MAY 2016 # 19

the Medicine Maker

The Great British Debate

How would a potential "Brexit" impact the pharma industry?

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Online this Month

More to Brexit Than Meets the Eye

On June 23, 2016, the British public will vote on whether the UK will remain a member of the European Union. What would a "Brexit" mean for the pharma industry? We ask this question in our cover feature on page 20, but if you're hungry for more information then check out our website.

Trials and Tribulations: Angus Dalgleish, Professor of Oncology at St George's University of London, believes EU overregulation ties the hands of clinical academics. He describes his experience with EU regulation – and why he thinks Britain should leave the EU.
http://tmm.txp/0516/Dalgeish

Helping or Hindering Science: If Britain votes to leave the EU, would the UK lose access to EU science programs? Could the UK make up the shortfall with savings gained by no longer contributing to the total EU budget? Two professors with experience of EU funding give their thoughts.
http://tmm.txp/0516/Merrifield

The BIA Says No to Brexit: Steve Bates, CEO of the UK BioIndustry Association, argues that a vote to leave the EU would harm British science and have a negative impact on the UK's bio industry. He gives the stats and facts about the potential impact in this online Q&A.
http://tmm.txp/0516/Bates

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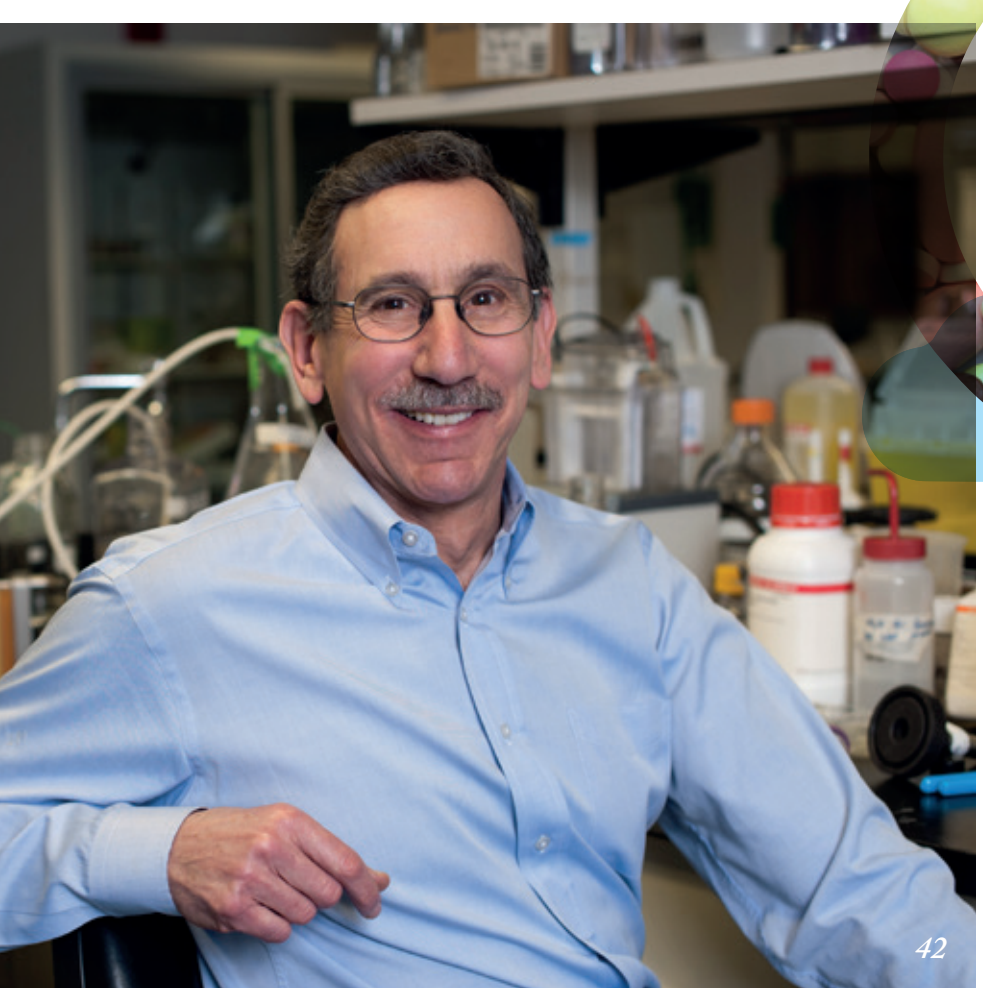

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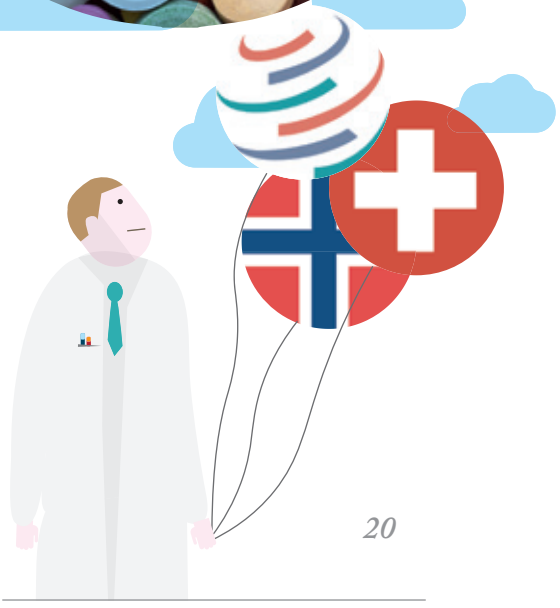

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On The Cover

Preparing for Britain's EU membership vote on June 23, 2016.

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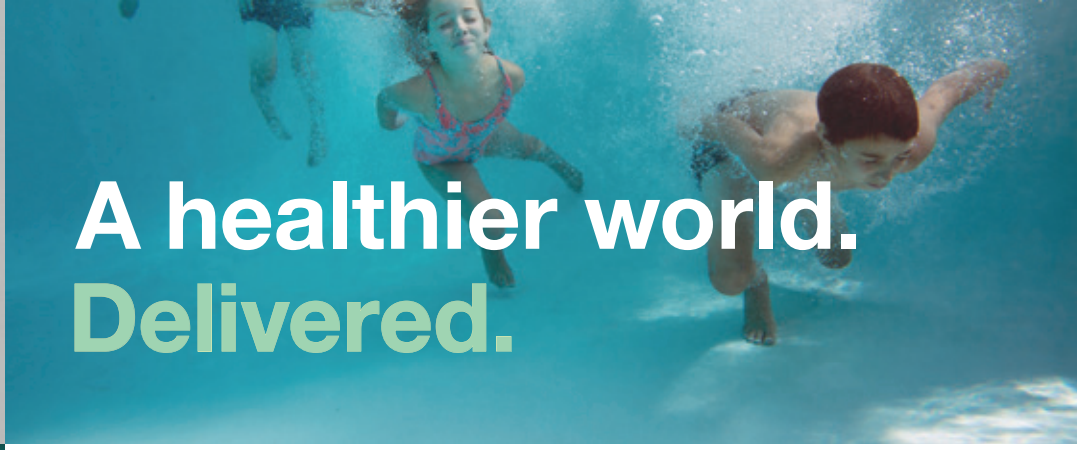

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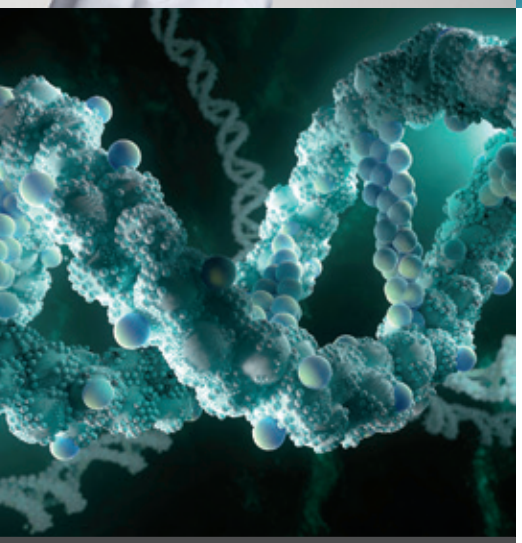

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Welcome to (Virtual) Reality

VR is creating a buzz, but is it a game changer or gimmick?

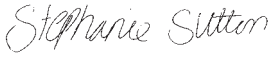
Attending the Interphex trade show in April, I can't deny that I was childishly excited to learn that a company was showcasing virtual reality (VR) headsets for use by pharma and biopharma companies. The technology is cool – and it's also expensive so it's not every day that you get to try it out. But I was also a little sceptical; VR certainly has the power to change video gaming, but is there a place for the technology in pharmaceuticals? Novel marketing campaigns quickly spring to mind; in March 2016, Pfizer launched a campaign to promote the benefits of its Advil Liquid Capsules, which incorporates VR in a "Tron-like bike experience" (1). But it seems that there could be potential for VR in manufacturing too.

VR headsets are now very advanced – and much lighter and more comfortable than I expected. If you've never experienced VR before then it's hard to imagine what it's like. You see the room around you, but you also see VR displays or objects. Apprentice Field Suite are promoting the use of VR for a number of pharma manufacturing applications. Glancing at a piece of equipment, for example, can bring up a display that shows the system is operating within normal parameters. VR can also be used to allow remote engineers to see equipment in real-time so that they can perform inspections or troubleshoot problems, or it can be used for training purposes or for instant access to standard operating procedures documents and batch records. A little gimmicky? Definitely. But these capabilities could be genuinely useful for a global pharma company.

Apprentice Field Suite aren't the only company active in this area. Also at Interphex, Pall were showcasing their HakaBio VR platform, developed with OUAT!, which allows companies to plan their own facility. And in 2015, Eon Reality developed a VR application for GlaxoSmithKline to help visitors to the Neural Pathways Discovery Performance Unit learn about Lou Gehrig's Disease.

Pharma is often accused of being conservative with new technologies, but VR is pretty 'safe'; it doesn't affect a manufacturing process directly, so won't require specialized regulatory approval. And I certainly believe that the technology is exciting enough to encourage companies to experiment. I'll be keeping a close eye on pharma's VR activities. And I'd love to hear your thoughts and experiences with the technology – both inside and outside the workplace. Game changer or gimmick?

Stephanie Sutton
Editor



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1. *S Canning, "Australian agency Matterhorn creates global VR first for Pfizer with Tron-like bike experience," Mumbrella, March 2016. http://bit.ly/1QXiA2p*

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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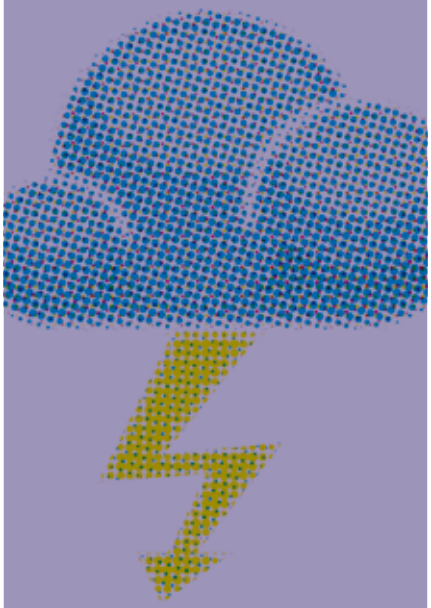

Microparticles, You've Been Thunderstruck

Scientists use hydrophobic plasma and AC/DC's 'Thunderstruck' to coat porous silicon microparticles for drug delivery

It was at a conference dinner when Nico Voelcker and his colleagues from the Future Industries Institute, University of South Australia, began bouncing around ideas for a new drug delivery method. "On the one hand we had porous silicon microparticles (pSi MPs) – which can be loaded with a multitude of drugs – but they dissolve too quickly for effective delivery," says Voelcker, Professor of Biomaterials and Nanomedicine. "On the other hand, we had a plasma reactor that is great at coating surfaces. By putting a loudspeaker into the plasma reactor and playing music to generate vibrations, we found that the particles bounced up and down, which resulted in them being coated evenly with a hydrophobic layer."

It seemed like the perfect match. The pSi MPs store the drug and the plasma acts as a barrier, slowing diffusion and thus release. But what music should be played? AC/DC seemed an obvious (and patriotic) choice, particularly the song "Thunderstruck" as the lightening that occurs in thunderstorms is also a plasma.

"Conveniently, 'Thunderstruck' possessed an adequate low-frequency beat to sufficiently bounce the pSi MPs in the plasma, without throwing them off and losing yield," says Voelcker. "But any song would have worked as long as the particles bounced high enough."

After evenly coating pSi MPs with hydrophobic plasma, the researchers were able to fine tune the kinetics of a given drug by increasing or decreasing the coating time (1). "For proof-of-concept, we used the anti-cancer drug Camptothecin – and we achieved up to 100 times slower release rates for the coated pSi MPs versus the uncoated pSi MPs," says Voelcker. "The pSi network protects the drug payloads from harsh conditions so the system could potentially be used to fabricate a delivery system that houses sensitive payloads."

Voelcker believes that the group can tune the chemistry of the pSi to hold virtually any drug or biomolecule – and they have already contemplated scale up. "pSi can be readily manufactured in high yields (gram quantities), thanks to a new etching technique we developed during the work," says Voelcker. "Secondly, plasma chambers are used on the industrial scale, so retrofitting them with a shaking system would be a relatively minor procedure."

For the moment, however, there is still much research to be done. Next, the group will be looking to correlate coatings with various hydrophobicities and thicknesses with drug release rates in order to allow for more versatile release profiles of the preloaded drugs.

The work has been widely reported by the media, but there is some confusion as to how rock music was involved. Since the group has experimented with a cancer drug, some people have wrongly formed the impression that chemotherapy will be more efficient if you listen to AC/DC while receiving it. "We do not play the music to help release the drug from the pSi MPs when they are being used for treatment; we play the music to fabricate the coated pSi MPs prior to administration," says Voelcker. "In fact, due to the plasma reactor being run under vacuum, we can't even hear the song playing whilst we do the coatings!" *JS*

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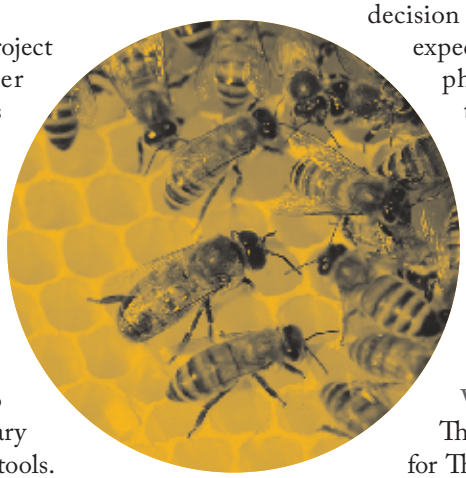
Hive of Industry

Are you a budding biotech or pharma startup? "The Hive" could be your chance to showcase your work

Nowadays, more than half of the industry's drug discoveries originate outside the walls of traditional pharma companies – with many firms supplementing their in-house R&D with external partners. But are the innovative startups responsible for much of the industry's early drug development getting the exposure they need?



"The Hive" is a project set up by Elsevier R&D Solutions where biotech and pharma startups can apply for the chance to be given a platform to share their work with the wider R&D community, and to receive complimentary access to Elsevier's tools. Christy Wilson, Senior Director, Pharma and Biotech Segment at Elsevier R&D Solutions, gives us the lowdown.

What?

The Hive aims to raise the visibility of promising work from biotech and pharma startups, and to share lessons in overcoming pharma R&D challenges with the wider community. Companies need to apply to have their work showcased.

