JANUARY 2018 # 37

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Online this Month

Q Exactive HF-X Hybrid Quadrupole Orbitrap Mass Spectrometer (Thermo Fisher Scientific)*

Register Your Vote in the Innovation Awards!

The Medicine Maker ended 2017 with a celebration of innovation in industry drug development technologies by compiling a list of the 15 top technologies to hit the market in 2017.

All of these winning innovations can make a mark on drug development and manufacturing activities, but which is the most ground breaking?

We will give one of our winners the chance to showcase the full development story behind their innovation in a future issue of The Medicine Maker. And we want you to choose! Vote for the innovation you would like to read more about at: http://tmm.txp.to/2017/innovationwinner.

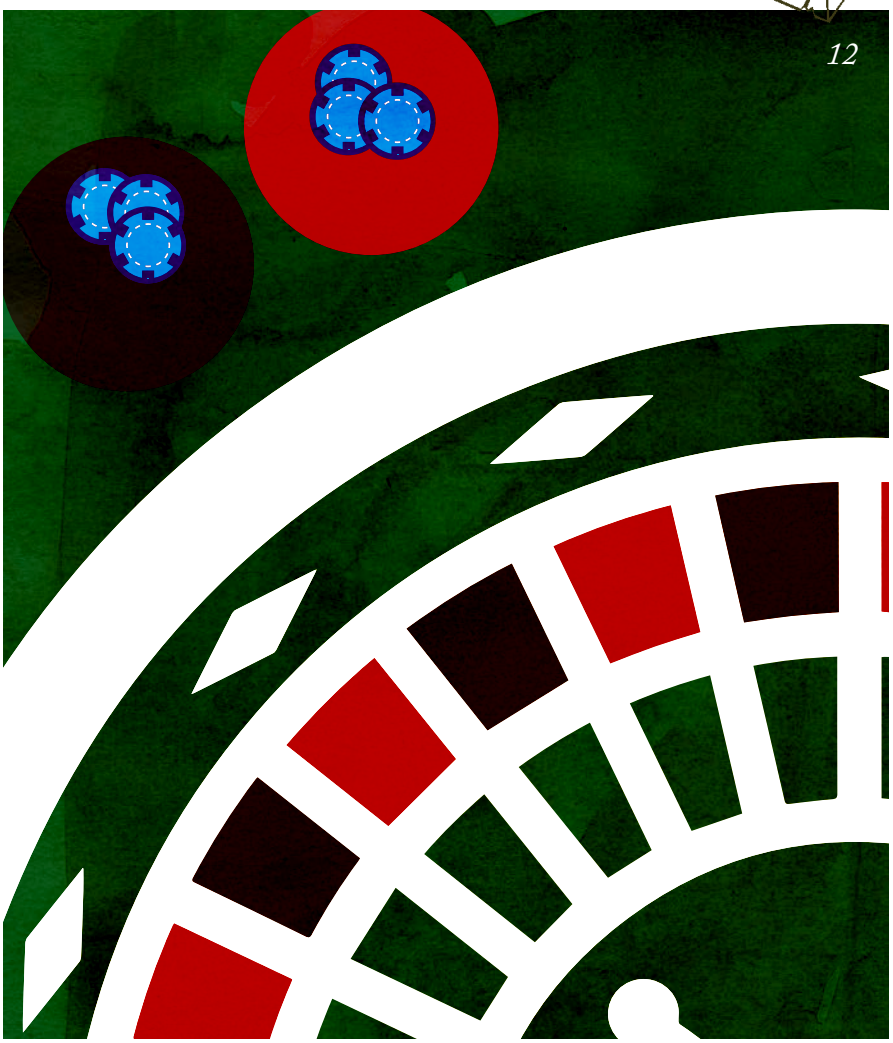
Voting closes on March 1, 2018.

Winners

- AFG 5000
- Cadence Inline Diafiltration Module
- Eshmuno P anti-A & Eshmuno P anti-B resins
- HakoBio
- H3N2 Challenge Virus
- iQ
- KLV 1360
- MabSelect PrismA
- MicroCal PEAQ-DSC
- Prodigi
- Q Exactive HF-X Hybrid Quadrupole Orbitrap Mass Spectrometer
- Valor Glass
- VarioSys Move
- VHP DC-A Decontamination Chamber Atmospheric
- X500B QTOF

Correction: An incorrect image of the Q Exactive HF-X Hybrid Quadrupole Orbitrap Mass Spectrometer was printed in the December 2017 issue of The Medicine Maker.

Contents



the Medicine Maker

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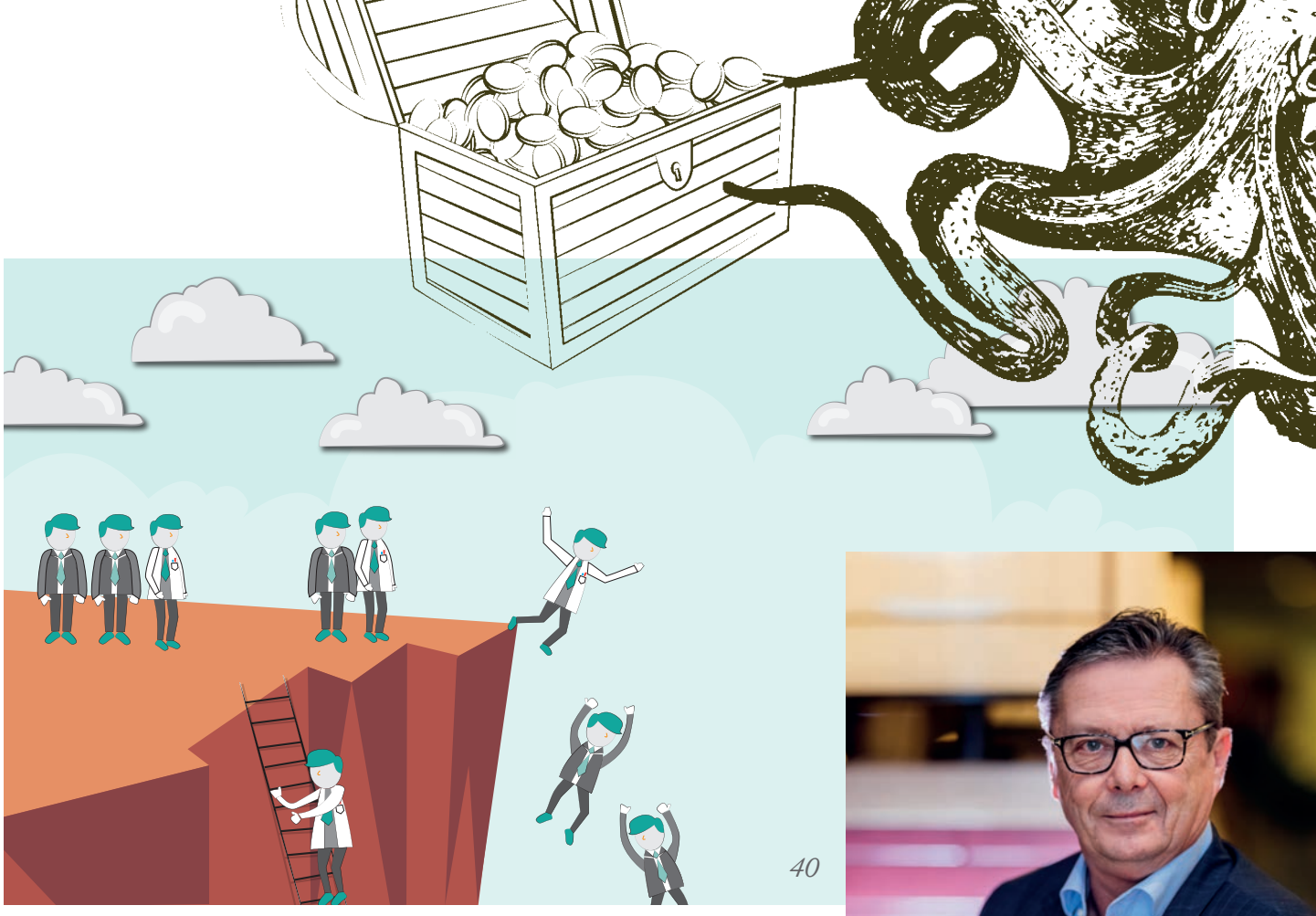

In My View

Feature

Best Practice

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There are many good reasons to register to The Medicine Maker. Here are just a few:

- We focus on the talents, passions and experience of the people involved in the development and manufacture of small molecules, biologics, and advanced therapies
- We showcase the industry's success stories and examine its biggest points of contention

Our engaging content covers the entire spectrum of drug development, keeping all medicine makers up to date with the most pressing topics, trends and technologies driving the pharma industry forward

Register now at **www.themedicinemaker.com/register**

Hopes and Fears

The year 2018 will be one of yet more drug approvals – but which areas will be neglected?

There's never a dull moment in the pharma industry, so never a shortage of great content. Progress (albeit slow in some areas) is relentless, with new research, technologies, and drugs – some truly revolutionary – emerging every year. Last year, two FDA approvals stand out: the US's first two CAR-T therapies, Kymriah (Novartis) and Yescarta (Gilead), which offer hope to cancer patients with few options. Overall, 2017 was a fantastic year for both FDA and EMA drug approvals, with several new medicines being first in class. New molecular entities approved by the FDA hit 46 as of November 2017 – the highest number since 1996.

