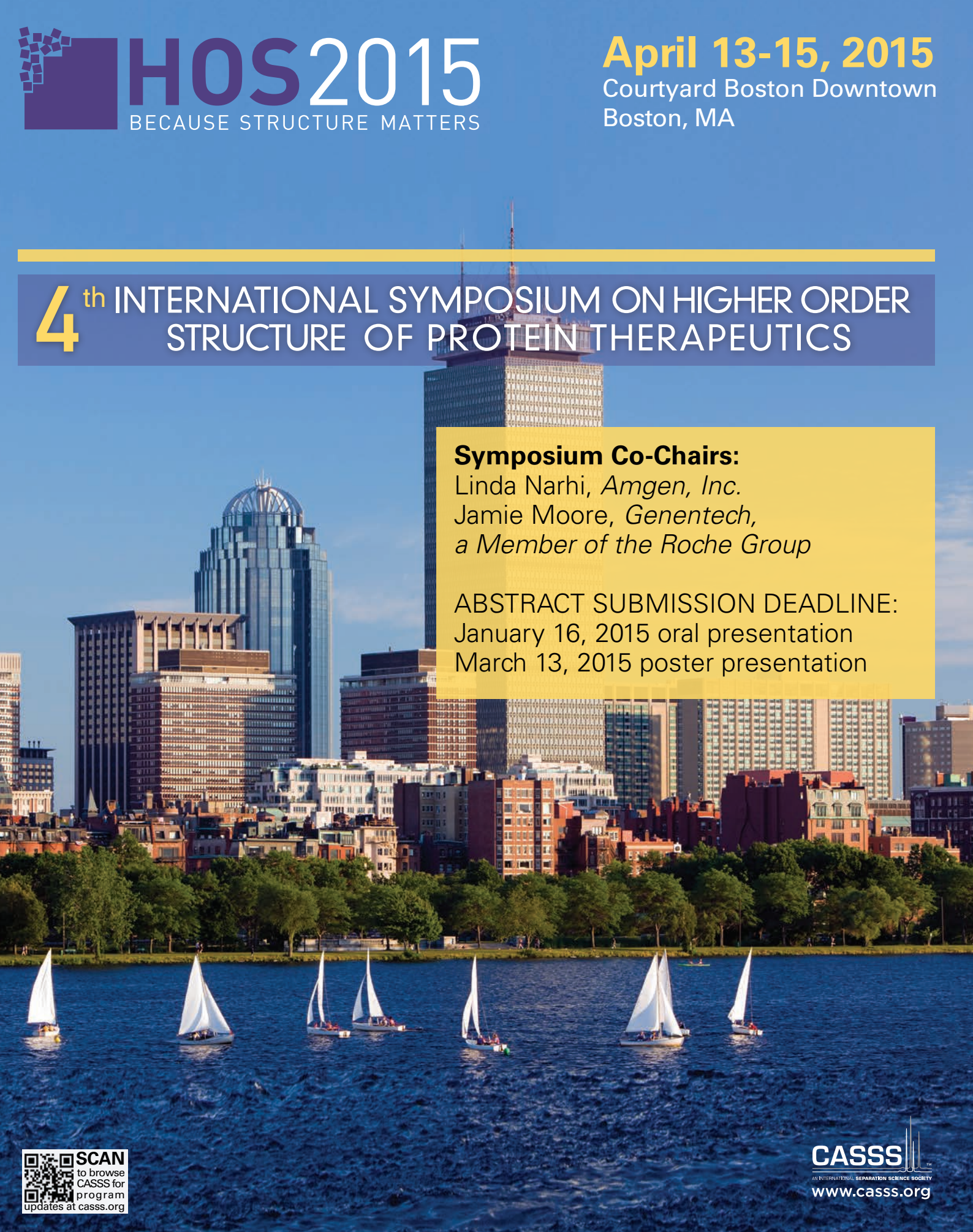

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Remote Controlled Drugs

The latest devices can deliver a drug in the right place and at the right time at the push of a button.

By Brian P. Timko and Daniel S. Kohane

Drug delivery technology evolved in part to address the deficiencies of conventional administration routes. When drugs are delivered by injection or in pills, it is difficult to achieve drug levels within the narrow window between toxicity and under-dosing. Furthermore, drugs with short half-lives have to be administered frequently or even continuously, potentially resulting in patient discomfort or inconvenience, or requiring tethering to external devices. Today, some of these limitations have been addressed by delivery systems that release therapeutics passively at a more-or-less constant rate for an extended period (1).

The problem with such systems is that they are not responsive to changes in the physiological state – or wishes – of the patient. Consequently, there has been a lot of research in developing drug delivery systems that can be triggered by the patient or physician to release drugs at the time and dose of their choosing or, in other words, on demand (2). These systems could be injectable, implantable, or in fact delivered by any means, and could be triggered multiple times. The potential stimuli for drug release include a wide range of energy sources, including light, magnetic fields, radio frequencies, or ultrasound. Triggered devices could make people's lives better in a number of obvious ways; for example, in chronic pain, the patient could adjust the level of analgesia relief precisely to match their level of pain and activity. More sophisticated designs would allow programming of complex dosing regimens, or have built-in sensors to detect fluctuations in blood or tissue levels of molecules of interest, and have automatic mechanisms to release drugs in response to them. Controlling the timing of drug release is clearly important, but using the same sorts of triggers to control targeting of drugs within the body is another area of research focus (though this can also be achieved by old-fashioned methods such as implanting or injecting the drug delivery device). Controlling the dosing regime and precise localization of a drug in the body has a clear impact on efficacy and toxicity.

Pulling the trigger

Near-infrared (NIR) light has attracted considerable attention as a trigger for drug release. It can penetrate relatively deeply into soft tissue because hemoglobin and water absorb the least light in that range of wavelengths (see Figure 1) (3). Moreover, NIR is already an established clinical tool, used for monitoring blood oxygenation levels within the body, deep-tissue fluorescent imaging or cancer therapy by hyperthermia (4). NIR light can be produced with relatively inexpensive and portable diode-based lasers that allow irradiation of only the target tissue. The devices are safe provided they produce light intensities below well-defined thresholds (5), and

could be readily adapted for point-of-care use.