Why?

The pharmaceutical community is facing a well-documented productivity challenge, and the costs associated with new drug development continue to soar. We think that the wider pharma R&D ecosystem can learn a lot from some of the younger, more nimble organizations. However, such companies can struggle to be heard and a lot of great research goes unnoticed.

How?

The Hive will publish case studies on successful companies, and we'll also be sharing work on social media channels. In addition, chosen firms will also receive complimentary access to Elsevier R&D Solutions' suite of tools; a collection of intelligence and technology tools designed to help improve discovery and development decision making. We also expect some traditional pharma companies to offer some of the innovative startups the capability to further develop and commercialize their innovations.

Who?

The best candidates for The Hive are biotech and pharmaceutical startups actively working in the early discovery stages through to early stage clinical development. Companies with three or more scientists on staff are ideal.

Potential candidates can apply to The Hive themselves or they can be nominated by someone else. Nominated candidates will complete a questionnaire about their research, funding, and goals over the next twelve months; selected candidates will then be invited to participate in a phone interview before the final selection.

When?

Rolling enrolment for The Hive commenced on April 20, 2016 and will continue throughout the year.

Getting the Message Across

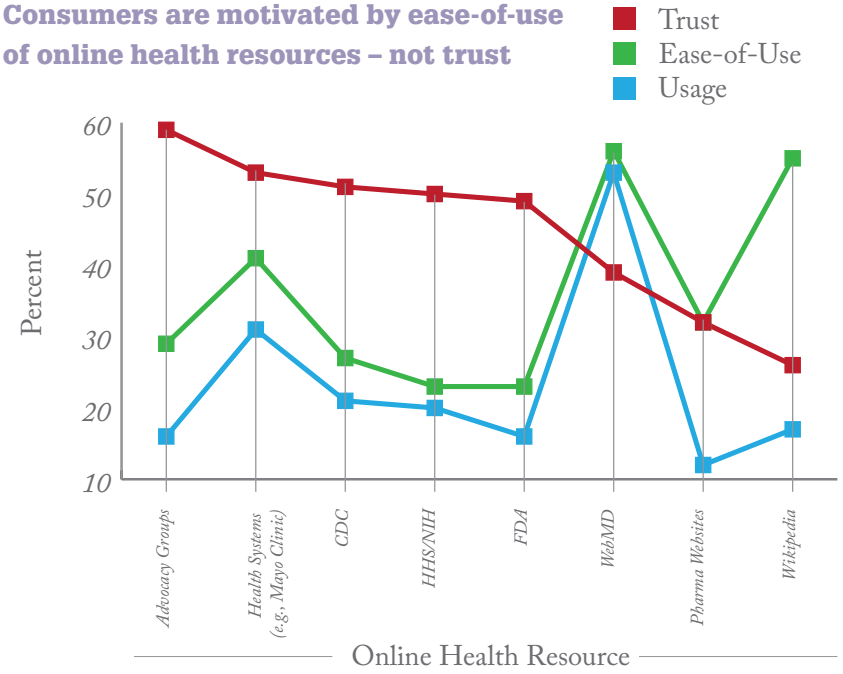
What's the best way to present a health resource? Apparently, ease of use trumps all other factors

People are becoming more healthcare savvy and more likely to use the Internet for research on medical issues, but what kind of resources are the most popular? In the US, where direct-to-consumer advertising is allowed, companies spend a great deal of money on developing marketing messages and resources about prescription medicines, so knowing exactly what makes a patient tick and grabs their attention is a high priority. Every year, Kelton and Makovsky Health conducts a US survey to glean insight into this area. For the 2016 Pulse of Online Search Survey, 1035 "nationally representative" Americans took part, and the results show that the most important factor influencing the use of an online health resource is ease of use (1). The fact that usability is important is not so surprising, but the fact that it typically outranks trustworthiness is interesting; 59 percent of people surveyed trusted advocacy group websites but only 16 percent visited them looking for health information – instead, they selected more user-friendly resources. *JS*

Reference

1. *Makovsky Integrated Communication, "Makovsky Pulse of Online Search Survey" (March 2016). Available at: http://bit.ly/1pzpXaW*

Consumers are motivated by ease-of-use of online health resources – not trust



Participants ranked websites in terms of their trustworthiness, ease-of-use, and whether or not they would use the website. Participant usage closely tracks ease-of-use, with Wikipedia slightly bucking the trend.

Doctors are trusted by 95 percent of consumers BUT...

63 percent of patients said they would research a prescribed treatment online following a visit to the doctor
53 percent would research an alternative treatment to the one prescribed by their doctor
61 percent are likely to ask for a specific prescription medication by name

Here are some other key findings from the 2016 survey.

The Millennial Generation* are the most responsive to pharma advertising

51 percent of Millennials, 36 percent of Gen Xers* and 26 percent of Baby Boomers*, would be motivated by an advertisement (TV, print, or online) to visit a pharma-sponsored website

1 in 5 Millennials trust celebrity endorsed products; as opposed to 1 in 10 among other age segments

42 percent of Millennials, **16 percent** of Gen Xers *and* **17 percent** of Baby Boomers said they visited Wikipedia because *"it was the first web link" appearing in their online search*

Patients increasingly research treatment info

Respondents conducting online health research:

2015: 24 percent
2016: 29 percent

Baby Boomers – born 1946-1964; Gen Xers – born 1965-1980; Millennials – born 1981-2000

Pharma on a Merger Mission

Abbott, Abbvie and Sanofi all make separate merger announcements – on the same day

April was a month of merger missions, with 40 billion dollars' worth of pharma deals being announced on just one day (April 28). Abbott agreed to purchase their competitor St. Jude Medical for $25 billion; AbbVie signed a $5.8-billion deal for cancer drug developer Stemcentrx; and Sanofi made an offer to buy the cancer drugmaker Medivation at $52.50 per share (valuing the company at around $9.3 billion).

Abbott and AbbVie's deals seem to be going smoothly. Abbott and St. Jude are excited to be forming a "premier medical device leader" with a focus on atrial fibrillation, neuromodulation, and structural heart and heart failure (1), while Abbvie is looking to complement its oncology pipeline. Stemcentrx has five novel compounds in clinical trials, including Rova-T, a biomarker-specific antibody drug conjugate that has shown promise for small-cell lung cancer in clinical studies.

Sanofi, on the other hand, is having a tougher time – Medivation rejected the unsolicited offer, arguing that it substantially undervalued the company, so Sanofi has threatened to take the offer directly to Medivation shareholders. "As you know, your shareholders have the ability to act at any time by written consent to remove and replace the Board. If the Medivation Board of Directors continues to refuse to engage with us, then we intend to commence a process to remove and replace members of the Board," a letter from Sanofi stated (2).

There are rumors abound as to what will happen next. According to Reuters, "people familiar with the situation" say that Medivation has opened its books to Pfizer and Amgen (3), and AstraZeneca and Novartis are also said to be interested in a bid and are reportedly talking to advisers about Medivation's value and possible next steps (4). Could we be about to see a bidding war?

With the blockbuster prostate cancer drug Xtandi on the market (which Medivation sells in partnership with Japan's Astellas) and the promising breast cancer drug talazoparib in late stage development, it's easy to see why Medivation could be a popular target for big pharma companies. However, whether any more bids roll in – and what effect the rumors may have on Sanofi's actions – remains to be seen. *JS*

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CSRxP Vs PhRMA

A US coalition seeks lower prices for US prescription drugs, but could their proposals undermine the competitive market?

The price of prescription drugs in the US is a hot topic – with Hilary Clinton, Bernie Sanders and Donald Trump all agreeing that something must be done to curb the rising costs. In fact, all three presidential candidates have endorsed a change in the law that would allow Medicare – the primary federal health insurance program for seniors – to negotiate prices with pharmaceutical companies. And they are not the only ones pushing for change. In April, the Campaign for Sustainable Rx Pricing (CSRxP) published a number of proposals for change, with the broad aim of keeping drug prices down and promoting generics. The coalition – which includes Walmart, and a number of healthcare providers and insurers – has focused their efforts on three main areas transparency, competition and value (1). Some of their proposed changes include:

- releasing details of drug pricing before FDA approval.
- disclosing the "true" R&D costs of a drug, including how much was funded by other entities, such as the National Institutes of Health.
- accelerating FDA approval of generics.
- reducing the 12-year exclusivity period for biologics.

The pharma industry, however, is not happy. In particular, CSRxP's proposals have faced fierce criticism from Robert Zirkelbach, Senior Vice President of the Pharmaceutical Research and Manufacturers of America (PhRMA). In a scathing press release (2), he said, "These so-called market-based proposals are nothing more than a litany of new government regulations and mandates that would undermine the competitive market and empower government bureaucrats and insurance companies to make one-size-fits-all treatment decisions for patients."

He argues that CSRxP's proposals would only apply to the small share of healthcare spending that goes toward life-saving medicines while exempting the largest healthcare cost drivers, such as hospital charges. He adds, "Importantly, these proposals would not improve coverage and access for patients, despite recent data showing that out-of-pocket costs are soaring and that insurers are continuing to discriminate against patients with chronic health conditions."

According to PhRMA, net prices for brand medicines only increased by 2.8 percent in 2015, when rebates and discounts negotiated by payers are factored in. CSRxP, on the other hand, claims that four of the top ten prescription drugs in the US have increased in price by more than 100 percent since 2011. It highlights a number of pharma companies, including Pfizer, which has apparently raised the prices on a number of brand-name products by 10 percent or more in the 2016 (3).

The debate continues, and is likely to rage on as the US presidential elections gather steam. *JS*

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Space Biology Awakens

Can the stress of space force fungi to produce novel therapeutics?

When placed under stressful conditions, certain fungi produce molecules known as secondary metabolites, which are not essential for growth or survival, but can be used as pharmaceuticals – penicillin and the cholesterol-lowering drug lovastatin are prime examples. Scientists have been able to shock fungi with some pretty stressful conditions here on Earth, but now they want to take it one step further… by blasting the fungi into space.

Researchers from NASA's Jet Propulsion Laboratory (JPL) and the University of Southern California (USC) decided to inflict a low-gravity environment on Aspergillus nidulans – a well-studied, filamentous fungus – after the USC conducted a genetic analysis and found that the fungus could potentially produce 40 different types of drugs – including some that could be used to treat osteoporosis. It is hoped that the low gravity, high radiation environment on board the International Space Station will prompt the fungi to produce therapeutic molecules that it hasn't been able to produce in experiments on Earth.

"This is the first project of its kind to send filamentous fungi to space and measure secondary metabolites as a potential drug discovery project," says Kasthuri Venkateswaran, a senior research scientist at the JPL. "This fungi is a well-established model fungi that showed production of novel compounds under stress. We have developed a few mutants that confirmed the production of secondary metabolites under stress, but no studies have yet tested the effect of microgravity yet."

Genetic analysis of Aspergillus nidulans has revealed the potential to produce metabolites with anti-cancer, anti-fungal and Alzheimer's disease properties, which would be highly beneficial to humankind back on Earth. But another drug that the fungi could potentially produce is an anti-osteoporosis compound, which is very relevant for astronauts who often face problems of decreased bone mass and density when in space. And producing drugs in space also has another advantage since astronauts don't have easy access to medicine when on a mission. "The ability to produce bio-active compounds in space will be very important to sustain life on a long duration flight – a journey to Mars for example, which NASA wants to do in the future," says Venkateswaran.

The JPL and USC researchers launched the samples into space on April 8, 2016 from Cape Canaveral Air Force Station in Florida – and Venkateswaran hopes to see some results within the next year. And if they are successful, the team will be looking to develop bio-engineering capabilities to perform larger scale experiments like this in space. *JS*

Cancer Static Shock

Are the metrics used to measure cancer drug efficacy inherently flawed?

When it comes to anticancer drug development, the difficulties of translating in vitro efficacy into clinical success are well known. But what if the metrics scientists use to measure a drug's effect on cancer cell growth, in vitro, are inherently flawed?

A group of researchers from the Department of Cancer Biology at Vanderbilt University School of Medicine, US, believe that in vitro cell proliferation assays suffer from a number of biases (1). In response, they have developed a new metric, called 'drug induced proliferation (DIP) rate'. Darren Tyson, Assistant Professor of Cancer Biology and lead author of the study, tells us more.

In what ways are current protocols flawed?

The use of a single measurement of cell number is widely employed across the scientific literature. Since it is based on a single time point measurement, we refer to this type of metric as "static". Static metrics are flawed in multiple ways. Firstly, because cells grow exponentially, an untreated population will rapidly outgrow a drug-treated population. Perhaps more critically, the ratio of control to drug-treated cells will steadily increase over time, creating the illusion that a drug's effectiveness is increasing over time. This is an example of what we call "time-dependent bias".

Another source of time-dependent bias in static metrics is that many drugs exhibit a lag time before their effect stabilizes within a cell population. This stabilization delay can cause drugs to appear more or less potent or effective than they actually are, which means ineffective compounds may be being improperly passed through the drug discovery pipeline or, conversely, effective drugs may be discontinued prematurely.

How does your proposed DIP rate metric differ?

The DIP rate quantifies the growth of a cell population, or more precisely, the rate of change of a cell population size over time. Since the most important characteristic of a cancer drug is whether it can halt or reverse tumor growth, DIP rate is a natural and accurate metric: on a plot of cell population doublings (log2 cell counts) vs time, it appears as the slope of a line. As such, it is independent of time, once any delays in drug action have been accounted for.

When developing the DIP rate metric, our biggest challenge was to determine when, after drug addition, a proliferation rate has stabilized. To support high-throughput drug screens, we had to develop reliable computational methods that could determine, in an automated fashion, when this occurs. The software is written in the R programming language and for academic applications can be obtained as free, open-source software (2).

What impact do you think this will have on the pharma industry?

If in the next few years proliferation rate-based metrics replace static cell counts in cell proliferation assays, we expect increased success rates in drug and biomarker discovery efforts to follow. We, in addition to our colleagues in companion papers, report examples of how DIP rate (and related metrics) can identify novel correlations and eliminate artifactual ones, providing a strong proof-of-concept for converting to time-independent metrics.

What are your next steps?

We want to measure DIP rates in large panels of cancer cell lines and search for novel molecular biomarkers of drug sensitivity, in addition to investigating DIP rate metric predictions of tumor cell responses in vivo. Both are translational tools for precision medicine.

We view the DIP rate as a metric of cell fitness in a particular environment, which extends beyond oncology. The DIP rate can act as a common currency, whether studying, for example, the influence of different drugs across a variety of cell lines, the effects of altering the microenvironment of stem cells, or the variation that exists at the single-cell level within a cell population (clonal heterogeneity, competition, or evolution).

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2. *D Tyson and LA Harris, "Code for Harris et al., Nature Methods 2016." Available at: http://bit.ly/23E8DOC*

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In My View

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

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

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

Better Together

Antibody drug conjugates offer a great deal of potential for drug targeting, but what's the best way of linking drugs and antibodies? Indeed, is there a single 'best way' in the context of the broad range of antibodies, drugs and diseases to which this modality is applicable?

By Vijay Chudasama, Lecturer of Organic Chemistry and Chemical Biology at University College London, UK.

Antibody-drug conjugates (ADCs) are constructed by covalently attaching drugs to antibodies, thus combining the specificity of antibodies with the therapeutic effect of cytotoxic drugs. Ideally, this approach confines the drug to the intended site of action, thereby limiting unwanted effects in healthy tissues and facilitating higher relative concentrations of drug at the target tissue. This is a powerful and exciting class of targeted therapy – and it has considerable promise in oncology; to date, two FDA-approved ADCs (Adcetris and Kadcyla) have reached the market, and around 40 ADCs are undergoing clinical evaluation.

