OCTOBER 2014 # 02

# the Medicine Maker



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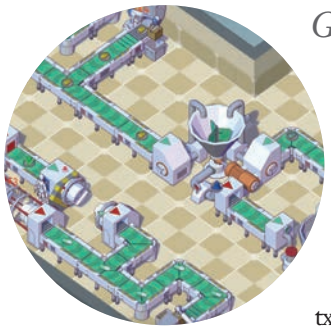
# Online this Month

## *Q&A with the EMA*

In March 2014, the European Medicines Agency (EMA) started inviting companies to submit ongoing medicine-development programs for prospective case studies in a pilot project on adaptive licensing. The agency received 26 applications and recently selected the first two 'live assets' for the pilot. Read our quick fire Q&A with Hans-Georg Eichler, Senior Medical Officer at the EMA, to find out why the pilot was launched and what the next steps will be. Read it online: tas.txp.to/1014/QAEMA or on the iPad app. You can read more about adaptive licensing from Lynne Baird on page 40.



## *Game On*

On page 10, we report on a new video game - Big Pharma - expected to launch in 2015. Online, you can find an interview with the game's developer that delves further into the inspiration behind the game and its mechanics, as well as insight into how someone outside of the industry perceives the business of making medicines. Read it online: tas.txp.to/1014/biggame or on the iPad app.

## *Putting ADRs on the Radar*

Mick Foy from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) contributes to our social media cover feature on page 20, but you can also hear more from him online where he brings us up to speed with the WEB-RADR project. The project will involve the development of a mobile app for reporting adverse drug reactions and new tools for mining social media data. The mobile app could be rolled out in the UK and Croatia within the next 6 months. Read it online: tas.txp.to/1014/ADRradar or on the iPad app.

## *Antibiotics Action*

In the last issue of The Medicine Maker we took an in-depth look at the problem of drug resistance and on page 43 you can read about how the pharma industry is rising to the challenge. Academia also has its part to play, from investigating how drug resistance occurs to identifying new classes of antibiotics. Read about some of the big academic developments of 2014 in this area online at tas.txp.to/1014/bioaction or on the iPad app.

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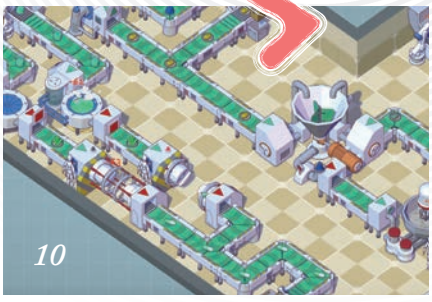




## On The Cover

*Ph replaces F to create a social media logo for the new face of pharma.*

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## In My View



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## Best Practice



## NextGen



## Profession



## Sitting Down With



the Medicine Maker

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# The (Un)fairer Sex?

*Our understanding of the differences in male and female biology is constantly growing – but can we translate that knowledge into better healthcare for all?*



Historically, clinical trials have been conducted in men – usually white men. Women of child-bearing age were excluded based on risks to the fetus should they fall pregnant, and there was a general belief that – beyond the reproductive system – men and women were biologically the same. Though women are still underrepresented in clinical trials in many diseases areas, times have changed. New research has opened our eyes to the myriad differences in how men and women respond to disease, and the drugs prescribed to treat it.

A well-publicized case in point was last year's relabeling of popular sleep aid zolpidem (Ambien) at the request of the US FDA, which halved the recommended maximum dosage for women based on new evidence from clinical trials and adverse event reporting. Apparently, women eliminate zolpidem 45 percent more slowly than men, leaving them more vulnerable to next-day impairment, as well as rare side effects like sleepwalking and even sleep-driving. If the new labeling is correct, women have been habitually overdosing on zolpidem for the past 20 years. In fact, the differences in metabolism between men and women were known when the drug was approved, but at the time there was no evidence that it would matter. FDA's Sandra Kweder told US TV show 60 Minutes, "If I saw this today, in light of today's science, I think we would go back and try to tease this out a little bit further. But I think at the time this was generally [...] business as usual for what you saw in clinical pharmacology studies."

Biased clinical trials are only half the problem; preclinical development work is still largely carried out on animals and cells of a single sex – most commonly male. The reason? To reduce variation by eliminating the hormonal cycle of female animals. The trouble is that female animals and cell lines are not biologically the same as those of the male. By excluding one sex in the early stages of research into new therapeutics, we are missing an opportunity to identify differentiation that could bring us closer to the ultimate goal of truly personalized medicine – potentially reducing risks and saving lives. In this month's Upfront, we explore new rules that require all NIH-funded research to include both male and female subjects wherever possible (see page 12).

Clearly, including both sexes in all preclinical and clinical research is not without its challenges, and requires cooperation from governments, researchers and physicians. But in the long run, a deeper understanding of the differences can only benefit us all.

*I'd like to know what you think – what is your organization doing to avoid sex bias in preclinical and clinical studies? What are your main challenges? Contact me at: charlotte.barker@texerepublishing.com*

**Charlotte Barker**
*Editor*

## Iain Moore

At university, Iain Moore spent time deciphering nuclear magnetic resonance spectra to determine the atomic structure of organometallic products that he had synthesized. It was an inspiring and captivating area, but didn't satisfy his need to apply the knowledge to real-world problems. "A career in industry – predominantly with the oleochemical supplier Croda – put all my problem solving skills to the test." Combining these skills with the desire to help people do better led him naturally to quality assurance, and then to working internationally on the definition of best practice standards for pharmaceutical excipients and now bio-based products. "Along the way, I like to think I've helped solve one or two real world problems." Iain describes his EXCiPACT expedition on page 30.

## Mike Rozembajgier

As the Vice President of Recalls for Stericycle, Mike Rozembajgier has managed thousands of recalls across a wide variety of industries including pharmaceutical, medical device, consumer products and food and beverage. "After holding various management positions at Guidant Corporation (now Boston Scientific) and at Deloitte in their Strategic Consulting practice, I knew the constantly changing recall landscape presented a unique challenge that would keep the next step in my career fresh and exciting." Mike received his BA in economics and computer applications from the University of Notre Dame, and an MBA from The Wharton School of Business. Get Mike's top tips for recall planning on page 34.

## Lynn Baird

After several years as an academic bench immunologist, Lynn Baird took her first job in biotechnology – a change that kept her at the bench for another year. Lynn assisted in the preparation of her company's first investigational new drug (IND) application. With responsibility for the company's second IND thrust upon her, she was hooked. "I enjoyed not only developing the scientific argumentation, but also having the opportunity to learn about all aspects of a product's development. After over 20 years in various biotech and pharmaceutical companies as a product development and regulatory executive, I was given a unique opportunity at MIT to help define regulatory policy of the future." Lynn gives her insight on the challenges of adaptive licensing on page 40.

## George Scott

George Scott has spent the last 20 years moving between academic, contract research and biotechnology organizations, and feels fortunate to have experienced many different sides to the scientific discipline. Whether in academia or industry, he believes that the right team is the most important factor for success. "What is really clear to me is that it is very difficult to make transformational change as a solo artist in our industry, but I truly believe that with the right people, you can create a team that can do absolutely anything." Currently, George oversees the bioanalytical organization within inVentiv Health Clinical. On page 48, he explains how to hire and retain top talent.

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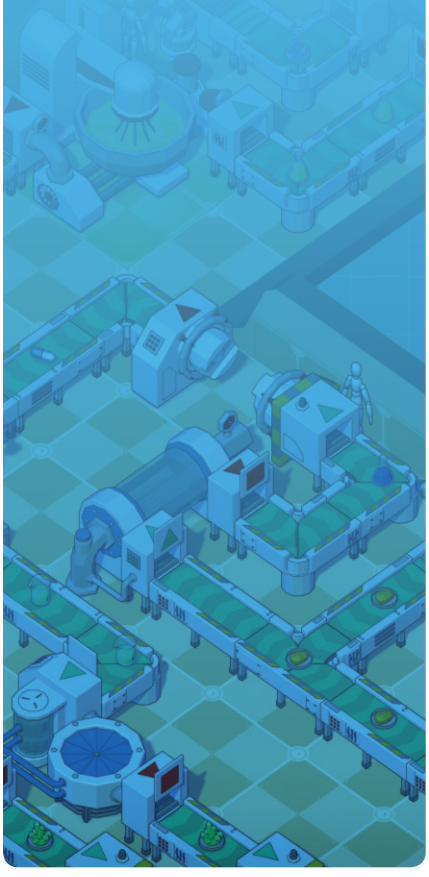
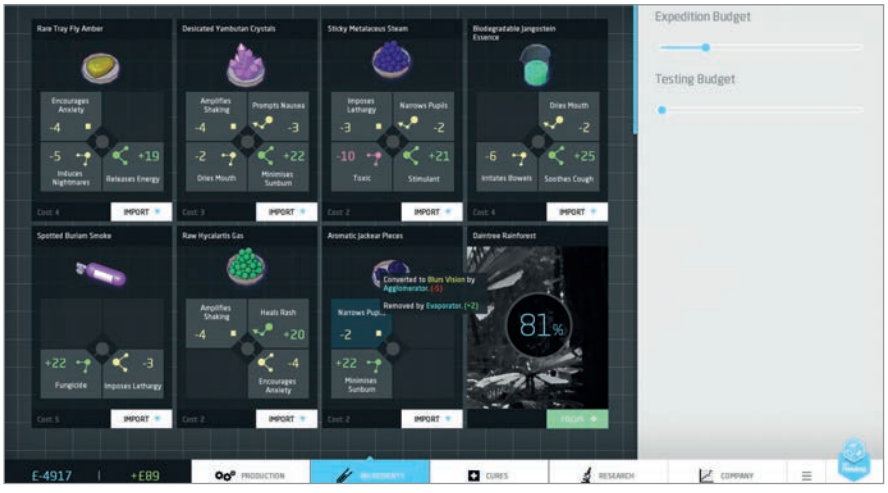
# Upfront

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

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

*Email: charlotte.barker@texerepublishing.com*




## All a Big Game?

**"Welcome to Big Pharma, where you can make a fortune and still maintain a healthy conscience. Or can you?"**

A new video game – Big Pharma – will apparently make its debut in 2015. The teaser is somewhat satirical: "What if you had it in your power to rid the world of disease, to improve the lives of millions, to ease suffering and cure the sick… and earn a tidy profit? As the head of your own Pharmaceutical Conglomerate you have this power resting in your hands. Will you use it for good? Being totally altruistic may not be the best business plan […] some remedies are more profitable than others and illness is good for business."

Is the game just an elaborate attempt to demonize the industry? Designer Tim Wicksteed says that isn't the case. "Some people are incredibly damning about the pharmaceutical industry, but then others are very grateful because a medicine has saved their life. I'm trying to stay neutral and represent both standpoints. I want the player to make up their own mind about how they build their pharmaceutical business, including the ethical challenges that go with that."

Gameplay is reminiscent of the 'Tycoon'

series of business simulation games. In Big Pharma, activities include exploring exotic locations for new ingredients and purchasing machines that can synthesize those ingredients into drug products. Players will have to compete against other companies, who may develop generic drugs at lower prices, and there will also be regulatory bodies and patents to deal with.

Wicksteed isn't intending for the game to be an entirely accurate representation of the industry and admits that drug synthesis is completely made up, for example. "It's a little bit cartoony with wacky, over-the-top machines. It's a game first and foremost, so it has to be fun to play," he explains. One area that he is keen to portray realistically is the marketplace of drug development. "I find it interesting that pharmaceutical companies have to align the goals of running a profitable drug company with making people healthy. As an example, there would be huge demand for something like an HIV vaccine, but many patients would be in developing nations and unable to pay hundreds of dollars for it. That kind of thing will be represented in the game and will give players a few things to think about. Do you make an HIV vaccine or something that panders to a richer Western market, like anti-wrinkle cream?"

Players will be under intense pressure if they want to progress and make enough money to unlock new machines, and Wicksteed hopes that it will give people food for thought.

"People have asked whether it'll be possible to sell a drug with a side effect that increases demand for another one of their products. But that might be taking the cynicism one step too far!" says Wicksteed. "There will be 'bad things' you can do – but there will always be consequences to those actions…" *SS*

*Would you play Big Pharma? Drop us a line at charlotte.barker@texerepublishing.com or tweet @medicine_maker.*

# Acquisitions Assemble

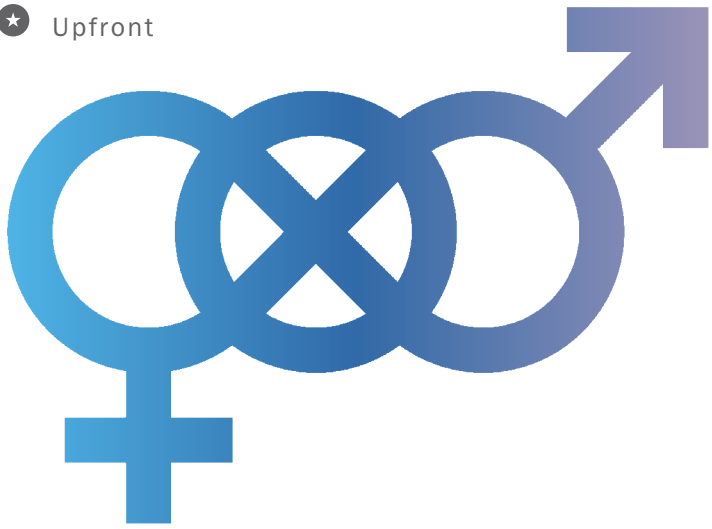
## Merck KGaA snaps up Sigma-Aldrich, Allergan fights Valeant, and Shire–Abbvie deal sours

Merck KGaA (not to be confused with US-based Merck and Co) will buy Sigma-Aldrich, headquartered in St Louis, MO, for $140 per share in cash, a significant premium for shareholders and a "quantum leap" for its life science business. Justifying the price, Merck CEO Karl-Ludwig Kley commented in a video released by the company online: "If you want to buy a Rolls Royce, you don't get it at a bargain price."

Kley described the $17 billion (€13.1 billion) deal as a "compelling value proposition", which will double Merck's US life sciences business and strengthen their position in Asian markets. He said that the acquisition fed directly into Merck's strategic plans for 2018 – its 350th (!) anniversary.

Relations are rather less friendly in Valeant Pharmaceuticals International's ongoing $49 billion (€38 billion) takeover bid for Botox-maker Allergan. Allergan has been fighting the deal since April, and exchanges between the companies have become increasingly heated. Allergan recently released a statement from its board of directors: "Our conclusion that Valeant's offer is grossly inadequate and substantially undervalues Allergan remains unchanged." Meanwhile, Valeant accused Allergan of "avoiding constructive engagement at all costs." At the request of eager shareholders, Allergan has scheduled a special meeting on December 18.