Going for gold

One way to trigger drug release with NIR light is by using gold nanoparticles, which come in a variety of shapes, such as rods, cubes or shells. Gold nanoparticles react to NIR light by producing heat in a process called surface plasmon resonance. The heat produced can be used to trigger another process; for example, to induce a change in a temperature-sensitive material built into the nanoparticle, resulting in drug release. In a seminal study, gold nanoshells were embedded in a macroscale hydrogel composed of the temperature-sensitive polymer poly(n-isopropylacrylamide) (pNIPAm) (6). Whereas most polymers swell when they are heated, pNIPAm hydrogels become hydrophobic and collapse when they are heated beyond 32°C. NIR light was used to heat (via the gold nanoshells) and collapse the polymer, expelling drugs. Many other systems have been developed based on the same general principle.

NIR-sensitive micro- or nanoparticles that contain drugs represent another route and offer the additional benefit that they are injectable. Temperature-sensitive liposomes, which typically release drugs passively, have been conjugated to gold nanorods to achieve NIR sensitivity. NIR irradiation disrupts the liposome, enabling release of the loaded drug (7). Hollow gold nanocages coated with pNIPAm have been loaded with drugs. NIR irradiation collapsed the polymer, opening pores through which the drug could be released. (8)

The wavelengths of light that cause heating of gold nanomaterials (based on absorption spectrum) are highly dependent on particle sizes and geometry. By tuning the shape and size of the nanoparticles, the drug delivery

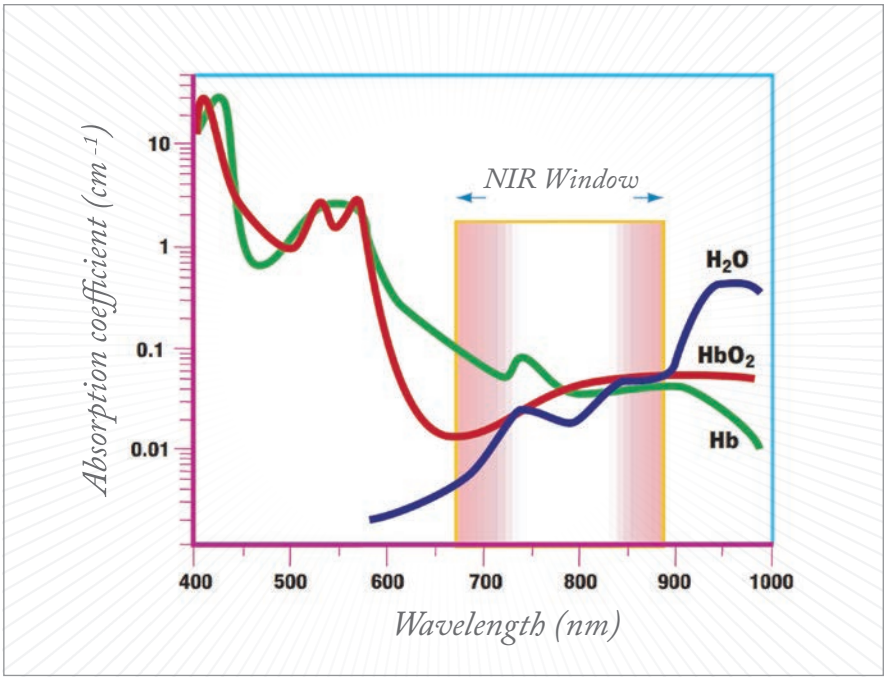

Figure 1. The NIR window, bound by hemoglobin (<650 nm) and water (>900 nm) exhibits minimal absorption. Adapted from (3).

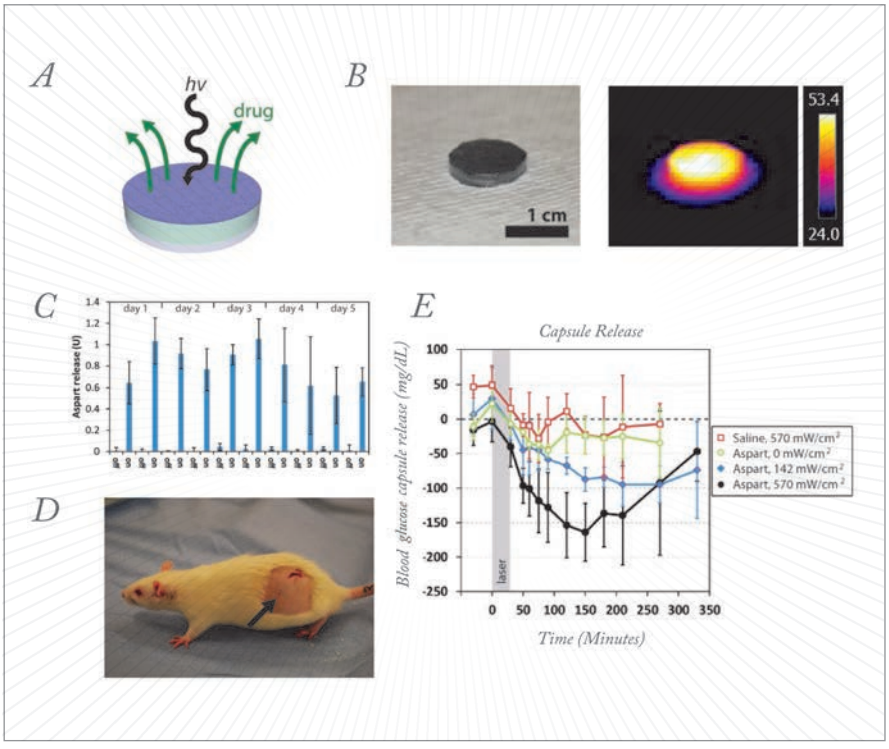

Figure 2. NIR-triggered capsules. (a) Schematic of device. (b) (left) Photograph of a typical device, and (right) thermal image of the same device uniformly irradiated with 808 nm light at 186 mW/cm². (c) Release from devices over 30-min dosing cycles. Devices were turned on with 570 mW/cm² laser light twice per day for 5 days. Off-state release was measured 30 min before laser triggering (n = 3). (d) Photograph of a rat with an implanted capsule (black arrow). (e) One day after device implantation, blood glucose levels were measured after triggered release from devices filled with saline (n = 4) or aspart solution by using an NIR trigger (30 min duration; gray box) of 0, 142, or 570 mW/cm² irradiance (n = 4, n = 3, and n = 6, respectively). All data are means ± SD. Adapted from (4)