ADC technologies are evolving rapidly, resulting in a correspondingly broad range of conjugation and linker technologies, each with their own advantages and limitations. One of the strongest approaches to gain access to next generation ADCs is through antibody engineering, which is technically challenging, but can result in a controlled, homogeneous product, and since homogeneity tends to mean predictability – this is a desirable feature for any drug. But there are alternatives, not least the application of relatively straightforward reaction protocols to modify native antibodies. These techniques have the advantage of simplicity, but may not always modify all the antibody molecules in precisely the same way. This type of quality issue needs to be balanced against the lower costs that are required for their use in ADC production. Moreover, it should also be noted that more homogeneous technologies in the class of native antibody modification are being developed at an astonishing rate.

At the moment, I don't believe that any one approach has advanced to the point where it could be considered the best/dominant technology; so there is no single, leading platform technology for ADC manufacture. And although the

"There is still no single technology that can be generally applied for the preparation of engineered, homogeneous ADCs."

current methods of ADC construction have gone some way to addressing the challenging issues of creating desired homogeneous antibody-drug conjugates, significant hurdles still remain. In particular, our understanding of the optimal combinations and precise interdependencies of particular features of an ADC – and the way in which these modulate its efficacy and pharmacokinetic profile – remains incomplete. Parameters of importance in ADC construction include the location of the drug on the antibody, the drug-to-antibody ratio, and the homogeneity of the ADC population. It is known that these will affect aspects of the product profile (for example, the required dosage, biodistribution, clearance rate, toxicity, and accumulation at the target tissue), but the nature of these links is not understood in great enough detail at present. In my view, much more work is required before we can completely and reliably predict key features of an ADC from the parameters applied in its design and the methods used in its construction.

Right now, it is unclear which site-specific strategies will be ideal for which drug types or drug-to-antibody ratios, or even which ones will best meet the basic requirements of safety, tolerability and low manufacturing cost. Even if we take the view that product homogeneity is an essential requirement, there is still no single technology that can be generally applied for the preparation of engineered, homogeneous ADCs with completely predictable attributes. Therefore, each site-specifically modified ADC must be constructed in a tailor-made fashion, building a method that works for the specific antibody and drug combination in question.

But it's not all negative – there is good news! I believe that we will gain a much better understanding of the influence and consequences of each site-specific modification strategy over the coming years, which means that the next generation of antibody-based targeted therapy will be based on a more rational design of bioconjugates, such that the "A" and the "D" can be connected with predictable effect. Will a single leading technology emerge? Perhaps – but it may be that particular technologies will turn out to be more suited to certain drug types, particular drug loads or specific antibodies. Regardless of the uncertainties around the optimal linkage strategy, I do know one thing: ADCs have an important role to play in the future of targeted therapeutics.

Beyond Counterfeiting

Our experience with implementing serialization, has shown us that anti-counterfeiting is just one of its potential uses.

By Izzet Senol, Maintenance and Energy Manager at Abdi İbrahim, Istanbul, Turkey.

When most people in the pharmaceutical industry consider serialization, they think about counterfeiting. But with a little outside-of-the-box thinking, track and trace has far more potential than simply deterring criminals. My company, Abdi Ibrahim (based in Turkey), began considering serialization back in 2009 – and since then, we've produced more than 826 million serialized boxes of medicine using 16 different packaging lines. But at the outset there were a number of concerns. Would implementing serialization lead to a drop in production efficiency or cause problems in cost and data management? Were there limitations with our current packaging lines or space limitations on our medicine packets? How would we integrate the serialization with our IT systems? All valid questions that we overcame – and we are now reaping the advantages. I'd like to share some of our experiences, in the hope that it may help other companies that are struggling to understand the benefits of serialization. Here, I'll briefly explain how we rolled out the solution – and how we've learned that there are benefits beyond counterfeit prevention.

"We also had to overcome the challenge of implementing the project without interrupting production."

Implementing serialization is not as tricky as it might seem. Once we had decided to go for track and trace, the first step was to conduct a detailed facility analysis. We had to study the layout of

"All in all, it was a lot of time and effort. Was it worth it? Definitely!"

our packaging lines to ensure that there was space for the new system on the line. And we had to check the dimensions of our packages and print designs – and then develop new designs with the appropriate space. It's useful to focus your serialization project on three main steps: box transfer, printing and data management. The most important step is the box transfer – transferring the packets to the serialization system. We decided to go with a standalone unit with a box intake system – this seemed like the best option after reviewing our existing line – and it also ensured good transfer, high-print quality and minimum rejection rates. I urge anyone considering serialization to look at the same aspects too. It's also beneficial to have a smart camera system that can read 2D code and carry out Optical Character Verification and Recognition checks, as well as software that can process the image correctly and minimize false rejects.

We also had to overcome the challenge of implementing the project without interrupting production. This isn't as difficult as you might think – we simply coordinated our project planning around our production schedules and other requirements. We arranged time for test boxes to be run on each line (an essential step – never forget to test your system!) and the results allowed us to optimize the mechanical solutions for optimum box transfer at each line.

We spent four months carrying out tests on the pilot line to check box transfer (all formats must be tested), print performance (must be checked at different temperatures and humidity), and print inspection (performance must be aligned with ISO 15415 norms). We also had to look at overall line performance to ensure it could cope with a real-size batch, and then there was data transfer. Data is essential in a track and trace system and you need to make sure that data flows smoothly from your line to the logistics warehouse, contract manufacturer, and so on. In addition, your server has to cope with multiple lines – we tested the server performance first at one line, then at three lines and finally at sixteen lines. The final step is an overall risk analysis.

Overall, the project took around 14 months and our reject rate is less than 0.3 percent (which is a relief given all of our concerns at the start of the project). All in all, it was a lot of time and effort. Was it worth it? Definitely! And once you've invested in serialization you'll see that it doesn't just deter counterfeiting. We've found that track and trace is also useful for other tasks like stock analysis – we can track amounts of our products both geographically and seasonally to help predict demand; for example, we'll be able to see a sudden increase in product demand and be able to respond appropriately. The track and trace system will also likely be invaluable during a product recall and can help to prevent tax fraud since all products are registered and there will never be more than one sale for one box.

Serialization is inevitable given regulatory requirements, and setting up the right system for your business can take time and effort. But the sooner you get on board, you'll realize that track and trace has potential well beyond keeping counterfeiters at bay.

Open Door IP

Intellectual property issues have suffocated many industry collaborations. And though IP is clearly valuable to pharma companies, there is also value in learning to let go.

By Charlotte Berg-Svendsen, Vice President Legal and IP at BASF Nutrition and Health, Norway.

By 2020, 10 percent of the global population is expected to be aged 65 years and older. In fact, the rapid increase in the aging population is a critical trend in the life sciences industry right now, because the elderly typically have more healthcare needs. In particular, there is a drive to address age-related diseases, such as cancer and Alzheimer's, but these significant challenges cannot be tackled by one stakeholder alone. There has never been a stronger need to collaborate.

However, collaborations, although commonplace in our industry, are not easy to get off the ground. After all, big pharma is based on big business, so all collaborations need to get over the first hurdle: negotiation. Each party involved is likely to have differing interests and, unsurprisingly, many collaborations

fail miserably before they even begin – sacrificed at the negotiation alter, with the death blow usually delivered by the intellectual property (IP) rights section of the agreement. Far too often, I've seen companies with IP strategies that do not mesh well with a collaborative business strategy.

Successful IP management is, in essence, about using IP to achieve your business targets, thereby creating value for your company's shareholders. Pharma is traditionally an IP-intensive industry – and for good reason; the large investments needed to develop a novel drug demand that companies secure any innovation through IP to ensure that those investments are recouped in the market.

But in my view, this is all set to change. The evolving infrastructure and challenges facing the life sciences industry will also affect how players approach their IP. Other tech-intensive industries have undergone similar changes; for example, we have seen a decline in focus on patents at tech companies with strategies instead centering around the notion that innovation needs to happen quickly – and that means in broad collaboration with other players. This is a far cry from pharma's gold standard: the coveted composition patent. I think there's a lot we can learn from these tech companies.

Fortunately, I think that the pharma industry is becoming increasingly open to ways to boost collaboration. As one example, we're seeing an increasing focus on open innovation (as emphasized in a recent cover feature in The Medicine Maker, http://tmm.txp.to/0316/Nilsson), and companies and academic institutes alike are offering innovation and R&D (as captured in their IP) to the public for further collaboration and development.

Developing platforms for this type of exchange is important. I think WIPO Re:Search is one good example of a multi-stakeholder platform. In 2011, a database was established by the World Intellectual Property Organization in collaboration with BIO Ventures for Global Health – and with the active participation of leading pharmaceutical companies and other private and public sector research organizations. The database provides information on the IP assets available for licensing, including compounds and enabling technologies, and the aim of the platform is to facilitate collaborations that can help fight neglected tropical diseases, malaria, and tuberculosis. The database demonstrates the commitment of the industry to solve some of the major challenges facing humanity with respect to these diseases.

The collaborative partnering and networking approach that we have seen in other industries should act as a healthy influence that can help us achieve even more in the life science fields. The outsourcing of R&D to smaller maverick players has also been trending for a while, and I believe that the interests of both big pharma companies and the smaller ones are aligned; both sides recognize the need for the others' contribution. The question is of course whether we can take this type of partnering to the next level, and develop communities that can cooperate in a structured way. BASF is currently exploring ecosystems – basically, small business networks – where selected players are invited to participate and achieve various goals. I like this approach and encourage others to try. Even when legal and IP challenges arise, flexible solutions can always be found.

Some think of open innovation as being contrary to good IP strategy and management. In my opinion, this is not the case. It is simply about dealing with reality and opening the door to a new environment.

THE GREAT BRITISH DEBATE

As politicians and the public argue over the minor point of the UK leaving Europe, we ask a more important question: what will a "Brexit" mean for the global pharmaceutical industry?

By James Strachan

The European Union (EU) is a coalition of 28 countries that have all agreed to cede certain aspects of national sovereignty in return for the benefits of global political influence and economic security. Whatever your opinion on the costs and benefits of this trade-off, there is no doubt that the EU, with a population of over 500 million citizens and some of the best-funded healthcare systems in the world, is a very important market for the pharmaceutical industry.

But the EU can look a little fragile a times. Unemployment is persistent (~9 percent on average and ~25 percent in some member countries); keeping weaker member countries afloat seems to be a constant burden; and developing a rapid, coordinated and effective response to external crises, such as an influx of refugees, is difficult when the disparate views of 28 members must be taken into account.

On June 23, 2016, the British public will be asked to decide whether or not the UK should remain a member of this complex coalition. How likely are the British to walk away from their cross-channel colleagues? Difficult to gauge. What are the likely consequences of such a 'Brexit' – not just for pharmaceutical companies based in Britain and Europe, but for those trying to sell into one or both of these markets? An even more complicated question. Our crystal ball is far from clear, but here we try to throw some light on the subject – and, importantly, what it means for the global pharma industry.

The past is a foreign country

Understanding Britain's sometimes strained relationship with EU institutions requires a short history lesson. In 1973, Britain joined the European Economic Community (EEC) – basically a trading bloc in which member countries agreed to impose no customs duties on each other's goods and services, while imposing common tariffs on products from outside the EEC. Two years later, in the 1975 referendum, pragmatic Brits voted to remain in the EEC. But since then, the EEC has evolved into the European Union – a very different creature, with its own flag, central bank, Supreme Court, parliament and president. "What was originally sold to the British people as an economic union has now become a political and social union," explains Neil Hunter, Life Science & Corporate Communications Director, at Image Communications Box Ltd.

With EU laws and courts superseding Britain's own, some Brits feel their country is being slowly absorbed into a foreign behemoth run by those with little regard for the UK's wishes or needs. "With each treaty, the EU accumulates more power," says Hunter. "The EU is marching closer to political unity with the end goal of a super-state: the United States of Europe." Given this fear, and given that the EU doesn't look as stable or as strong as the EEC of the 1960s and 70s, it's not surprising that the same pragmatic citizenship that voted to join the EEC may now be wondering about leaving the EU.

Polls have suggested that the majority of British citizens are 'Eurosceptic' (1) – which is to say, critical of the EU and its institutions. Despite this, it would seem that the UK is also nervous of change. Indeed, at the time of writing, most opinion polls suggest that the population is slightly in favor of remaining in the EU. Nevertheless, with older voters more likely both to support the 'leave' camp and to actually make the effort to vote, the result could be a very close call (2). Whichever way the British vote falls, the fact that the referendum is happening at all signals discontent and instability within Europe. And if Britain leaves the EU – taking with it a large contribution to the EU budget – the costs of events such as the Greek bail-out and the migrant crisis will have to be shouldered by a smaller core of wealthy member countries. Consequent tensions could fuel Eurosceptic parties in other EU members – and potentially lead to more referendums. The potential of a 'Grexit' (Greek withdrawal from the Eurozone) has been in discussion since around 2010, and there are rumblings of discontent in other EU countries too; thus, there is potential for a Brexit to cause a domino effect and to fragment the EU. "A number of countries are already talking about having their own referendums if Britain votes to leave the EU," says Hunter. "A vote to stay could strengthen the EU in its ambitions for closer union. But a vote to leave could lead to the unraveling of the entire project."

Who cares?!

Even if you live outside of Europe, the scale of the decision and potential for further change is important. In a speech made at the end of April in London, Barack Obama stated, "Ultimately, this is something that the British voters have to decide for themselves [...] And speaking honestly, the outcome of that decision is a matter of deep interest to the United States because it affects our prospects as well," (3).

Pharma is a global industry and the EU is one of its most important markets, so the potential for a Brexit matters. In particular, the UK often serves as an entry point to the EU market for foreign companies. If Britain lost – or ended up with limited access to – the EU "single market", these firms may need to look elsewhere when launching new products. There may also be consequences to global supply chains, such as the flow of ingredients, equipment and consumables.

Indeed, one of the concerns expressed by anti-Brexit campaigners is that Britain might lose access to the EU single market. Whether or not this would actually happen is debatable. EU treaties stipulate that if no agreement is reached within two years, the UK would revert to World Trade Organization (WTO) rules, whereby the UK's exports to the EU and other WTO members would be subject to tariffs. The UK would also likely introduce an import levy on goods coming from the EU to provide equal treatment between goods imported from EU member states and other third countries – but there are other options (see Post-Brexit Realities).

With the US and the EU currently negotiating the Transatlantic Trade and Investment Partnership (TTIP), a vote

"The precise effect of a Brexit will depend on how the UK responds in terms of future legislation."

to leave could position Britain outside of both the European single market and the new EU-US market. In that case, British goods exported to the US would face tariffs and so British companies could be at a disadvantage to EU-based competitors. In his speech, Obama explained, "Down the line, there might be a UK-US trade agreement, but it's not going to happen anytime soon, because our focus is in negotiating with a big bloc, the European Union, to get a trade agreement done [...] trying to do piecemeal trade agreements is hugely inefficient."

But the TTIP is by no means a done deal, and has taken a very long time to get to this stage – a consequence, Eurosceptics would say, of needing to take into account the wishes of 28 different members.

According to Angus Dalgleish, Professor of Oncology at St George's University of London (and a member of the 'Leave' campaign), one of the frustrating aspects of being tied to the EU is the red tape associated with EU regulation. "90 percent of companies in the UK don't even trade with the EU, but they still have to adhere to EU regulations," he says. Moreover, an individual country within the EU, such as the UK, cannot negotiate trade agreements with non-EU countries. Such deals are done on an EU-wide level on behalf of all member countries, which can take a significant amount of negotiation since all 28 EU stakeholders need to agree.