Finally, the $54 billion takeover of UK pharma company Shire by US-based Abbvie is in jeopardy. Abbvie released a statement on October 15 saying that its board of directors had withdrawn its support, following changes in US tax regulation, which they said had introduced too much uncertainty into the deal and eliminated a number of financial benefits. The new rules are designed to make 'tax inversion' – moving the tax base of the company out of the US to reduce the tax paid – more difficult. *CB*



# Sex Matters

## New NIH policies aim to correct the sex bias in preclinical research

Despite progress being made against sex bias in clinical studies, preclinical research often relies on male animals or cell lines. To tackle this disparity, the US National Institutes of Health (NIH) are making inclusion of male and female subjects mandatory in NIH-funded studies. Moreover, $10 million in supplemental grants is available to explore sex differences in ongoing preclinical research (1).

We know that drugs can exhibit different rates of metabolism, efficacy and side effects in men and women. "Examples abound of where failure to consider the impact of sex differences have led to harm and/or missed therapeutic opportunities," says JoAnn Manson, Chief of the Division of Preventive Medicine, Brigham and Women's Hospital, and Professor of Medicine.

There are also important differences in prevalence and outcomes between men and women in a whole host of common conditions. "Sex differences affect nearly all organ-systems, and differences are particularly prominent in the vascular/cardiac, endocrine, metabolic, brain/neurologic, immunologic, and respiratory systems," explains Manson. In a recent retrospective study, researchers at Yale University found that among young heart attack patients, women had higher rates of in-hospital mortality, suffered more co-morbidities and stayed longer in hospital than men (2).

In fact, the NIH has required the inclusion of women in all NIH-funded clinical research since 1993 – and just over half of clinical trial subjects in NIH-funded trials are now women. It makes sense to now turn the spotlight on preclinical studies, especially given a recent study of published preclinical research in surgery, which found that 22 percent of studies did not report the sex of the animals used and, of those that did, 80 percent used only male animals (17 percent used only females, and only 3 percent included both) (3).

"The consideration of sex as a biologic variable in all forms of research is long overdue, and holds promise for new discoveries that will provide clinical benefits for the entire population," concludes Manson. *CB*

*References*


1. *NIH Press Release, "New supplemental awards apply sex and gender lens to NIH-funded research", 23 September (2014). www.nih.gov*
2. *A. Gupta, Y. Wang, J.A. Spertus et al. "Trends in Acute Myocardial Infarction in Young Patients and Differences by Sex and Race, 2001 to 2010", J. Am. Coll. Cardiol. 64(4), 337-345 (2014).*
3. *D.Y. Yoon, N.A. Mansukhani, V.C. Stubbs et al. "Sex bias exists in basic science and translational surgical research", Surgery 156 (3), 508–516 (2014).*


# The Harsh Economics of Ebola

## Opportunistic investors surf the wave of experimental treatments

Share prices for makers of Ebola drugs leapt following the first case of the disease diagnosed on American soil. Thomas Eric Duncan, who is thought to have contracted the disease in Liberia while helping a sick neighbour, only developed symptoms after reaching the US. Tekmira Pharmaceuticals, who produce lipid nanoparticle TKM-Ebola, saw a 25 percent jump in their share price following the news, while Sarepta Therapeutics and Hemispherx Biopharma also saw increases. Makers of biosafety equipment have also seen large gains on the stock market since the first US case was confirmed.

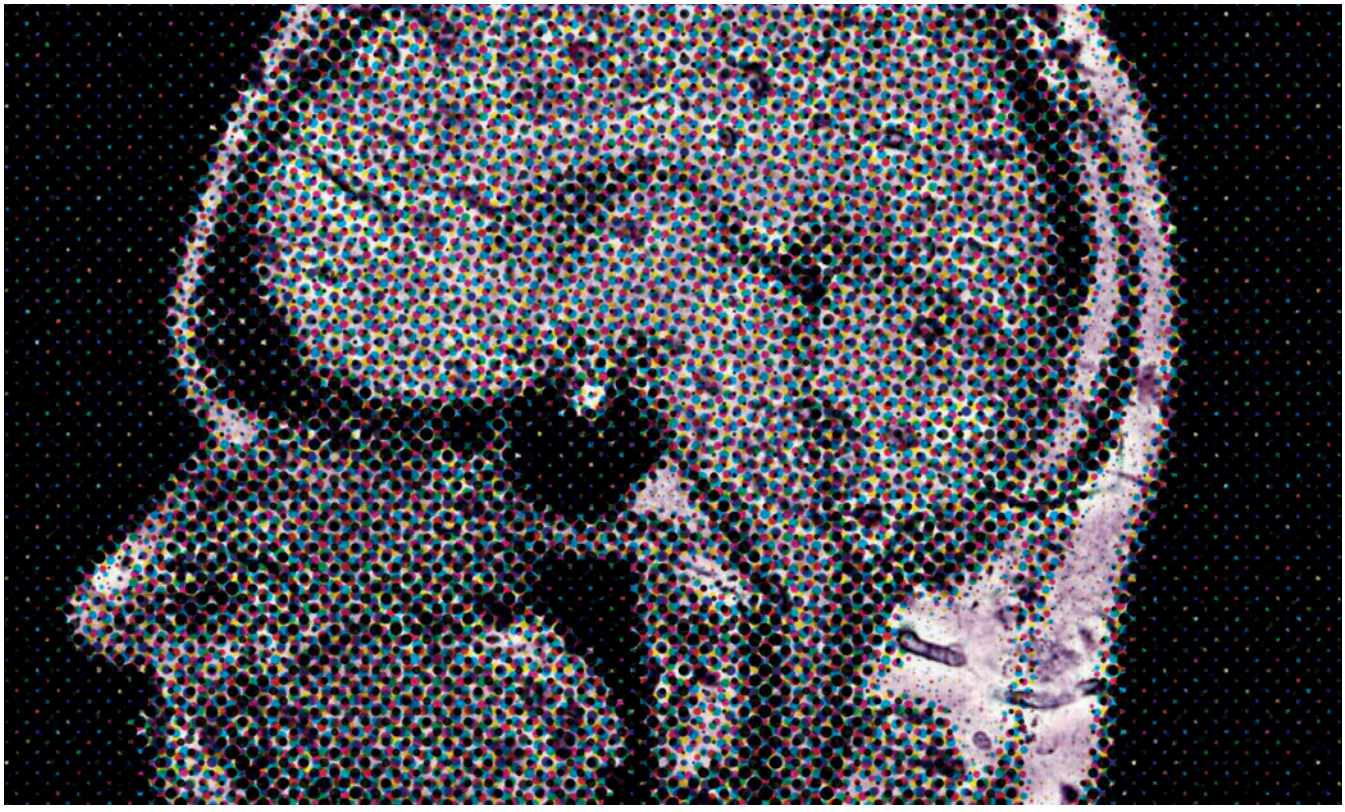
Many commentators were shocked by the reaction to Duncan's death: within minutes, stocks in Chimerx – whose experimental treatment had been used – dropped, while stocks in Tekmira saw another spike.

Ebola cases in the US and Europe have led to a number of companies offering sham Ebola treatments to worried members of the public. In the US, the FDA and Federal Trade Commission have sent Warning Letters to several companies who claimed that their products can treat or prevent Ebola.

In a recent notice to the public, the FDA wrote: "Unfortunately, during outbreak situations, fraudulent products that claim to prevent, treat, or cure a disease all too often appear on the market [...] Consumers who have seen these fraudulent products or false claims are encouraged to report them to the FDA."(1) *CB*

*Reference*


1. *FDA Press Release, "FDA warns consumers about fraudulent Ebola treatment products", August 14, 2014. www.fda.gov*



# Shared Risk, Shared Reward

## New Alzheimer's treatment gets $500 million collaborative boost

In May 2014, AstraZeneca announced that it was seeking a partner for its experimental Alzheimer's drug, the oral beta secretase cleaving enzyme (BACE) inhibitor AZD3293. Now, Eli Lilly has stepped up to help move the drug through Phase II and III trials (1).

AstraZeneca previously highlighted the potential revenue from the drug at $5 billion per annum during Pfizer's unsuccessful takeover bid in May 2014. However, they gave it only a 9 percent chance of success.

Neurology is no longer a core area for AstraZeneca, which is focusing its efforts in cancer, diabetes, respiratory and cardiovascular medicine. Lilly, on the other hand, has maintained a strong interest in Alzheimer's research, with the goal of making Alzheimer's dementia preventable by 2025. Lilly's own BACE inhibitor, LY288672, had to be scrapped after abnormal liver function was detected in Phase II clinical trial patients, joining a string of failures in the field.

The few drugs available for Alzheimer's disease only mitigate the symptoms temporarily; so there's certainly a big potential market for more effective drugs. A spokesperson for Lilly said that they were encouraged by AZD3293 Phase I results that showed a reduction in levels of beta-amyloid in the cerebrospinal fluid of both Alzheimer's patients and healthy volunteers; beta-amyloid forms plaques in the brains of Alzheimer's patients, so inhibiting its formation is thought to slow disease progression. But AZD3293 is not the only BACE inhibitor on the block – Merck remains one step ahead and will move its candidate, MK-8931, into Phase III trials in December 2014.

As for the AZD3293 collaboration, Lilly will lead the clinical trial program, while AstraZeneca will manufacture the drug. The companies will share both the risks and potential rewards of the experimental treatment, with costs and global revenues to be split equally. *CB*

*Reference*

1. *AstraZeneca Press Release, "AstraZeneca and Lilly announce alliance to develop and commercialise BACE inhibitor AZD3293 for Alzheimer's disease", September 16, 2014. www.astrazeneca.com*

# Beware the Dragonfly

## Mysterious cyber attackers are hitting pharma manufacturing systems

The pharma industry is being targeted by a cyber-espionage campaign known as Dragonfly, which uses a variety of 'weapons,' including spam emails, web watering holes (that infect websites with malware) and Trojan malware that allows unauthorized system access and information disclosure. Most organizations are aware of the dangers of malware, but Dragonfly is unusual as it specifically targets manufacturing systems. We spoke to Joel Langill, a security expert at RedHat Cyber, and Eric Byres, chief technology officer of Belden's Tofino Security, to find out more.

### Are we sure Dragonfly is targeting pharma?

The actual list of named victims is contained in "restricted" documents that cannot be shared. However, security provider Kaspersky Labs (Russia) offered descriptive information of the victims at various stages of the attack. This information, along with personal knowledge of the operation of pharmaceutical and life science facilities, led to the conclusion that the attack was not likely targeting the energy sector, as previously assumed. At this time, the campaign appears to be limited to reconnaissance or information theft, but the attackers possess the capability for more destructive acts, including system sabotage or disruption to operations.

### How does Dragonfly work?

The malware used in Dragonfly targets common services that run on industrial control systems found within the manufacturing networks of an organization. It "scans" a network for potential targets, and then probes them for specific communication services. The attackers placed the malware in legitimate software that would then be used by suppliers common in pharma and life sciences, allowing the malware to be introduced into the final organization via the "trusted supplier" that was carrying the malware.

### Is it unusual for the pharma industry to be targeted?

No. The pharma industry has been a potential target for years. According to security analysts, pharma companies have become more vulnerable to cyber-attacks over the last year than even the retail industry (and Target and EBay recently suffered high-profile data breaches). The pharma industry's focus on federal regulations, like 21 CFR Part 11, with the absence of any cyber requirements, makes them easy targets. This technical weakness is amplified by a socio-economic motivation for countries to obtain intellectual property or other information that would allow them to establish local manufacturing capabilities.

Kaspersky Labs released information of an ongoing attack against the pharma industry they called "Epic Turla" that is believed to have begun in late 2013. The overlap of the Dragonfly and Epic Turla campaigns led us to believe that both attacks may be coordinated, and that Dragonfly was actually used to obtain information about the industrial control systems that was not previously available from Epic Turla.

### Any recommendations?

Dragonfly shows that cyber-attacks are becoming more sophisticated, and that the tools used are beginning to focus on critical systems within manufacturing operations. Recommendations to help defend against Dragonfly and similar attacks are discussed in more detail in Belden's white paper series 'Defending Against the Dragonfly Cyber Security Attacks' (1).

*Reference*

1. *Belden, "Defending Against the Dragonfly Cyber Security Attacks", (2014). http://info.belden com/a-cyber-security-dragonfly-bc-lp*

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*Presented by* Life Sciences Index

# 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 editors at edit@texerepublishing.com*

## Future Proofing Track and Trace

**The US is finally introducing regulation on drug serialization and traceability, but gaps remain that could leave patients vulnerable.**

*By Allan Coukell, Senior Director, Drugs and Medical Devices, and Gabrielle Cosel, Manager, Drug Safety, The Pew Charitable Trusts, Washington, DC, USA.*

The US has finally joined the European Union and other regions in requiring a 'track and trace' serialization and traceability system for medicines, with major implementation steps just a few months away. Although the changes are significant and welcome, more must be done to realize the system's full potential to protect our drug supply against stolen, counterfeit, or diverted goods.

Approved by Congress last year, the Drug Quality and Security Act (DQSA) requires manufacturers and repackagers to apply unique serial numbers to each carton or vial of prescription drugs sold in the US, allowing trading partners (drug companies, repackagers, wholesalers, and pharmacies) to check the legitimacy of any individual package. In addition, all stakeholders involved in drug distribution are to establish interoperable data exchange systems to share information on product movement that permits a reverse look-up of a drug's chain of custody.

But the statutory requirements for the use of these new tools will not tap into their full potential. The FDA should recommend – and the industry should support – the creation of a system that allows trading partners to go beyond mere baseline requirements.

Serial number verification is a clear example of how the letter of the law falls short. Assigning a unique serial number to each drug package could potentially create a proactive screen for counterfeit or diverted products. In Turkey, for instance, where drugs have been serialized for several years, every pharmacy must verify a drug's unique serial number before it is dispensed to the patient. DQSA doesn't require any entity in the supply chain to routinely or proactively verify serial numbers, except for drugs that have been returned to a wholesaler or manufacturer and are intended for resale. It is only when a company believes that a product may be suspicious that the serial number must be checked. Because counterfeit drugs can be expertly crafted and packaged, reliance on human screening defeats the main purpose of serial numbers: discovering bad products that a human might miss.

The threat of counterfeit drugs has been seen over and over in the US, placing patients at risk. A counterfeit version of somatotropin – a human growth hormone used to treat AIDS-related wasting – was found in at least seven states in 2001 and passed through multiple wholesalers. In 2002, falsified bottles of high-dose erythropoietin (a costly injectable drug to treat anemia) were actually low-concentration products that were relabeled at a higher strength and sold to wholesalers and pharmacies. And as recently as 2013, counterfeit versions of the cancer drug bevacizumab that contained no active ingredient were distributed in the US.

DQSA could also be improved by deactivating the serial number after a drug is dispensed. If serial numbers

for dispensed or expired drugs remain active, nothing prevents criminals from reusing those numbers to market their drugs as legitimate. A single serial number might appear on hundreds of boxes and pass repeated verification checks. Post-consumer 'recycling' of dispensed drugs is common and can be exploited by criminals. In 2012, the US attorney for southern New York uncovered a large-scale drug diversion and relabeling scheme that cost the state Medicaid program more than $500 million. Under the scheme, 'collectors' purchased the drugs from patients and sold the medicines back into distribution through pharmaceutical wholesalers. Unsuspecting consumers who received these previously dispensed drugs may have been exposed to expired or contaminated medicines. This and similar schemes in other states can be prevented through verification of the package serial number, but only if serial numbers are decommissioned after use…

Finally, although DQSA requires interoperable systems capable of checking a drug's transaction history, it fails to specify details. A system that permits automatic verification of each transaction between trading partners could flag products offered for sale that do not have verifiable transaction histories. This type of automated checking would help buyers to avoid purchasing illegitimate products, thus protecting both businesses and patients.