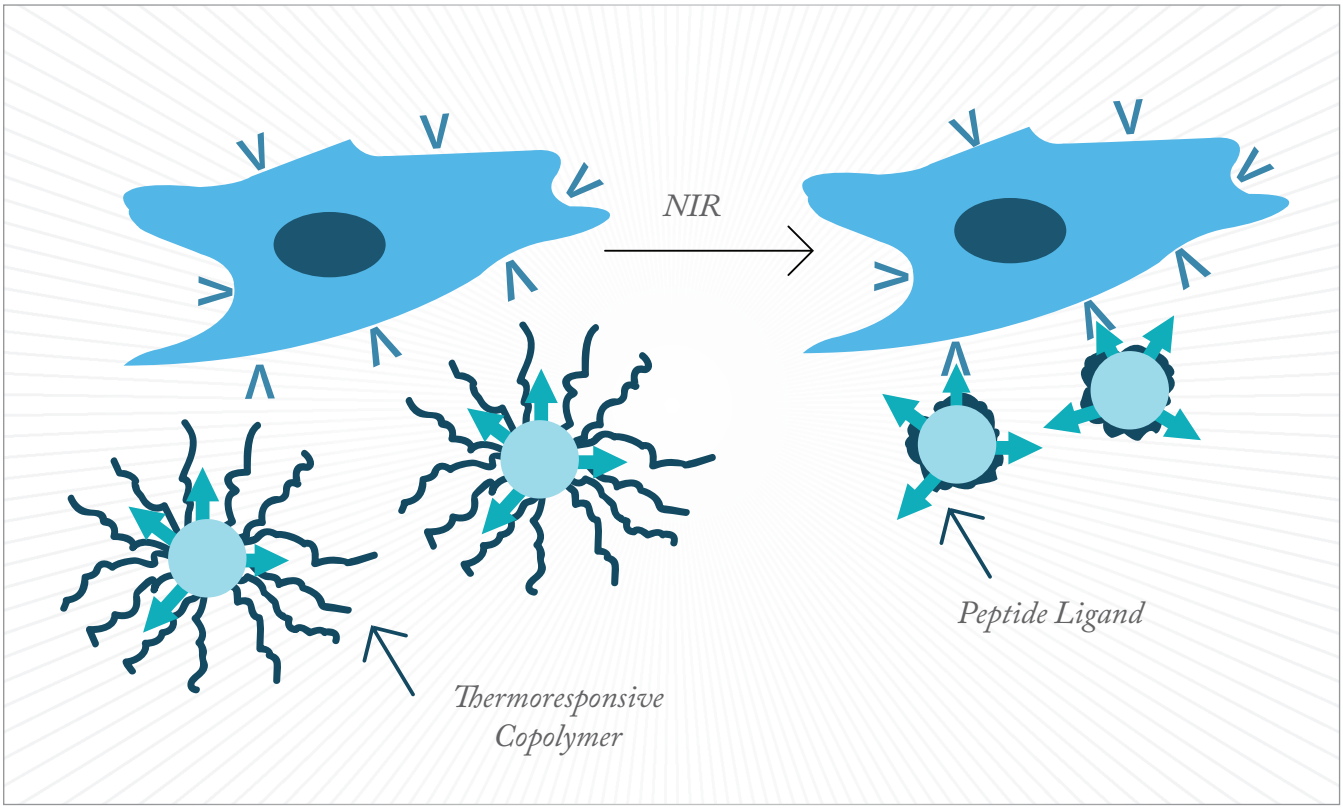

Figure 3. Schematic illustration of photothermally targeted nanoparticles. Adapted from (11). Gold nanoshells are covalently functionalized with a peptide sequence that binds to a receptor that is ubiquitous in the body. The peptide ligand is blocked by a layer of a heat-sensitive polymer. When the particle is irradiated with NIR light, the gold nanoshells heat and the carpet of polymer shrinks, revealing the ligand and allowing the nanoparticles to bind to cells and release drug payload (12).

system can be adapted to any light source within the visible or near-infrared range. Systems can also be composed of two populations of particles that are triggered by lasers firing nonoverlapping spectra, enabling independent dosing of two or more distinct drug types (9).

Reservoir drugs

Remotely-triggered drug delivery systems must be designed so that the range of achievable drug release rates is therapeutically acceptable. Moreover, the ratio between the fully-on and fully-off states of the device should be as high as possible so that baseline drug leakage, which reduces the lifetime of the device and could cause side effects, is minimized.

One way to achieve consistent, reproducible drug release is with reservoir-based systems, in oral, transdermal or implantable formulations, designed to achieve sustained or pulsatile release profiles. Some have already undergone clinical trials for treating conditions such as diabetes, osteoporosis or macular edema (10), and contain enough drug for weeks or months of therapy.

We recently developed an implantable reservoir that could be loaded with tens or hundreds of doses of drug and triggered with NIR light (see Figure 2A). The drug is contained in a capsule bounded by a hydrophobic membrane that is impermeable to the drug. The membrane contains an interconnecting network of nanoparticles based on pNIPAm and gold nanoshells. When irradiated with NIR light, the drug is released through pores that are created in the membrane via pNIPAm collapse (see Figure 2B) (4).

Drug delivery rates could be modulated by adjusting the thickness or composition of the membrane. More importantly, the specific rate of drug release could be modulated by adjusting the intensity of the NIR light. As a proof of concept, we designed devices that could treat diabetic rats. Typically, a dose of 1 unit of insulin – or, in our case, a fast-acting analog such as aspart – is enough to reduce blood glucose to normal levels. We built devices loaded with over 100 doses of aspart, sealed with a membrane designed to

release approximately 1 unit of aspart when triggered for 30 minutes with a laser (see Figure 2C). The devices were implanted beneath the skin of diabetic rats (see Figure 2D), and could be triggered multiple times over a 14-day period. Figure 2E shows the typical glucose response after a 30-minute NIR pulse. The blood glucose level reached a minimum about 150 minutes after triggering, but notably the magnitude of glycemic reduction could be controlled by the intensity of the laser pulse – a stronger pulse achieved a greater reduction.

If coupled to a glucose monitor, systems like these could tailor dosing to the level of hyperglycemia. They could also be used to achieve localized drug release. For example, they could be placed on a nerve, giving the patient the capability for precise titration of local analgesia to match actual needs and circumstances. These devices can moreover be used to deliver a wide range of drug types from small molecules to macromolecules, and therefore could be useful for treating a wide range of disorders (11).

Safety

Despite the abundance of triggered drug delivery systems, relatively few have made it into the clinic. Systems that show potential in humans will certainly need to undergo a thorough battery of tests to ensure patient safety; for example, the NIR light itself could cause burns at sufficiently high powers and/or irradiation times, which is particularly relevant in patient-controlled devices, where the a device may be activated repeatedly. Materials for drug delivery should be designed so that the irradiance required to fully activate the device is minimized, particularly in the case of systems placed deep within tissues, where a substantial portion of the light is absorbed and scattered, leading to heating.