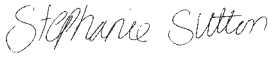
Cancer remains a priority, but what about other diseases that are in dire need of new treatments, such as Alzheimer's? Unfortunately, 2018 has already started out on the wrong foot in that regard; earlier this month, Pfizer announced that it was ending its neuroscience discovery programs – axing around 300 jobs, as well as its work into Parkinson's and Alzheimer's. Of course, from a business point of view it makes sense – the company has already spent billions on both diseases, without a single drug to show for it. Axovant Sciences, a biotech dedicated to neurological conditions, is also struggling with Alzheimer's – the company's lead drug candidate, intepirdine, failed a phase III trial in 2017, and the development program was subsequently scrapped.

The woes of Alzheimer's drug development are well known – no new drugs have been approved in either Europe or the US in well over a decade – so perhaps it's no surprise that so many companies have pulled the plug.

However, I'm reminded of an inspiring comment in our final issue of 2017 from Eric Weaver (University of Nebraska): "It may be impossible to make a universal vaccine for everyone [but that] should not be a limitation to the pursuit of new vaccine research." Should we really give up on the quest for an Alzheimer's treatment, even if it does feel like an insurmountable challenge?

In a recent column, Bart De Strooper, Director of the UK Dementia Research Institute, suggested that it is time to move away from expensive phase III trials and look back at the biology of the disease with fresh eyes (1). Despite ditching its Alzheimer's programs, Pfizer also indicates that earlier research is the way forward – and the company says it will launch a venture fund, specifically to invest in biotech companies with intriguing neuroscience research programs (2). So perhaps big pharma doesn't give up that easily...

Stephanie Sutton
Editor



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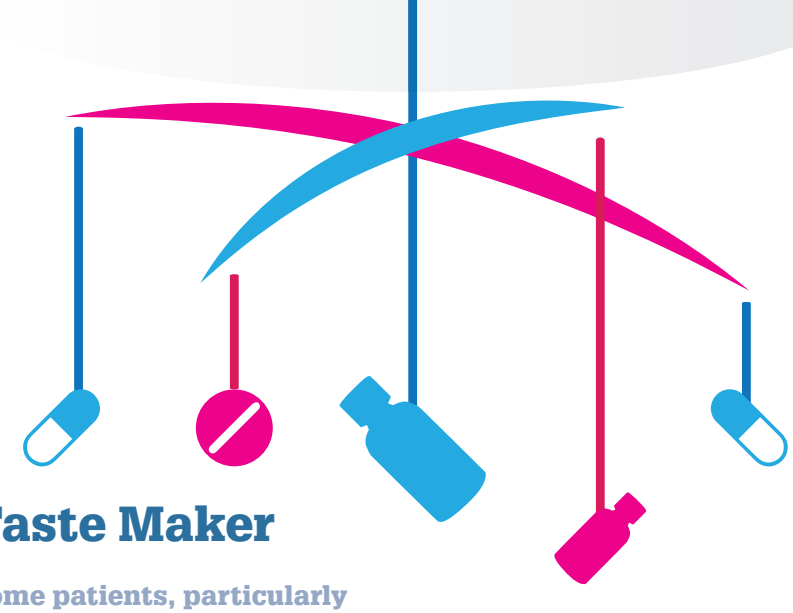
1. *B De Strooper, "Dementia is too big a problem to walk away from – for Pfizer or any of us", The Guardian (2018). Available at: http://on.pfizer.com/2D9nKxg. Last accessed January 15, 2018.*
2. *Pfizer, "Learn more about our neuroscience decision R&D decision", (2018). Available at: http://bit.ly/2CUKjlR. Last accessed January 15, 2018.*

Upfront

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

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com



Taste Maker

Some patients, particularly children, find medicines unpalatable – and genetics could be the cause

According to the World Health Organization, around half of all pediatric patients do not take their medicines correctly (1). "Taste is the number one issue," says Julie Mennella, researcher at the Monell Chemical Senses Center. "Young children often can't swallow pills and tablets, which encapsulate the bitter tasting drug or active pharmaceutical ingredient. This means they instead have to take bitter-tasting liquids, which have flavor ingredients to mask the bad taste, but they don't always work for all children."

When Mennella attended a lecture at the University of Pennsylvania, she met Elizabeth Lowenthal from the university's Perelman School of Medicine. "Elizabeth relayed issues encountered when giving Kaletra, a pediatric HIV drug, to infants: some infants accepted it readily while others strongly rejected it. It sparked off an interesting conversation about why some people find medicines unpalatable, and we formed a collaboration to investigate whether we could see the same variation in adults," says Mennella.

The researchers used a panel of genotyped adults to document the range of individual differences in the taste and palatability of the liquid formulation of Kaletra, which contains a number of flavor ingredients including sugars, salts and menthol. Panelists rated their taste sensations, which the researchers used to determine a genotype-phenotype relationship. The results showed that those who experienced less bitter and sweeter taste sensations had a different genetic signature than other participants. Bitterness and irritation ratings of Kaletra varied by the orphaned bitter receptor gene (TAS2R60), whereas sweetness ratings of Kaletra varied according to the cold receptor gene (TRPM8), which is activated by menthol, an excipient of Kaletra (2).

"Essentially, we systematically used the adult palate as a screening tool to identify those drugs where there is wide variation in acceptance to uncover a genetic basis," says Mennella. "Our hope is that this knowledge may lead to molecular targets to improve taste, as well as systematic assessment of other pediatric drugs to determine which ones are problematic for some children. A drug, no matter how powerful, is not going to work if the child rejects its taste."

Read more about the challenges of pediatric medicines on page 38.

This research was supported by a grant from the National Institute of Deafness and Other Communication Disorders (NIDCD).

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1. *World Health Organization, "Adherence to Long-Term Therapies: Evidence for Action", (2003). Last accessed January 08, 2018. Available at: http://bit.ly/2EiL9IH.*
2. *JA Menella, PS Mathew, and ED Lowenthal, "Use of adult sensory panel to study individual differences in the palatability of a pediatric HIV treatment drug", Clin Ther, 39, 2018-2058 (2017). PMID: 28923290.*

Battling the Bugs

London's Science Museum highlights superbugs and the stars that fight against them in a new exhibition

What? "Superbugs: The Fight For Our Lives" is a free exhibition in London that highlights the danger that antibiotic resistance poses to human health, as well as the stories of those tackling the issue head-on. Some of the displays included in the exhibition are 12 real bacterial colonies (including nine classified by the World Health Organization as a significant threat to human health), penicillium mould recently grown from Fleming's original samples, 14,000 pills that illustrate the two-year treatment needed to combat multi-drug resistant tuberculosis, and an interactive game where visitors can try to halt the worldwide spread of a superbug. It will also be possible to learn about Komodo dragon blood and watch as researchers from the University of Illinois dive into Icelandic fjords – both potential sources of new antibiotics. Experts will share thoughts on superbugs and how to prevent them from spreading.

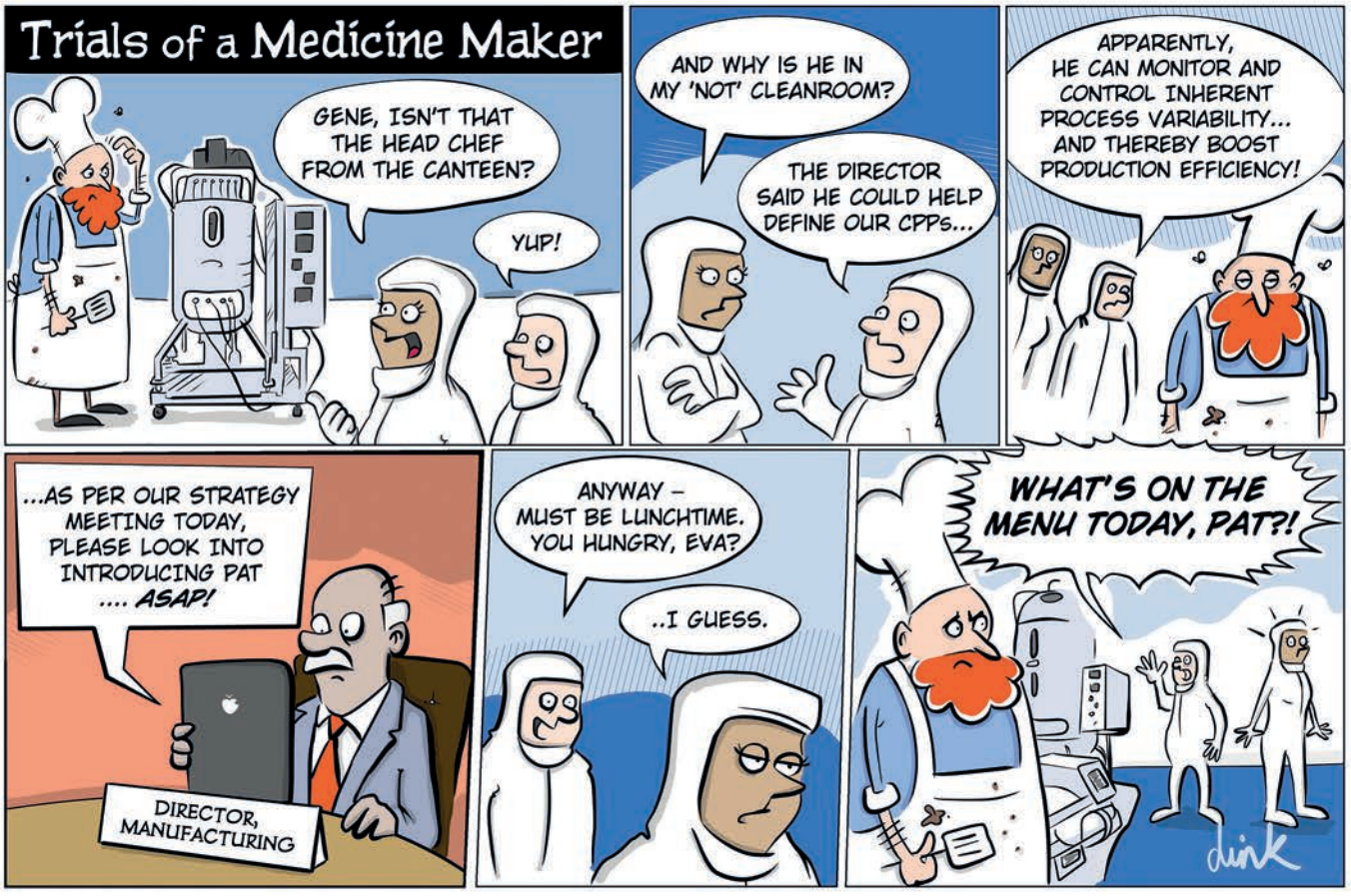
Four prototypes made by teams across the globe vying for the £8-million Longitude Prize will also be on display for the first time. Submissions for the Longitude Prize launched in 2014 – the goal: to invent an affordable, accurate, rapid and easy to use test for bacterial infections that will allow health professionals to administer the right antibiotics at the right time.