*"Reliance on human screening defeats the main purpose of serial numbers: discovering bad products that a human might miss."*

The most effective way to detect compromised medicines in the supply chain is to build an enhanced drug distribution security system that takes full advantage of the new tools created by the DQSA. To achieve this goal, both the FDA and industry have a role to play, as do other agencies and, potentially, third-party payers. The FDA is responsible for developing guidance, coordinating pilot programs, and holding public meetings to implement the law, all of which are meant to ensure that the new tools are used in an optimal way. Meanwhile, affected stakeholders, including drug manufacturers, distributors, and pharmacies, must engage with the FDA and with one another to make sure that systems and protocols are feasible and support the deeper functions described above. The Medicare program or other insurers could also require verification of serial numbers, particularly for high-risk products, that are independent of the requirements of DQSA.

The time to begin this collaborative work is now. Although the US serialization and traceability system will not be fully implemented for several years, the process has already begun in earnest. Stakeholders are already investing resources and working hard to comply with first-phase requirements. Industry and FDA should work together to build a system that reaches its full potential to protect consumers and companies from the health risks and enormous economic toll of counterfeit and contaminated products.

# Don't Forget CDx Developers

**Many drug developers are going 'full steam ahead' with personalized medicine strategies. They would be wise to consider a more equitable business model for an essential partner in the process: the developer of the companion diagnostic.**

*By Mark J. J. Roberts, Director, Diagnostics Development at Covance, Indianapolis, IN, USA.*

It is now a well-established principle that not every patient responds to a therapy in the same way. To that end, the pharma industry is evolving from a 'one-drug-treats-all' model to one based on better-directed, personalized medicine. By pre-screening individuals with one or more analytical tools, we can more easily ensure that they are treated with the drug most likely to produce a favorable clinical outcome. In essence, personalized medicine is all about matching the right patient with the right therapy. The prescreening tools – usually biomarker tests performed in a clinical laboratory – are designed as an accompaniment to the safe and effective use of the drug, and are thus termed companion diagnostics (CDx).

*"Adoption is often slow – and the disparity in the revenue generated by the drug and the accompanying CDx is striking."*

While experienced in drug development, most pharma companies do not have the expertise required to develop a biomarker assay and commercialize it as a CDx. Instead, drug developers look towards external partnerships with diagnostic manufacturers. For a diagnostic industry that has experienced low single-digit growth over the past decade, you'd think that a pipeline of CDx assays would be considered a revenue driver and would be widely embraced, right? Wrong. Though smaller diagnostic companies benefit from funded R&D that allows them to commercialize (low volume) tests in which they would not otherwise invest, a number of factors have led many diagnostic companies to question the sustainability of the current model. In many cases, investment in the CDx program only takes place once it is certain (or at least highly likely) that the compound will progress through the clinic, which leaves the CDx developer with very tight timelines to meet first-patient screening targets. Even then, there is still a real possibility that the compound will fail or that the biomarker will not be clinically useful as a CDx, and its use discontinued. Such waste is extremely onerous for the CDx developer.

Even if the drug and accompanying CDx receive regulatory clearance, adoption is often slow – and the disparity in the revenue generated by the drug and the accompanying CDx is striking. I have particularly observed this inequity in assays that accompany drugs designed for use in a limited population, where the volume of testing and resulting revenue is low. In addition, low volumes push testing towards a centralized (specialty reference lab) solution that may not be able to generate the results in the timeframe required for optimal patient management.

To overcome these issues, the industry needs to consider an alternative business model that more appropriately considers risk sharing and more equitably rewards a successful launch of the CDx in support of a high-revenue targeted therapy. At Hanson Wade's recent World CDx Congress, I saw a number of diagnostic manufacturers proposing a profit-sharing model whereby they would receive a percentage of the sales of the drug. While I doubt that the biopharmaceutical industry would universally embrace this approach, I do feel that a new model should be developed that better rewards the diagnostic manufacturer for achieving development and commercialization milestones, with more balance across upfront revenue versus revenue from ongoing sales.

Additionally, I would encourage all parties to provide open access to non-proprietary CDx assays to avoid several companies addressing the same target with different CDx assays, all independently manufactured. In addition to the confusion that this would cause the prescribing physician, it would fragment the potential market size and limit adoption of a number of drugs because it is unlikely that clinical laboratories would offer several different assays for the same analyte…

The future of drug development is singularly focused on tailored therapeutics centered on a strong companion diagnostic strategy. A forward-thinking partnership between the drug developer and their companion diagnostic development partner will strengthen commercial return and help deliver on the promise of personalized medicine.

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# Terminal Inertia

**It is clear that terminal sterilization is the gold standard for sterile drug manufacture, so why are companies so reluctant to pursue it?**

*By Jeanne Moldenhauer, Excellent Pharma Consulting, Mundelein, IL, USA.*

Terminal sterilization should be used wherever possible when manufacturing sterile medicines; not only does it provide a higher level of sterility assurance than other sterilization processes, it is also the preferred approach of regulators, both in the US and Europe. The FDA indicates in its Aseptic Processing Guidance that "it is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible" (1). Similarly, the European Medicines Agency's Decision Tree provides guidance on the sterilization parameters to be evaluated prior to determining that a product should be sterilized using aseptic processing. It states: "Those products intended to be sterile should be terminally sterilized in their final container as clearly stated in the European Pharmacopoeia, and in the CPMP Notes for Guidance. Where it is not possible to carry out terminal

sterilization by heat due to formulation instability, a decision should be taken to utilize an alternative method of terminal sterilization, filtration and/or aseptic processing," (2).

And so it continues to amaze me that surveys show no significant change in the number of drugs aseptically processed versus terminally sterilized. Approximately 80 percent of sterile drugs manufactured use aseptic processing versus just 20 percent for terminal sterilization (3-6).

Apart from a few exceptions, manufacturers of large-volume parenteral medicines (those with container sizes of 100 mL or more) must terminally sterilize their products. However, many of these medicines are also manufactured in vials or syringes in smaller volumes, which are not terminally sterilized. Some companies think that terminal sterilization cannot be used for their products because of a misunderstanding that 121 °C for at least 15 minutes is the only acceptable cycle. In reality, you can select cycles with lower temperatures and longer times, or higher temperatures with shorter times, and still meet the regulatory requirements for terminal sterilization. For example, some products that cannot be successfully sterilized using standard steam cycles can withstand high temperatures for very short periods of time. As long as this provides a probability of a non-sterile unit of less than 0.000001, it is considered successful terminal sterilization. Depending upon the product formulation and its packaging configuration, you could also choose other types of moist heat sterilization, such as saturated steam, air–steam mixtures, air–steam–water mixtures, water immersion or rotary sterilization to meet the necessary sterilization requirements.

There is a lot of guidance to help manufacturers. The Parenteral Drug Association updated their technical report on moist heat sterilization in 2007 (7) to provide a significant level of detail on the various types of sterilization approaches that can be performed, including overkill cycles, or product-specific cycles (formerly called combined bioburden biological indicator based cycles or absolute bioburden cycles). Despite the detailed methods provided, companies have been reluctant to pursue product-specific cycles. In some cases, they do not want to perform the additional biological indicator testing to determine spore log reductions – they prefer total kill cycles.

*"It continues to amaze me that surveys show no significant change in the number of drugs aseptically processed versus terminally sterilized."*

Another roadblock is that companies often don't want to evaluate terminal sterilization for existing products because a regulatory submission is required to approve the new cycle. When the submission is made, it will also be evaluated for compliance with all current regulatory requirements, and the company may be concerned whether all the various chemistry and microbiology parameters will be met. In some cases, there are also costs associated with making the submissions, which may be prohibitive.

Yes, there are hurdles – some real, some perceived – but the huge advances made in sterilization science and methods in the last 35 years allow the terminal sterilization of even challenging formulations. With so many cycles available, and so much guidance at hand to develop and implement them, it is disconcerting to see how few companies are moving towards terminal sterilization of more of their products. Companies need to accept that terminal sterilization ultimately benefits patient safety – and that's something we should all be striving for.

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Ph

# Liking Social Pharma

Patients and physicians are tweeting, snapchatting, pinning and posting about healthcare, and although many pharma companies still have no idea what any of that means, some are making the leap into the digital world – and seeing results.

*By Stephanie Sutton and Charlotte Barker*

Pharma has been slow off the mark when it comes to social media. Only half of the top 50 global pharmaceutical companies use Facebook, Twitter or YouTube – and only ten use all three, according to a 2014 report from IMS Health (1). A survey from the Digital Health Coalition (DHC) and Google agrees, with nearly two thirds of respondents (DHC members) claiming that the pharmaceutical and medical device industry is lagging behind other sectors (2).

Despite the slow start, a number of social media campaigns are generating genuine interest and engagement from patients. Such campaigns are the result of focused strategies that step away from the use of singular, one-way channels to disseminate press releases, and they prove that some companies are starting to take social media much more seriously.

James Musick, head of digital communications and social media at Novartis, says, "Most companies are now on the cusp of realizing a more structured strategy where they are more deliberate about the areas they want to be active in." Previously, individual staff members or departments might engage in a particular channel that suited a particular need; "For example, human resources may have decided to use LinkedIn for recruitment because someone in the department thought it was a good idea," he adds.

However, as knowledge of the platforms – and how to use them effectively – grows, so too does the industry's understanding of the potential benefits. For those unfamiliar with the advantages, the IMS Health report nicely groups the use of social media into three core areas:

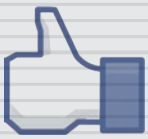
- Gathering information about attitudes, actions and behaviors of consumers.
- Broadcasting messages.
- Engaging people on healthcare-related topics and stimulating public discussions.

In addition, regulators see potential for social media in terms of pharmacovigilance and the identification of regional quality issues through geomapping.

Still unconvinced? "The benefits for pharma are significant," explains Stacey Bernstein, senior vice president and director of digital health at the public relations firm, Weber Shandwick. "The reality is that social media is where people get their health information, where they engage with brands and companies, and where they share their health experiences with one another. For a pharma company that wants to be patient-centric in today's social world, you have to be in social media. It's an opportunity to break down the big, bad pharma persona and to show a more human side."

And yet, many remain wary. What about regulatory backlash? How exactly do you keep a firm grasp on platforms that are constantly evolving? How do you accurately measure the benefits and return on investment? And how do you handle reports of adverse drug reactions (ADRs) or Individual Case Safety Reports (ICSRs) on your social media channels…?

As the questions mount, any degree of trepidation starts to make sense. Here, we explore some of the biggest fears – and how you can overcome them.



## "Like"

*Boehringer Ingelheim: #ChatAFib*

Boehringer Ingelheim's three-part live tweetchat on atrial fibrillation won an Excellence in Digital Communications Award at Communiqué in July. This followed on from their #COPDChat events, which were highlighted by Twitter as a case study in how pharma can use the platform while remaining compliant. Each event lasted an hour, with contributions from experts, journalists and patient advocates. Some were timed to coincide with major scientific conferences in the relevant disease area, to maximize the impact. Clear rules were set by the moderator (for example, no individual medical advice could be given) to manage expectations of participants and any adverse events mentioned were followed up by direct message.

*Sanofi: The DX*

Sanofi runs an integrated online community for diabetic patients and carers across several digital and social media outlets, giving patients a choice of how and where to engage. Three dedicated websites – a discussion site, an encyclopedia of diabetes terminology, and a community site bringing all the information together in one place (diabetes.sanofi.us) – are supported by active Facebook and Twitter accounts. The focus of the community is on supporting patients and encouraging healthy behavior, with lots of blog posts, profiles of members, tips, recipes and interviews.

*Novartis: Music in the Noise*

"Music in the Noise" tells the story of the company's research programs at Cambridge, MA, in a fun, immersive way. The company developed a website and Twitter feeds, but also made use of Flipboard, Instagram and Pinterest, including using location pins to explore the scientific hub in Cambridge. According to the company's social media team, the aim was to design the campaign with a "digital first" mentality, rather than retro-fitting traditional communications into a digital environment, so that audiences can engage with the topic on their own terms.

*Common sense update*

The regulatory environment is clearly a challenge. A number of Warning Letters have been issued to companies regarding their use of social media (3-7). For international pharma companies, there is also the headache associated with operating across different regulatory environments, where 'offline' guidance may vary significantly.

At present, the only specific social media guidance for promoting medicines is from the FDA – and it's only a draft. The guidance comprises two documents that were released in June 2014: "Internet/Social Media Platforms with Character Space Limitations –Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices"; and "Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices" (8, 9). The documents have already ignited much discussion (mainly critical) and the comment period for both was reopened for 30 days at the end of September.

The FDA actually held a public hearing about social media and medicinal products back in November 2009 – the length of time it has taken to produce the guidance documents is testimony to the difficulty in tackling such a nebulous topic. "People expected guidance within the year, but it's taken five," says Bernstein, "but imagine what would have happened if they had issued guidance back in 2009; they'd be completely out of date because of the high velocity at which social media changes."

"The FDA is in the same difficult spot that the rest of us are," adds Musick. "Social media channels change extraordinarily quickly and the FDA is trying to create something, structured and futureproof, which is the right thing to do, but of course they have hundreds of critics. While some of the feedback may be fair, the big picture is that they are trying to give guidance that recognizes that social media is useful and fit for consumers and patients, and to provide signposts that tell us how to use it responsibly. They have the best interests of consumers and patients at heart."

It is possible to be highly successful on social media without stepping on the toes of regulators (see sidebar, "Like"). After all, pharma companies are well used to working within tight regulatory guidelines. "We know how to be compliant," says Musick. "There may be a few fuzzy edges where we have to talk to a regulator, but we know what the intent is; to put forward fair and balanced information. The big question is how to overcome the hurdles; for example, the 140 characters on Twitter."

## Top Tip "Tweets"

*James Musick, Novartis*
Keep trying new things – you learn from this and succeed by learning.

*Andy Malavsky, inVentiv Health Clinical*
Set specific goals. Use social media's collective power. Tie all together: LinkedIn, Twitter, web....

*Stacey Bernstein, Weber Shandwick*
Keep your content personal and genuine.

*Alex Maw, Aesica*
Social media is not about selling a service to as many people as possible; it must be part of a wider strategy to build customer engagement.

*Benedikte Larsen, Novo Nordisk*
Make sure you have the right people in place to monitor your channels.

*Joe Montano, Catalent*
Information is the currency of social media. Those who create meaningful content reinforce their brand integrity and can create new demand.

Bernstein believes good judgment is key: "There may not be guidelines for social media, but there is common sense. A lot of regulatory bodies say you should follow the offline guidance; whatever you do offline you should do online too. You'll often see that the missteps companies have made in social media would probably have resulted in the same regulatory consequences if they had happened offline too. It's not usually the social channel that's the problem but the content."