Accordingly, many in the UK are frustrated with the speed at which the EU negotiates trade deals; Eurosceptics point out that smaller non-EU nations, such as Iceland, have been able to rapidly negotiate agreements with countries like China. And for European pharma companies, there are many markets outside of the EU that are clearly of interest. "As Asia, South America, and Africa continue to develop, there will be a huge demand for pharmaceuticals," says George Chressanthis, Professor of Healthcare Management and Marketing at Temple University, US, and former Senior Director for Commercial Strategic Analysis at AstraZeneca. "Brexit would certainly give the UK a much greater, freer hand to negotiate free trade agreements with the growth markets in the developing world."

Helen Roberts, a lawyer at BonelliErede, concurs: "If Britain could negotiate bi-lateral trade deals with non-EU nations, for example with China or Latin America, UK-based pharma companies might benefit from freer trade – in the form of reduced customs duties, for example – if it could offer a significant trade benefit over trading with the EU market."

But there are warning voices too. "Trade between UK and EU pharmaceutical companies may be significantly restricted if the UK does not arrange a free-trade deal with the EU post-Brexit," says Davide Levi, Managing Director of Navigant's Life Sciences Practice. "Due to greater ease of generic entry in the UK, prices in the UK often decrease faster compared to markets such as France and Germany, making exportation attractive. UK drug prices may be removed from other states' international reference pricing baskets; potentially reducing prices across Europe as prices in the UK are typically higher than average. If this occurs, it could serve to make product launches in the UK less attractive."

Similarly, UK-based biopharma companies are currently free to sell their products to the EU without trade barriers, and the same goes for companies in the EU selling to the UK market (which was ranked in the top ten global markets in 2013 [4]). A Brexit may require these companies to change their domicile to an EU country to continue to enjoy the same tariff-free trade with the EU.

Scientifically speaking

As well as impacting pharma companies via trade, a Brexit could also have a more direct impact on scientific research. At present, the EU, via the European Research Council (ERC), supports EU-based scientific research through grants allocated on the basis of "peer-reviewed excellence", regardless of political, economic or geographic considerations. The UK contributed nearly £4.3 billion for EU research projects from 2007 to 2013, but received nearly £7 billion back over the same period, so some UK scientists fear that a Brexit would result in a net loss of research funding (5). However, Eurosceptics claim that the shortfall would be made up from savings gained by no longer contributing to the total EU budget.

Another point is that the EU facilitates collaborations between EU scientists. "Science is such a large-scale collaborative undertaking these days that viewing it in national units makes little sense," says Mike Merrifield, a professor at the University of Nottingham. However, Chris Leigh from Liverpool John Moores University, argues that, if anything, collaborative work outside of the EU would increase. "In order to control overall inward migration, the UK government is having to restrict entry from non-EU countries to counteract migration from EU countries, which means that non-EU scientists are having to cover additional costs and jump through many hoops to work in the UK." For more discussion about the impact on science, see Helping or Hindering Science?

Finally, when it comes to the regulation of medicines, being in the EU has advantages for the globalized pharma industry; harmonized regulations mean that pharma companies don't have to adhere to multiple regulatory systems to sell to different EU nations. Thus, companies from outside the EU can launch

EU timeline

1951
Treaty of Paris signed by Belgium, France, Germany, Italy, Luxembourg, the Netherlands, establishing the European Coal and Steel Community (ECSC)

1957
Treaty of Rome creates European Economic Community with the six founding members

1973
Denmark, Ireland and the UK join the European Economic Community

1975
A British referendum shows 67.2 percent in favor of UK remaining a member of the Community

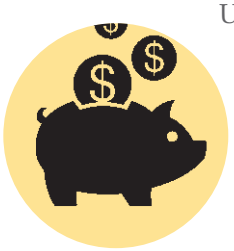
1978
European Council establishes the European Monetary System based on a European currency unit (the ECU) and the Exchange Rate Mechanism (ERM). All the community's members – with the exception of the UK – join the ERM

1981
Greece becomes 10th member of the European Community

1986
Spain and Portugal join the Community

1991
Treaty of Maastricht creates European Union and paves way for the euro

1995
Austria, Finland and Sweden join the Union, bringing membership to 15



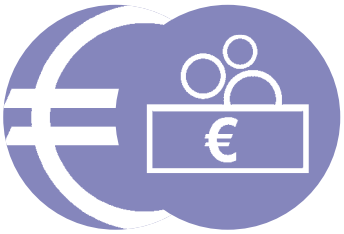
1997
Amsterdam Treaty signed, emphasizing citizenship and the rights of individuals, more powers for the European Parliament, and the beginnings of a common foreign and security policy (CFSP)

1998
Establishment of the European Central Bank

1999
Entire Commission led by Jacques Santer resigns following report by the Committee of Independent Experts on allegations of fraud, mismanagement and nepotism

2000
September: Danes vote against joining the single currency. December: formal proclamation of the Charter of Fundamental Rights of the European Union

2001
Treaty of Nice signed, reforming the institutional structure of the European Union to allow for eastward expansion



2002
Euro coins and notes enter circulation in the 12 participating member states

2004
European Union's biggest enlargement as 10 new countries join – Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Slovak Republic and Slovenia

2007
Bulgaria and Romania join the EU, bringing membership to 27

2009
European Parliament elections, the biggest trans-national elections in history

2013
Croatia joins the EU

2016
UK has a referendum on EU membership

Helping or Hindering Science?

How important are EU science programs to UK science?

Mike Merrifield: The main attraction isn't actually the funding, but the structures provided by Horizon 2020 and other EU initiatives. For example, the EU provides very effective mechanisms for setting up exchange programs of both junior and senior researchers, with integrated training programs and other ways of sharing expertise.

Chris Leigh: There are some universities and research groups that rely on EU funding, but for the bigger picture, the EU only funds around 3 percent of the UK's research and development base. Even in the extremely unlikely event that we cut all ties with EU science networks, it would be hard to argue that the overall impact would be much greater than this 3 percent figure. It's also important to note that EU science funding represents around 3-4 percent of our net contribution to the EU project.

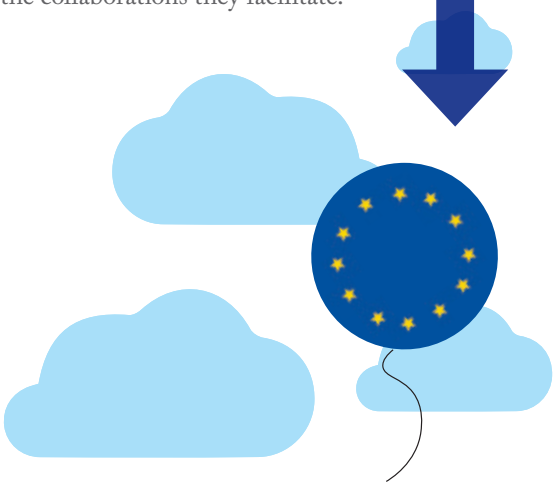
Steve Bates: The UK is a net recipient of EU funding for its health research, accessing more funding per capita than any other country. Since 2007, UK scientists have received around £3.7 billion from the EU. As of 2011, the UK won 16 percent of all FP7 funding to EU member states and 27 percent of European Research Council funding. These fractions are higher than the overall UK contribution to the EU budget (about 11.5 percent) and the UK's share of overall EU spending (about 5.6 percent).

Would Brexit mean an end to the UK's participation?

Merrifield: Those in favor of Brexit point to countries like Israel, who are "associated countries" of the Horizon 2020 program, and hence can benefit from the funding that it offers. Those opposed to Brexit point to Switzerland, which has a longstanding involvement with these programs, but their agreement is tied in with free movement of people between Switzerland and the EU, and unless they extend their current free movement arrangements to include Croatia, they will lose access to EU science programs at the end of 2016. One cannot say definitively how closely the UK would remain associated with these programs post-Brexit.

Leigh: Switzerland had an agreement in place with the EU but, after they voted against free movement in a referendum, they reneged on that agreement. The UK situation would be different as any negotiations and subsequent agreement would have to be determined in the two years after a Brexit vote. I'd also point out two things. Firstly, Israel is a net beneficiary from their involvement in EU science networks and yet has no free movement agreement with the EU. Secondly, CORDIS data shows that Switzerland is still very much involved in EU science networks – more so than the UK on a per capita basis. The only difference is that the Swiss government picks up the tab for some of the projects.

Bates: Outside the EU, it seems likely that UK life sciences would be shut out from such funding schemes. There has been no proposal put forward for the sector to consider where the money might come from to replace this in the scenario of the UK leaving the EU. Several UK life science companies have found the Horizon 2020 process difficult and over burdensome to manage. However, this process issue can be overcome. What access to equivalent funding and collaboration would look like if the UK left the EU is not clear, and hence not a compelling alternative to the current situation. The value of funding schemes is not only in the hard cash they provide, but also in the collaborations they facilitate.



"From a more logistical point of view, a Brexit could have implications for the EMA."

their drugs in the UK and throughout the EU via a single regulatory body. In the case of a Brexit, companies that wanted to launch their drugs in the UK may have to go through a UK-specific regulatory body (the Medicines and Healthcare products Regulatory Agency [MHRA]). Dealing with any regulatory body can be a headache for pharma – and there are already frustrations at the differences between EMA and FDA procedures.

"Sharing a common regulatory agency and common market with the entire EU is a benefit for the UK. While the UK is likely to strike trade deals with non-EU nations in the event of Brexit, it is unclear whether this will make up for the loss of EU and EMA membership," says Levi. "From the perspective of a large pharmaceutical firm, the need to work with an additional regulatory agency, while somewhat inconvenient, would not be a significant cost and is unlikely to discourage investment in the UK but the challenges for small companies may be greater."

From a more logistical point of view, a Brexit could have implications for the EMA itself; EU rules stipulate that the EMA must be based within the EU, so it would likely have to move its headquarters from London. Some European countries would perhaps rejoice at this news; Anders Blanck, Director General of the LIF group representing research-based drug-makers in Sweden, has already been encouraging the Swedish government to immediately launch an intensive lobbying campaign to make Sweden the new host country for the EMA (9).

Conversely, those campaigning to leave point to the cost of EU directives for small businesses and medium sized enterprises. Dalgeish claims it costs UK business more than £33 billion a year. He decided to campaign for Britain to leave the EU after an anti-cancer drug he was working on was denied approval by the EMA because of the Clinical Trials Directive. "Without the backing of a large pharmaceutical company there was no way to carry out further studies of the scale the EMA wanted – it would have cost over £2 million," says Dalgleish. Work on the drug had to stop, but Dalgleish believes that had it been left to UK regulators, the drug probably would have been approved. "There's some evidence that even people in big pharma find the barriers and costs too high to do the clinical studies they want to," he adds.

Daniel Hannan, a Member of the European Parliament and another member of the 'leave' campaign also targeted the directive. "Britain has just 1 percent of the world's population, but in 2004 we were carrying out 12 percent of the world's clinical trials, but when the directive came in, this went down to 1 percent. I think we can do better without those directives."

The Clinical Trials Directive has been criticized by many in the global pharma industry, so much so that a reformed version will come into play after May 28, 2016. The new directive has not settled all of the critics, but a functioning clinical trials regulation encompassing the EU inarguably has its benefits because you can use one process to apply to conduct clinical trials in multiple EU countries. What would happen if the UK were to be outside of that process? Would companies bother going through a separate process or would they just use an EU site?

The Picture of Divorce

Levi suggests the UK could strike a deal to remain in the EMA, or create a regulatory agency that manages to mirror much of the EMA's guidance, with the ability to opt out of any directives and regulations it doesn't want. "The thought of Britain leaving the EU creates a lot of uncertainty as to what potential effects it might have – especially if policy developments are required," adds Chressanthis. "Companies may not like the current environment, and a different path may even lend itself to something better, but change creates

You Spin Me Right Round

In the run-up to the 2015 General Election, David Cameron, promised that he would hold an in-out referendum on the country's EU membership – after a "renegotiation" with the EU. His words appeased his Eurosceptic voter base – and after he won, there was no backing out. Cameron deliberated with European leaders and then presented to the British people a letter containing the details of some – arguably small reforms (mainly to in-work benefits EU migrants are eligible for) and proclaimed the negotiation a success. Since then he been strongly campaigning for Britain to remain in the EU. Others calling for the UK to remain within the EU include Barack Obama (President of the US) and Shinzo Abe (Prime Minister of Japan).

Post-Brexit Realities

Is leaving the EU really a "leap in the dark" for the UK? Helen Roberts, solicitor at BonelliErede and a former member of the UK Regulator for Promotion of Medicines (PMCPA) attempts to shine a light on the possibilities for Britain post-Brexit.

World Trade Organization model

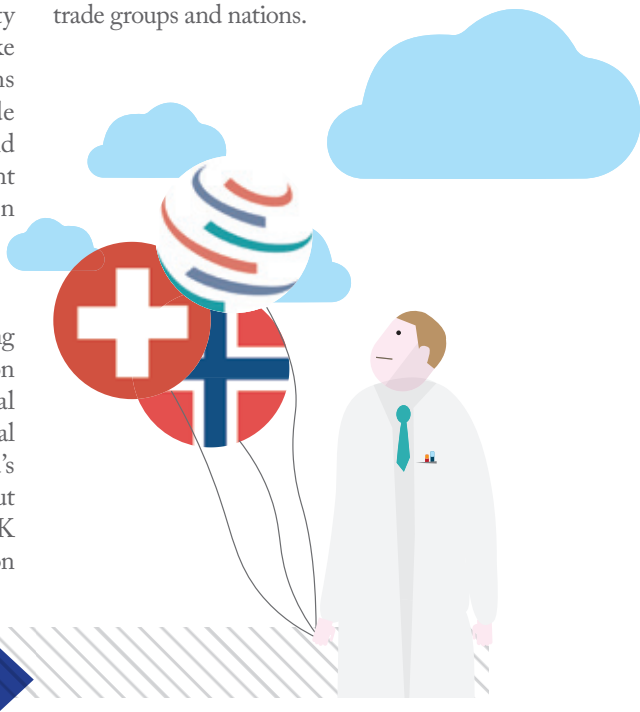
Under WTO rules, each member must grant the same 'most favored nation' (MFN) market access, including charging the same tariffs, to all other WTO members. As a WTO member, the UK's exports to the EU and other WTO members would be subject to the importing countries' MFN tariffs. Compared with EU or EFTA membership, this would raise the cost of exporting to the EU for UK firms (9).

The Norway model

The Norway model would involve joining the European Economic Area (EEA) alongside Norway, Iceland and Liechstenstein, and these members would have the right to veto the UK's entry (as they did for Slovakia). The UK would still need to pay a contribution to the EU Trade through an 'EEA Grant' – likely to be about 75 percent of the current contribution the UK makes to the EU – without the opportunity to be represented in, to vote in, or take part in EU negotiations or decisions relating to the EU or to the trade partners of the EU. The UK would then be required to adopt a significant number of EU laws that have been adopted by the EEA members.

The Swiss model

The Swiss model would involve joining the European Free Trade Association (EFTA) through a series of bi-lateral agreements, continuing to make financial contributions to the EU. Switzerland's current contribution to the EU is about 50 percent of the UK level. The UK would probably adopt the EU legislation voluntarily, and would gain access to the EU market if it agreed to free movement of EU goods, services and capital. The UK would lose the opportunity to be represented in, to vote in, or take part in EU negotiations or decisions relating to the EU, or to the trade partners of the EU; however, the UK could negotiate a series of trade agreements with other trade groups and nations.



uncertainty – and businesses by and large don't like uncertainty."