Why? According to the exhibition, superbugs today kill almost 700,000 each year – a figure that could rise to 10 million by 2050. Tackling the issue requires both public awareness and collaboration between industry, governments and health providers in the creation of new policies, educational programs and medical interventions.

Who? The exhibition is sponsored by Pfizer and Shionogi, and supported by UK Research and Innovation and the University of East Anglia.

Where? The Science Museum, London, UK.

When? The exhibition will run until April 2019.



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You've Got the Power!

Who will be chosen for The Medicine Maker 2018 Power List? The power is in your hands

A new year means that another Power List is on the horizon. The Medicine Maker annual list of the best and brightest in the pharma industry will be published in April. From academics and philanthropists, to business leaders and entrepreneurs, to technicians and regulators, everyone involved in pharma is eligible for entry.

Nominations for this prestigious list will close on February 1 – and it's up to you to decide who will be considered. Will it be dominated by returning names or will new nominees take the list by storm?

All nominations will be put to an expert judging panel who will decide on a final list that will be divided into four categories: Masters of the Bench (celebrating researchers), Business Captains (business innovation and leadership), Industry Influencers (those guiding the industry forward), and Champions of Change (those driving groundbreaking changes).

To nominate, fill out the short form at http://tmm.txp.to/2018/powerlist. Or email stephanie.sutton@texerepublishing.com

Your selection may join the ranks of 2017's illustrious winners:

#1 Master of the Bench: Robert Samuel Langer; Institute Professor, Massachusetts Institute of Technology

Considered one of the most prolific inventors in medicine, Robert Langer has over 1100 issued and pending patents. He previously served on the FDA's Science Board and has been elected to the Institute of Medicine of the National Academy of Sciences, the National Academy of Engineering, and the National Academy of Inventors.

#1 Industry Influencer: Richard M. Johnson; President and Chief Executive Officer, Parenteral Drug Association

"I became active in PDA 25 years ago, and this has given me the opportunity to help lead the way in promoting science-based solutions for challenges the industry faces, and to work with health authorities to improve the understanding and implementation of best practices. Serving patients is and should always be the focus of our efforts. At PDA, I am committed to working to advance our knowledge, promote best practices, and drive quality through collaboration between all stakeholders: manufacturers, suppliers and health authorities."

#1 Business Captain: Joseph Jimenez; Chief Executive Officer, Novartis

Joseph joined Novartis in April 2007 as Division Head, Novartis Consumer Health, after spending eight years running the North American, European and then Asian operations of H.J. Heinz. He was named CEO of Novartis in 2010. He is also President of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and Chairman Elect of Pharmaceutical Research and Manufacturers of America (PhRMA).

#1 Champion of Change: Susan Desmond-Hellman; Chief Executive Officer, Bill & Melinda Gates Foundation

Trained as an oncologist, Sue spent 14 years as head of product development at Genentech – where she played a role in the development of Herceptin and Avastin – before spending five years as Chancellor of the University of California, San Francisco.

You can read The Medicine Maker's full 2017 Power List at https://themedicinemaker.com/power-list/2017/

Beating the Resistance

Should we target minor rather than major infections with new therapeutics to best fight antibiotic resistance?

An oft-suggested solution to antibiotic resistance is to curb prescriptions for relatively small infections, but this only solves half the problem, as patients still have to deal with minor infections – before they turn into major ones. The current fight against antibiotic resistance revolves around alternative therapeutics for the most severe diseases, but these are difficult to develop. A recent study suggests that alternative therapeutics for minor bacterial infections may be a better solution to help reduce microbes' growing drug resistance (1).

After reviewing previous studies of antibiotic use and using an evolutionary framework to analyze the data, Kristofer Waldetoft and Sam Brown from the Georgia Institute of Technology, USA, believe that it is plausible that the widespread use of antibiotics against certain mild infections may contribute significantly to the development of antibiotic resistance. For example, one common and relatively mild infection is pharyngotonsillitis, which is treated with penicillin. It represents a large contribution to antibiotic use, and so may affect the evolution of resistance in other bacteria.

"Systemic antibiotic treatment selects for resistance throughout the patient's microbiota, not only in the pathogen it is aimed to target. Thus, when weighing the benefits of treatment against the problem of selecting for resistance, one needs to look beyond the infection at hand and take the whole microbiota into account," Waldetoft and Brown write in their study.

Using alternative therapeutics for minor infections, such as antivirulence drugs that limit the infection and make it asymptomatic or bacteriophages, which actively kill the bacteria, would reduce the selection pressure of antibiotic resistance. "This [approach] should slow the spread of resistance and keep the remaining antibiotics effective for more severe infections. In addition, new treatments for mild infections may also be easier to develop," says Waldetoft. As mild infections allow more time for diagnostics, they also lend themselves to therapeutics that have a narrow spectrum and, thereby, a reduced negative impact on the commensal biota.

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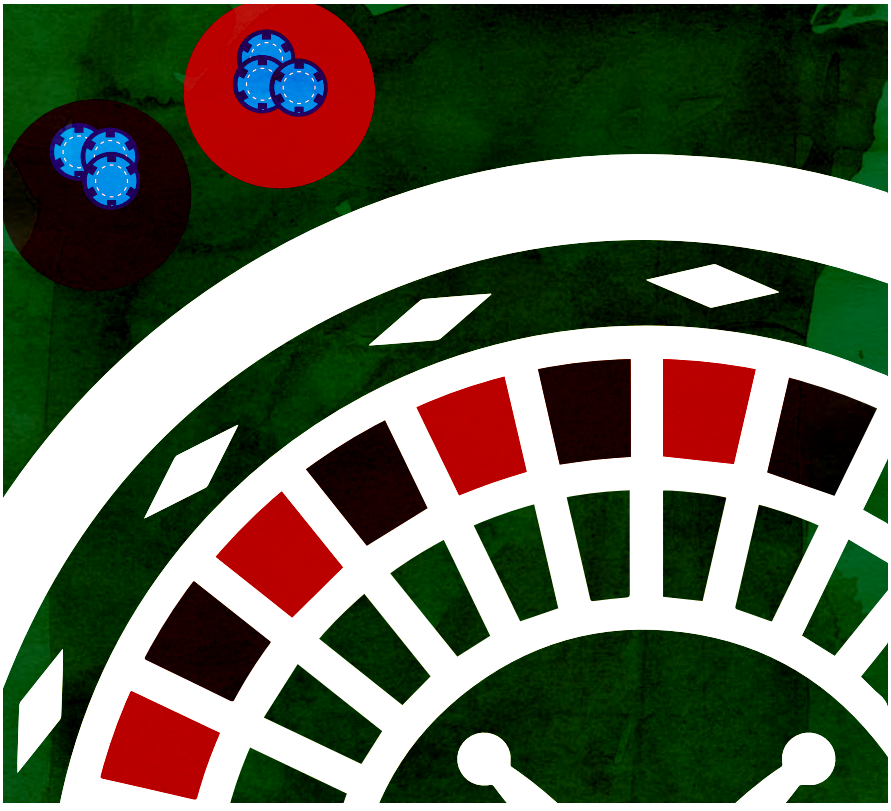
Forgotten, but not Gone

A half-century-old "bet hedging" hypothesis explains the effectiveness of many common cancer drug combinations



Why do drug combinations work? Many targeted therapies are combined based on molecular reasoning or evidence of additive or synergistic effects in cell line and animal models – and many clinical trials based on such reasoning have been successful. But what if that isn't the full story?

While treating cancer cells grown in the laboratory with various anti-cancer drugs, Adam Palmer and Peter Sorger (both researchers at Harvard Medical School) observed that some cancer cell lines were more sensitive to drug A than drug B but, conversely, other cell lines of the same type of cancer were more sensitive to drug B. It occurred to the researchers that the variability in single drug response could partly explain why a population of patients may respond better when treated with two different drugs rather than one – a kind of "bet hedging," where introducing a second drug boosts the likelihood that a patient will benefit from at least one.