Companies can also take heart from the fact that the FDA and EMA are no strangers to social media, using Twitter, Facebook and YouTube; in fact, if the FDA was assessed alongside pharma companies on the IMS Health report rankings, they would sit in the top 3 (1).

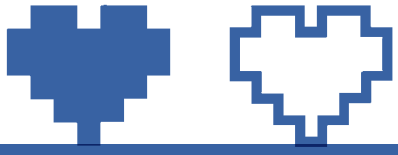
### *ADR alert*

Another prime concern surrounds the obligation to report all known ADRs; it's not necessary to monitor every blog and social media post in the world, of course, but you do have to monitor social media accounts that you control. It's an extra layer of work that some would prefer not to take on, but Daniel Ghinn, CEO of healthcare engagement consultancy Creation Healthcare argues that it's not as tricky as companies may expect. "There is the idea that a company's pharmacovigilance team might be inundated with reportable events, but in practice this is rarely the case, although it varies on the therapy area, drug and market," he says. "A practical way that some of our clients manage this risk is to agree a threshold when launching a campaign or initiative: if an agreed limit of reportable events are discovered, then the initiative is paused pending a review. This limit might be set at say 5 or 10 reportable events and in my experience has never been reached."

In fact, rather than being worried about ADRs, some companies are exploring data mining as an information-gathering exercise. "For monitoring social media for ADRs and reportable ICSRs, at the moment action varies," says Mick Foy, Group Manager, Vigilance, Intelligence & Research group at the UK's Medicines and Healthcare products regulatory Agency (MHRA). "EU Regulations say that if you see something when mining that meets the criteria of a valid case you need to report it. Some innovative companies have gone beyond this and are using it from a marketing perspective to see what people say about their products, or to actively look for new pharmacovigilance signals, whereas others are concerned about compliance with the regulations and not much more, so tend not to look."

Ghinn adds, "We have some clients who would actually like to deliberately look for events like off-label use, or product complains, in order to learn more about their customers and perhaps identify new indications for their products. It's an exciting area, but not for the faint-hearted, as searching for adverse events or conversations about off-label use is a minefield to many in the industry!"

The potential for digital and social media in pharmacovigilance



## Loving Social Media

James Musick: "I love the combination of complexity and simplicity. On one side, social media is about detailed systems, data, networks, mathematics, analytics and insights, but it's also about a simplicity and clarity; do you have a clear message and are you putting it in the right place?"

Stacey Bernstein: "I like the creativity that social media allows. If you look at the most successful digital health campaigns over the past few years, they will give you chills because they're that good! If you want people to see and share content in a digital world, you have to push the limits of creativity to break through the clutter and truly have an impact."

Mick Foy: "On the regulatory side, for me at least, it's not about ICSR or ADR reporting. I'm excited about what the mass of social media data can tell us about new safety signals, or how it can perhaps support signals that have been reported through the traditional reporting methods. For example, the MHRA's Yellow Card reporting scheme may raise a signal that we could perhaps strengthen or refute with social media data – if social media is shown to be a reliable source of robust information of course. The jury is still out on that one."

Daniel Ghinn: "The most cutting edge thing in my mind is pharma using social media as a market research tool by listening to conversations among healthcare professionals taking place in public social media. This was virtually impossible until two years ago, when Creation Pinpoint first piloted a new technology that distils the healthcare professional voice from public conversations."

was recognized by Europe's Innovative Medicines Initiative (IMI), which put out a call in 2013 for proposals to leverage technologies to introduce a mobile app for reporting ADRs and a platform for mining social media data. The IMI call generated a lot of interest, with around 19 bids put forward, but the final project was awarded to a consortium organized by the MHRA.

For the project – now called WEB-RADR (Recognizing Adverse Drug Reactions) – the consortium is developing a mobile app, which could be introduced in the UK and Croatia in the next six months and examining technologies for social media mining, as well as looking to develop a policy framework (10).

"Developing the mobile app is very clear-cut, in so much as it will be used for the reporting of ICSRs and accessing medicines information," says Foy, "but the social media side is more difficult. We also need to consider the ethics. At this stage I'm not a fan of using individual posts or tweets as a basis for identifying ISCRs, but we would have the ability to respond to tweets or posts and say, 'It looks like you have experienced an adverse drug reaction. Would you like to report it?' But is this an intrusion? Will the poster/blogger/tweeter be expecting or welcoming a response out of the blue from MHRA? We'll be seeking opinions from legal and ethical experts on that matter."

Foy also sees great potential for social media in other aspects. One area he is really interested in – and which the consortium will be looking at – is geomapping where public tweets and Facebook posts raising issues have occurred. Potentially, this could identify batch issues, counterfeits and isolated defects in regions where there appears to be an increase in quality-type events. "It could lead us to investigate batches and even medication errors; perhaps there are bad practices in certain regions, for instance," he explains.

### *Follow me!*

Once you've got to grips with what you need to do from a regulatory and ADR standpoint, internal buy-in and a clear strategy is essential to recognize the value of social media. Both Bernstein and Musick believe that the biggest barriers to implementing social media actually lie within the company itself. Musick points to the Gartner Hype cycle. "This cycle is so accurate that it's funny – whether it's talking about social media or anything else! People see an opportunity and put in the early effort, but then – especially in a big company – people start asking you to quantify results, which is difficult in an emerging space.

You then have the period of disillusionment and attention may wane, but then as you push through that and learn more about the platform, you steadily see progress."

Companies who have been present on social media since the early days have been steadily growing their Twitter and Facebook audiences for many years, which gives them a big advantage – and larger reach – than those just starting out. With so many companies now boasting large social media accounts, there is a danger that new starters might expect it to be easy. But the reality is that successful social media strategies require significant changes to operations. Musick warns that the structure of communications departments can also be an issue. "Historically, communications departments were structured around traditional one-to-many communication methods, whereas social media tends to be about engagement and dialogue, which is more one-to-one and requires a different set of skills. It's a daunting task and it's also not easy to find social media experts," he explains. "For companies that started using social media early on, no matter how disparate, you'll usually find that they have internal champions, who can stand up and say that even though social media is difficult to fully harness, it's the future of communications – so you need to do it."

For Bernstein, the biggest issue internally is lack of digital confidence. "There can be a lot of fear, anxiety and uncertainty about what you're doing and whether it's right. Before you jump into launching a social or digital program, you really need to figure out your internal guidelines and educate people internally about what they can or can't do, as well as the benefits."

Indeed, many companies, including AstraZeneca, Roche and Novartis, have published their own internal guidelines for social media, detailing what behaviour is expected from their employees. "I think rolling out concise, clear guidelines, which are easy to read rather than being full of legal language, is a very important milestone in a social media strategy because it can quell employee misconceptions," says Musick. "People have many different feelings about social media and what they should and shouldn't do, so it's important to establish a framework. Rolling out guidelines at a big company isn't easy, but it sparks a lot of positive social media activity."

"At Novo Nordisk, we have also developed extensive guidelines about social media," adds Benedikte Larsen, team leader in corporate branding at Novo Nordisk. "We have decided that we don't communicate about products on our social media platforms - though there are a few exceptions in US."

## Didn't "Like"...

While it's true that the FDA does monitor pharma's use of social media, Warning Letters for violations in this area are relatively rare, mainly directed at companies promoting unapproved drugs or dietary supplement and health products. However, there are a few lessons that can be learned.

### *Watch out for text limitations*

On July 29, 2010, the FDA sent a letter to Novartis about a Facebook Share widget on the company's Tasigna website, which allowed visitors to share Tasigna information on their Facebook profile, or on the profiles of their friends (3). Although the shared content directed users to the Tasigna website, which contained a full risk profile, the shared content itself did not explicitly disclose the risk information. Novartis quickly removed the widget.

### *Be transparent about risks*

The first Warning Letter specifically against a pharma brand's Facebook page was sent in February 2014 and related to Tirosint, distributed in the US by Akrimax Pharmaceuticals (4). The FDA claimed that the page neglected to mention any risk information at all.

### *Be careful about Likes and Reposts*

A 2012 Warning Letter chastised a dietary supplement company for 'liking' comments on Facebook, which the FDA said could be seen as implied endorsement (5). For example, AMARC Enterprises received a Warning Letter after they liked and reposted a comment from a customer crediting the companies' supplements with helping her beat cancer. An article published by the Regulatory Affairs Professionals Society added that 'favoriting' tweets on Twitter could also be risky (13).

### *Pinterest isn't immune*

Pinterest focuses on images, which are more difficult to scan and regulate than text. But the first Warning Letters to cite Pinterest were issued in September 2014 against two dietary supplement companies (6, 7). The companies, Young Living and dōTERRA, received the Warning Letters for marketing various products to treat a range of conditions (including Ebola) on their websites and social media channels.

### *Damage control*

When it comes to social media you need to be prepared to fail. IMS Health's report says, "It is likely that companies will make mistakes in the application of social media, so it is also advisable to be prepared and have a protocol ready for damage control in that event and respond quickly and appropriately."

*Channel choice*

As well as developing guidelines, you also need to decide what channels to focus on. Twitter? Facebook? LinkedIn? Pinterest? What about Flipboard or Xing? The number and variety of platforms can seem overwhelming, but it's best to avoid a scattergun approach. Musick advises picking a set number of channels with a 'quality over quantity' mindset. "Look at the strengths and weaknesses of each channel," he says. "You don't just grab a piece of content or a topic that you want to talk about and throw it out in all the channels, which is the old way of doing it. You should consider what you want to talk about, and then look at which channels are connected to the audience for this topic. You then need to develop the content in a way that works for the channel."

Larsen also emphasizes a carefully considered approach. "We launched our first platforms in early 2009 – an internal video sharing platform and an external graduate blog. The strategy was to start small, learn as we go and only with platforms where we could see a clear business value. The strategy has evolved in the sense that we now have more platforms: Facebook, Twitter (several accounts, focusing on different topics and target audiences), Google+, Pinterest, LinkedIn, Instagram, Flickr and YouTube. All platforms have been launched one by one."

Bernstein adds, "You need to give people content that they actually want to read. There are still so many companies out there pumping out content that just sounds like a press release. It's obviously not been written for social media."

*Snapshot of success*

The successes of social media can be difficult to measure and quantify, so it's challenging to single out specific companies or campaigns, but there are a few companies who are generally agreed to be ahead of the pack. The IMS Health report ranked Johnson & Johnson as the top performer in terms of reach (number of listeners, likes, shares, and so on), relevance and relationship. J&J's news account @JNJNews has over 75,000 followers on Twitter and the company's Facebook page has attracted over 645,500 likes. That's streets ahead of the competition; 12,000 more Twitter followers and over 500,000 more 'likes' than GlaxoSmithKline, who took the runner-up spot in the report. Other top performers included Novo Nordisk, Pfizer and Novartis. In September, Novartis was ranked as the Digital Pharma Company of the Year in the UK at the PM Society for Digital Media Awards (11). At the same event, Novo Nordisk took home an award for digital pioneer, which was awarded to Adam Boucher, who played a key role in the company's 'Decisions in Time' series.

Another company regularly singled out by digital consultants and online bloggers is Boehringer Ingelheim, which has won praise for its informal style. Their live tweetchats and Facebook game Syrum have really got the industry talking. We've listed three high-impact social media campaigns in the sidebar, "Like".

And what about the future of social media? Only time will tell. "I don't think anyone can say with any degree of certainty what the future of social media and digital technology will look like because technology changes so much," says Foy. "Phones have more power than main frames had 10 years ago! People are definitely using

## Timeline

*August 6, 1991: First website launched by CERN, the European Organization for Nuclear Research*

*October 1996: FDA holds hearing about the Internet titled 'World Wide Web 101'*
*December 1996: 16 million Internet users**
*September 1998: Google*

*January 2001: Wikipedia*

*August 2001: 513 million Internet users**

*May 2003: LinkedIn*
*February 2004: Facebook and YouTube*

social media more and more – and in the future we'll see more platforms, some more serious than others. A couple of years ago, no one had heard of Instagram or Snapchat and look where they are now. In years, they could be gone and something else could be around the corner… As for how we'll use them, hopefully projects like WEB-RADR will help to inform us."

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## Welcome to Digital Health

A recent report from IMS Health was packed with fascinating statistics about our brave new digital world (1):

- Use of social networking sites in the US has grown from just 8 percent of adults in 2005, to 67 percent in 2012, and 72 percent in 2013.
- In the UK, Facebook is reported as the fourth most popular source of health information.
- In the US, 42 percent of people seek health information on social media.
- Many people are turning to 'Dr Google' for health advice. 35 percent of US adults have searched online for a diagnosis; of those, 41 percent said that a medical professional subsequently confirmed their diagnosis, while 18 percent found that their doctor disagreed (12).
- Wikipedia is increasingly seen as a valid source of information, both amongst patients and doctors. The top three most visited healthcare pages in 2013 were tuberculosis, Crohn's disease and pneumonia, with around 4 million visits each.
- Health professionals themselves are also digital-savvy, with physicians spending twice as much time using online resources compared with print when making clinical decisions.
- Doctors are fans of online professional education, spending on average three hours per week watching online videos for professional purposes.