The precise effect of a Brexit will depend on how the UK responds in terms of future legislation and incentives for the pharma industry, and is difficult to predict. However, many executives, such as Andrew Witty from GlaxoSmithKline and Eli Lilly's John Lechleiter, have support Britain remaining in the EU (7). The European Federation of Pharmaceutical Industries and Associations (EFPIA) has also been vocal on this issue, claiming that "the UK's continued membership of the EU is in the best interests of the pharmaceutical industry in the UK and across Europe" (8). UK industry bodies, such as the BioIndustry Association (BIA), are also supportive of the UK remaining with the EU. "Feedback from BIA member companies of all sizes has been unanimous in calling for the UK to remain in the EU as it acts as a catalyst for scientific collaboration and development across all member states," says Steve Bates, CEO of the BIA. "By being part of the EU, the UK has the opportunity to demonstrate the benefits of its progressive science based approach to the wider EU members and has a strong and powerful voice to influence change in the European market."

The best of times, the worst of times

Ultimately, no one really knows how a Brexit will affect the wider world – or pharma in particular. Roberts says that a worst case scenario for pharma could include some or all of the following: "A short transition phase for Britain to leave the EU, sterling fluctuating at a high exchange value, fast withdrawal of R&D funding, doubling of customs duties for UK exports into Europe, fast departure of UK-based pharma companies to other countries, resourcing and funding difficulties for MHRA when it tries to recruit staff it needs to provide guidance, relocation of EMA, legal action against UK authorities for the costs of Brexit, and delays in implementing EU initiatives, such as anti-counterfeit coding on packs of medicines."

Meanwhile, Levi raises the possibility of a drawn-out creation of a new regulatory agency to replace the EMA and a complex approvals process within the new regulatory framework that could potentially discourage companies from launching products in the UK, depending on the complexity of the process. "UK prices may also be removed from international reference pricing baskets across the EU, which could have the effect of driving down pharmaceutical prices in many markets across the continent," he adds.

And what about the best-case scenario? Roberts describes an orderly withdrawal of Britain with the opt-outs it seeks, with no change to how it trades inward and outward products and services, with no resistance from other EU member states to Britain's proposals.

"A best-case scenario would be one in which the UK strikes a deal to remain in the EMA or creates a straightforward regulatory agency quickly," says Levi. "The new regulatory agency develops a streamlined approval process and loosens restrictions on research; corporate taxes are reduced significantly to encourage pharmaceutical investment; UK prices are retained in all international reference pricing baskets across the EU; and a free trade agreement eliminating all importing restrictions between the UK and the EU is negotiated."

The vote will take place on June 23, 2016. Look out for the announcement of the results on our social media channels – and our thoughts on the future of pharma! And let's not forget that a Brexit isn't the only political issue that may be shaking pharma's world in 2016. In November, the US – the largest pharmaceutical market in the world – will be holding its Presidential elections. We'll be reporting on this – and how each candidate's plans could affect the pharma industry – closer to the time.

James Strachan is Associate Editor of The Medicine Maker.

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The Beginning of the End of Quality by Design

Where did Quality by Design come from? Where will it lead to in pharma? And is there a day when the concept will no longer exist?

By Jasmine

"Begin with the end in mind" is a very sensible principle for success in almost any aspect of life. In pharma manufacturing, this principle is encouraged by Quality by Design (QbD), which urges manufacturers to manage sources of potential variability in a process and to "get it right first time" when it comes to manufacturing. But when thinking about the quote "begin with the end in mind," I was inspired to write this piece on QbD – and unlike many traditional best practices guides in this area I wanted to take a different angle by discussing the very beginnings of QbD, where it has ended up today and its ultimate 'end'. Can there ever really be an end to QbD? Read on…

At this point, you may be asking why it is important to reflect on the past of QbD at all. The answer is clear – reflecting on the past allows us to understand a subject better, and to make improvements. Very early on in my career as a QbD practitioner and champion, I realized that understanding the history of quality is very important if we want QbD to become entrenched in the pharma industry. History teaches perspective and proportion, and I feel that both of these are lacking in the debate on how and why QbD will provide better drugs and healthier lives. In addition, an awareness of quality history reduces the risk of yesterday's mistakes being repeated; in healthcare, mistakes can be fatal! So let me take you on a historical journey of the birth of QbD in the pharma industry. As fellow pharmaceutical professionals, I hope you find this fascinating – and I look forward to seeing how history inspires you and modern pharma.

Let there be quality

The beginnings of modern quality control can perhaps be traced to the mass-production manufacturing techniques that started during the industrial revolution. Large-scale manufacturing methods were further modulated by the demands associated with the two World Wars of the 20th Century; for example, the need for making large numbers of interchangeable parts for military equipment created more stringent requirements for precision and accuracy. Eventually, the lessons learned during this period filtered through into peacetime industry.

Even so, for many years most industrial processes assured quality by inspecting the end product only. But by the 1930s, a new approach to quality was apparent; notably, Walter Shewhart, an American engineer and statistician, shifted industrial emphasis from the quality of the final product to improving the process that creates the product. To this end, Shewhart advocated the use of engineering principles to build quality into the product, and introduced statistics for quality assurance purposes – in particular the measurement of variation as an indicator of process stability. Shewhart's methods were espoused by Deming and Juran, his colleagues at Western Electric in Chicago (1).

While Shewhart brought the maths, Deming and Juran developed the management perspective on quality. They believed that quality improvement required, above all, management commitment and action; and that these, when effectively applied, motivated the

workforce to attend to quality. Deming's approach can be summarized as follows:

- emphasize the need for change
- institute firm leadership
- reassure the workforce
- break down barriers between departments
- eliminate numerical targets and slogans
- promote continuing education
- eliminate the need for mass inspection by building quality into the product in the first instance, and continuous improvement of the production system.

According to Deming, a real improvement in quality was impossible without profound knowledge, which requires in-depth understanding of the following closely interrelated elements: systems approach, knowledge theory, variation analysis, and human psychology. In short, Deming proposed a systematic approach for continuous improvement, which balanced the technical aspects of quality with the human dimension (2).

Surprisingly, however, the US did not remember these lessons for long, and in the absence of competition, the US industry mistakenly came to believe that it had reached the ultimate stage in production and management systems. But at this time, in the eastern edge of the world, occupied post-war Japan desperately needed to reinvent its economy. The Union of Japanese Scientists and Engineers (JUSE) was formed in 1947 with the purpose of guiding Japan's economic rebirth. Deming and Juran collaborated with JUSE to formidable effect, leading to the improved benchmarks of quality that we see in many of today's industries. This period saw the emergence of influential quality leaders including Kaouru Ishikawa, Genichi Taguchi and Shigeo Shingo; these individuals, in association with JUSE, Deming and Juran, revolutionized Japan's automobile industry by blending American theory and innovations with Japanese cultural influences and reinventions.

"Understanding the history of quality is very important if we want QbD to become entrenched in the pharma industry."

Contemporaneous developments in other industries included Fisher's Design of Experiments (DoE) innovation in the UK, designed to optimize the potato yield in the UK's post-war agriculture industry. DoE enabled experimental and observational inquiries to be conducted so as to maximize the information obtained for a given expenditure (3), and is now a common tool used in QbD-based product development. Similarly, the period just after the Second World War saw the insurance industry develop risk management systems to safeguard their own, as well as their customer's interests. Risk management soon became another significant tool employed in QbD.

The effect of this systematic attention to quality soon became evident. In particular, Japanese industry became increasingly powerful, and by the 1970s, Japanese product quality had far surpassed that of America. The watershed event that would emphasize the increasing industrial competition that the US was facing from Japan – and catapult the theories of Deming and Juran back into American manufacturing – was a 1980 NBC television documentary titled, "If Japan Can, Why Can't We?" (4). Following this, there was a renewed American focus on quality management, aided by individuals such as Armand V. Feigenbaum and Philip Crosby. Before long, improved concepts such as Six Sigma were developed.

There is a common thread to all these stories – namely, "needs to means". Thus, over time, the evident need for quality assurance led to innovations with far-reaching consequences for industry: statistical process control by Shewhart, QbD by Juran; acceptance Sampling for the US military; design of experiments by Fisher; risk management by the insurance industry; the Toyota production system (now popularly known as lean management); quality circles in Japan; and Six Sigma in Motorola.

What about pharma?

The story of quality in pharma is also a "needs to means" tale – quality issues led to quality legislation, and quality legislation led to quality improvements. We now live in times when the stated regulatory goal is to create "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight" (5) . It has been a long journey to reach this point, and the FDA is an interesting yardstick to use for understanding how system-based thinking has evolved within the regulatory bodies. A number of incidents have affected the FDA's regulation of (see Shaping Regulation Today) the drug industry, and hence influenced the development of quality legislation in the pharma sector (6).

Given that Juran trained the management of Takeda Pharma in quality systems in the 1950s – it is perhaps extraordinary that it took another fifty years before QbD really became the

"Modern quality systems like this help us to avoid medicine-related disasters of the past."

regulatory and then the industry's choice. The systems approach visualized by Deming – i.e., the holistic view of industry operations as a system of interrelated processes, and the latter as sub-systems of interacting factors – was embodied in the FDA's regulatory framework "Quality Systems Approach to Pharmaceutical cGMPs" and the ICH Q10 Guideline on "Pharmaceutical Quality Systems" – and then adopted by pharmaceuticals in the early 2000s. In its report on cGMP for the 21st century, the FDA identified particular aspects of pharmaceuticals manufacture that are incompatible with modern quality principles. In particular, the regulators asserted that (7):

- pharmaceutical processes are static
- the functionality of material characteristics in relation to process is not well understood
- out-of-specification values occur frequently
- measurement systems suffer from variability
- differentiation between inherent and special causes variability is difficult
- information needed for continuous improvement is segregated in different departments.

The FDA further endorsed QbD, as per the PAT Guideline (2004), the Process Validation Guideline (2011), and the Analytical Method Validation Guideline (2014). ICH's Q8, 9, 10, 11 and the upcoming Q12 also are embodiments of patient-centric systematic development and manufacturing.

The End

In most industries, quality management tools are seen as a way to forge a closer connection with the consumer while also reducing variance and waste. The pharma industry, however, is perhaps the only industry making products that consumers often wouldn't really "choose" to buy – in many cases consumers may not even be in a position to decide by themselves on their choice of product. At the same time, the difference between a good and bad quality product can be a matter of life and death for a consumer. As such, it is difficult for our industry to gauge customer satisfaction – and we must also admit that the potential for harm is not always easy to detect. All drugs are subject to highly stringent regulatory requirements and yet some unfortunate effects can still come to light after a drug has reached real-life patients. Safeguarding the consumer –

Shaping Regulation Today

A number of unfortunate events have contributed to the development of today's drug regulation.

Publication of "The Jungle" in 1906

Upton Sinclair's novel was written to expose the way immigrants were exploited in the US, but readers were more worried about the book's description of the health violations and unsanitary practices of the American meatpacking industry. The book fostered the creation of the Pure Food and Drug Act, 1906, as well as a meat inspection law.

The Elixir Sulfanilamide incident in 1937

Sulfanilamide had been used safely in tablet and powder forms, but when the company, by popular demand, created an oral liquid form it resulted in many patient deaths, including a number of children, across the US. The liquid drug was not tested for toxicity because there was no law at the time that required safety studies. The incident accelerated the enactment of the 1938 Federal Food, Drug, and Cosmetic Act.

the patient – is paramount in the drug industry. This is why we must embrace QbD, as well as lean manufacturing and Six Sigma. Modern quality systems like this help us to avoid medicine-related disasters of the past.

Change, however, is the only constant and today's quality systems are challenged by the pressure for high volume, high quality manufacture, coupled with the need to reduce energy costs and carbon footprints. In addition, pharmaceutical manufacturing is being affected by the rise of personalized medicine (how do we manufacture them at a commercial scale?) and by changes in information technology and knowledge management (how do we make use of big data?).

There is still much to do so can we ever truly reach an "end" to QbD? One of my managers once told me that if I can make my job as the QbD champion cease to exist – i.e., if product development doesn't need QbD proponents anymore – then I will have done my job well. In a way, that would be the "end" of QbD – when pharma doesn't need to be reminded about developing and manufacturing products with the patient at heart. So when conferences and publications centered around QbD no longer exist, and when even articles like this are passé, the QbD story in pharma will have come to a happy ending. In many other industries it has almost reached that conclusion already – a Google Scholar alert with the search terms "Quality by Design" for many months now has affirmed my opinion that QbD at present is only pharma's pet. And I hope we too soon evolve to make it a standard part of our way of developing and manufacturing better products.

I know there is a great deal more to be discussed – and in future articles I'll be discussing lean Six Sigma tools in product development, capability building for QbD, the use and misuse of statistics in QbD, and risk assessments in product development.

Jasmine is Principal Scientist, Quality by Design, at Dr. Reddy's Laboratories SA. The views expressed are personal and do not necessarily reflect those of Jasmine's employer or any other organization with which she is affiliated.

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Thalidomide incident in the 1950s

Thalidomide was licensed in Germany in 1956 as an over-the counter sedative and became popular among pregnant women because it could help relieve morning sickness. In the following years, more than 10,000 children were born with disabilities. The disaster prompted the introduction of more stringent drug testing and licensing rules for drug safety and efficacy in a number of countries, including the US and the European Union.

Generic drug scandal in the late 1980s

Noting that its application to manufacture generic drugs was being repeatedly delayed, Mylan began to investigate the FDA. In 1989, a number of FDA officials pleaded guilty to accepting bribes from generic drug companies. It was also found that several manufacturers had submitted falsified data when looking to market their generic drugs. Dozens of drugs were suspended or recalled, and in the early 1990s, the FDA established the Office of Criminal Investigations (OCI).

Heparin adulteration in 2008

Following a number of deaths, and hundreds of adverse events, heparin manufactured in China on behalf of US pharmaceutical companies was found to be contaminated with oversulfated chondroitin sulfate (OSCS), which at the time was difficult to detect in the standard safety tests. The incident led to greater scrutiny over global supply chains and changes were also made to the heparin monograph in the US Pharmacopeia.

Biopharma's Continuous Future

Traditional pharma manufacturers are already dipping their toes in the waters of continuous processing, but what about when it comes to biopharmaceuticals?

There is tremendous pressure on companies to reduce the cost of developing new medicines, while at the same time maintaining high standards for quality and safety. In addition, there is a shift towards flexible manufacturing methods that can readily be duplicated at multiple sites worldwide to enable companies to meet local market needs. It's clear that changes are needed in the bio/pharma industry's manufacturing models – and Martin Smith, Chief Technology Officer at Pall – believes that continuous processing may be the answer.

What trends are driving increased interest in continuous processing for biopharmaceuticals?

For biopharmaceutical manufacturing, process intensification has led to the higher product titers needed to make continuous manufacturing a viable option. Single-use technologies, which are ideally suited for use in continuous operations, are also being more widely adopted at the commercial scale.

Continuous manufacturing can help reduce manufacturing and environmental footprints, as well as manufacturing costs. Continuous processes are monitored on an ongoing basis to ensure that process parameters are maintained at optimal values, leading to more consistent processes and product quality. Smaller bioreactors run for longer times can provide the same quantities of product obtained from batch reactions in large reactors – and a smaller footprint often equates to reduced capital expenditures, allowing for reduced energy, water and raw material consumption, resulting in lower operating expenses. Continuous processes are also more automated, which minimizes human intervention and the potential for error.

There has also been discussion around mobile continuous processing, which could, for example, take place in remote regions of emerging countries or anywhere outside of traditional factory walls. Because of this, technologies that are brought to the market for continuous unit operations should consider both traditional and mobile settings.