They later found this to be a 50-year old hypothesis, called "independent action," which had been inexplicably forgotten, and not tested against contemporary clinical trial data. They went and carried out those tests, with some surprising results (1). We spoke with the pair to find out more.

What is "independent action"?

From 1956, the Acute Leukemia Group B (which included many giants of oncology, including Emil Frei III, Emil Freireich, and James Holland) tested combinations of anti-leukemic drugs. They observed in patients how variable cancers were in terms of drug sensitivity. In trials of sequential treatments, an individual patient's response to one chemotherapy had little relation to their subsequent response to a different chemotherapy, which justified the "independent action" model in which a combination of two drugs will induce a remission if either one of those drugs is able to induce remission by itself (without invoking any synergistic drug interaction). Emil Frei III's independent action model accurately predicted remission rates in acute leukemia. We suspect that the theory fell out of use because improved methods for survival analysis came to dominate the interpretation of clinical trials in oncology.

What did your study involve?

We set out to distinguish between drug interaction and independence by: i) re-analyzing human clinical trial data in which single and combination therapies are compared, ii) mining a database of drug responses for patient-derived tumor xenografts, and iii) using a computational model of drug responses in a heterogeneous population of tumors.

We found that the independent drug action model (adapted to survival data and accounting for drug cross-resistance) was a sufficient explanation for the entire survival benefit of most of the clinical trials that we analyzed. It was a big surprise – we expected independent action to explain a fraction of the benefits of the combination therapies, but not this much. Combinations of cancer therapies with compelling molecular justifications, and strong evidence of synergy in pre-clinical studies, were not displaying synergy or even additivity in individual human tumors. Conversely, a fraction of combinations were identified as truly synergistic, using this model as the benchmark for the identification of synergy in clinical trial data.

Why do some drugs exhibit synergy in preclinical studies, but not in clinical studies?

We hypothesize that pre-clinical synergy often fails to translate into a detectable clinical benefit because even if drug synergy occurs in human tumors, its effect is overwhelmed by patient-to-patient variability in drug response. For many combination cancer therapies, some patients will be resistant to drug A and some resistant to drug B – resistance to either single drug may exclude the possibility of synergistic interaction. Conversely, some patients may have a durable response to one or the other single drug, and synergy will be not evident in survival data that is within the duration of the most long-lasting single-drug responses.

How could this work affect trial design?

When selecting anti-cancer drugs to include in a combination, this research (and the Acute Leukemia Group's historical data) suggests that synergistic interaction is unnecessary for benefit: it is sufficient that two drugs each have a good rate of single-agent activity, and critical that they have tolerable toxicity together and non-overlapping mechanisms of resistance.

This research cautions that when a clinical trial shows "drugs A plus B" to be superior to "drug A," it is not necessarily evidence that the simultaneous combination "A plus B" is also superior to "A, followed by B when needed." If the toxicity of a drug combination is readily tolerable then the upfront combination may be justified, but when a combination has challenging side-effects (perhaps requiring dose adjustment) there may be value in testing a sequential regime (perhaps without requiring dose adjustment) for non-inferior therapeutic benefit. Whether this is true for a given combination depends on many factors, including possible costs of waiting to see whether drug A was effective. This is likely be relevant to immunotherapies combined with other anti-cancer drugs.

Our research suggests that many cancer therapies are, today, commonly applied with inadequate stratification of patients or tumor subtypes. In the future, clinical trials on more finely stratified patient cohorts may contain less variability in drug response – and therefore might be better able to identify which tumor subtypes, if any, benefit from a clinically impactful synergy.

Reference

1. *AC Palmer and PK Sorger, "Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy", Cell 171, 1678, (2017). PMID: 29245013.*

In My View

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

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

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

Manage the Relationship

Outsourcing partnerships aim to reduce costs and improve efficiencies, but they can rapidly fall apart if you overlook the human elements.

By Muna Kugler, Global Strategic Sourcing Manager, Idorsia Pharmaceuticals, Switzerland.

Outsourcing certain services to competent business partners is often essential to securing value in drug development. The idea behind outsourcing is to reduce costs and increase efficiency by hiring experts who can do the job in less time, with less costs, and to a high standard of quality. It sounds straightforward, but management conflicts and mistrust in the relationship – commonly encountered in outsourcing partnerships – can counteract these goals. Relationship management is incredibly important in the outsourcing relationship and I believe that the industry must learn to set adequate performance metrics that not only reflect milestone achievements within a set timeframe, but further extend to measure the quality of the work in terms of issue management and efficiency.

According to Jean Toth-Allen, "Quality is characterized by the ability to effectively and efficiently answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) procedure, while ensuring protection of human subjects" (1). Quality is the main goal in our industry. Quality is constantly at risk during drug development and when conducting clinical trials, whether managed in-house or outsourced. However, there are methods and techniques that can address these risks – and these should be agreed upon at the start of a contract services relationship. In particular, teams need to be supported in dealing with the real-life challenges and issues that emerge during the course of the relationship. I specialize in clinical trials – here, the human element is vital. All issues in clinical trials are usually directly or indirectly related to human interaction. Unfortunately, I find that this element is often neglected and left to the individuals managing the contracts to attend to without sufficient support. These individuals may not have any experience in relationship

"Long-term strategic partnerships seem to better deal with relationship management aspects because of the commitment and mutual risk sharing."

"The industry is not aligned on vendor management expectations outside of deliverables and milestone definitions."

management, or may be ill resourced and overworked (increasingly common in today's economical environment), which leads to relationship management falling between the cracks. This major deficiency must be addressed at both the sponsor and service provider ends. Long-term strategic partnerships seem to better deal with relationship management aspects because of the commitment and mutual risk sharing. But not all companies are able to form (and sometimes do not require) long-term relationships.

Outsourcing, whether short or long term, must be seen as a relationship between human beings that do not always share the same values, culture, visions, objectives, and practices. One party fills the other's gap, but for the piece to truly fit the puzzle, the various differences need to be thoroughly identified, discussed and aligned. Falling short in giving the human element of the relationship due attention and care will inevitably lead to delays, inconsistencies, and relationship failure, which will damage the outcome in one way or another.

The industry is not aligned on vendor management expectations outside of deliverables and milestone definitions. In my view, we need an industry tool that addresses and defines the key aspects of the sponsor/contractor relationship required for success. Ideally, such a tool would include clearly defined issue resolution scenarios and escalation paths for CRO performance problems (vendor managers must be involved and trained accordingly). A strong structure must also be in place to encourage a shift in mindset related to vendor oversight – namely, a solid multiple level governance system. In addition, sponsor in-house teams must be trained on managing outsourcing partners on a cooperation level rather than just focusing on deliverables and timelines. The overall aim is to educate companies about the important role that human factors play in the success or failure of outsourcing.

Reference

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Beyond the Rule of Five

We need to explore the chemical space outside of Lipinski's rules.

By Simon Pearce, Market Segment Manager for Organic Chemicals, Thermo Fisher Scientific.

Two decades on from its initial publication, Lipinski's "rule of five" is arguably one of the most influential concepts in modern drug discovery. Yet it is also one of the most controversial. Developed with the aim of prioritizing the progression of drug candidates with the most promising oral bioavailability properties, Lipinski's rules have had a lasting effect on drug discovery strategies and the curation of compound screening libraries. They have also inspired the creation of other similar selection criteria, such as GlaxoSmithKline's 4/400 and Pfizer's 3/75 rules.

The origins of the rule of five lie in a study of the favorable absorption properties of orally administered drugs and clinical candidates, conducted by Chris Lipinski and colleagues at Pfizer

"The origins of the rule of five lie in a study of the favorable absorption properties of orally administered drugs and clinical candidates."

in 1997 (1). For four key physicochemical properties, cut-offs were calculated that covered 90 percent of the molecules studied. In short, molecules with the best solubility and permeability were found to have:

i. molecular weights less than 500 Da
ii. calculated octanol–water coefficients (CLogP) not greater than five
iii. no more than five hydrogen bond donors
iv. no more than 10 hydrogen bond acceptors.

All numbers are multiples of five – hence the name "rule of five". However, what was originally intended as a rule-of-thumb soon became dogma. The pharmaceutical industry can be heavily influenced by precedent – or rather, motivated by a fear of missing out. Somewhere along the way, these guidelines for oral bioavailability became confused with rules for drug likeness, and I find that the industry often prioritizes Lipinski's rules at all costs.

With attrition still a significant problem for the industry – 2016 saw FDA new drug approvals fall to a six-year low (2) – and the cost of bringing a new medicine to market still eye-wateringly high (as much as $2.6 billion per approval, according to figures published by the Tufts Center for the Study of Drug Development), many people have questioned the value of a rigid interpretation of these rules. For starters, the hard cut-offs used to de-prioritize hits could lead to missed opportunities. Is a drug candidate with a molecular weight of 501 Da really worth losing over a candidate with a similar structure but a molecular weight of 499 Da? Perhaps... perhaps not.

I believe that drug discovery should be based on measurement rather than theoretical prediction. There are certainly many notable examples of successful drugs that violate at least two of Lipinski's rules: take the HMG-CoA reductase inhibitor atorvastatin, for example, or leukotriene receptor antagonist montelukast. Rigid interpretation of Lipinski's rules comes at the expense of chemical diversity. Indeed, some of the biggest challenges in drug discovery require us to think beyond our current design space.