*December 2005:*
*>1 billion Internet users**
*March 2006: Twitter*

*November 2006: Xing*
*November 2009: FDA holds Public Hearing on 'Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools'*

*March 2010: Pinterest*
*September 2010:*
*1.97 billion Internet users**
*September 2011: Snapchat*

*June 2011: Google+*
*March 2014:*
*2.93 billion Internet users**

*June 2014: FDA releases draft social media guidance*

**source: www.internetworldstats.com*

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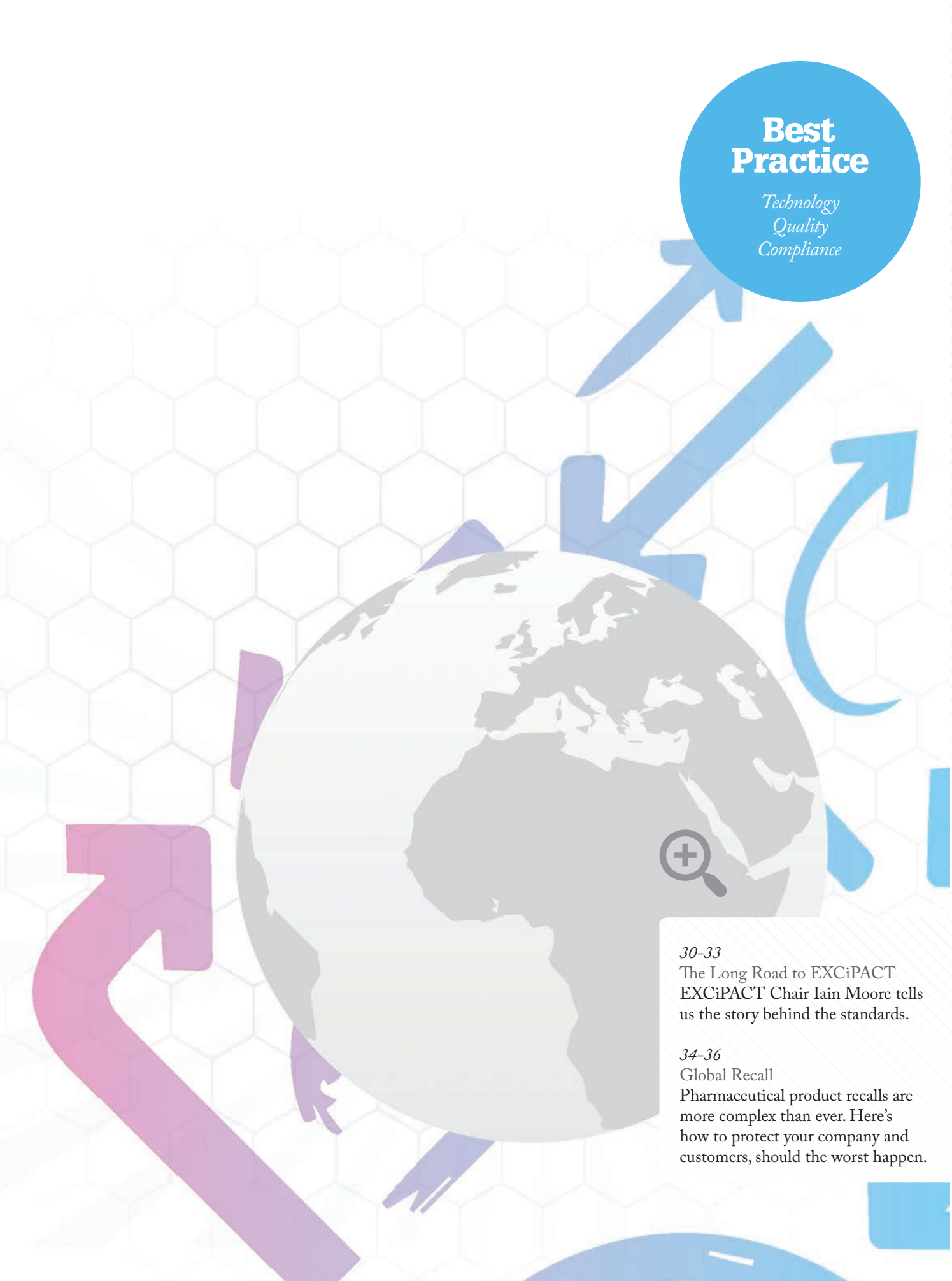

# The Long Road to EXCiPACT

**If I knew six years ago just how much of my time EXCiPACT would take up, would I have even started? A good question! But, actually, I have no regrets; the story of EXCiPACT and its impact, even today, on the pharmaceutical industry makes every second worthwhile.**

*By Iain Moore*

*One distant day in the last century…*
*I was annoyed. I had travelled halfway across Europe to meet with an industrial customer to promote our new metalworking products but the majority of the meeting had been taken up by discussing poor product quality for our existing business. Sadly, it wasn't the first time I'd heard about these problems, so I decided to go down to the manufacturing plant to find out what was happening.*
*The answers were not comforting: while there was control over the process, there was insufficient understanding of the chemistry involved, so when abnormal situations were encountered they did not know what to do. As a chemist I knew I could help.*

And so began my journey into quality assurance (QA) and, indirectly, down the long road to the establishment of EXCiPACT.

If you work in pharma manufacturing, you will almost certainly have heard about EXCiPACT, a global, third-party certification scheme for pharmaceutical excipient suppliers. Here, I tell the story behind the standards.

## The trauma of audits

When I graduated from the University of Bristol with a BSc and PhD in organometallic chemistry, I had no idea where my career would take me. I took a research position at BP, before joining Croda in 1987, where I have had a great career ever since. In my first Croda role, I provided technical support to sales teams, but I found my vocation in QA. By drawing on my experience in chemical research I was able to help the manufacturing team increase product quality and manufacturing efficiency. Croda customers were much happier and this freed up time in our meetings to discuss new products and ideas. An opportunity presented itself to work in R&D and although I loved the customer interaction, the chance to go back to my roots in the laboratory was too strong to resist. But this was just a stepping stone, and a new role in quality allowed me to use all my skills and knowledge across the business. All too soon another customer-centric problem came to my attention.

I was completely perplexed by the variety of outcomes from customer audits. The majority of customers were perfectly happy with our processes and quality standards, but a few would audit the exact same product, made in the exact same way, and then be very unhappy and worried. Clearly, some auditors were assessing us with very different standards, and those differences seemed to arise chiefly from the intended use of the product. At that time, I knew of no uniform standards or best practice for excipient suppliers. I was pointed in the direction of the UK Pharmaceutical Quality Group (PQG), and they provided me with some very helpful guidance. Rashly, I commented at the launch event that if they ever needed help with a revision of that guide I'd be happy to help. Well, that comment was the beginning of my involvement in setting standards for excipients.

Working with the PQG in the UK in the late 1990s, we designed a new GMP standard for pharmaceutical excipients – PS 9100. At its core was a tiered approach, based on an initial risk assessment, with increasingly strict standards of quality and purity depending on the use of the excipient and other factors. These allowed different standards to be applied for topical creams, oral products and injected medicines. When PS 9100 came out in 2002, it was leading-edge – even revolutionary, I might say. It took the rest of industry and the authorities 12 years to catch up. PS 9100 already contained many of the building blocks of what would eventually become EXCiPACT.

At the time, PS 9100 was controversial in using a risk-based approach to determine the degree of GMP that was required. It attracted a lot of criticism and was not widely adopted, not least because it was a UK standard, but I always knew the approach was fundamentally correct

in terms of assuring patient safety. A little later the International Pharmaceutical Excipients Council (IPEC) –PQG GMP guidance for excipients was published in 2006. The IPEC-PQG excipients GMP Guide used many of the same concepts as PS 9100 but in a less formal manner. It was more a document of its time and as a result it has been very well accepted by regulators and industry worldwide. Many companies adopted it and used it to audit their suppliers, but as a guidance document, rather than a standard, it was not ideally suited for this purpose.

Guidance is primarily educational; it sets out the principles to follow and provides an explanation of them in various scenarios. Guidance is a "how to do" approach, which is great to educate and inform on best practices but causes problems with audits. An example: a favored word in guidance is "where appropriate". Well for me that begs the question – who decides what is appropriate? Is it the auditor who comes to assess your compliance? Or the excipient supplier? The lack of clarity is not helpful. By contrast, a standard is a "what to do" document – if you want to know how, then read the guidance. A highly respected member of the UK's Medicines and Healthcare products Regulatory Agency (MHRA) was always amazed that PS 9100 was so short: "I can't believe you have reduced GMP to so few words". Less is more, as they say.

## Tragedy triggers change

While most manufacturers were making progress in quality, it became clear that the industry as a whole was not doing enough. Heartbreakingly, in the late 2000s, the industry saw several serious instances where GMP failure, or failure to secure the supply chain, led to patient deaths. One of the most widely reported cases was the adulteration of heparin with counterfeit ingredients from China, which caused more than 80 deaths and 700 serious adverse reactions. There were also a number of instances worldwide of glycerin, used in cough syrups and baby teething medicine, being contaminated with toxic ethylene glycol, with hundreds of fatalities. The tragedy is that these deaths were avoidable – implementation of very simple GMPs would have prevented them all.

The string of tragedies understandably alarmed the authorities, who needed to tighten up regulation and increase control of all ingredients – not just the finished dosage form and active pharmaceutical ingredients, but also the excipients and other ingredients. Tighter regulation generally means more audits. I went to my sales team and asked how many pharmaceutical customers we were working with. The number was large. Assuming each customer audits every three years, we were looking at several audits every week at every site. We couldn't keep up with that, and on the other side of the fence pharmaceutical companies were making a similar calculation and realizing they would need an army of auditors.

It wasn't just the number of audits causing concern. If regulators started to inspect excipient suppliers, in Europe at least, they could only audit them to Part I or Part II GMP. These standards are designed for the world of medicinal products, and while the principles of ensuring product purity are the same in excipient manufacture, the actual detail is fundamentally different. The classic example is an auditor used to working with medicinal products coming to a chemical plant and citing absent hairnets as a noncompliance. The plant management then point out that everything is encased in stainless steel reactors and pipes, running at several hundred degrees centigrade and extreme pressure – if anyone came into close enough contact with the product to drop a hair in it, contamination would be the least of their problems! In this environment, protective clothing is worn to protect the workers, not the product. That's not to say the product should not be protected from contamination, but a hairnet is not likely to be much use in that situation. The risks to product quality stem from the technology used to make the excipient. A one size fits all rule is not going to be effective in all circumstances, especially given the complexity of excipients, their varied sources and methods of manufacture.

*"Heartbreakingly, in the late 2000s, the industry saw several serious instances where GMP failure, or failure to secure the supply chain, led to patient deaths".*

For many excipient suppliers, like Croda, pharmaceutical excipients are only a part of the business. If the GMP or auditing requirements became so onerous that it was financially unrewarding to supply this market, suppliers would simply stop providing excipients. The impact of withdrawal of suppliers from the pharmaceutical industry on the availability of modern medicines would be huge. It was clear we needed to raise the bar for excipients, but I also knew that it had to be done at a pace that was viable for the whole industry. PS 9100 had taught me that lesson.

## EXCiPACT is born

Excipient suppliers and pharmaceutical manufacturers all agreed that something

## EXCiPACT Timeline

*October 2007*
EFCG position paper published proposing certifiable standards for pharmaceutical excipients

*Early 2009*
Several organizations formed a project consortium to jointly develop a set of cGMP and cGDP standards for pharmaceutical excipients. Global Steering Committee formed to manage the project – now called EXCiPACT

*December 2011*
Standards finalized

*January 2012*
EXCiPACT European public launch in Barcelona

*April 2013*
US Launch of EXCiPACT at ExcipientFest Baltimore, MD, USA

*July 2013*
First two EXCiPACT Certificates issued to Merck KGaA and Aug. Hedinger in Germany

*January 2014*
EXCiPACT becomes a not-for-profit association ("asbl") registered in Belgium

*September 2014*
The number of sites with EXCiPACT certification reaches 14

Croda manufacturing site.

must be done to stem the rising tide of audits. The obvious solution was third-party certification – an approach that had been successfully applied before in industry – just look at the way ISO 9001 has been adopted worldwide. But the weaknesses of ISO 9001 were well documented and understood. So in July 2008, there was a meeting of a number of organizations representing suppliers, distributors and pharmaceutical companies. The meeting is still sharp in my memory, since it did not get off to as good a start as I expected. I suspect I wasn't alone in this!

We could all see that there was a problem, and we were all very passionate about protecting patient safety. But everyone had different ideas about what should be done. Many of us had never met before and several times during that first meeting I found myself thinking, "I can't work with these people!"

But despite the stormy start, gradually we found some common ground. Once we had the basis of that initial agreement, everything quickly lined up. EXCiPACT was born! The energy of that meeting really carried us forward over the next few months as we formed working teams for GMP, good distribution practice, defining standards for auditors, and certifying bodies.

It took nearly three years to define, design, develop and consult on those standards. We consulted widely, with regulators and other stakeholders. This was the most crucial part of the process and we built on the success of the IPEC document in this respect – the wide-ranging consultation and visible review of those comments has been instrumental in getting acceptance of EXCiPACT and building quality into the whole scheme. There were many other trials and tribulations during that time, and several points when I nearly regretted taking on the project. It was clear that it was not going to be a short haul process. But equally I and the EXCiPACT team were convinced we had a really good solution to the problem of audits, and like many quality professionals, I don't like to give up.

In these early stages, we tragically lost one of our key members, Arnulf Heubner, who died suddenly. His leadership was very important in forming EXCiPACT and we felt – and still feel – his loss greatly.

Writing and preparing standards was only one part of the solution. Having been in QA for some time now, I thought I was aware of the business systems and processes needed to run and make a success of an organization. But I had been quite insulated from money matters and my education was about to get a rude awakening as we brought EXCiPACT to its launch.

At the start of 2012, we formally launched the scheme in Barcelona at the IPEC Europe Annual Meeting. Suppliers pay what we believe to be a modest fee of €5500 every three years for certification, revenue that EXCiPACT uses to provide direct oversight of both certifying bodies and auditors. We are working very hard to make sure standards are kept high. EXCiPACT already has its very own QA manager – and now a Treasurer too, because all that oversight and QA requires financing. The irony of learning about the theory of businesses through QA and the reality of financial matters is not lost on me!

EXCiPACT delivers more than a certificate – an audit report is provided to the customer by the supplier, so they can evaluate the quality systems in place and perform their own risk assessment. The supplier can then decide whether they need to carry out their own audit, or whether the EXCiPACT certification is sufficient.

Importantly, at the launch, we were joined by representatives from the UK's MHRA and the US FDA, who were very positive and made it clear that EXCiPACT matched their requirements for demonstrating GMP. Though regulators have the authority, in reality they do not have the resources to routinely inspect excipient suppliers, so they view the scheme as a welcome development in helping to assure the quality and purity of excipients.

## Impact of EXCiPACT

Initial reactions to the scheme have been very positive. Currently, there are 14 certificates held by different suppliers. Our initial goal is to get 20–30 organizations certified, and expand the scheme in the US and Asia. Companies, both suppliers and users of excipients, have reported that they have significantly cut down on the number of customer audits. We believe passionately that we have a good product – one the industry can use, that is cost effective and which doesn't compromise on quality. But ultimately the customers – the excipient users – will decide if it is a success or not.

*"Though regulators have the authority, in reality they do not have the resources to routinely inspect excipient suppliers, so they view the scheme as a welcome development."*

Of course, people do have concerns. One thing that suppliers have remarked on is the length and thoroughness of the audit. At least one supplier has told us that they have never had a customer audit as difficult as the EXCiPACT audit. But I take that as a compliment – we need to set a thorough standard. We need pharma companies to know that they cannot do an audit better than one by EXCiPACT. That said, anyone who thinks EXCiPACT is going to stop all customer audits is dreaming; that is never going to happen. However, I do believe it will certainly halt the increase in audits that many manufacturers have been facing.

## The road ahead

When flying over to Paris for a conference, most of us don't typically think about all the hard work and effort that has gone into getting that plane into the air (and down again). It's the same with medicines. Patients have an expectation that a medicine is going to work, and that it's not going to harm them. But it takes a coordinated effort from manufacturers, suppliers, regulators and many others to make sure that is the case. We all use excipients – you, me, our families – and we all want those products to work and be safe.

When I look back to where we were over 25 years ago at the beginning of my time with Croda and where we are today with the quality and purity of our products, I can hardly believe the progress we have made. It's absolutely astonishing. I see the next 20 years as a continuation of that. I don't think we can or should stop now, when there is still so much more we can do to ensure patient safety. EXCiPACT is certainly part of that journey, but it's not the final destination.

The last six years have not been easy, that's for sure. But I'm proud to have been able to work with a large number of equally committed people, who have given up their time as volunteers, to make EXCiPACT happen. In ten years' time, I'd like to look back and see that I started something that has helped make medicines safer.