As with all drug delivery systems, the biocompatibility of the NIR-activated carrier and the drug contained within is important (12). The biocompatibility, biodistribution and other biological parameters of some materials – including nanomaterials – is still ill-defined. Local tissue reaction to the drug released is another important concern, particularly in the case of sustained-release systems, where pharmacokinetics may differ substantially from those of injected doses. In particular, local drug levels may be much higher for much longer duration than with systemic delivery. Finally, the device may be susceptible to biofouling, degradation (which may be a good thing), and biodistribution of any possible degradation products.

Looking ahead

As NIR-triggered devices can, in principle, release drugs in any temporal profile – pulsatile, sustained, crescendo, and so on – they enable dosing regimens that are not achievable by conventional means. NIR can also be used to target nanoparticle carriers to specific tissues (13), enabling localized drug delivery after systemic intravenous injection (see Figure 3). Such targeted release may help to reduce side effects for drugs that are locally effective but systemically toxic – a great example is cancer chemotherapy.

In short, NIR-triggered drug delivery systems could enhance efficacy, reduce side effects, increase patient compliance and, ultimately, give patients greater control over their lives. Certainly, there is much to consider in terms of both safety and efficacy in the future, but we feel the huge potential benefits are well worth the effort.

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Gary Meek, Georgia Tech

Nonthreatening Needles

No-one likes getting injections. Fortunately, patients may soon have a pain-free alternative in the form of microneedle delivery systems – a hot area of research for our group and others around the world.

By Lifeng Kang

So what is a microneedle? The simple answer is that it's just like a normal needle, but on a micrometer scale. Microneedles also differ from conventional needles in that they are almost always found in an array, with several hundred tiny needles arranged in a grid. Drugs can be incorporated inside the needles or as a coat over the surface of the array.

The needles are small but there are big advantages to the technology. The most obvious benefits come when we consider using microneedle arrays in place of a traditional hypodermic injection. Children are often afraid of injections, and it's thought that more than 10 percent of adults have a needle phobia (1) – see "Needle Phobia Facts". While we may call them needles, microneedles are almost invisible to the naked eye and painless to apply – they feel like a piece of Velcro and so shouldn't trigger the same concerns.

Importantly, while the needles are tiny compared with standard needles, they are big enough to allow delivery of even large biologic molecules, which are in serious need of new delivery options. Even for those without a phobia, injections are typically painful and inconvenient, especially for drugs like insulin that require regular dosing. There is also the embarrassment factor of having to use injector pens or syringes in front of friends or colleagues – this is a real concern for teenagers particularly. Microneedles can be assembled into single-use, disposable patches, so it should be easy for patients to self-administer.

Other transdermal delivery mechanisms – patches, creams, gels and lotions – have been explored in the past, but the skin is a very strong barrier that most chemicals or biologics cannot penetrate. Microneedle arrays create many micro-scale passages

across the outer layers of the skin, allowing the drug to enter the body in much larger quantities. It could be said that microneedles combine the best of both worlds – the effective drug delivery of injection and the pain-free, easy administration of a cream or transdermal patch.

Micromanufacturing

One method for producing a microneedle array is by micro-molding. Long before being applied in healthcare, micro-molding was being used in the electronic industry to manufacture computer or smart phone chips, so the technology is already well established. Microchips are usually made of silicone, but for healthcare applications we usually use metals or polymers that have an established safety profile in medical devices. Polymers used in microneedles can be designed to dissolve once inserted into the skin, releasing the drug as they do so.

My group has recently developed a new method for creating microneedle arrays using photolithography (2). The needles are made from a light-sensitive liquid, which polymerizes when exposed to light. We apply a photo-mask – essentially an opaque sheet of plastic with small transparent windows at regular intervals. Then we turn on the lights and see the microneedles form as the liquid solidifies. This simple procedure, potentially scalable for mass production, offers the possibility of conveniently incorporating the therapeutic agent inside the microneedles.

Expanding applications

Given the potential advantages of microneedles, it's no surprise that their use is being explored in a whole host of clinical and non-clinical applications. In the less regulated cosmetic market, microneedles in the form of 'derma rollers,' are already in widespread use. And though it's hard to test claims

"Microneedles combine the best of both worlds – the effective drug delivery of injection and the pain-free, easy administration of a cream or transdermal patch."

Needle Phobia Facts

In **1994**, needle phobia was officially recognized in the DSM-IV (Diagnostic and Statistical Manual, 4th edition)

23 deaths due to vasovagal shock during injections were reported in a 1995 review (1)

10% of Americans suffer from a fear of needles (1)

There are at least **6** separate phobias relating to injections:

Aichmophobia:
an intense or morbid fear of sharp or pointed objects

Algophobia:
an intense or morbid fear of pain

Belonephobia:
an abnormal fear of sharp pointed objects, especially needles

Enetophobia:
a fear of pins

Trypanophobia:
a fear of injections

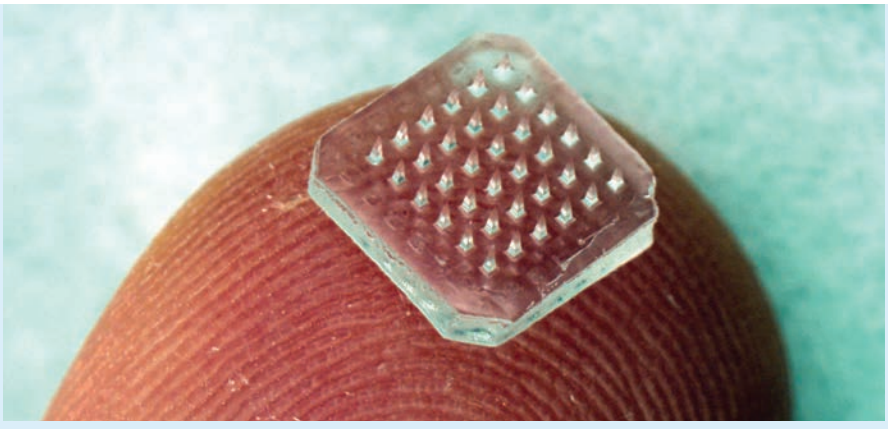
Vaccinophobia:
a fear of vaccines and vaccinations

"The pioneering smallpox vaccination developed by 'father of immunology' Edmund Jenner was first administered by scratching the skin."

that microneedles (alone or used with creams) rejuvenate the skin, we have conducted studies on topical delivery of collagen and copper peptide, which play important roles in skin regeneration and healing, but are too large to easily pass through the skin barrier. Using microneedle pretreatment increases the uptake of both molecules into the dermis significantly, with potential applications in medicine as well as cosmetics.