"Somewhere along the way, these guidelines for oral bioavailability became confused with rules for drug likeness, and I find that the industry often prioritizes Lipinski's rules at all costs."

In the urgent search for new and effective antimicrobials, for example, tweaking the structure of existing molecules will not be sufficient – we need to identify entirely new structures. A focus on natural products, the vast majority of which violate Lipinski's rules, could be one effective solution.

Moreover, genomic approaches to target discovery suggest that we've only just scratched the surface as far as modulating biological pathways are concerned. It is becoming increasingly apparent that the vast majority of potential targets cannot be modulated according to the "lock and key" model. To disrupt more challenging targets, such as transcription factors and scaffolding proteins, interfering with protein–protein interactions will be key. Here, larger, more hydrophilic molecules, including macromolecules and natural products, could be more effective than conventional small molecules.

In our search for diversity, it is worth remembering that Lipinski's rules were developed with oral delivery in mind. For localized treatment of pulmonary targets, for example, these Lipinski-like attributes can actually reduce therapeutic effectiveness. Though the rule of five has helped to further our understanding of the effects of physicochemical properties on oral bioavailability, careful consideration of how and when it is applied is crucial as we start fully exploring the chemical space available to us. Otherwise, we will unnecessarily limit our creativity, which could be harmful to drug discovery.

So, just like Captain Hector Barbossa in Pirates of the Carribean: The Curse of the Black Pearl, we should consider that "the code [rule of five] is more what you'd call 'guidelines' than actual rules."

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Adopting an Orphan (Drug)

The search for new cancer therapeutics is arduous, but new treatments may be lying right under our noses – if we are willing to take a commercial risk.

By Pan Pantziarka, Senior Researcher, and Gauthier Bouche, Medical Director, both from the Anticancer Fund, Belgium.

The Anticancer Fund and GlobalCures are two separate organizations, but both are dedicated to developing new treatment options for cancer patients. Independently, we both stumbled onto positive clinical trial results involving repurposed drugs that had apparently gone completely unnoticed – and that seemed shocking. After performing due diligence, we realized that the common theme behind these neglected potential therapies was the lack of financial incentive – the treatments had been dubbed "financial orphans" because they did not offer commercial opportunities and return on investment.

In some ways, the pharma industry is very active in drug repurposing, but usually only for young, proprietary drugs; tocilizumab, for instance, has been repurposed many times. Often, the drugs that are of greatest interest to repurposing researchers are generics because of their low costs. The potential for return on investment with repurposed generics, however, is constrained as other manufacturers can profit from the positive results generated by investment in new trials and new licenses. In some cases, manufacturers are looking to reformulations as a means to secure IP protection of their repurposing investment, but when it comes to using existing medicines "as-is" for other diseases there is a definite funding gap that needs to be filled.

The Repurposing Drugs in Oncology (ReDO) project is a partnership between the Anticancer Fund and GlobalCures that aims to identify non-cancer medicines that have evidence of potent anti-cancer effects and, therefore, the potential to be developed as new oncology treatments (1). In particular, we focus on financial orphans – and there are many out there with great potential. We have adopted a literature-based approach that maximizes the range of data that we can access; we make use of data from in silico, in vitro, in vivo, case reports and clinical trials. To date, we have identified over 230 existing medications that have published evidence of anti-cancer activity, over half of which is made up of relevant human data. We have identified high-priority drugs – including propranolol, cimetidine, diclofenac, and clarithromycin – and published review papers summarizing the available evidence, and suggesting appropriate cancer implications in which the drugs could be applicable (2).

One of our most recent papers focused on two malaria medicines, chloroquine and hydroxychloroquine (3). These drugs were interesting because there is a large but scattered corpus of data that we were able to draw on. In addition to extensive pre-clinical data sources, there are also a large number of active clinical trials in a range of cancer types. Mechanistically, it is clear that there are multiple relevant mechanisms of action and that the drugs synergize with existing therapies. As with many of the other ReDO drugs, these can be viewed as multi-targeted agents and have the potential to be rapidly adopted clinically, should efficacy be shown in well-designed clinical trials. The results in glioblastoma and metastatic disease in the brain are especially intriguing given the lack of clinical progress in this area.

As part of our work, we collaborate with clinical groups across the world to develop and support clinical trials using repurposed drugs. We have met many investigators who have kept their enthusiasm about repurposing hidden, knowing it was not the most financially rewarding avenue of research. We believe it is important to raise the profile of drug repurposing as a strategy. Repurposing existing drugs could offer tremendous potential for patients in many disease areas, but we cannot move forward unless we solve challenges around funding and regulation. Drug licensing is a key obstacle. And though ReDO is not interested in licensing per se, we are interested in the cascade of events that follow the granting of a new FDA or EMA licence: updating of national formularies, inclusion in clinical guidelines, reimbursement analyses, and excitement amongst clinicians and patients. The current drug system is still largely geared around commercial players. We need to change this – it is not good enough for positive clinical trials to go no further than a nice journal article or conference presentation. Existing generic drugs can help patients with unmet needs – we just need to ensure they are identified and used.

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Island of Personalized medicine
End of the blockbuster era
Here be monsters

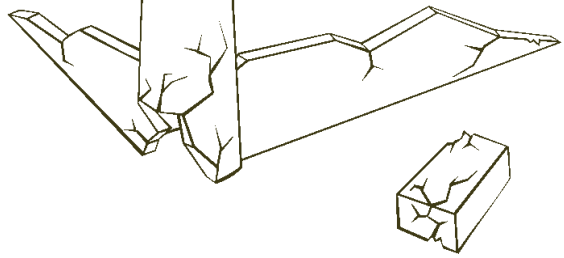
What Lies Ahead for Manufacturing?

What trends and new technologies await the pharma industry in 2018 and beyond? We seek the help of three gurus to map the way forward.

By Stephanie Sutton

At the start of a new year, it is customary to review what has happened in the preceding months and to make resolutions for the future. It is fair to say that 2017 – and recent years in fact – have not been kind to the industry. Costs of manufacturing continue to rise, return on investment for R&D is low, and there is increasing rebellion from payers and pressure to lower drug prices. Slowly, the industry has accepted that the old, traditional ways of working aren't good enough to get medicines to market faster – and with acceptable price tags. And so there have been many discussions about the best way forward – and what technologies could help. Despite the challenges, the many conversations between The Medicine Maker and experts across the industry throughout 2017 suggest a positive outlook; continuous processing, single-use technology and other innovations that could lead to lower cost and more flexible manufacturing are starting to gather pace. Change happens slowly in the industry, but we are certainly moving in the right direction.

We asked three gurus – one in academia, another from a contract development and manufacturing organization, and a third representing suppliers – for their views on the state of innovation in manufacturing operations.



The pharma industry is often described as being behind when it comes to manufacturing innovation. Do you agree?

Johannes Khinast: My answer is a resounding yes! The technology has not changed significantly in decades; today, a tablet is essentially made the same way as 50 years ago. Although designed much later, biopharmaceutical manufacturing processes, such as cell cultures, chromatographic separations and other steps, are also still far from their potential optimum state. In my view, the problem stems from the fact that 99 percent of processes have been designed based on trial and error (or "design of experiments"). To date, a predictive science framework has not been adopted widely by pharmaceutical engineers to design processes precisely, enabling peak efficiency and robustness. As a result, current approaches require extensive quality-assurance costs, wasted batches and lost material. Moreover, process development from small laboratory samples to large-scale manufacturing is often hampered by unexpected scale-up issues that can cause delays, supply shortages and enormous associated costs. A rational, science-based approach to manufacturing is pharmaceutical engineering, which combines material and process science to predict product and process performance based on fundamental science. The industry and its regulators seem to understand that change is necessary and progress is being now made.

"Facilities are getting smaller, more flexible, less CAPEX-intense, all while still being able to produce several different drugs."

Thomas Page: I actually believe that the industry is not so much behind because of a lack of technical competence, but simply because of the nature of the work in itself. With any highly regulated industry, the cost of change is innately high. Let us consider biologic drugs: the product is the process by nature, so making changes to adopt new technologies is not simple and is very costly. Until very recently, the industry has focused on "blockbuster" drugs, which typically call for high volume production in purpose-built facilities with traditional stainless steel technologies. Today, new technologies are emerging – and are being investigated for new products – but making changes to legacy products is particularly challenging.

To increase uptake of new technologies, I believe that we need to increase analytical power – in particular, the industry needs to focus on characterization. The concept of a well characterized biologic is not new but it must really take precedence, as it will help support the efficiency of new technologies and minimize the innate concerns related to process changes. Understanding how your molecule behaves from the very early stages will be key to minimizing risks introduced by technology/processing changes.

Daria Donati: It is true that the industry is slow to adopt innovation, but I agree with Thomas that it's because it is highly regulated. The industry is, understandably, reluctant to disrupt everyday manufacturing operations, so the evaluation time for new innovations is long and diluted, leading to a less effective response to new technologies and solutions. I don't think we can really say the industry is "behind" as such though because companies are certainly innovative in terms of exploring new proteins and molecules to treat formerly untreatable diseases – drugs are becoming more complex and advanced all the time.