Is continuous processing for everyone?

One factor that is preventing some companies from actively pursuing continuous processing is perceived regulatory uncertainty, but the FDA, in particular, has been an advocate of continuous manufacturing and has been very vocal about the advantages. Perhaps the biggest challenge to continuous processing is the industry's existing infrastructure – and existing processes that are already cost effective are unlikely to be completely converted to continuous. However, there is an opportunity for companies to adopt a 'hybrid' system comprising both batch and continuous processes for operations where there is clear evidence that continuous will provide benefits.

In my experience, it is in newer, multi-product, flexible manufacturing facilities that continuous technologies are being more widely implemented, often in conjunction with disposable systems for biomanufacturing. One of the challenges we face at Pall is the wide variation in customer needs and expectations. It is a bit like the Wild West at times because there are multiple ways of doing things. We don't know how it will all play out yet, but we are having many conversations about how the new technologies we are developing can provide the widest applicability range.

"The discussion around continuous processing is very vibrant and I'm seeing keen interest at the unit operation level."

Despite the hurdles, the discussion around continuous processing is very vibrant and I'm seeing keen interest at the unit operation level. Most companies, including drug manufacturers and contract manufacturing organizations, have recognized the potential benefits and are at least exploring some aspects of continuous manufacturing. There is no example yet of a completely integrated end-to-end continuous bioprocess on the commercial scale, but people are definitely interested in technology solutions for continuous unit operations. Several biologic drug substances are already being produced using continuous processing (perfusion).

How are new technologies responding to the challenges of continuous processing?

There are three main challenges associated with the implementation of continuous processing. First is the need for cost-effective continuous technologies for some unit operations, such as large-scale filtrations in bioprocessing and continuous crystallization for small-molecule manufacturing. Second is the need for clearly demonstrated performance under cGMP conditions at the commercial scale. Third is the need for process analytical technology that can truly enable real-time analysis of manufacturing processes from end to end. The industry is making great strides in all of these areas, with new developments announced almost daily. Pall has actively expanded its portfolio of continuous bioprocessing solutions and has a number of new technologies under development, as well as some recently launched. For example, our Cadence Acoustic Separator (CAS), which is based on acoustic wave separation, was introduced in April 2016 and reduces the buffer volume required to perform large-scale depth filtration by 75 percent. We are also in the process of developing a state-of-the-art clarification solution suitable for use with perfusion processes. In addition to these technologies for specific unit operations, we are looking at technologies to manage waste, as well as being involved in discussions about managing plastic waste.

Gazing into your crystal ball, do you have any predictions for the future of continuous processing?

In the next 3 years, I believe that an increasing number of companies will, to some degree, adopt continuous manufacturing on a commercial scale. Within 5 years, we are likely to see the first examples of fully integrated, continuous biopharmaceutical manufacturing at production scale, and 10 years from now, I believe that continuous manufacturing will be accepted as the norm. I also expect to see continuous processes used for the production of more advanced biological products, such as cell and gene therapies, viral vaccines and virus-like particles. The processing dynamics of such medicines are very different to proteins and antibodies, and both the industry and equipment suppliers will need to develop very specific processes and technologies that can handle these sensitive products.

Is there a risk that late-movers will be left behind?

If a company has a novel drug then they will have a unique position in the marketplace regardless of how it is made. Having said that, it is becoming increasingly difficult for drug companies to get their products listed on insurance company formularies. Payers are expecting differentiated performance at a cost-effective price. Drugs that can't meet both requirements won't be successful in many markets. Therefore, accelerated manufacturing at lower cost is crucial. Early adopters of continuous processing are already realizing the benefits of continuous manufacturing and late adopters could see their product portfolios losing competitiveness.

The benefits of continuous manufacturing have been clearly demonstrated in many other sectors, but these advantages can reach to pharma too! Changes in our industry are driving the need for more efficient manufacturing strategies that consistently provide higher-quality drug products. We are currently seeing the advantages of process intensification and the first steps are being taken to couple unit operations, such as concentration and chromatography, together. As regulatory aspects and the questions surrounding process monitoring are addressed, we will see further movement toward integrated continuous processes.

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Packaging the Future

The term 'packaging' may not immediately evoke excitement – but without innovation in the field, some therapies wouldn't even reach market. In other words, don't judge a box by its cover because there's more to packaging than meets the eye… and even more lies on the horizon.

By Mike Schäfers

I often feel that there's a perception that packaging is not a particularly interesting subject – perhaps because drug containers don't always look that exciting. Indeed, patients barely notice the container at all unless there's a problem – but that's the way it should be. If the package does its job properly then it should be invisible to the patient and this is the aspect that I find so exciting about pharmaceutical packaging; the products are understated and unnoticed, and yet they can make the patient's life much easier. Visible to the patient or not, certain therapies would not have reached the market without innovation in packaging technology. The primary packaging container is essential for the efficacy and quality of the drug product, and has a critical impact on the product approval process. In addition, it also affects patient compliance because packaging is key to addressing the human aspects of product use – for example, by making drug administration easier, more convenient, or less painful. This is quite a complex aspect of packaging design, because it's important to understand the needs of your targeted patient group and how to make the packaging fit those needs. Things that are easy for young people may not be so for older people, for example.

A growing number of packaging innovations are being seen in the pharmaceutical industry and it's very much an evolving field at present. In the future, I believe that we will see new delivery methodologies that we can't even dream about today.

Containing biologics

Perhaps the biggest trend impacting innovation in packaging is the growth of biopharmaceuticals. Today, the 10 best-selling drugs are biologics, and by 2020 about 80 percent of all pipeline products are expected to be biologics. Just as these medicines are harder to manufacture than small-molecule drugs, they are also harder to package because they are so sensitive. For example, biologics can be very sensitive to environmental conditions, such as light or temperature, and the packaging components have a role to play in protecting the drug during transportation and storage. This is one aspect of packaging that is starting to receive more attention, but right now I'd say that there is a big focus on 'clean' ready-to-use packaging components that minimize interaction between the drug and the packaging material. Using the wrong material for the container can result in unwanted interactions with the drug product, which, in extreme cases, can be very dangerous for patients. It's important for packaging manufacturers to produce comprehensive extractables profiles for their components. In addition, some manufacturers apply a barrier film or coating that protects against extractables. Broadly speaking, there is a lot of work being done to identify the right materials for making components and to give drug manufacturers confidence in their performance. In particular, quality by design practices – which have been adopted by both pharma and biopharma manufacturers – are also making inroads into packaging manufacture. After all, quality by design is about building in quality from the very beginning – such as meeting a quality target product profile determined at the start of the design project – and just as it can help produce better drugs, it can also help produce better packaging solutions better suited to their needs. This is particularly important as packaging components become more advanced to match the

"Most patients don't get overly excited about injections – therefore across the drug delivery field as a whole there is quite a large focus on alternative technologies to improve patients' acceptance."

demanding needs of biologics – we need to minimize variations just as much as drug manufacturers do.

As well as developing effective containers for biologics, packaging companies also need to ask how the drug can be administered in a way that is both comfortable and convenient for patients. In some cases, a biologic medicine must be injected several times a day so it's understandable why there can be issues with therapy compliance. There has been a big trend towards self-administration so that patients do not have to travel to a healthcare provider for their injections. Devices such as auto-injectors and pen injectors have become quite commonplace – and we're also seeing innovations moving away from these traditional devices completely. For example, in the future you'll see more 'wearable' drug delivery devices. We've been working on a wearable injector that is placed on the body that is designed to apply large volumes of a biologic drug over a certain time period. This is a very new and unique technology, called the SmartDose electronic wearable injector – and you can expect to read more in a future issue of The Medicine Maker. SmartDose is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company..

These sort of innovations are really important because they are better adapted to the needs of patients – generally speaking, most patients don't get overly excited about injections – therefore across the drug delivery field as a whole there is quite a large focus on alternative technologies to improve patients' acceptance and therapy compliance. There is also a move to make the package combine the functions of container and delivery system – an auto-injector acts as both packaging and drug delivery system, which is a good example of how the field of packaging is becoming more comprehensive. There are specific regulatory frameworks and quality expectations that apply to these combination products, but you should never overlook the human factor. The system should be effective, but it should also be easy to use, safe and convenient for the patient to help boost compliance.

There's also a lot of potential for using mobile technologies to help promote patient adherence, such as by reminding patients to take their medication, or by educating them on how to take it (which is particularly important if a drug delivery device is more unique). I also think that there is potential for us to incorporate electronic features into packaging; for example, using a mobile phone to check that a drug has always been stored at a certain temperature without ever exceeding certain thresholds. I think this kind of connectivity will have a major impact on the packaging industry, as well as on the pharmaceutical industry as a whole.

Safe and smart

One issue that affects the packaging of all drug products – small molecule as well as biologics – is quality. Product recalls related to glass breakage or particulates are unfortunately more commonplace than you would think – and there is huge pressure from regulatory agencies to reduce these problems. On the other side of the fence, there is also constant pressure for manufacturers to reduce their production costs. This means that packaging companies have a bigger role to play – because one way for drug manufacturers to save costs is to outsource aspects, such as packaging component processing. The requirements for increased quality, however, are becoming more stringent all the time. This is a very well-known challenge – but that doesn't make it easier to address. Some solutions are to invest in better clean rooms and in vision-inspection technologies, which are advancing really fast and can also be used by packaging companies to better ensure the quality of their components. This can help reduce the drug manufacturer's rejection rates by around 1 or 2 percent, based on data points shared by customers. And although that doesn't sound like a lot, it is significant when you consider the fact that a biologic can cost thousands of dollars. And of course reducing the chance of defects by even a small amount can still mean improved safety for patients.

Looking ahead, the key issue for packaging providers companies is how to better serve the patient by making products of very high quality in terms of administration and delivery. And related to that is the human factor; the critical issue of guiding and helping the patient with the therapy. Because even if you have the best drug in the world, it won't be a success if they patient doesn't take it correctly.

Mike Schäfers is Vice President, West Pharmaceutical Services.

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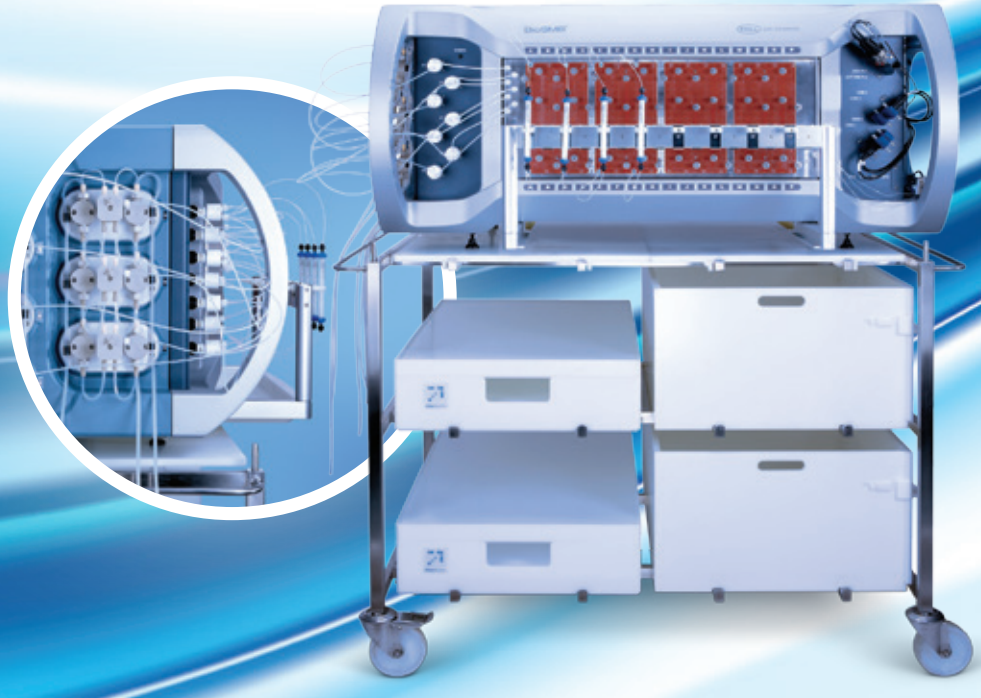


Profession

Your career
Your business
Your life

The Conjuror of Conjugation: Lessons Learned with Andrew Lees

Andrew Lees lightheartedly states that he has built his career on two tenets: multivalency and being lazy. And it's worked out well; while moonlighting as a magician, he has developed the conjugation chemistry behind some of the world's most-used vaccines. Here, he explains how he learned to combine science and magic.

A scientific career is not straightforward

I grew up surrounded by science. My mother was a neurochemist. She was the first woman to attend Harvard's graduate biochemistry department and later became President of the American Neurochemistry Society and editor of their journal. She was a wonderful mentor – both to me and many students. My father started out at the Massachusetts Institute of Technology developing gyroscopes for guided missiles, but ended up doing pioneering research into the structure of teeth and bone. Our house in Boston was always full of visiting scientists and there were times when I had future Nobel Prize-winners babysitting me.

In that environment, a science career seemed inevitable for me and my brothers. My older brother walked a conventional path from PhD to industry and my younger brother ended up in finance, but I became a little lost as I advanced in my academic career. I was my high school valedictorian and I went on to read engineering at Harvey Mudd College in Claremont, California, but after one class I realized that I'd made a mistake – engineering was too rigid and it didn't fit my personality. Chemistry seemed interesting so I switched. However, after getting my degree I didn't know what to do – so I ended up going to graduate school, an effective way of deferring decisions! Larger institutions intimidated me, so I chose John Hopkins University, which had a small biophysics department.

Some scientists need an outlet

When you're in grad school, options start to open up and you have to take a good look at yourself and start to make decisions about your life. Obtaining a PhD can be as much about psychological pressure as it is about actual research. Indeed, I think grad school is psychologically difficult for many students and I don't think everyone gets the help they need. For me, part of the problem was that I was suffering from the perceived expectations I felt from my parents. I was also absolutely terrified of giving scientific talks.