Another area in which microneedles show promise is in topical pain relief, and this has been a major research focus in my lab. Specifically, we have developed a microneedle patch for administration of lidocaine. Lidocaine in gel or patch form is already in common use as a topical anesthetic before injections, or to relieve local pain. However, it is relatively slow to act, taking 20–30 minutes to cross the skin and start working. If you imagine a busy vaccination clinic, that's a significant wait between applying the patch and being able to administer the vaccine. In animal studies, we have shown that lidocaine penetrates the outer layer of skin in less than 5 minutes using microneedle patches.

Vaccination is another area in which microneedles could represent a major advance. After all, the pioneering



Jeong-Woo Lee, Georgia Tech

Microneedle Trials to Watch

Eye disease (Georgia Institute of Technology)

Scientists at Georgia Tech have developed a microneedle patch for use on the eye. The patch could be used in place of eye drops for conditions like glaucoma. Eye drops, while convenient, require daily use and have poor compliance – by giving a pain-free microneedle injection in the doctor's office, patients may be less likely to forget their medication. Hypodermic injections into the center of the eye are increasingly common, but the researchers think a microneedle patch may be more effective as it delivers the drug exactly where it needs to go.

Polio vaccination (Georgia Institute of Technology and Micron Biomedical)

Polio is one of the success stories of immunization, with cases down 99 percent since 1988. To hit 100 percent, it is essential that children continue to be vaccinated, even where the risk is very low. However, the cheap and convenient live attenuated oral vaccine carries a small risk of developing the disease, so its use is being phased out in regions where polio is no longer a threat. The problem is that the inactivated vaccine must be injected, meaning it is more expensive and must be administered by healthcare workers. Georgia Tech and Micron Biomedical recently received a grant from the Bill and Melinda Gates Foundation to develop a microneedle patch that could combine the ease of use and low cost of the oral vaccine with the safety of the injectable.

Osteoporosis (Zosano)

Eli Lilly recently bought the rights to Zosano's ZP-PTH, one of the few microneedle delivery systems that has already undergone clinical trials. ZP-PTH delivers parathyroid hormone to stimulate new bone development in patients with osteoporosis, giving doctors and patients an alternative to injection. It was found to be safe and effective in Phase II trials, and is now moving into Phase III development.

smallpox vaccination developed by "father of immunology" Edmund Jenner was first administered by scratching the skin. Recent research indicates that if a self-administrated patch were available, significantly more people would opt for an annual flu vaccination (3). The same study found that most people were able to successfully apply a prototype patch themselves. Many groups are exploring microneedle vaccination, with promising preclinical results for flu, anthrax and others.

With multiple microscale passages created inside the skin, the delivery of various fragile biomolecules becomes possible. Microneedles, therefore, may have big potential in the world of pharmaceutical products (see "Microneedle Trials to Watch").

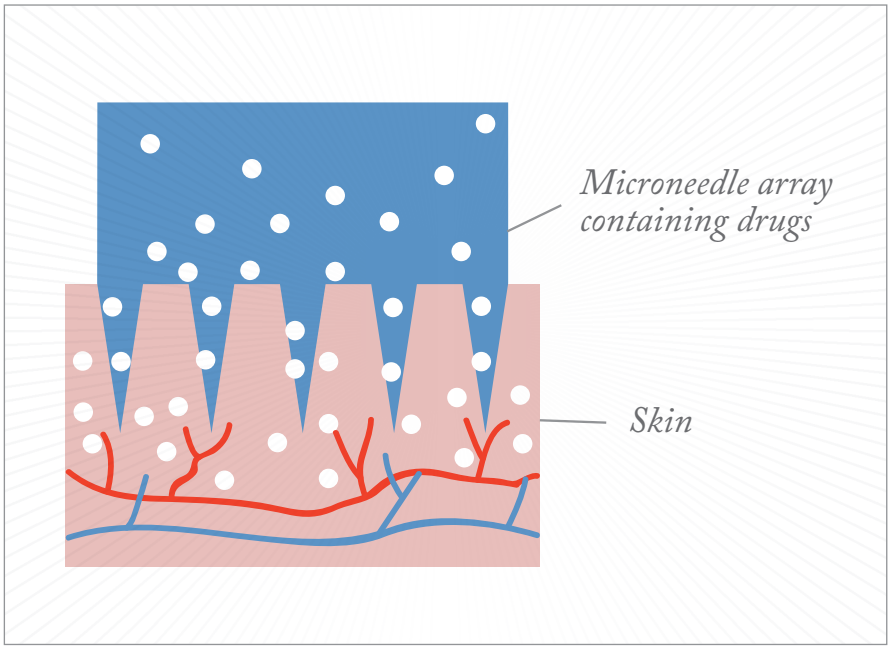


Figure 1. Microneedle patch.

Big future

Microneedles may even move beyond the skin, with at least one lab exploring the potential for 'microneedle pills' (4). Insulin was encased in an acrylic capsule covered in microneedles, with a coating that dissolves in the acidic pH of the stomach. In pigs, the pills succeeded in injecting insulin into the digestive tract lining, and did not appear to cause any tissue damage. Such advances could open up whole new fields in the microneedle area.

Drug delivery is the most obvious application of microneedles, but let's not forget that they are still needles and could also be used to collect samples. Rather than taking a blood sample, microneedle patches could be used to painlessly collect a sample of fluid from the skin. For example, a recent study showed that biomarkers of malaria infection could be collected from mice using a wearable patch – one day this could be used to diagnose infection quickly and easily in resource-limited settings (5).

Regulatory hurdles

Microneedles are still a long way from the clinic in most cases. A few systems are now in clinical trials, like Zosano's ZP-PTH, which delivers parathyroid hormone to osteoporosis patients. However, regulatory approval is complicated by the fact that a microneedle array is both a medical device and a drug delivery system – they have to be proved safe and effective from both perspectives. Furthermore, it is a new area for regulators as well as scientists – prior experience in regulating microneedles is lacking. There is still a lot of basic preclinical work needed to elucidate the biocompatibility of different materials and the geometry of microneedles. These factors are likely to be different for each new drug, so researchers may have to come up with a unique microneedle delivery system, compatible with that specific drug, for each medicine. Researchers will have to do more to show the nature of this new technology, but I believe once one product is approved, it will open the floodgates and we will see microneedles taking a prominent position in the drug delivery toolbox.