The industry must be risk-adverse, given that the stakes are so high: changes in regulated manufacturing processes need to be documented and validated, and they might even demand re-filings to prove product quality, efficacy and patient safety. These activities are highly time consuming and costly. I think we need to create more robust processes to drive innovations forward – and we also need more collaboration. Collaborations between drug producers and technology providers can ensure that innovative technologies are designed to meet real-world needs, and I would also like to see more collaborations that give start-up companies and academia opportunities to test and verify their innovations in an authentic environment.

What are the biggest trends driving innovation in manufacturing operations?

JK: In my view, the biggest trend right now is the personalization of medicine; cancer therapies, for example, are slowly but surely becoming personalized, replacing decades of chemotherapy. In addition, the individual microbiome is being recognized as a major factor in disease progression and therapy outcome. Individual metabolism is another well-known factor in this whole puzzle – and there is still more to be discovered, such as a

detailed understanding of the systems that control epigenetics.

Right now, biopharmaceuticals, including human monoclonal antibodies, are currently among the most sophisticated drugs coming to the market. Their manufacturing is complex, as is their formulation. Enormous cost is associated with just 1g of drug substance, and therapeutic programs often start to exceed the ability and willingness of public health systems to fund costs. Significant advances have been made and lots of research has been dedicated to biotechnology and the related production. For many decades to come, large-protein drugs will be an important sector in the drug market, but I don't believe these molecules are the final answer. Indeed, I expect that novel approaches will steadily become more relevant, including gene-based vaccines (with advanced vectors), small molecules that mimic the actions of proteins, gene-altering systems, and much more. Moreover, delivery forms will change, possibly leading to a reduction in parenteral forms and an increase in advanced oral applications, inhalable drugs, topical (also via micro-needles) and buccal delivery. Thus, we must prepare the formulation and manufacturing science for these challenges.

As for large-scale manufacturing, continuous manufacturing is becoming an important and irreversible trend of the future. In my view, the greatest advantage is that it is based on real-time analytics, making it possible to monitor a product's quality. This requirement transforms old-fashioned manufacturing into a modern approach, which is long overdue.

TP: Secular trends are leading to big changes in how we manufacture drugs. In biopharma, for example, improvements in cell line development, a move towards process intensification and a paradigm shift in new products being developed, particularly in the gene therapy space, are driving a new era of manufacturing operations. Drug developers are moving towards treatments that provide cures rather than treatments, which means smaller to medium volumes that can be supported by a "scale out" approach. To achieve this, future manufacturing facilities must be more flexible and nimble.

DD: I agree that more flexible manufacture is a must to meet today's drug development needs. Facilities are getting smaller, more flexible, less CAPEX-intense, all while still being able to produce several different drugs. In manufacturing, productivity and yields have increased significantly, partly because failures and contamination risks are now reduced.

The industry is also starting to see greater uptake of innovative

technologies; for example, right now I see many companies seriously looking at closed and continuous bioprocessing. The use of single-use technologies, combined with more automated unit operations, finally provides the opportunity to run closed systems, which reduce contamination risk and time-to-market while increasing production efficiency. I also agree with Johannes in that continuous processing – an alternative to batch-based manufacturing, where raw materials are continuously fed into the process train, while finished product material is continuously removed from the other end – could be very beneficial for the industry in terms of improving product quality, reducing capital investment, and increasing scalability.

Flexibility and throughput are often cited as important factors in manufacturing, but what about energy-efficiency?

JK: Energy-efficient manufacturing is already a priority for other industries, and is now receiving greater attention in pharma. Most modern manufacturing approaches require extensive exhaust air and water treatment, which is energy- and cost-intensive. Though not considered a top priority in the pharma industry currently, energy efficiency is increasingly being taken into account, as it adds to the bottom line of a product.

"Closed processing supports the flexible, multi-product ballroom facility that goes along with the concept of nimble and more efficient facilities."

TP: Energy savings are, of course, a goal that anyone running a facility would like to achieve, but as manufacturers our first and foremost responsibility is to keep the facilities running. Patients depend on us. As we look into energy conservation and efficiencies, we must ask ourselves, what does the process need? Can costs be offset without compromising quality standards and regulatory requirements? Single-use technology has already started a trend in energy conservation efforts by eliminating certain activities, such as steam and clean in place, and other technologies are engineered to conserve energy while not in production; mobile clean rooms, for example.

DD: Energy efficiency is one factor that can lead to a reduced carbon footprint – it's a recurring topic that I find comes up whenever companies want to improve their production processes, or are evaluating the need for additional manufacturing capacity. We have a long way to go, but progress is starting to be made. As Thomas explained, single-use technologies are one way of reducing energy and water use in a facility – and uptake of single use is growing. It is estimated that single-use manufacturing technologies can help reduce capex costs by up to 50 percent (1), and water and energy use by up to 80 percent (2), compared to a traditional facility.

What are the most exciting and positive advances in manufacturing technology or equipment in recent years?

JK: Without a doubt, the transition from bulk to continuous manufacturing has had a tremendous impact on manufacturing operations, in terms of quality, costs and reduction of production times.

TP: I am really excited by the uptake of single-use systems bioprocessing – and closed processing is one of the up-and-coming advances. Closed processing supports the flexible, multi-product ballroom facility that goes along with the concept of nimble and more efficient facilities. We must also consider the latest uptake of viral vectors.

DD: I am excited by the advances in biomanufacturing in general. Upstream processing has really come a long way and the efficiency with which cells produce antibodies has improved radically. But these gains have put pressure on downstream purification technologies, sometimes leading to increased processing times and larger chromatography columns to deal with the greater upstream output. Fortunately, purification is catching up, with new generations of high productivity chromatography resins contributing to reducing the cost, scale and time consumption of downstream operations. As Thomas says, single-use systems are also exciting because of their capability to boost production flexibility, help avoid quality issues, and reduce capital investment. The industry is aiming to reduce facility footprint, while increasing throughput – and single use can really help.

Another key advance affecting pharma and biopharma is the application of digital technology to manufacturing. Combining

data analysis with predictive analytics can help reduce the failure rate of manufacturing, as well as predicting positive and improved outcomes from a quality and productivity standpoint. Moreover, better utilization of automation and network systems can create truly integrated manufacturing platforms that can be overseen and controlled remotely through smart interfaces. In addition, tighter connection of systems between drug manufacturers and suppliers can reduce risk and decrease the time from production to release of the product.

How do you think advances in 3D printing, robotics and other emerging technology will shape the near future?

JK: As the demand for new drugs and medicines grows, pharmaceutical companies are continuously looking for new ways to increase productivity and increasingly rely on automation. The use of robotics is ever on the rise in pharma, especially in sterile manufacturing. People are considered the major source of contamination in clean rooms, so automation and robotics are already becoming a prerequisite for the modern manufacturing of parenterals. I'd also welcome more automation for lyophilization, such as real-time analysis of defects.

As for 3D printing, I think its capability and potential to solve major problems is limited. Does a precisely shaped 3D object have a major advantage over a regular capsule that is filled with precise amount of powders? In a typical setting, the answer is no, and 3D printing is likely to remain a niche technology in pharma manufacturing.

However, I am interested in a very different type of "printing". Integrated drug development approaches (including more effective clinical programs), novel delivery systems (targeted delivery to areas such as the brain and inner ear) and completely new manufacturing methods are a prerequisite

for the next-generation of medicines. Standardized and robust methods to make drugs for individual patients, in real time, on demand should be available by 2030 – and drug printing could be an effective solution. Drug printing allows precise combinations of multiple APIs (including large molecules, DNA, RNA, vaccine vectors, and so on) to be printed into a single dose on a dissolvable strip, microneedle patch or other dosing devices. It makes individual delivery possible – and it's something I am very excited about pursuing. Another field I am interested in is micro-fluidics of granular systems. Though a few microliters of a fluid can easily be dosed, it is very difficult to generate individual powder doses precisely in the mg range, but this is required for personalized medicine that involves solid components. The focus of my research is increasingly shifting to this field.

DD: Personally, I am very interested in 3D printing! True, the applications may be niche but I think it could be very useful for for manufacturing equipment and perhaps some consumables. In October 2017, GE Healthcare opened a 3D printing lab in Uppsala, Sweden, called the Innovative Design and Advanced Manufacturing Technology Center. The center will use 3D printing technologies to help speed up the launch of new products for the healthcare industry, especially within bioprocessing. We believe that we can improve the performance and shorten the lead time of bioprocessing equipment with additive manufactured parts. Reducing the number of parts will improve reliability and enable additional benefits, such as lighter products. Additive manufacturing can also improve product design, as it offers more freedom for engineers – and sometimes better economics for complex, low-volume components and products. The computer-oriented design process enables quick design iterations and improves the design process, meaning that better products reach the market quicker. It is also possible to collect data as parts are built. I think, for some applications, additive manufacturing will be a useful tool in the engineer's toolbox that will coexist with traditional techniques.

Another key technology for me is robots. Robots are already seeing increased use in the industry. We deploy collaborative robots (also known as "cobots"), which allow us to better allocate resources. Cobots do not replace employees, but rather take on mechanical, repetitive tasks within a factory, allowing employees to concentrate on more meaningful work. That said, given the huge variety in products and production processes, and the

fact that even robots need to be "trained" or programmed by humans, it seems highly unlikely that human workers could ever be completely replaced by robots in the foreseeable future.