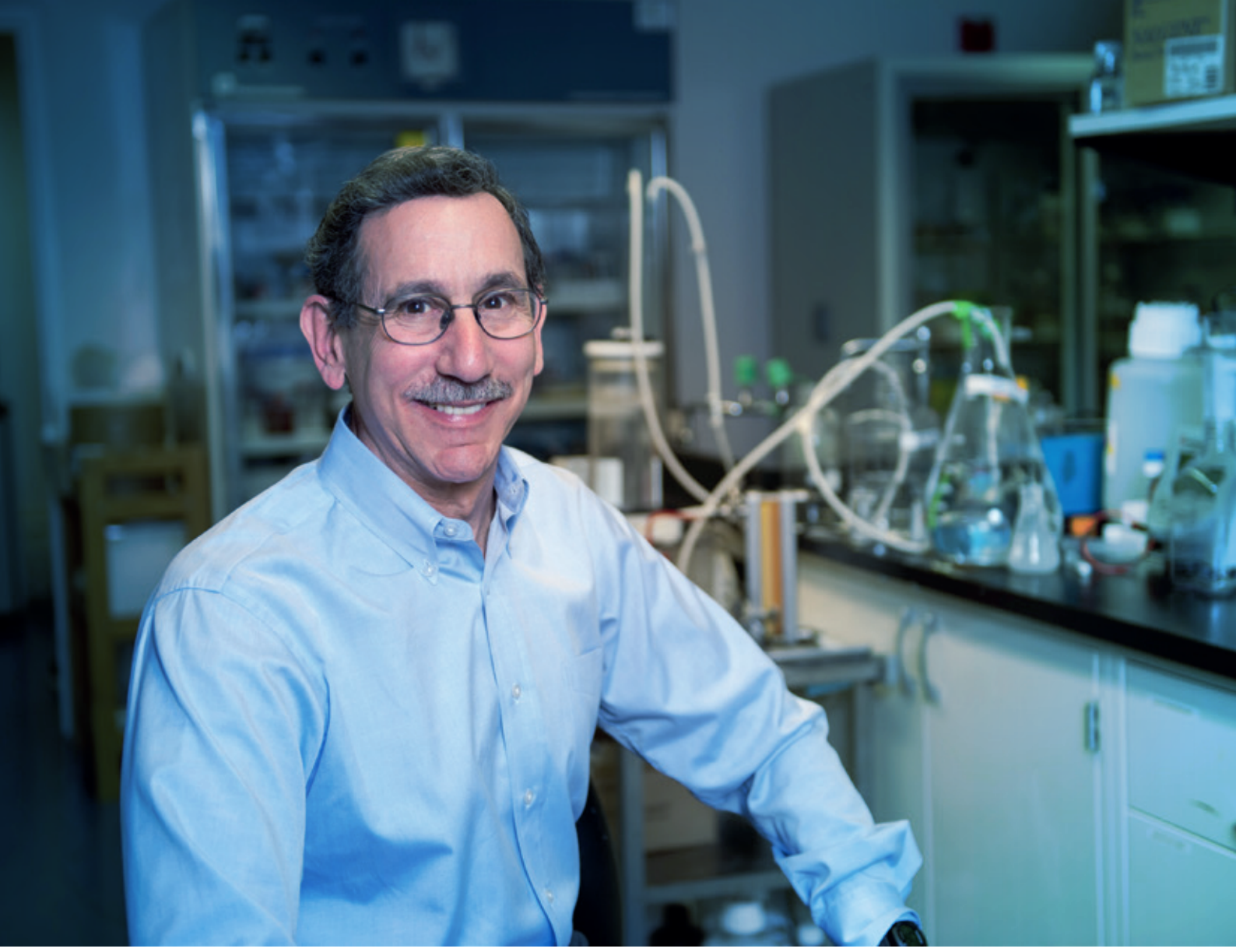
I needed an escape route. I'd always been interested in magic tricks so I reverted back to the hobby. It was strange that I couldn't present my work in front of 10 colleagues, but I didn't have a problem performing in front of hundreds as a magician. I loved it and I started a street-performing troupe in Baltimore called the Freelance Fools. Next, I began performing for private parties, and then I started working at a restaurant doing table magic… I was pretty good at entertaining people. I was even featured on the cover of Baltimore Magazine as one of their "84 People to Watch in '84". It was great fun, but I wasn't a very good graduate student. In fact, there was talk of throwing me out because I didn't seem to have much interest in being a scientist. Fortunately, one of the professors defended me, even though he didn't particularly like me (or at least that was my impression). They let me stay and I obtained my PhD.

After I graduated, I still didn't have a clear direction in mind about what I wanted to do. I became a full-time magician and only went back into research because my student loans could be paid back by working in the field in which I was trained. I ended up as a post-doc in Howard Dintzis' immunology lab at Johns Hopkins, looking at the multivalent interactions behind immunological signaling. I was interested in the subject but not enough to actually work very hard at it... But though I didn't know it at the time, it was the beginning of the multivalent thread that was to run through my career.

You never know when the "eureka" moment might strike

After a couple of years as a post-doctoral fellow, I had to move on to a new position. I wanted to work in industry but I only got one job offer – an academic post at the Uniformed Services University (and I think that was only because I changed a one dollar bill into a 100 dollar bill at the interview). In terms of career, I was just drifting along without really knowing where I was heading. I split my time between on-campus work and working at the National Institutes of Health in a collaboration with John Inman – a conjugation chemistry expert (and a real gentleman). The group was particularly interested in understanding the immune response to T-cell-independent antigens, such as polysaccharides. Polysaccharides are long strings of sugar repeat units – effectively, highly multivalent epitopes. These long strings of repeating epitopes can engage and crosslink the antigen receptors on B-cells, generating activation signals. Jimmy Mond, Fred Finkelman and John Inman, following up on the work of Howard Dintzis, developed a model of T-cell independent antigens by chemically linking anti-Ig antibodies to long dextran polymers to create multivalent constructs capable of crosslinking B cell antigen receptors, just like polysaccharides.

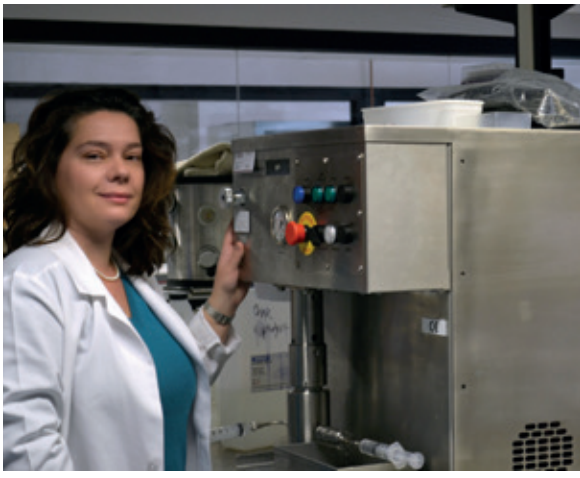
For many years, I made these multivalent constructs for immunologists.



"It was strange that I couldn't present my work in front of 10 colleagues, but I didn't have a problem performing in front of hundreds as a magician."

Immunologists would give me antibodies to a cell surface antigen and I would construct a multivalent antibody-dextran polymer so they could study the effects of crosslinking the target. I found the immunology to be too complex and not that interesting, but I became pretty good at making these things and I was listed as a middle author on lots of papers. I could make enough conjugate in one day to keep the immunologists happy for months. This meant that I could disappear from the lab and reappear as a magician at parties and fund-raising events – after all, I still loved magic and I didn't see why I couldn't balance the life of a scientist and a magician (and nobody seemed to notice).

As controls for the antibody dextrans I was synthesizing, I put a nonsense protein, bovine serum albumin (BSA), onto dextran polymers. We found that making the protein multivalent in this way enhanced the immune response to the protein and I learned that chemically linking proteins to sugar polymers was the basis for making conjugate vaccines. Conjugate vaccines, such as Pfizer's Prevnar for Streptococcus pneumonia, are vaccines consisting of a protein chemically linked to a bacterial polysaccharide antigen. Conjugation changes the immune response to the polysaccharide from a T-cell independent one to a T-cell dependent one and makes the polysaccharide immunogenic in infants. This class of vaccines is remarkably effective, but also very complex and expensive.



Top left: Natalia Oganesyan and Andrew Lees at Fina Biosolutions. Top right: a visit to Biological E in Hyderabad, India. Andrew Lees: "The guy in the red shirt is Dr Akshay Goel, Senior Vice President of R&D. And the poster behind us is titled 'Finding Pneumo'." Bottom right: Morgane Ollivault-Shiflett microfluidizing polysaccharides at Fina Biosolutions. Bottom center: a visit to the Korean Demilitarized Zone when attending a seminar at the international Vaccine Institute in Seoul, Korea. Bottom left: Andrew Lees and Pippin the Magic Rabbit in 1984 when Andrew was in grad school.

My supervisor, Dr Mond, and I tried to generate interest in our immune adjuvanting system and this was the start of my career in vaccines. This applied work, as opposed to more academic research, grabbed me. Perhaps it was that engineering gene I got from my father…

I was assigned to start making conjugates, using tetanus toxoid and relevant bacterial polysaccharides using cyanogen bromide, but it's dangerous chemistry for neophytes and I didn't have the right equipment or knowledge. While hiding in the NIH library, I came across an interesting chemistry (using 1-cyanodimethylaminopyridinium tetrafluoroborate, CDAP) that had been used to link proteins to chromatography beads. I decided to see if it would work in solution phase using my favorite system of BSA and dextran.

During this time, my wife was pregnant with our second child and was on complete bedrest so I could only work at night. I was alone in the lab at around 11pm when I mixed BSA with CDAP-activated dextran and it turned to jelly – I had made something through a cross-linking reaction. It was the "eureka" moment that changed my life! It took months of work to learn about controlling the reaction and to make a soluble product suitable for immunization, but the conjugate vaccines I created with CDAP chemistry were potently immunogenic in mice.

Solutions can find problems

Unfortunately, BSA and dextran weren't clinically relevant, so nobody cared about my discovery very much. Even my boss didn't pay full attention. He was chatting with his seatmate while I gave a seminar and that person suggested reaching out to GlaxoSmithKline, which turned out to be a great suggestion – GSK was making decisions about what chemistry to use for their conjugate vaccine program. They ended up licensing the CDAP technology, and that was a game-changer. Now, I had some income from the license and the laboratory had funding to do work I enjoyed. It was the start of a wonderful collaboration with GSK, which lasted until they started scaling up for vaccine manufacture. I later developed a twist on CDAP chemistry while trying to improve the reaction selectivity. At the time, it was more of a "solution in search of a problem" but the approach later became the method of choice for CDAP-mediated conjugation.

CDAP conjugation is one of the easiest and most efficient ways of making conjugate vaccines. I think I only succeeded because I didn't know any better; if I'd had a better understanding, I might not have tried what I did. But perhaps this is how many scientific discoveries are made.

My next commercial involvement was with two biotech companies – Virion Systems and then Biosynexus, in Rockville, Maryland. Again, I was developing new conjugation technologies, and was based partly at the Uniformed Services University and partly off-site, so I mostly worked unsupervised. But when I was moved to the main company facility, I began getting into all kinds of trouble... (I'd been used to working alone in a basement laboratory and my style of interaction was often inappropriate for a company environment.) Once again, I was protected – this time by my boss. I'm very grateful for that.

During this period, I developed another conjugation technology, using oxime chemistry, which grew from my efforts to further improve upon the CDAP method. Oxime chemistry has been around for a long time, but I developed approaches to make it more useful in the context of conjugate vaccines.

Shortly afterwards I decided it was time to leave Biosynexus before my being a "difficult employee" caught up with me. But in the end I didn't have to resign – there was a layoff, which was perfect timing because it helped me to set up my own business: Fina Biosolutions.

"CDAP conjugation is one of the easiest and most efficient ways of making conjugate vaccines."

Always leverage your connections

Starting Fina Biosolutions was the first time I had made an intentional, decisive career move rather than just drifting along from one job to another. I wanted to take more control over my work life. At age 53, I felt that I had developed some useful technical skills, had some financial independence and I wanted to be able to make my own mistakes – and be responsible for them.

At this point, all of my previous experience – as both a scientist and an entertainer – began to pay off. In particular, I realized I'd made a lot of good connections. For instance, I met the Director of the Serum Institute of India, Subhash Kapre, while at Biosynexus. He had been very interested in the oxime chemistry and when I started up FinaBio he came to visit me – and we eventually signed a research and development agreement, which allowed my company to grow. We went from occupying just a single bench and a desk to taking up more space than the company I was subletting from!

Shortly after that, at a conference in Beijing, I bumped into somebody I'd known at the NIH who had become Director of Conjugate Vaccines at the Cheng Du Institute of Biological Products in China. We ended up negotiating a contract, under which they sent scientists to my lab for a year for training. By now, we had moved into our own space: 5,000 square feet of laboratories and offices.

Cheap vaccines change lives

FinaBio is a "consulting laboratory" because we both consult and do lab work – we train scientists, develop processes and help with technology implementation. One problem we've addressed is the cost of the protein component (the "carrier protein") of protein-polysaccharide conjugate vaccines, specifically the protein CRM197. This carrier protein has historically been difficult to make and very expensive to buy. A member of our staff – a wonderful person who came to us after being laid off by GSK during their takeover of Human Genome Sciences – became the first person to express CRM197 as a soluble protein in E.coli, which cracked the problem. We now produce CRM197 for research and pre-clinical use, and we're looking to license the process to vaccine companies.

My approach to commercializing our CRM197 is to do our best to make it affordable and to make it widely available to researchers and vaccine companies. Our efforts have helped to change one of the more expensive components of the vaccine into an insignificant factor in conjugate vaccine cost. From a business sense, it is unusual not to try to maximize profit but it feels good to know that we have made a real difference to vaccine production

Fina Biosolutions Laboratory in Rockville, MD, USA. Andrew Lees: "I like toys. I have the best equipped lab of my career."

in countries that desperately need lower cost drugs.

Much of FinaBio's work is done as contract work, which tends not to provide steady income so I've tried to create a reliable revenue stream by developing products. I went back to my basics – modifying dextran polymers. We use our expertise from the carbohydrate conjugate vaccine area to make well-characterized, functionalized dextran polymers. Sales of our fluorescent dextrans are particularly strong – revenues from this line have been doubling every year. And there's a whole world of possibilities for our antibody-dextrans as they are now being used for drug discovery.

Our mission statement is: "Doing good, while having fun, while trying not to go broke". And we can only use this model because we're not backed by investors who would, of course, want a large return for their investment.

Play to your strengths

My work and my work style would not have been possible without the support of my wife, Julie. She took care of the home and spent way more time raising our two children. It's not always been easy and I am most appreciative of her efforts. Julie has a graduate degree in medieval studies, as well as an MBA. I think she was prescient in knowing that studying to be a saint would be handy when married to a scientist-entrepreneur...

I like giving back to the community and helping people. I feel I was born with a scientific "silver spoon in my mouth". Not everyone is so lucky and I frequently meet young people who have not had much exposure to scientific life – I like to invite them to visit FinaBio. Other people's work is always more fun than your own and it's not a bad thing to take an interest – I've made many friends this way. And ironically, all of my goofing off as a magician over the years has had its benefits – I've learned to sell myself, which is incredibly useful now that I'm in business, and it's also a nice icebreaker and a way to form relationships. For example, I used to make balloon animals for the sales reps, and one rep asked me to do a magic show for her kid's birthday party, which I did. Today, she's in charge of emerging biotechnology companies at a multinational pharma, and invited me to do a video interview for their website.

You never know where things will lead. Once, I did a performance to raise funds for the American Lung Association and I met someone who later became director of the University of Maryland's Technology Enterprise Institute. A decade later, she remembered me favorably and I was engaged to teach bio-chromatography, which is how I became part of the faculty. And that also led to something else – being aware of my conjugate vaccine background, the director of the Center for Vaccine Development at the School of Medicine asked me to help with a salmonella vaccine project. He persuaded the Wellcome Trust to fund their salmonella conjugate vaccine program. The vaccine is now moving through the process of GMP manufacture in partnership with an Indian company. I'm now an associate professor of medicine at Maryland.

In starting Fina Biosolutions, my intent was to work to reduce the cost of conjugate vaccines for lower income countries by working with emerging market companies. Between developing efficient conjugation chemistry and reducing the cost of the carrier protein I feel that we have gone a long ways towards this goal.

In short, I've made a career from two things: multivalency and being lazy (though in fairness, I think I've worked hard to be lazy). Acknowledging that we're all human, I've tried to make FinaBio a forgiving place. For example, we don't have "vacation time" at FinaBio – if you take time off, then it's because you need it. (Also, vacation time needs to be tracked and that's more work...)

I actually like to work and I think everyone in my lab is the same. I would say we're consistently achieving two out of FinaBio's three mission statement goals: doing good and having fun. The third one – not going bankrupt – is a constant challenge; it's a bit of magic trick to keep pulling that one off.