*Iain Moore is Head of Global QA at Croda Europe and Chair of the Excipient Certification Project at IPEC Federation (EXCiPACT).*

# Global Recall

**It is the nightmare scenario for any drug firm. And yet, in a world of regulatory rigor and complex supply chains, product recalls are becoming increasingly challenging. Here's how you can protect your company and customers, should the worst happen.**

*By Mike Rozembajgier*

The increasing globalization of the pharmaceutical supply chain has caused a headache for drug manufacturers. Increased international regulatory collaboration and oversight, stricter requirements for imported products and raw materials, new sourcing and supplier verification processes, the need for traceability protocols... the supply chain is more complex than ever before. With all these different factors to keep an eye on, it's perhaps no wonder that pharmaceutical product recalls have also significantly increased in complexity.

## Globalization of recalls

No one is feeling the effects of the globalization rollercoaster more than Indian drug manufacturers. India has risen rapidly to become the number two exporter of pharmaceuticals to the US, but has hit a few 'bumps' along the way. A recent FDA Warning Letter to an Indian manufacturing facility was widely reported in the media after noting problems from falsification of data to "dead and decaying frogs" near the exit dock. Indeed, the FDA has been monitoring foreign drug companies much more closely and has banned multiple Indian drug makers from importing products to the US over the past year. Added to a series of FDA recalls for Indian pharmaceutical manufacturers, it's clear that these are not just warning shots, but the result of strict ongoing oversight that is not likely to stop in the foreseeable future.

For me, the main lesson from these recall woes is that manufacturers must be prepared to implement quality control measures on a global scale, if they want to effectively compete in the global economy. They must also be prepared to handle subsequent recalls in a way that complies with regulations; for example, it's a good idea to devise country-specific recall plans and on-site assessments to identify risks in standard operating procedures. Companies also need surge capacity to handle the complexity of

*"The main lesson from these recall woes is that manufacturers must be prepared to implement quality control measures on a global scale."*

large-scale, geographically distributed events. Companies are generally good at doing forward logistics and shipping, but may not be as evolved on the reverse side. Today's recalls often affect more than one country, which makes the process more challenging. For instance, translation services or additional linguistic capabilities at call centers may be required. Product collection, storage, shipment and destruction will also vary between geographic regions based on local regulatory requirements and border control.

The sheer size of a major recall is often daunting enough, but when a manufacturer starts to look at the laundry list of other potential issues in the recall process (communication, logistics, supply chain management, and so on), it can seem like an insurmountable task. However, this 'recall sprawl' can be conquered by preparing for the worst in advance with a strong recall plan.

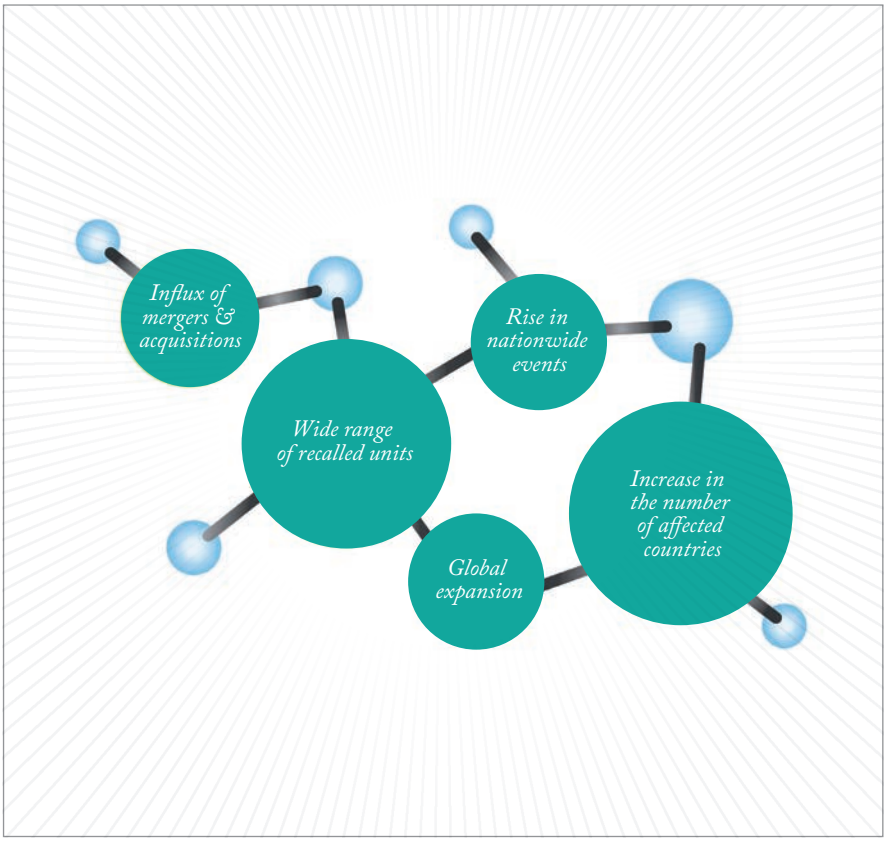


Figure 1: The increasing complexity of pharmaceutical recalls.

## Recall planning: the importance of being earnest

There are 5-10 product recalls issued every day in the USA alone. And yet, I can't tell you how many times I have given my card to the regulatory manager or CEO of a company and been told "We have a good process in place. We've never had a recall and I don't think we ever will." Weeks, months, or sometimes years later, I'll receive a call: "We need some help…"

No manufacturer wants to believe that its product may be the subject of a recall, but to deny the possibility completely is a dangerous business; especially given that the best way for an organization to cope well in such a situation is to ensure that it is adequately prepared. It's true that there is now more awareness about recalls, and most companies do have a recall plan. Whether it is an effective, comprehensive plan or not is a different story. Fortunately, there are some specific precautionary steps that all companies can take:

### 1. Involve the right people

In essence, an effective recall plan empowers organizations to quickly and efficiently locate recalled product and remove it from the marketplace. Your first task is to make sure you have the right people involved, from the planning stage onwards. It's not just the quality and regulation teams that will have a role to play in a recall – you will need operations, sales and marketing, logistics, communications and others to play their part. Having robust discussions between departments before a crisis occurs is critical. Leaving out a key department at the planning stage can really hamper your efforts – for example, your sales teams can often be your most direct route to reach customers so they need to be kept up to speed. Another common omission is the finance department. The cost of recalls can be massive – by bringing finance into the discussion early on, you can identify ways to minimize costs without compromising patient safety.

### 2. Clearly define roles

To succeed, you must very clearly define the role and responsibility of each member of the recall management team. This section of the plan should also drill into the scope of authority and responsibilities of each individual, department, and affiliate, so that all members are clear on what needs to be done and when. Communication within your core team is critical. You should plan for daily, sometimes twice-daily calls, to make sure everyone knows

*"Whatever the size or complexity of the recall, addressing the situation efficiently and calmly is key."*

what is going on in every region, and the response from customers, the media, and senior management.

### 3. Communicate the plan

You can assemble a great team and create a watertight plan but when it comes to an actual recall, it isn't just your own team involved. Whether they be distributors, wholesalers or pharmacies, it is crucial for your business partners to understand their role in the plan. Companies throughout the supply chain should revisit the plan annually to ensure it takes current operations and personnel changes into consideration. The whole supply chain needs to know how and when you will communicate in the event of a recall and how the recall will be carried out. When a recall occurs, it should certainly not be the first time you are talking to them about your plans.

### 4. Be proactive, not reactive

When creating recall plans, a lot of energy is put into the launch – making sure that the communication is right and that the plan will be executed properly. Equally if not more important is to plan how you will respond during the recall. You need to know how quickly you can expect to see a response in different regions and track returns, questions and complaints in real time. This allows you to not only answer current questions but to anticipate upcoming questions.

### 5. Don't underestimate social media

Don't underestimate the power, both positive and negative, of social media. It can be a great friend in the midst of a recall, if you use it correctly and keep the message clear and concise. On the flipside, it can be critically damaging if the wrong information starts circulating. Confusion can spread very quickly and compound the crisis, so you will need to monitor and respond to social media traffic as it happens.

### 6. Test the plan

Planning alone doesn't guarantee an effective recall – no orchestra performs perfectly by reading music sheets once! And so, like a well-practiced orchestra, you must rehearse your recall plan to ensure that all aspects have been considered. Recalls involve multiple phases and processes, so testing potential scenarios and the recall management team's ability to respond will enable you to make adjustments where necessary. There are a variety of approaches to rehearsals. One of the most common is to simply 'lock' people in a room with a recall scenario, perhaps introducing a curveball halfway through to really test the strength of the team. Such exercises allow your team to respond to a real-life situation with critical, decisive thinking.

Taking things a logical step further, a mock recall (that is to say, actually sending out a mocked-up product) can test how reverse shipping would work in practice. I remember taking part in one simulation where, at a critical stage when testing had revealed that the recall needed to be expanded, it became apparent that no one on the team had access to the data needed to identify affected lots. This might seem like a trivial problem, but in an emergency you don't want to lose valuable time waiting for a fix from the IT team. If you can't pull the data quickly enough in a real-life scenario, the recall may have to be expanded – at considerable extra cost.

### 7. Look back

If you have a recall, it might be tempting to put it behind you as quickly as possible. But you would be missing an opportunity to learn a lot about your business and your supply chain. After every rehearsal or recall, meet with the team and make sure any lessons learned are shared with all relevant team members.

Having a good, well-rehearsed plan is clearly essential, but it is also imperative for manufacturers to stay informed on the safety standards of imported pharmaceuticals, as well as the distribution, handling and practices of global distribution networks. Having a deep understanding of current regional regulatory and legal mandates is of utmost importance, as multiple regionally targeted plans will be needed to adhere to local regulations.

Unfortunately, I think recalls are likely to become more complicated, not less; the increasing market demand for cheaper products is putting greater pressure on all manufacturers to spread supply chains even wider. But whatever the size or complexity of the recall, addressing the situation efficiently and calmly is key.

Companies that have practiced and prepared for the worst will be able to initiate a prompt, organized recall, which enables them to more quickly turn their attention to even more serious matters: correcting the problem that caused the recall in the first place.

*Mike Rozembajgier is Vice President of Recalls at Stericycle Indianapolis, IN, USA.*

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# Adapting to the Future of Licensing

**With an EMA pilot scheme underway, and ongoing discussion at regulatory agencies worldwide, it looks likely that adaptive licensing will feature in the future drug development landscape. But what will this mean for the development process and the working relationship between regulators, payers, patients and sponsors?**

*By Lynn Baird*

Currently, authorization is the magic moment in the drug approval process. A "yes" answer catapults a therapy from the experimental stage into routine use by thousands of patients – including potential off-label indications. At this point, the medicine is considered to be safe and effective; however, there can be unpredictable effects in real-world patients because assumptions on safety are based on data from narrowly selected patient populations enrolled in clinical trials. For example, patients over 60 and those with pre-existing conditions are often excluded. To address these challenges and others, a new approach is under discussion by regulators, drug developers, payers and patient advocates worldwide: adaptive licensing.

Adaptive licensing (also known as staggered approval or progressive licensing) is an iterative process that may begin with the early authorization of a medicine in a restricted patient population, followed by proactive monitoring of newly treated patients. If the safety and efficacy profile in these patients is positive, the marketing authorization can be adapted to expand the patient population little by little, based on accumulating data. I sometimes describe it as building out from the center of an onion, where layers of data from broader patient populations are progressively added. With each layer, the regulators make new decisions on whether to expand, or indeed contract, the patient population, as supported by the data.

A key benefit of adaptive licensing is the potential to get medicines to patients faster, particularly if the therapy addresses an unmet medical need. Indeed, it is anticipated that the first adaptive licensing medicines may initially target niche indications before being expanded. Regulatory pathways already exist for speeding up the approval process, such as Accelerated Approval in the US and Conditional Marketing Authorization in Europe, but adaptive licensing represents a more comprehensive framework that goes beyond licensing – it covers everything from early development right through the lifespan of the product.

It also offers advantages in terms of monitoring safety and efficacy after the initial marketing approval. In the current system, the patient populations and conditions in clinical trials are very controlled, but this all changes after approval. In fact, very few data are collected to evaluate the safety or efficacy of the drug in a real-world setting, beyond the passive reporting of adverse events. With adaptive licensing, the initial patients are followed much more closely and there is the potential to supplement clinical trial data with real-world data, which is useful for regulators, payers, sponsors, and patients alike. In today's system, these stakeholders do not have a great deal of confidence that they will get the postmarketing data they want and need. If everyone agrees upfront what data are going to be collected, there are much clearer assurances that this will occur.

## Can it work?

So far, I've focused on the potential benefits of adaptive licensing, but there are a number of hurdles to overcome before such a system becomes the norm. First of all, the interactions among drug companies, regulators, payers and others will need to be much more transparent and collaborative. Frequent and extensive dialogue within and among stakeholder groups will be required to build trust and arrive at an acceptable solution for all. This will be particularly important for payers and health technology assessment (HTA) bodies, who already take a variety of approaches to assess comparative effectiveness of traditionally developed medicine. These differences will almost certainly be magnified when considering adaptively developed medicines.

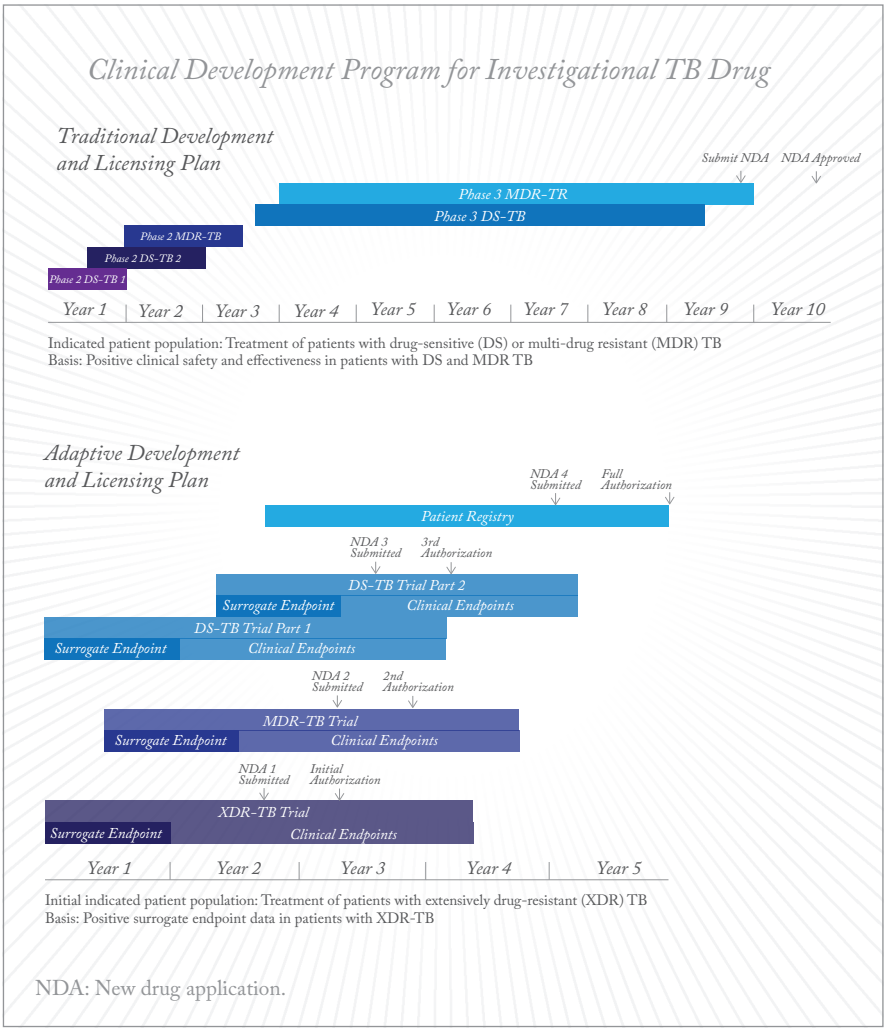
Adaptive licensing involves an element of risk sharing – all stakeholder groups are going to have to compromise, to give up something in order to get medicines to the patients who need it. For instance, regulators and payers will need to be comfortable with making initial decisions based on a smaller dataset and feel confident that additional data will be forthcoming; payers and sponsors will need to come up with more flexible pricing strategies that can be modified as additional data are accumulated; patients will need to accept more uncertainty about a medicine early in its lifespan in order to obtain its potential benefits; and sponsors must be willing to accept a small initial market in order to accelerate the availability of medicines to the patients who need them most. There aren't many particularly good examples of this type of multi-stakeholder interaction and collaboration in drug development. To make this work, we must get each

stakeholder group to focus on achieving a greater good.