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The Toolbox of 2025

Previously, in our series – "Connecting the Dots in Drug Delivery" – we examined the current status of drug delivery. We saw how today's new therapeutics pose tough challenges for formulation scientists, and how companies are tackling those challenges with a range of tools, from micronization to hot melt extrusion. But what techniques will be in the toolbox 10 years from now? We speak to academic and industry experts to find out.

On Target

With Hamid Ghandehari, Professor at University of Utah, Director of Utah Center for Nanomedicine and member of Catalent Applied Drug Delivery Institute Advisory Board

What do you think will be the most important future trends in drug delivery?

For one thing, we are going to continue to see the approval of targeted drug delivery systems, including polymeric systems. There are several micellar polymer structures that are in various stages of clinical trials, and I expect to see those in the clinic in the next few years.

In the next decade, we are going to see local triggered-release drug delivery. Here, the drug delivery system is delivered to the target site and activated by local or external triggers to enhance the delivery of the active agent.

What is needed to drive continued innovation?

Two decades ago this was a very specialty field, but now a lot more research is going on. It is very satisfying to work with a younger generation of scientists and see their enthusiasm. I think the field needs more innovation and new minds to take it to the next level. In particular, we need more clinician–scientists in our ranks to help translate technologies for the clinic.

Broad support from the pharma industry is essential to bridge the gap between academia and industry, and speed up commercialization. To that end, the Catalent Applied Drug Delivery Institute is reaching out to the broader scientific community, as well as the younger generation with workshops and academic prizes.

How did you get into the field?

I was really in the right place at the right time. I completed my undergraduate degree at the University of Utah in the late 1980s and stayed on for my PhD in the early 1990s. At that time, the university had some of the pioneers in drug delivery, including my PhD mentor Jindrich Kopecek – one of the world leaders in polymer therapeutics. I was inspired to continue this great work.

To deliver the drug to the right site at the right time is so important – it really impacts on patient's lives by reducing side effects and improving efficacy.

What are you working on right now?

A lot of drugs, such as cancer chemotherapies, are fabulous at what they do, but have devastating off-target side effects, so can only be used in small doses – or not at all. We aim to confine the delivery of those drugs to the target tissue, for example cancer cells, by using novel drug delivery systems.

In our lab, we tailor-make recombinant polymers for gene delivery applications. These polymers are made using genetic engineering, which gives us a high degree of control over the sequence and length. In particular, we use them to deliver genes to accessible head and neck solid tumors. The particular polymers we use are made of silk and elastin blocks. They are liquid at room temperature and when mixed with viral gene carriers and injected they solidify at body temperature and improve localization and duration of gene transfer.

In another project, we use local hyperthermia to target delivery of polymer–drug conjugates to prostate tumors. We use plasmonic photothermal therapy or other means of hyperthermia, such as ultrasound, to maximize the delivery of the polymeric systems to the site of action. This improves blood flow in the tumor and enhances cellular uptake of the cytotoxic agents.

Where have you seen the most promising results?

There are a couple of areas where I think we have had particular impact. By using recombinant techniques we have been able to sustain the expression of adenoviral systems locally in head and neck tumors. More recently, we have developed recombinant polymer systems that are responsive to local enzymes, such as matrix metalloproteinases, that are overexpressed in tumors. This allows gene therapy to be delivered primarily in the tumor.

In the area of targeted delivery using hyperthermia, we have shown that by carefully controlling local temperature we can magnify the so-called enhanced permeability and retention (EPR) effect, whereby certain sizes of molecules tend to accumulate in tumor cells.

Dissolving Delivery Challenges

With Rosie McLaughlin, Director, Scientific Affairs at Catalent Pharma Solutions

What's the focus of your work?

Right now, I'm looking at innovative ways to expand on the Zydis® drug delivery platform – a freeze-dried, orally dispersible tablet. We start with a dispersion of active pharmaceutical ingredient (API) in the formulation matrix, and freeze-dry it to create a very porous, lightweight product, which dissolves in the mouth in around three seconds and without the need for water. The drug can enter the body either by standard gastrointestinal absorption or through the oral mucosa, depending on the API. The sublingual area (under the tongue) is highly vascularized so certain APIs can be quickly transported through the oral mucosa and into the bloodstream, bypassing first-pass metabolism and potentially improving bioavailability.

What are your most exciting projects at the moment?

There's always something new and exciting! The best thing is when we push the boundaries. At the moment I'm working on two new developments – one is a new API coating process developed exclusively for Catalent by the New Jersey Institute of Technology. The process involves a Resonance Acoustic Mixer, which uses sound energy to generate vibrations for dry-coating very fine particles, increasing drug loading and improving taste masking. Previously, we haven't been able to use coated APIs in Zydis, so this expands the number of drugs we can develop in the platform. We've also been doing proof-of-concept work on oral delivery of vaccines, starting with influenza.

An oral flu vaccine could be quite a breakthrough…

We're using influenza in our proof-of-concept preclinical trials because it is so well characterized, but we hope the technology may be applicable to a whole range of vaccines. The availability of a noninjectable, room temperature-stable vaccine delivery system could certainly transform the whole field. This is particularly true of the developing world, where the logistics of cold chain storage are a big challenge, causing significant wastage, and where trained healthcare workers may not always be available to administer injections.

What approach are you taking?

Vaccines, except for some live attenuated viruses like polio, are generally destroyed in the gastrointestinal tract if swallowed. Using Zydis Bio, we're administering the vaccine sublingually, to bypass the acidic environment of the stomach and enzymes of the digestive system and go directly into the bloodstream via the oral mucosa.

Proteins, being large molecules, have less tendency to cross the oral mucosa. But we know it is possible because we have already used Zydis Bio to deliver an allergy vaccine. The active ingredient is a protein extract, which is delivered sublingually and induces tolerance in hay fever sufferers. Our work on oral vaccines is a natural continuation – the difference is that we're now trying to trigger an immune response, rather than immune tolerance. The results so far have been encouraging, although it may be several years before we see clinical trials.

What challenges will tomorrow's drug development scientists face?

Bioavailability challenges will continue to be a problem for drug manufacturers. As more and more biologics become available, the Holy Grail is to find new routes of administration to improve the patient experience – whether that's oral, inhalation or microneedle delivery.