TP: As Johannes and Daria say, robotics are seeing increased use – and I believe they will substantially reduce risk to patients over time. The next step will be driven by the FDA's desire to move more processes into isolators without human intervention. Eliminating risk to patients from direct and indirect contamination from operators will require use of robotic manipulation in place of glove ports. Down the road, transitioning to continuous operations, which are by their nature highly automated and controlled, will reduce the front line manufacturing labor, but increase the need for highly trained robotics technicians, software engineers and savvy validation and quality assurance management. For manufacturers, 3D printing may find a place in quickly providing replacements for broken parts; thereby maintaining manufacturing schedules.

Where do you think the industry's priorities need to lie in 2018 and beyond?

JK: Continuous manufacturing is in the process of being widely recognized as an important improvement. Early adopters have registered products and created certified plants (for example, Vertex, J&J and GSK). Others are following closely, and some companies will wait until the trend is inevitable. My first workshop on continuous pharmaceutical manufacturing was held at Rutgers University around 1998 – and we are still only in a start-up phase, which shows how slowly new technologies can be adopted across the industry.

I think we also need to pay more attention to researching advanced manufacturing solutions for personalized and patient-centric healthcare; it will become one of the main issues in the decades to come and engineers have to be ready to provide solutions. As the individual consumer may become the pharmaceutical company's most strategic partner, the focus has to shift from the product to the patient.

Ultimately, I think we need to move to future facilities that use continuous manufacturing to produce personalized medicines in a highly energy-efficient way – making them affordable for everybody.

"Continuous manufacturing is in the process of being widely recognized as an important improvement."

TP: The Holy Grail for all drug developers is not just to treat diseases, but to bring actual cures to market. This will have a profound effect on how we, as an industry, approach manufacturing operations. Companies will have to change their current models, moving from the large volume blockbuster drug production to lesser volume products. But I think we are in a great place to develop effective facilities of the future. Biologics are likely to dominate the industry for the time being so facilities will need to focus on these drugs. The BioPhorum Operations Group is doing a lot of great work in this area through their Technology Roadmap initiative – a collaborative effort with a number of industry leading organizations to define future needs, challenges and potential solutions. In my view, the facility of the future will be nimble, flexible, designed to decrease manufacturing costs and, most importantly, will ultimately help increase patient access to life saving medicines all over the world.

DD: Flexibility will definitely be crucial for the facilities of the future. Already, there is a trend towards smaller, less CAPEX-intense facilities that can produce several different drugs. There is also a trend towards more manufacturing delocalization, with local production gaining more importance. To make this possible, the integration of new digital technologies is key. Smaller modular facilities with manufacturing processes that are standardized, integrated and automated on the same platform will allow the "copy and paste model", where facilities can be replicated in different regions, while adapting to local manufacturing requirements. We have a lot to learn from other industry sectors when it comes to digitalization, and not making the most out of this opportunity would be unacceptable. Using predictive digital solutions, automation control and automation integration, we can bring significant operational and financial benefits for manufacturing that should eventually help increase access to new drugs.

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TAKING DOWN A GOLIATH

Big pharma, vulnerable supply chains, an international religious network… The story of the Global Pharma Health Fund reads like the plot of a conspiracy novel. But for its developer Richard Jähnke – winner of the 2017 Humanity in Science Award – the reality of fighting counterfeit medicine is far more prosaic. Equipped with his sling – a case full of chemicals, a basic TLC test, and a training manual – his aim is simple: to help spot fakes before they reach consumers.

By Joanna Cummings

Counterfeit medicines are a problem of epidemic proportions, particularly in resource-poor countries. In 2000, the World Health Organization (WHO) reported (1) that of all poor quality and substandard counterfeit falsified products, 80 percent do not contain any active ingredients, do not contain enough active ingredient, or even contain the wrong ingredients – leaving patients with drugs that are at best ineffective, and at worst potentially fatal. Complex supply chains provide too many opportunities for adulteration, while understocked labs and expensive analysis equipment only compound the problem of detection, particularly in countries with limited financial resources and patchy power supplies. What is needed is a simple, low-cost and transportable analytical toolkit to protect the supply chain – and, ultimately, consumers.

A tough challenge, perhaps. But Richard Jähnke, as part of the Global Pharma Health Fund (GPHF, based in Frankfurt – a charitable intiative led by Merck, Germany) has spent the last 20 years working with a small team of chemists and pharmacists from universities and the pharmaceutical industry in Germany to develop and deliver a life-saving solution. Its name? The "GPHF-Minilab."

A bicycle built for… chemical analysis

How did the Minilab come into being? Jähnke, a former Principal Scientist at Beecham Pharmaceuticals, UK, and Business Development Manager at the German branch of PCI Pharmaceutical Services, Philadelphia, recalls his bold (and wonderfully naïve) declaration on finishing his pharmacy degree in Bonn: "I was talking to friends about what we were going to do with our lives. I said I wanted to go into international health development work – and that I would try to make sure the pharmaceutical industry was paying for it. It was a big statement at that time!" In search of a worthy venture after being awarded a Master of Business Administration (and brushing up on his English language skills), a fortuitous meeting with the GPHF – and a subsequent discussion with the WHO – led to the birth of the Minilab project.

The WHO provided a clear but also challenging specification for the project: a test kit for rapid medicine verification and quality monitoring in the field, for low- and middle-income countries. The kit needed to be transportable, reliable, affordable, and unsophisticated, allowing people on the ground to monitor medicine quality with minimal training. It needed to be used by health or medicine-supplying facilities, as well as drug supply organizations in the private and public sectors, and in places with little access to fully fledged operational laboratories. But Jähnke is quick to point out that the Minilab was never intended as a laboratory replacement. "We wanted a 'complement' to the lab – when it's not in full working order, or one simply doesn't exist." He spent the next two years developing the Minilab.

Jähnke in no way takes full credit for the idea behind the kit, acknowledging the importance of good timing – and the foresight of his colleague Tom Layloff (Senior Environmental Health Advisor at the Partnership for Supply Chain Management), who he dubs the "grandfather" of the Minilab. "In 1985, there was a big WHO conference in Nairobi, about the quality of medicine in sub-Saharan Africa. People were aware of the circulation of fake medicine, and wanted to discuss ideas for improving pharmaceutical supply," he says. "Lots of observers from the industry were getting involved – but we needed to stop talking and take action. Tom was working for the FDA at that time, and started to develop some simple thin-layer chromatography test methods – but didn't have an appropriate toolbox and couldn't get funding for it. It wasn't the right time. Ten years later, it started to gain momentum."

Jähnke realized that to be a success, the Minilab must improve upon the accuracy of previous dye-testing methods, yet be cheaper than the HPLC methods used in the lab. "HPLC is the Mercedes Benz of instrumental analysis, but we only needed a bicycle," Jähnke explains. "In this context, we did not need fully fledged, sophisticated testing – detecting the absence of a drug is relatively easy." The resulting Minilab uses thin layer chromatography to test for the presence of 90 drugs, and also includes physical tests for degradation or solidification, which can prevent adequate release of the drug and thus render them useless.

As well as working with input provided by the WHO, the team consulted churches and faith-based organizations who are involved in health initiatives in low- and middle-income countries. "Such organizations gave input as to the cultural background, and what would and wouldn't work," Jähnke says. "For example, when I came to develop the manual, they told me I needed far more extensive operational procedures than in the British or US pharmacopoeia. On the other hand, I was told the list of materials in the pharmacopoeia is too long; when people

> "We did not need fully fledged, **sophisticated testing** – detecting the absence of a drug **is relatively easy.**"


USAID
GPHF-Minilab
BBPOM
DKI JAKARTA

"When you order or use a Minilab, **what is written in the text can be instantly performed.** There's a starter kit of chemicals, **and everything you need to do the job is right there.**"

have to do a test on, say, amoxicillin, they would normally consult the pharmacopoeia, then run around the lab, identifying the equipment and chemicals needed – of which 50 percent were likely to be missing." To prevent the problem, the team had to include all the chemicals, reference standards and solvents needed, so that testing could be performed on the spot. "When you order or use a Minilab, what is written in the text can be instantly performed. There's a starter kit of chemicals, and everything you need to do the job is right there," says Jähnke.

Have lab, will travel

From a logistical standpoint, the Minilab comes in a heavy-duty flight case, which contains all the appropriate labware and consumables. The 'hub' weighs approximately 25kg, but a starter kit of about 20 boxes of chemicals and solvents is also included in the shipment. Sending scientific equipment to remote regions is a challenge, but Jähnke is proud to note a solid track record in his own supply chain. "We have sent Minilabs to every corner of the world – to the Philippines, to Tanzania, to Ghana – and although they have arrived late in some cases, we've never lost one in transit completely," he says.

The bulk of the Minilabs go to national medicine control labs or public health facilities run by the state. "At the beginning, we focused on the quality of antibacterial and antimalarial medicine. These are public health concerns, so it's the responsibility of the state to make sure the medicine is accessible and of good quality for people in that country," says Jähnke. If there is no manufacturing capability in the country itself, the state buys the medicine by tender process, probably cheaply from China or India. Medicine is delivered to central medical stores, then distributed to regional medical stores – and from there goes to general and referral hospitals. Faith-based drug supply can be even more complex.

For African countries in particular, churches have proved to be an invaluable partner in interactions with local communities. "UNICEF and other global tender organizations might order 10 Minilabs for Congo, but they will not tell me precisely where they are going. We procure and send the kits, but are disconnected from their use," he says. "I find with church groups, there is more of a rapport – I talk to them, I know them, and it's more transparent." And though the state might have to answer to its people, faith-based groups answer to a higher power. "They don't have much money and are quick to spot when they are being cheated. They track fake medicine down even more effectively than the police – because in their eyes, delivering counterfeit medicine with nothing inside is 'like cheating God'."