At the New Drug Development Paradigms (NEWDIGS) program, led by the MIT Center for Biomedical Innovation, we wanted to move beyond theory and explore how adaptive licensing could work in practice; we wanted to see whether this level of stakeholder collaboration was realistic. With that in mind, we have been holding quarterly two-day workshops over the past four years. The goal of these workshops is to get stakeholders together early to talk about the common goal they all share and work together to improve the efficiency of that process.

In these workshops, trial sponsors discuss real-life case studies of drugs in development. They describe the current regulatory pathway, and propose how an adaptive licensing approach could be applied. To date, 14 different candidate medicines have been discussed across a wide range of therapeutic areas and drug types – small molecules, biologics, combination therapies and vaccines.

The discussions at the workshops are carried out under confidentiality agreements. Proprietary information about the candidate medicine stays in the room, although the ideas developed during the workshop can be shared more broadly. In the room, there are multiple pharma companies, regulators from a number of agencies, payers and HTA representatives from several jurisdictions, patient advocates and physicians. A company typically presents a proposal, and then everyone weighs in with suggestions on how the plan could be refined to make it more robust from a scientific standpoint, or how it might be refined to more effectively get regulators and payers the information they need, as they need it. The conversations are surprisingly interactive, with a great deal of idea cross-fertilization, which is impressive to see in an industry that is so often focused on the proprietary nature of what they are doing. The sponsor participants, regardless of whether they have chosen to pursue adaptive licensing for their product, also get a lot out of the discussions, benefitting from the diverse perspectives that are voiced. Indeed, several companies have brought their development candidates back for two, three, even four follow-up sessions, as new information is accumulated and/or to continue to refine their approach.




## Supporting implementation

Having seen such a positive reaction to the workshops, we hope to broaden stakeholder familiarity with this type of collaborative environment with a recently launched program called the Janus Initiative. From development to clinical outcomes, the Janus Initiative is being designed to bring together a diverse group of experts (not only from multiple organizations but also from multiple functional areas within those organizations) to capture the key information about a therapeutic program. Specific factors that will be considered include: patient population structure, clinical trial programs, registration, reimbursement, adoption, public health impact, and even caregiver impact.

Janus collects multiple stakeholder views on the strength of evidence for each input and the range of estimates, using both retrospective and prospective case studies. If consensus cannot be reached, enhanced visualizations of the various perspectives facilitate stakeholder dialogue to define the range of scenarios to explore. Janus employs a linked series of simulation models to quantify the effects of adaptive licensing across time and according to each stakeholder's perspective. Wherever possible, Janus will leverage and link existing tools rather than create entirely new ones.

The successful adoption of adaptive licensing will also require proactive collection and analysis of safety and efficacy data across the lifespan of a medicine, not just up until the time of authorization. Therefore, a more diverse dataset, beyond that collected in randomized, controlled trials, will be required, including real-world data from observational studies and/or patient registries, as well as emerging data sources such as social media, electronic medical records, and wearable sensors. The NEWDIGS Data Program has been established to evaluate data sources, quality, and requirements to support adaptive licensing, as well as the technologies, policies, and processes that will be needed for their analysis.

## One step at a time

Until we understand more about what adaptive licensing is, how it works and the potential benefits and drawbacks, the initial drug candidates (such as those in the pilot program now underway in Europe) will likely be medicines to address an unmet medical need. In this context, an unmet medical need is not necessarily a first-in-class molecule, but could be a 'rescue' therapy for a group of patients where all other available therapies have failed. For these therapies, the benefit/risk ratio is clearly weighted in favor of intervention. An example would be a therapy for Duchene's muscular dystrophy, a progressive degeneration of the muscles affecting 1 in 3600 boys with an average life expectancy of 25; if the treatment could be made available in three or four years rather than 10, many lives could be saved.

*"It is easy to simply stick with what we know, rather than do what makes sense from a patient perspective. With adaptive licensing, industry could put the focus back on the needs of the patient."*

As we learn more, I believe that adaptive licensing will be applicable to a broader range of medical products, not just those for unmet medical needs. By definition, adaptive licensing is very flexible – the development program is designed specifically for each product – so it gives us the opportunity to put together more rational development plans rather than following established precedents or being purely reactive. It is easy to simply stick with what we know, rather than do what makes sense from a patient's perspective. With adaptive licensing, industry could put the focus back on the needs of the patient.

## Regulators on board

Regulators are already moving in this direction. Several national regulatory agencies have been discussing the potential of adaptive licensing for a number of years, but there was a big step earlier this year when the EMA launched a pilot scheme. Such bold moves are likely to move the discussion of adaptive licensing forward, with an emphasis on its practical aspects. In particular, the EMA wants to understand how future adaptive licensing pathways might work for different types of products and indications. Two medicines have been chosen to take part in the pilot, and although the EMA can't reveal the names, it says it has selected the products based on several criteria including: unmet clinical need, an early stage of development that will allow for actionable input, positive prospect of expanding from a restricted indication to broader populations, and the potential for real-world data in fulfilling expansion requirements. As the pilots progress, the European Commission will be examining the legal and policy aspects of adaptive licensing.

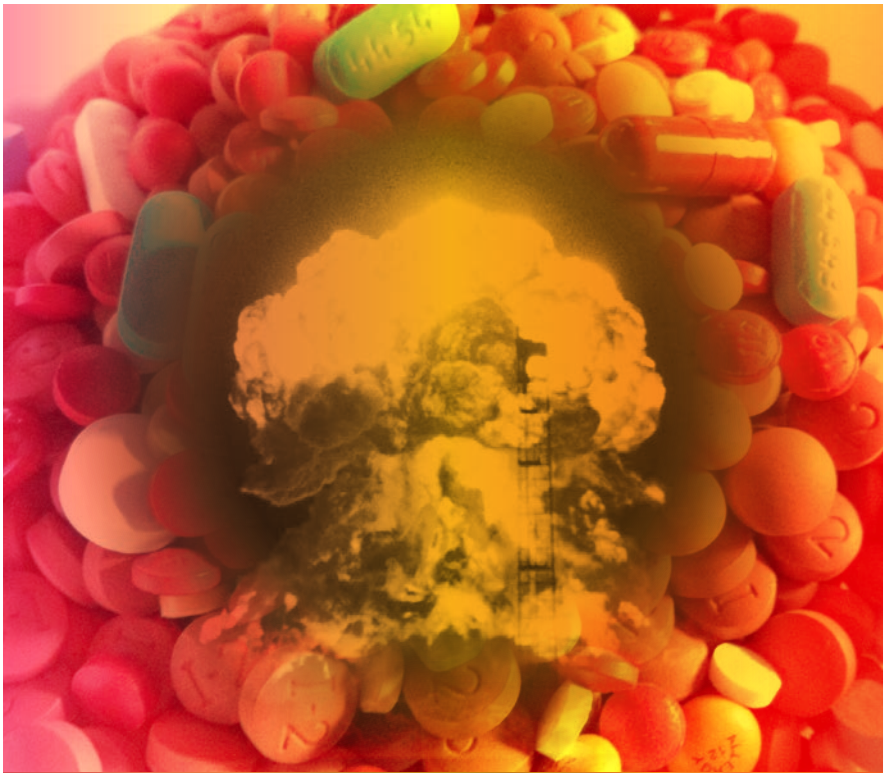
A new and more sustainable paradigm in drug development has been talked about for a number of years and now seem to be poised for launch. I hope that the experiences gained in EMA's adaptive licensing pilots, NEWDIGS Janus Initiative, and the work of other groups, will provide stakeholders with the foundation on which to build and refine drug development policies and procedures of the future, and the confidence to adopt them widely.

*Lynn Baird is Program Director, Regulatory Science at the MIT Center for Biomedical Innovation, Cambridge, USA.*

# Antibiotic Apocalypse: Part II

**The rise of drug resistance has left us facing a future with few effective antibiotics. Do the next-generation antibiotics in the pipeline offer hope?**

*By Stephanie Sutton*



"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant." So warned Alexander Fleming in his acceptance speech for the 1945 Nobel Prize in Physiology.

It's not easy to buy antibiotics over-the-counter in most countries, but lax prescription practices and poor compliance have led to an increase in drug-resistant microbes. A UK study published at the end of September claimed that in 2012 prescribed antibiotics could have been failing 15 percent of the time – up 12 percent from 1991 (1).

Last month in Antibiotic Apocalypse: Part I (tas.txp.to/1014/AAone), we covered the problem of drug resistance and the initiatives being launched to help kick start development. Here, we look at the 'fall and rise' of antibiotics.

## Abandoning antibiotics

Many pharmaceutical companies have been neglecting antibiotic R&D for years. As well as being scientifically challenging, new antibiotics carry a significant business disadvantage. Despite being expensive to develop, they are only used in small amounts and for a short duration, so the return on investment is often not attractive – a fact that is compounded by payers who are reluctant to shell out for newer, expensive alternatives when cheaper antibiotics are available – however ineffective they may be.

Pfizer's 2011 decision to close its antibiotic research facility in Connecticut came as a big blow to the antibiotic space. Originally, the company said that it would move its antibiotics research to China, but that hasn't yet happened – despite Pfizer indicating the move would take around two years (2). In July, Sanofi withdrew from a partnership with KalaBios to develop the monoclonal antibody KB001-A. Sanofi was developing the drug against Pseudomonas aeruginosa (Pa) pneumonia in intensive care patients; KaloBios was focused on treatment for Pa lung infections in cystic fibrosis patients. In August, Novartis rehomed its experimental TB drugs by licensing them to the Global Alliance for TB Drug Development, a non-profit organization. The deal included the indolcarboxamides class of drugs, which are active against drug sensitive and multi-drug resistant strains of TB.

Fortunately, there are rays of hope. Several small companies have seen opportunity amongst the challenges. And there are some big pharma players too; Roche recently announced its intention to return to antibiotics R&D after quitting in 1999 (see sidebar "Roche Returns" on page 44). And Merck, AstraZeneca and GlaxoSmithKline (GSK) are all still active in the field. With several new antibiotics receiving regulatory approval and the pipeline finally picking up, we could be at the beginning of an antibiotic research resurgence.

## The year of the antibiotic

The FDA approved three new antibiotics in 2014 through its Generating Antibiotic Incentives Now (GAIN) program, which was introduced in

## Roche Returns

We caught up with Janet Hammond (Global Head of Infectious Diseases at Roche Pharma Research and Early Development) about the company's return to the antibiotic field.

Roche has a history in antibiotics – why did it move out of the space?

Roche indeed has a long history of antibiotics development; it introduced Bactrim in 1969, and its active ingredient co-trimoxazole has since been administered in about two billion doses. Bactrim and its generic forms have become a standard treatment for infection, particularly in developing countries. In 1982, Roche launched Rocephin, a broad-spectrum once-daily injectable antibiotic used to treat a wide range of bacterial infections. Rocephin quickly became Roche's top-selling drug and the world's number one injectable antibiotic.

We exited the antibiotics space in 1999 – at that time, it seemed that the unmet medical need was largely addressed.

What prompted Roche's recent return?

The incidence of drug-resistant infections is creating an urgent demand for new therapeutic options, so we believe that this is now an area of unmet need and have accordingly decided to re-enter the antibiotics R&D arena.

In our antibiotics efforts we will focus on targeting a single pathogen. For example, RG7929 is an investigational compound targeting the lipopolysaccharide-assembly protein located on the outer membrane of Pseudomonas aeruginosa. A phase II clinical trial evaluating RG7929 as an antibacterial therapy is ongoing.

How can governments and regulators help?

Governments and regulatory authorities have already created special pathways for new antibiotics given the very high unmet need. Moreover, regulatory agencies have provided major incentives for antibiotic developers to research and develop new compounds. For instance, the FDA recently created the Qualified Infectious Disease Product designation for antibiotics in development that are active, both in vitro and in animal models, against multi-drug resistance species. The EMA has recently introduced guidance for the pathogen-specific approach.

Separately, we are convinced that the development and approval of point-of-care, pathogen-specific assays that can be used at the bedside is necessary to avoid or reduce empirical prescribing and thus potentially reduce the development of resistance. Therefore, pathogen-specific diagnostic methods are being encouraged by both regulators and infectious disease experts.

How do new antibiotic development programs differ from pre-1999 efforts?

Our understanding of microbiology has advanced considerably since the 1990s – we now have the bacterial genome sequenced for all pathogens, we understand much more about bacterial metabolism, and other ways in which bacteria are able to colonize and invade to cause infections. This new knowledge allows us to address and find new targets and ways of diagnosing and treating infection.

Bacteria will continue to evolve to elude our attempts to control them and it is increasingly apparent that we will need to continue to develop new ways to address what will be an ongoing problem. To combat the growing threat of resistance, Roche has established three pillars of antibacterial research: overcoming resistance, identifying new targets and tackling virulence or host factors. We have identified the need to not only develop broad-spectrum antibiotics but also pay attention to the requirement for narrow-spectrum agents.

2012 to provide stimulatory benefits, such as extended exclusivity and fast-track and priority review status. The new drugs – Dalvance (dalbavancin), manufactured by Durata Therapeutics; Orbactiv (oritavancin), manufactured by The Medicines Company; and Sivextro (tedizolid phosphate), manufactured by Cubist Pharmaceuticals – all target skin infections.

Cubist Pharmaceuticals is clearly looking to make a big impact. It has another antibiotic currently under FDA and EMA review called ceftolozane/tazobactam for the treatment of complicated urinary tract and complicated intra-abdominal infections – and other potential antibiotics are undergoing clinical trials at the company. In mid-September, Cubist announced the opening of new international headquarters in Zurich (its corporate headquarters are in Massachusetts in the US), and its intention to focus on the launch of potential new antibiotics in Europe in 2015. In 2014, the company planned to spend $400 million on antibiotic R&D. "Bringing antibiotics to market under current conditions is hard, but we've proven our strategy works. Our therapies aren't appropriate for every bacterial infection; we tackle the serious bugs and that is why resistance to our therapies is very low," said a spokesperson.