Innovation Events

Get the inside track on the future of drug delivery at these Catalent Applied Drug Delivery Institute events.

Addressing the Challenges of Drug Delivery

April 30, 2015 - *3M Customer Innovation Center, Bracknell, UK*

- Dr. Ralph Lipp on using patient insights to design drugs
- Dr. Mark Tomai on increasing the effectiveness of vaccines
- Professor Claus-Michael Lehr on innovative drug delivery methods

Advanced Drug Delivery Applications

September 17, 2015 - *University Of Tokyo, Japan*

- Bioavailability challenges
- Patient-centric drug design
- Innovative technologies

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Business

Economic drivers
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The Challenge of China

As the world's most populous country and the second largest global economy, the potential for growth is significant. But how does a company break into China?

By Fadia AlKhalil

Much has been made of the advantages of doing business in China in recent years. Unlike western markets, it is far less mature – the pharma sector is growing at double-digit rates, for example. In fact, it is already the world's second largest pharmaceutical market, and the IMS Institute for Healthcare Informatics predicts the annual spend may reach $185 billion by 2018 in its report, 'Global Outlook for Medicines through 2018', published in November 2014.

Per capita spending may be low, but the huge population bumps up the total, and this per capita spending is predicted to grow by more than 70 percent in the next five years; even then, it will still be just nine percent of the level in the US. Little wonder then that western pharma companies see China as a huge opportunity.

Alongside this burgeoning market for pharma products is a growing outsourcing market, thanks to western pharma companies' eagerness to outsource the more routine pharma research operations to Chinese companies, from chemical synthesis to biological screening, with the aim of saving money. Although it is not the cheap option it once was, there is still a heavy reliance on outsourcing research to China. The authorities' requirement that any medicines licensed in China must have undergone Chinese trials has also encouraged western companies to carry out clinical studies there. And let's not forget that the large, untreated population can offer a huge pool of potential trial subjects.

The tide is turning

Growth has now started in the other direction, as well. China has a well-established manufacturing industry but Chinese companies in the pharma sector are increasingly outsourcing to the western companies, who have set up operations within China.

Even with the flood of returnees – young scientists trained in western universities and pharma companies heading back to China (often to care for aging parents) – there is still an enormous need for the experience, knowledge and skill set offered by western experts. I have visited many small-to-mid sized Chinese pharma companies and found that while they have money and enthusiasm, they are often very short on technology and know-how.

Yes, many large Chinese pharma companies have already collaborated with partner companies in the west to secure the expertise they are missing or hired the talent they need to run their operations from overseas. Indeed, most of the large western pharma companies have entered the Chinese market via some form of joint venture with a big local rival; brand names are everything and while some of the Chinese companies have managed to develop their own brands fairly successfully, the additional cachet of big western brands is perceived as extremely advantageous to their prospects. However, their smaller counterparts frequently have not entered into such arrangements. I think if it is properly packaged, marketed and targeted, an annual growth rate of 10 percent, if not 15 percent, should be easily achievable for companies looking to work with smaller Chinese companies. As well as technology and knowledge, western partners can offer quality improvement and organization, with more streamlined business processes and expertise in GLP and GMP procedures. Western partners can also act as a conduit to help Chinese companies to expand globally by using their knowledge of markets and regulatory demands.

Analytical opening?

There is another area ripe for partnerships between western and Chinese companies in the pharma sector: analytical services. Outsourced analytical services is still a fairly young market and, therefore, offers plenty of potential for growth. SGS established its Life Science Services operations in the Chinese market in 2006 at a time when there was huge demand in the country for testing, a lack of fundamental knowledge and, crucially, an absence of that all-important international accreditation which allows a business to create products that will be acceptable for export to international markets. In 2006, SGS began its Life Science Services operations with a

small team of 10 employees in response to a request from a global client. By mid 2014, the laboratory space had increased to 1,500 square meters with 75 employees. Recently, SGS announced additional investments to increase the laboratory to 2,000 square meters, also increasing its capabilities to include extractables–leachables packaging testing, inductively coupled plasma mass spectrometry (ICP-MS) to address upcoming USP<233> Elemental Impurities guidelines, a dissolution lab for generic drug stability studies, and a highly active compound testing laboratory to meet growing market demand.

As the Chinese start to develop this know-how, acquire the skills and develop potential, they will surely start to become more protective of their own companies. Though they were sadly lacking before, the money and market are now there, and their knowledge and expertise are growing, so why allow foreign companies to compete? And another notable factor that must be taken into account is that as Chinese exports stagnate or even decline, companies are starting to put a much greater focus on serving their own domestic market. After all, a population of 1.4 billion generates a lot of consumers! The upshot? Well, I would say that unless a US or European company providing analytical services already has a foothold in the Chinese market, they will find it increasingly hard to enter. In other words, the clock is ticking...

However, despite the steadily growing challenges, China still offers great potential to western companies in terms of analytical services. In many cases, Chinese companies remain behind the bar when it comes to implementing and complying with international standards, such as ICH and GMP, because they simply cannot keep up with the growing demand. As they struggle to become a major force in overseas markets as well as at home, they need western companies to help them bridge the quality gap. Even at home, as the wealth per capita increases, consumers are ever more likely to want products that offer them quality rather than just simply being cheap. And quality is what the west has experience in providing.

One country – five markets

The tactic of providing a one-stop shop service to customers across the whole of China is very unlikely to succeed. Quite simply, China is far too big a country, with far too many people. My advice would be to treat China as four or five distinct markets, based on its different regions and dialects, including Mandarin, Wu, Yue (Cantonese), Min and Jinyu. The one-stop shop approach would mean having to find a way to satisfy the unique conditions of all five of these separate market segments, which would be complicated (and therefore costly) and doomed to fail.

Of course, there are local Chinese suppliers who meet some of the needs of local pharma companies. There is an abundance of local laboratories who offer contract analytical support. That said, adherence to those all-important GLP and GMP standards remains somewhat questionable. Many analytical service providers in China – both local and western companies with Chinese operations – aim to service western companies from their operations within China. And herein lies the big opportunity: working with the pharma companies whose needs are still under-served.