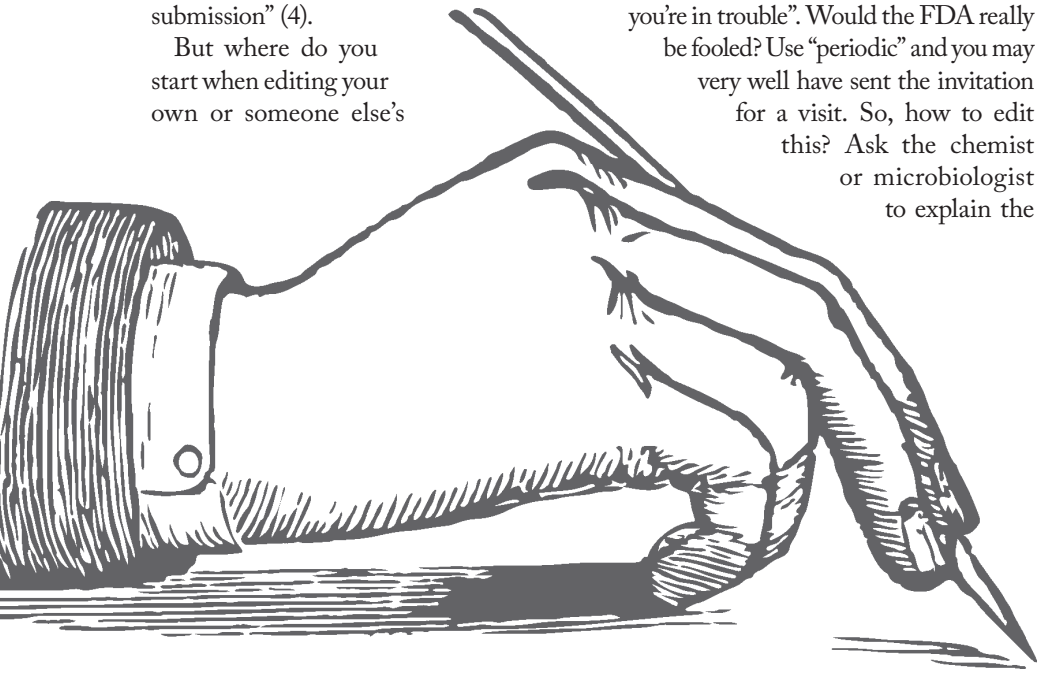
Language as Quality Control...

... or sonicate until the cockroaches disappear. When writing is central to the job of assuring health, safety, and quality, can you afford to be loose with language prone to misunderstanding? Why take a chance? Here are a few strategies to edit your written work for quality control.

By Steven Schultz

Advice on writing is plentiful – whether for writing short stories or scientific articles: "Avoid vague statements, jargon and laboratory slang" (1); scientific writing must be "precise and unambiguous"(2); "the writer should so write that his reader not only may, but must, understand" (3); and "read closely and revise your own manuscript at least three times before submission" (4).

But where do you start when editing your own or someone else's work? What do you look for? In "How to Fail an FDA Quality Audit", Mort Levin states that based on "sampling statistics, if 1 percent of [written] procedures have problems, the probability of finding one or more in a group of 100 is 63 percent" (5). In other words, if you find one cockroach, dozens more surely lurk in the dark. So, my advice for a first editing step is to examine the language and look for the cockroaches; they thrive in vague wording, jargon, and ambiguity.



Non-specific language

When introducing a unit on language in writing seminars, I often start with an excerpt from a pharmaceutical standard operating procedure I once edited: "Inspect the vials periodically for microbial growth." Is the directive "periodically" up to quality standards? Many defend it. Since this vague word is found in so much documentation, some believe there must be a successful strategy behind it. I have heard explanations, such as "you don't want to be too clear because if the FDA comes in and you're inspecting the vials on the eighth day when it should be done on the seventh, you're in trouble". Would the FDA really be fooled? Use "periodic" and you may very well have sent the invitation for a visit. So, how to edit this? Ask the chemist or microbiologist to explain the purpose of inspecting the vials and the best time to make the inspection to assure the intended outcome. Revision: Inspect the vials for microbial growth every seven days after incubation.

This is not an isolated example of unclear scientific writing. Examine every batch of writing intended to provide specific direction and quality assurance, and you will find more:

- *"All exposed jewelry must be removed if in close proximity of operating equipment."* How close is close proximity? (And close proximity itself is redundant.)
- *"Select 10 biohazard autoclavable hazardous material bags (or equivalent)."* Would someone new to this method know what's autoclavable, as well as its equivalent?
- *"Objective: To detect any obvious high and low filled vials."* What's obvious? Could the high and low range be measured?
- *"Some solvents can damage the appearance and function of the instrument."* Which solvents? How will the reader know?
- *"Unless otherwise directed, non-company personnel are required to wear safety glasses."* Directed by whom or what? And who are non-company personnel?
- *"This uncalibrated capper count appears to be more accurate than the average tray count."* Is the uncalibrated count more accurate or not? What's the basis of this appearance?
- *"When necessary, identify isolates using an appropriate microbial identification system."* When would this be necessary, and what system would be appropriate?
- *"Minimize reaching over open containers, syringe baskets, etc. on the tables and the number of people moving at one time in the rooms during operations in the class 100 areas."* Is reaching over sterile components acceptable at all? How many times

and how many people moving at one time jeopardize product quality? What other types of items could etc. refer to?

Not all of these examples will jeopardize quality or safety or prevent a scientist from reproducing another's results. But why take a chance?

When editing for clarity, ask yourself, is this specific enough, will this produce consistent results, could two people interpret it in more than one way? If it's fine as is, move on. If there is a probability for misunderstanding, then rewrite so readers must versus may understand. Vague language shifts the burden or responsibility to the reader, who will either find out what's necessary, appropriate, obvious, or guess and make a decision based on subjective, loosely chosen language.

Jargon – the bottom line, if you will, of synergistic scenarios

Jargon is so pervasive in English that it's often hard to recognize or see what's wrong with it and why writing guides decry it. We use jargon, as we do slang, in everyday conversation, not realizing it – I'm going to "scoot to" the store, "pick up" groceries, and "whip up" something for dinner. In science, the jargon might sound more technical, but it's just as potentially vague, imprecise, and troublesome. Here are some examples:

- *"The new study has been performed for optimization purposes."* Sounds great; who isn't for optimization? The study's objective, however, buried pages later in the study, was to increase a product's shelf life by six months.
- *"Products in question will be formulated and held at their required storage parameters per their respective master records by the Formulation Department."* Who doesn't love a parameter... and its melodious sound on the tongue, sprinkled with a little "per" and "respective"? But the writer could have stated the point directly and simply – the products will be formulated and stored as their master records require.

The biggest cockroach in the jargon family is "utilize" and its fellow hatchlings "utilizing" and "utilization":

- *"Laboratory documentation was reviewed to determine the number of samples that were utilized in the testing performed."* Possible revision: We reviewed the documentation to determine the number of samples tested.
- *"Biologically, perchlorate interferes with the utilization of iodine and disrupts hormone production by the thyroid gland."* What's the actual causation described here? What is utilizing the iodine and the relation between iodine and the thyroid? When writers make a commitment to avoiding the jargon (in this case, not using utilization), they choose more descriptive verbs and concise phrasing: Perchlorate interferes with (or inhibits) the thyroid's uptake of iodine, which is essential for hormone production.

Again, because jargon and imprecise language are so pervasive, it would seem the scientific professions condone it, even though all scientific style guides – whether from the American Chemistry Society or the Council of Biology Editors – devote chapters that discourage it. Why, when so well documented in these sources, is jargon hard to exterminate? Possibly because it sounds (to the writer) intelligent, sophisticated, in the know, and part of the profession. Using jargon may make the writer feel good. It's also easy to use.

Nonetheless, jargon makes the job of reading more complicated, abstract, and longer than necessary. Is there a compromise? For an editor, I'd say no. Scientific peer reviewers, however, may be more tolerant, focusing on accuracy, precision, or reducing the probability for failure. If the jargon creates inflated, sluggish prose that is difficult to read, fine (but still try to improve it). But if the language is potentially ambiguous, not technical and accurate enough (as illustrated in this article's examples), simpler, more specific language is a must.

It's always been done this way... and they should know this

The most difficult obstacle to overcome as a writer and editor might be a resistance to change based on an unfounded belief that because a practice is so common, it must have been proven scientifically infallible. When it comes to writing, it can be difficult to prove a case for applying best practices because the metrics are often subjective. Even though an editor can demonstrate jargon's shortcomings or how to delete wordiness, it's difficult to overcome statements like, "that's just our style, this is the standard language we always use, and if they are working in this field, they should know this."

Two common examples I've found yield some metrics and support for avoiding jargon and using plain yet specific language. One is based on research; the other, on interviews with QA personnel in R&D and manufacturing and their on-the-job experiences.

i. *"For external use only."* A study of prescription drug warnings at Northwestern University (Evanston, Illinois, US) has centered on how to improve the warnings – the standard warnings now in use – to assure patient comprehension and reduce the risk of errors (6).

The research compared adult patients' responses to current standard drug warning labels with responses to drug warnings that were rewritten in more plain language with less text. See Table 1 for

Standard Warning Label	*Revised Simplified Warning*
FOR EXTERNAL USE ONLY	Use only on your skin
IT IS VERY IMPORTANT THAT YOU TAKE OR USE THIS EXACTLY AS DIRECTED. DO NOT SKIP DOSES OR DISCONTINUE UNLESS DIRECTED BY YOUR DOCTOR.	Do not stop taking unless directed by your doctor.
OBTAIN MEDICAL ADVICE BEFORE TAKING NON-PRESCRIPTION DRUGS. SOME MAY AFFECT THE ACTION OF THE MEDICATION.	Talk to your doctor before using any over-the-counter drugs.

Table 1. Standard prescription drug warning labels alongside drug warnings that were rewritten in more plain language with less text

three of the nine labels and revisions that the study used. The researchers found an 80.3 percent rate of correct interpretation of the standard drug warnings and a 90.6 percent correct interpretation of the revised simplified ones.

ii. *"Sonicate until dissolved."* The industry need for simple, direct, and unambiguous instructions is no less important for reducing the probability of misunderstanding in methods, lab protocols, or analytical studies. The threat of lab jargon – assuming stock phrases and language are as universally understood as, say, the symbol for benzene – is also no less intense.

In reviewing a method, ask a chemist, does "sonicate until dissolved" need to be explained? You might hear a sigh or a statement like "why should we have to tell an analyst that?" For a standard operating procedure (SOP), this language leaves the step open to interpretation and one that can be completed differently each time by the same person; one analyst will use the sonicator to prepare a sample for 15 minutes over a coffee break, but another may take an hour for lunch...

QA managers and directors attest that the latitude embedded in "sonicate until dissolved" is prone to error. It can be cited as the cause for low assay results and results out of specification, even though nothing was wrong with the product. Such variances waste resources, time and money (through additional testing), delay the release of product or, in stability testing, delay reporting the results to the FDA. Why take the chance?

There's no perfect solution, but there are ways to reduce this risk – through language and science, and by making instructions method-specific, not analyst-dependent. A possible translation in plain language might be "prepare the solution using x and z. Sonicate it until the solution is clear and no particles can be observed." However, for photosensitive testing that uses amber glassware, an analyst can't see what's dissolved. A more reliable and consistent approach would be to base the directive on experiments that identify the time required for this method to eliminate possible variances in results, and state it in unambiguous language: When using Method A, sonicate the solution for 15 minutes.

There is no such thing as a good writer

To allude to a line in the sales profession, writers are only as good as their last written communication. Writing is work, and no simple formula is going to produce the quality product desired every time. Rigorous editing and rewriting will increase the chances. So give yourself a hard time – and ask others who review your work to do the same. As the legal scholar Bryan Garner advises, "Review your writing ungenerously, as a harsh critic might... If you approach your own writing mercilessly, your readers are sure to be merciful" (7). Great advice, too, for professionals involved in the health and safety of the public. Why take a chance?

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Doyenne of Discovery

Sitting Down With... Ann Hayes,
Owner, The Ann Hayes Consultancy,
Stevenage, UK.

How did you get into science – and drug discovery?

I always wanted to be a scientist. Ever since I can remember, I've been interested in learning about the world around us and finding out something that people didn't know before. After obtaining a PhD in pharmacology, I felt there were two paths in front of me if I wanted to continue my research: academia or the pharma industry. And I opted to go into the pharma industry. Today, I don't work in the lab anymore – and haven't done for quite some time – but I still love looking at and analyzing scientific data when I can.

What I really like about drug discovery is the chance to start from the patient and work from there. You start off by thinking about the patients, the disease and the medical needs, before you even start coming up with molecular targets. I've always found it very rewarding because, if successful, I felt I could make a real difference to patients.

You have a long history in big pharma...

That's right. I worked at Glaxo and then GlaxoWellcome for 22 years, eventually becoming Director of Drug Discovery. Most of my time was spent in central nervous system (CNS) drug discovery (neurology, psychiatry and pain), and I was working at Glaxo in Pharmacology when two major first-in-class drugs were discovered – one for migraine and one for chemotherapy induced emesis. It's just so exciting to be involved when a treatment becomes available where there wasn't one before. Imigran is a great example; there really was no good treatment for migraine before it. Doing clinical trials in migraine can be a challenge given the size of the placebo response, but I remember talking to the team leader, Pat Humphrey, who said he knew it was going to work even after the first two or three patients. We used to hear stories from the commercial team about how much patients appreciated the drug and how much it changed their lives. It gave us a real boost.

How do you feel about the negative press coverage of pharma R&D?

Sometimes it seems as though the press only report negative stories about big pharma, but many of these companies really do some amazing work, especially in research and drug development. Think of how much has changed in just 15 years. We've seen some phenomenal new drugs in multiple sclerosis and we have a cure for Hepatitis C. I also heard a heartwarming story from an oncology clinician at an advisory board meeting. Every day, the oncologist has to pass through the rheumatoid arthritis (RA) clinic to reach his own. Ten years ago, he said, the RA clinic was full of wheelchairs, but today, there are no wheelchairs at all – mainly the result of life-changing new drugs like TNF inhibitors. It's good to hear such clear success stories from time to time; it's easy to forget how far we've come.

What challenges face modern drug discovery?

For certain diseases, we still don't know enough about etiology or pathophysiology to easily validate targets. And, of course, animal models often don't translate well into humans.

The other big challenge is finding a molecule that can be used as a drug – there is a laundry list of requirements to be met. Beyond simply interacting with the target, it must be potent, selective, and reach the right site of action in the body. Ideally, it's got to be cheap to make, easy to formulate, and not have too many side effects... Then you've got to take it though toxicology, scale-up synthesis, clinical trials, and so on. I don't work in big pharma any more, but I still get a buzz when I hear about successes, particularly in CNS, because there are so few new drugs in that area.

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Has all the low-hanging fruit gone?

There is certainly an element of truth in that. A lot of the diseases with unmet needs today are chronic, so pretty much by definition you're talking about extensive clinical trials. You've got to show that your drug is better than what is already out there. You can't just take somebody with epilepsy or diabetes off their existing medication, so you've got to do add-on trials. And that means the hurdles are higher.

Have you enjoyed your move to consultancy?

I loved my years at Glaxo – you really learn the business. But since leaving the industry in 2001, it's been great working with smaller companies and using all my experience to help them. A lot of smaller companies need help in drug discovery, particularly spin outs from universities, but they are fun to work with – what they lack in infrastructure and experience, they make up for in dynamism and rapid decision making. I've co-founded two small drug discovery companies, sat on boards of others and I consult for small companies and investors like venture capitalists. For a few years, I also chaired the industry committee for the British Pharmacological Society. I find having a wide breadth of activities very satisfying.

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