In terms of big pharma, Merck has also taken advantage of the GAIN framework with its investigational antibiotic relebactam, which received designated status at the start of September 2014 for treating complicated urinary tract infections, complicated intra-abdominal infections and hospital-acquired/ventilator-associated bacterial pneumonia. The drug is currently in Phase II trials in combination with another Merck antibiotic, imipenem/cilastatinm. Phase III trials are planned for 2015.

Merck claims its scientists were among the first to investigate penicillin and that the company was also one of

the pioneers in the mass production of the antibiotic. Currently, it has two new drugs in development – MK-3415A and MK-8228 – that target *C. difficile* recurrence and human cytomegalovirus (CMV)-related infection, respectively. MK-3415A is a combination of two monoclonal antibodies, actoxumab and bezlotoxumab, that target two C. difficile pathogenic toxins (A and B). The idea is to use MK-3415A to neutralize the toxins, while using antibiotics to kill the bacteria. Letermovir (MK-8228) is currently undergoing Phase III clinical testing for preventing CMV infection in high-risk bone marrow transplant patients. It is administered once daily, either as an oral tablet or intravenously.

AstraZeneca's investigational AZD0914 drug for treating uncomplicated gonorrhoea was also awarded fast-track status through GAIN and is currently entering Phase II. AstraZeneca has the largest pipeline of all the big pharma companies. As of June 30 this year, the company had nine compounds targeting a range of infections (including TB, MRSA, and serious *S. aureus* infection) in Phase I and II trials, and three in Phase III or registration: CAZ AVI RECLAIM for serious infections, CAZ AVI REPROVE for hospital-acquired pneumonia (both are being developed with Forrest Laboratories) and Zinforo, which launched in the EU in 2012 for serious skin infections or community-acquired pneumonia, and has now also been filed in China.

GSK has taken a slightly different approach to boost its antibiotic pipeline by making use of public–private partnerships. In particular, the company is heavily involved in programs run by Europe's Innovative Medicines Initiative (IMI). The company told The Medicine Maker that, "Tackling antibiotic resistance is a challenge we want to be part of solving but no one company can do this alone. Antibiotics research is one of the areas where we believe taking a more open-minded approach to sharing information and engaging in public–private partnerships will help to address some of the key barriers to the development of effective new medicines."

*"Many investigational drugs don't make it to market, but we can at least expect more drugs to enter the pipeline as GAIN and other recent incentives gather momentum".*

GSK has several antibiotics in very early development and a topoisomerase inhibitor (2140944 ) in Phase II that has received significant funding from the US Biomedical Advanced Research and Development Authority. GSK described the partnership as "unique" since it allows the company to work on various projects rather than a single molecule. If a molecule fails, focus can quickly switch to something more promising without the need for new contracts. 2140944 is expected to move into Phase III in 2015/16.

As noted, Roche has returned to the antibiotics space and several other companies are also having antibiotic R&D success. For example, Wockhardt received GAIN status for two MRSA drugs, WCK 771 and WCK 2349, and Cempra Pharmaceuticals, which specifically focuses on antibacterials, recently received a $10-million milestone payment from Toyama Pharmaceutical for its work on solithromycin, a ketolide antibiotic under development. The payment was made after Toyama received regulatory clearance to begin a Phase II trial of solithromycin in Japan. At the end of September, Cempra itself announced that it had finished enrolment for the global Solitaire-Oral Phase III clinical trial of oral solithromycin for severe community-acquired bacterial pneumonia. The data are expected to be announced in the first quarter of 2015. A second antibiotic, Taksta (CEM-102), is also in clinical trials for prosthetic joint infections.

Of course, many investigational drugs don't make it to market, but we can at least expect more drugs to enter the pipeline as GAIN and other recent incentives gather momentum.

All things considered, it has been a good year for antibiotics. But the war on resistance is far from over and we are still seeing antibiotics being prescribed in inappropriate situations; this was highlighted recently when it emerged that Thomas Eric Duncan, the first patient to develop Ebola in the US, was originally sent home with antibiotics from the hospital he visited after falling ill.

Continued (or better yet increased) focus from pharmaceutical companies, academia, and world governments will help to give us a fighting chance for the future, but we'll also need to see increased vigilance from medical staff with regards to curbing overuse.

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# The Talent Trap

**Hiring gifted new employees is tough enough, but how do you keep them within your organization once you've got them?**

*By George Scott*

Talent is one of the major challenges we face as managers or leaders in the biotech and pharma industries. A recent study from Randstad suggested that over 50 percent of our talent is actively looking for employment elsewhere and that more than 65 percent would be likely to accept a new job offer (1). The reasons for this can vary from compensation issues to professional advancement to relationships with coworkers and supervisors. The cost of attrition can be counted not only in economic terms, but also as a loss in productivity; recruiting and training activities may take weeks or even months, depending on the role. As managers in a highly competitive industry, achieving stability in our organizations is important for future success. Two big questions need to be addressed. First, what makes an organization highly attractive for talented individuals? And second, what makes those individuals want to stay?

Numerous metrics regarding salary and compensation levels are published annually, and most companies ensure that they are at least competitive at the first level of talent engagement. In this article, I'll leave the obvious element of money aside to instead focus on the environmental attributes that contribute to a healthy, engaging and vibrant workplace that is attractive to both new and existing talent. After all, there's more to our working lives than money…

## The right fit

Growth and attrition are the typical reasons that set us off down the path to find new talent, and there are at least three factors to consider in the hiring process. We need to understand what the candidate will bring to our existing talent pool, whether or not they can perform the role adequately, and how they will "fit in" with the existing team or even strengthen the group culture.

In the pharma industry, we place a premium on high technical capability, believing it will transform our teams and give us a competitive advantage. How many times, however, have we targeted a candidate based on expertise alone, only to find that our new superstar didn't contribute or fit into the organization in the way we'd hoped? "All too often," is a common answer. But many of us have also instinctively prevented disaster by holding back on a hire because we felt they did not fit. As unscientific and unquantifiable a feeling as this is, it is this powerful recognition of the non-technical attributes of potential hires that can make or break your team.

Technical capability is often a normalizing factor, in that the candidates applying for your position should all have the credentials to perform the tasks you need based on their CV alone. A PhD and 10 years of industrial experience may get you to the negotiation table, but it's a small part of the equation and needs to be balanced against their less tangible attributes. Technical expertise can be built or acquired; personal traits can only be coached. I believe that the emphasis we place on a candidate's technical capability and experience, and the balance between this and the ability to personally invest themselves in a new organization, is in fact the defining factor when it comes to successfully building – and retaining – your dream team.

## The right environment

Hiring the right person is only the start. As I stated at the beginning, the next big question is: how do you keep them? When you have a great team, your priority should be to keep it intact. Compensation is not always the key factor. A pay rise wouldn't tempt most people to stay in a job with poor career development and poor colleague or supervisor relationships. In contrast, a highly engaged and motivated person, with room to grow in a collegiate and supportive environment of like-minded friends is unlikely to leave all that for a few extra dollars. Extreme non-equity in compensation will be a destabilizing factor, of course, but if this is normalized, the key elements of success lie in the working environment. A common mistake that many leaders and managers make is to assume that this environment is generated by their team while absconding themselves from responsibility. In fact, it starts and ends with you. To help, I offer five straightforward considerations to create the right environment:

### 1. Accept that you are not the smartest person in the room

And if you think you are, then don't feel the need to remind everyone. It is important to acknowledge that everyone needs to feel as if they are part of the solution when you are building your team. The best leaders recognize that there

are facets of their organization in which they are not the expert, and their hiring strategy reflects the need to fill these gaps with motivated and empowered individuals. Put someone in the right place and then empower, challenge and trust them – I've seen people flourish in a way that is almost unimaginable.

### 2. Expect mistakes

Mistakes will be made, of course, so you should expect them, but view them as part of the continuum of learning and experience. A manager whose first instinct is to blame and punish people when they make a mistake will stifle creativity. An environment where mistakes are managed as learning events can alleviate the fear of failure and transform risk-averse conservatism to risk-based advancement. Having the trust of leadership can instill self-confidence and motivate an individual to feel truly invested in the team.

### 3. Know your team

I can almost guarantee that there is talent and capability embedded within your organization that you don't know about. Many of us have abilities and expertise that we don't harness in our daily roles, or that were a footnote in our role-targeted resumes. When transforming an organization, give opportunities to those who are currently invested in your company's success wherever possible, rather than recruiting externally. It is always a pleasant surprise to find out that someone in your organization is a six-sigma black belt just as you are planning to force-fit a process improvement initiative to an unsuspecting research scientist. In many companies, employees with diverse talent end up leaving because they feel unrecognized; often unintentionally overlooked through a lack of awareness.

### 4. Create lateral opportunities

Many of us see the logical progression of our career as a vertical ascendance. More often than we want to believe, lateral progression can be as fulfilling and even more rewarding. Expanding a role laterally can allow someone to step outside the boundaries of their current experience and build their skillset, develop a more integrated and inclusive viewpoint of their organization, and allow them to engage intellectually in a new environment with new people. In the scientific and technical fields, many do not want the extra managerial burden that comes through the acquisition of a higher title, but want to expand their experience through new and challenging opportunities. Those opportunities do not need to be vertical, and it is a common yet fatal mistake to "elevate" technical staff to a higher role that makes them lose their identity – there is no quicker way to lose a hardcore scientist than to make them a manager.

*"Put someone in the right place and then empower, challenge and trust them."*

### 5. Remove obstacles quickly

One of the most damaging elements to the morale of a high-performing team is a toxic element left unchecked, for example, a poorly performing or obstructive individual. In many cases, the group itself can resolve the problem, but if the issue is unresolved and management fails to react, it can be a death sentence for team cohesion. When your team does not believe you have the capability or intention to remove obstacles, your credibility as their leader is lost, and they will find another leader that they trust and respect.

### Parting on good terms

It is inevitable that attrition, like death and taxes, will exist at some level. You will lose key talent, for family, health, geographic or other reasons, but what they take away with them will be as important as what they have left behind. The experiences, opinions and perceptions of departing staff can have a huge impact on the reputation of both you and your organization, and will impact your ability to attract new talent. If someone has to leave an organization then we should plan that they leave with more than they started with, and that our team has had a positive influence on them both professionally and personally. The pharma community is well connected and it reflects well on you if the talent acquired from you is of a high caliber.

Developing a positive working culture of inclusion, empowerment and recognition undoubtedly comes at a high price; it's an all-consuming effort and it may take months or years for you to fully realize the benefits. Difficult decisions and candid discussions will be daily events, and your time investment will be considerable. But the rewards do outweigh the effort. It is worth remembering that friends do things for friends that others will not, and any organization that has a culture of celebrating each other's success will be a difficult place to leave. A team with this culture can only win, and nobody wants to leave a winning team.

*George Scott is Vice President of Bioanalytical Services at inVentiv Health Clinical, Seattle, WA, USA.*

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# Singular Head of Generics

**Sitting Down With…**
Nick Haggar, Head of Western Europe, Middle East & Africa, Sandoz, and President of the European Generic Medicines Association (EGA).

How did you get into the pharmaceutical industry?

My father suffered with cardiovascular disease and diabetes for most of his life; as a child, I remember being determined to do something that helped people like him get well. The difference that the right medicine can make to people's lives is one of the things that continues to inspire and motivate me, even now. I started my career working in technical roles, first at Baxter Healthcare, then at GlaxoSmithKline. While at GlaxoSmithKline, I decided to make the move to the commercial side of the business, and I have been in commercial roles ever since.

What motivated your switch to a commercial role?

The main motivator was the opportunity to be entrepreneurial, to drive growth and to compete; my current role as Head, Western Europe, Middle East & Africa at Sandoz certainly gives me that opportunity, but also taps into my technical knowledge of the supply chain. I absolutely love what I do and consider myself to be in a very privileged position to work for one of the strongest companies in the generics space.

How has the generics market evolved in recent years?

The industry has grown significantly over the last decade. In Europe today, 55 percent of all prescriptions are for a generic medicine. In another 10 years, I expect that to have risen to 75-80 percent. The generics industry is now central to public health in Europe, which is a tremendous transformation but also a tremendous responsibility. The growth and diversification of the industry is driving a change in the way generics are perceived – there is increasing recognition that all medicines, whether generic or branded, are far too important to be considered purely as commodities.

What is the key challenge right now?

After the rapid growth of the past decade, the last few years have been a time of significant reflection for leaders in the industry, including here at the EGA. One of the biggest challenges to creating a sustainable industry – and sustainable access to medicines – is the perception of value. There is a perception that medicines are expensive. But I would ask: compared with what? The generics industry saves European payers around €40 billion per year. As an example, across Europe, we supply medications to control Type 2 diabetes at an average of €0.25-0.30 per day, wholesale. When meeting with payers and regulators, we often discuss the fact that the coffee we just shared costs the same as three months of diabetes treatment. Payers face an ever-increasing demand for medicines and subsequent pressure on their cost base. But continual, year-on-year price cuts that go beyond the efficiency gains a highly regulated industry can expect to achieve are just not sustainable.

What is the EGA's approach?

We believe there is a more profound discussion to be had about medicines – not as a cost, but as an investment in the health of Europeans. We want to partner with governments so that we can be seen as part of the solution, not a procurement target – and that means looking at the healthcare industry from different points of view and trying to find common ground. Since adopting this multi-stakeholder approach, our dialogue with payers, patient associations, pharmacy associations and others is already much more positive and dynamic. We believe that, if there is willingness to make compromises on all sides, we will achieve a better outcome for patients.

What else do you hope to accomplish as EGA President?

There is a huge amount of work to do in the coming years. The first priority is to work in partnership with stakeholders around Europe on implementation of the falsified medicines directive. Second, we intend to put in place a new code of conduct for the industry. The global pharmaceutical industry's reputation has suffered in recent years and at the EGA we want all our members to commit to a stronger, clearer code of conduct. The industry must do more to re-establish its reputation and communicate the importance of its role in society.

You're clearly passionate about your work – what is your proudest achievement?

I feel proud of the difference we are making to access – especially in Africa. I spend a lot of time in Africa and have seen first-hand what it means when effective medicines are not available. Opening up access to medicine is something Sandoz takes seriously. One example is our work with UNICEF and the UN on pediatric amoxicillin. A few years ago, they identified a need for a pediatric formulation of amoxicillin to fight childhood pneumonia, and we worked with them to develop a low-strength, dispersible form of the drug. The first shipment of the drug will go to UNICEF any day now, and we're working hard to scale that up. Pneumonia kills around 900,000 children worldwide every year so if we can get the drug to those who need it, it could have a significant impact on child mortality. More broadly, I'm proud to have been part of an industry that has brought effective medicines to so many people around the world. The pharma industry has been instrumental in turning HIV from a death sentence to a chronic disease, developing breakthrough treatments for malaria, and improving quality of life for millions of people with respiratory disease.

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