When it comes to keeping the Chinese regulators happy, it has to be said that they appreciate companies working with

Six Tips for Success in China

1. Hire locals with international knowledge
2. Train globally (especially in terms of quality/compliance)
3. Follow both local and global regulations closely
4. Understand the local and national culture
5. Offer capabilities based on your clients' needs within each region
6. Focus on global clients' needs and grow your capabilities accordingly

western partners, because they are more likely to adhere to international quality standards. However, they still expect those partners to respect and meet all relevant local regulations. Therefore, to be successful, it is vital that companies fully cooperate with the Chinese regulators and demonstrate that Chinese criteria are being fully satisfied. For SGS, having a laboratory in Shanghai means that we have local accreditation, and our scientists and quality experts have a good understanding of the local regulations. Importantly, this lab is part of the global SGS Life Science Services network, and therefore automatically works under our global quality standards, ensuring high quality and compliance with western regulations as well.

Chinese requirements

In recent years, the Chinese FDA has revised its guidance, and it now tracks very closely to the guidance set by the US FDA. This converging approach is also reflected in other documents. For example, the Chinese Pharmacopeia strives to harmonize with the existing guidelines set by the US and Japanese pharmacopeias.

Even though the Chinese FDA is now trying to streamline its processes, many overlaps in authority, requirements and agency oversight exist within the Chinese government. It is therefore very important to identify the correct regulatory agency prior to moving forward in business to ensure compliance with local and global regulatory agencies. The real area where western quality testing labs can make their money is in final testing of products for export. The importing country will have different testing requirements to those for the Chinese domestic market. And in many cases the requirements will be more stringent than those for internal use. The west does not fully trust the quality of testing work carried out by the Chinese regulatory agencies, so a western company in China with international accreditation for its laboratories can charge a premium to Chinese pharma companies wanting to export goods.

Chinese consumers often have a deep mistrust of their own regulatory agencies too, and this boosts the demand for outsourced testing of products for consumption at home. The most recent restructuring of the Chinese FDA has provided consumers with the ability to have an input into the formulation of food standards, the selection of risk assessments, the reporting of crimes, and even criminal punishment; we should never underestimate consumers' knowledge and awareness – after all, they drive the future success of any product.

The most important piece of advice I can give to any company looking to set up as a service provider in China is to remember the essential point that it really is not a single market. Western companies tend to cut China up into homogeneous regions, but I would actually consider it as five different countries, each with their own unique culture, people, resources and business environment. Making generalizations that what's right in Shanghai is also right in Chengdu or Hainan is guaranteed to hinder your growth – or even lead to failure.

SGS's success in China is rooted in an understanding of the importance of China in the global market as well as the local market, local culture, hiring qualified local people and offering continuing training from our global quality and compliance.

"The Chinese FDA has revised its guidance, and it now tracks very closely to the US FDA."

Fadia AlKhalil is vice president of Global Alliance & Partnership, SGS Life Science Services, Fairfield, New Jersey, US.

Webinars

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Regulatory bodies such as the FDA and EMA require that these biotherapeutics are thoroughly characterized. As a result, extremely high resolution accurate mass spectrometry is required for a complete understanding of the protein structure.

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Advocate of Change

Sitting Down With… Phyllis Greenberger, President and CEO of the Society for Women's Health Research (SWHR), Washington, D.C., USA.

It must be rewarding to have been involved in SWHR from the start…

It's very rewarding. And it's been fun and exciting, partly because we look at so many conditions, from neurological conditions to cardiovascular. I have had the opportunity to work with so many researchers, academic centers, regulators, and government officials. And though every day has been a challenge, it's always been interesting.

How was SWHR founded?

SWHR was founded in 1990 by a group of physicians, medical researchers and health advocates. Dr Florence Haseltine – who was working at the National Institutes of Health (NIH) at the time – realized that women's health issues were almost entirely focused on reproductive issues, and maternal and pediatric medicine. Florence went to Congress and talked to them about the need to pay attention to the full range of health issues that women experience. In particular, we lobbied for an audit of NIH's policies and practices regarding inclusion of women in clinical trials. As a result, President Clinton signed legislation in 1993 that established the Office of Women's Health at the NIH, appropriated a significant amount of money for women's health research, and mandated the inclusion of women in clinical trials.

And how did you become involved?

In the early 1990s, I was working for the American Psychiatric Association, and I was aware that women were not being adequately represented in clinical trials, particularly in areas like depression, which we knew disproportionately affected women. I was also working with a physician at NIH who invited me to a meeting on AIDS, where they discussed the fact that no one was paying attention to women; all the focus was on gay men and the only consideration for women was during pregnancy. Women weren't even being included in clinical trials. That really captured my interest, so when Florence asked me to join the board of a new voluntary organization in 1990, I accepted. After that, I got involved in President Clinton's first presidential campaign and was introduced to Hillary Clinton. I worked with Hillary's staff on women's issues and they really picked it up and made several speeches on the subject. That publicity set us on a path to become a fully-fledged organization, and in 1993 we were able to get properly off the ground.

"Though every day has been a challenge, it's always been interesting."

What was the main focus of the Society in the early days?

We first focused on the inclusion of women and minorities in clinical trials. We worked with the handful of people at the FDA who supported what we were doing, to encourage inclusion of women in drug trials. In 1996, we went to the Institute of Medicine (IOM) and asked to do a report on sex differences in health and medicine. It was difficult to get the funding for it and there was a lot of pushback by people that didn't believe in it, but the IOM report – "Exploring the Biological Contributions to Human Health: Does Sex Matter?" – came out in 2001. That gave us a more official document, which had to be taken seriously, and couldn't be dismissed as simple political correctness. Before that, there was a general belief from pharma companies, researchers and regulators that men and women were pretty much the same and that if something worked on men it worked on women. It wasn't until the IOM report came out that it became a much bigger issue – a number of researchers, many of whom we worked with and funded with small grants, started finding major differences between the sexes.

How does the Society promote research?

Our research networks bring together researchers from a range of disciplines to look at issues like Alzheimer's, mental illness, pain and cardiovascular disease. They have been publishing papers in journals to educate researchers and physicians about sex differences. It's interesting that when you bring all these people together from different disciplines and they start comparing notes, they often quickly find differences in diagnosis or treatment. We're working hard to get enough funding to continue the research.

What's next?

There's still a lot of work that needs to be done. We'd like to start a fellowship for medical students, so that the next generation of doctors better understand sex differences, as it's not really being taught in medical schools yet. There's still a lot that we don't know, but we want to make sure that new physicians can apply the knowledge we do have in clinical practice.

What do you love most about your job?

I always felt that I didn't want to be just talking about one disease because that would get monotonous after a while. I enjoy being able to get involved in a lot of different issues and meet a lot of different people and, frankly, I like the challenge. It's been difficult at times and extremely frustrating, but it's been exciting as well.

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