The human factor

Jähnke believes that cooperation with partners has played a crucial part in getting the Minilab in front of the right people and into the hands of those who benefit the most – describing the Minilab as "a success not only of science, but also of public relations." Recognizing the value of the Minilab, the US pharmacopoeia has helped to market the kit as part of its global health impact program.

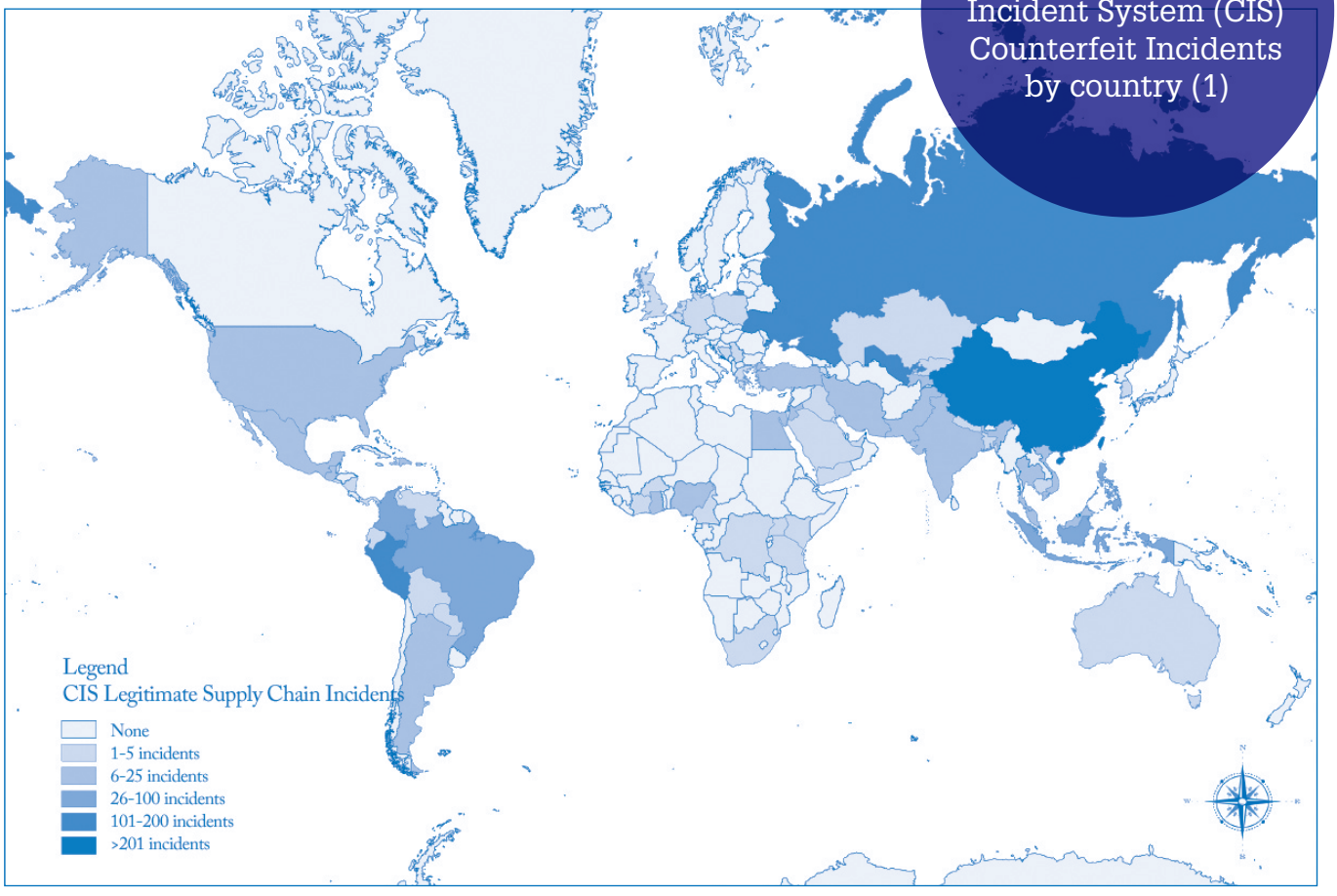
"They are very well connected, with access to many governmental labs… but most importantly, they care about the technology," Jähnke says. The result of such support is few limitations in geographical reach, or in funding. "They were very good at negotiating with the US Agency of International Development to get the funding and, through the Center of Disease Control (CDC), they had access to every embassy. In terms of marketing, when they became involved in the project it was like a hot knife going through butter."

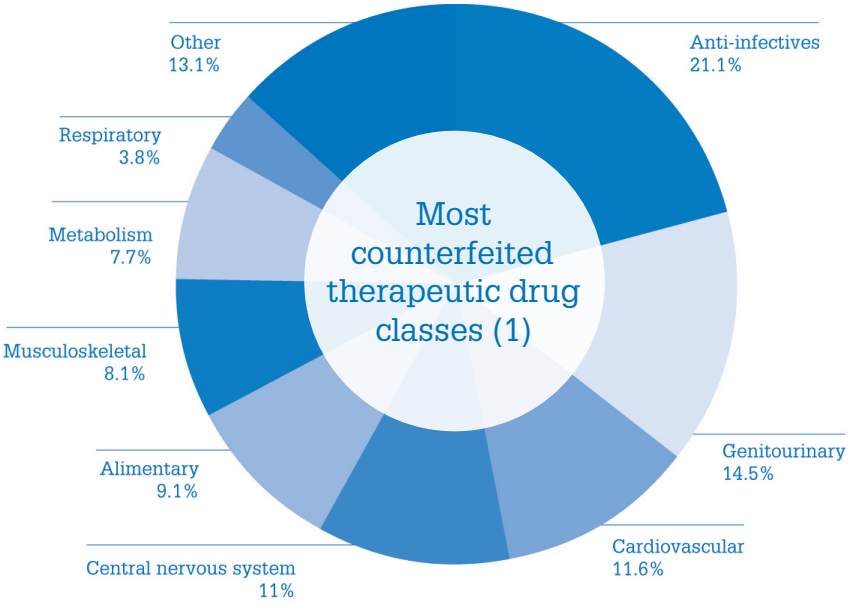
Working closely with the WHO has also been a real boost to the Minilab team, affording a type of protection that might otherwise have been difficult to attain for a micro enterprise; Jähnke describes the relationship as "a gentleman's agreement" rather than contractual protection. "They told me that to survive as a small operation, I should follow them as long as I can."

Jähnke's own visibility has helped build public trust in the product. "I gave a presentation in Africa, and an audience member said, 'This is the first time I've seen a professor and not a politician!' They trust me because they can see I have no hidden agenda – I'm not telling them what they want to hear. The most interesting parts of this

Counting the Cost
of Counterfeit Medicines

Global map of Counterfeit Incident System (CIS) Counterfeit Incidents by country (1)





Most counterfeited therapeutic drug classes (1)

An estimated **1 in 10** medical products in low- and middle-income countries is substandard or falsified (2)

References

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What's Inside the Minilab?

- Glassware for sample extraction, preparation, pipetting and spotting
- High performance chromatographic plates
- Developing and detection chambers
- Electronic pocket balance
- UV lamps with different wavelengths
- A hot plate
- Calliper rules
- A full collection of secondary reference standards for 90 active ingredients
- A set of manuals providing simple operation procedures.

A three-point plan

Testing with the Minilab involves three steps:

1. A physical inspection scheme of dosage forms and associated packaging material for an early rejection of the more crudely presented counterfeits
2. A simple tablet and capsule disintegration test in order to verify label claims on enteric-coating and other modified-release systems
3. Easy-to-use thin layer chromatographic tests for a quick check on drug content, thus verifying label claims on potency.

Supplies include sufficient quantities in order to perform about 1,000 assays while ensuring that the total material costs for one test run do not exceed two Euros.

https://www.gphf.org/en/minilab/index.htm

job go beyond the professional – wherever I go, I travel there as a human being and, ultimately, that's how you make connections."

But that's not to say that he has never caused a stir. The authorities in certain countries have been known to keep a watchful eye on his activities. "One Minister of Health admitted that the state was unable to carry out the testing themselves, but went on to say that it doesn't mean anyone else is allowed to do it. They reminded me that they were observing me – and that they could have thrown me out of the country at a moment's notice! But we always find a way around..."

Put to the test – and then further optimized

Jähnke was delighted to have the impact of the Minilab retrospectively confirmed by a WHO report. In a study to identify the scale of the problem of falsified medicine, the WHO checked 100 publications in 88 countries from the last ten years (2), comparing the Minilab with HPLC and other technologies. They checked the reports on 48,000 samples, of which 20,000 were tested by the Minilab – and of these, 1,000 were found to be fake or of extremely poor quality.

"We now know the impact of the Minilab statistically. Case by case, we knew we were doing well, but our claim that the Minilab saves lives has now been backed up by the authority of the WHO. The GPHF is a micro enterprise, so it can feel like David versus Goliath!" The constant observation that goes hand in hand with a higher profile has increased the pressure on the team, however. "We've essentially been developing test methods in the public arena, so there is nowhere to hide!"

The Minilab covers a broad spectrum of drugs within the anti-infective arena – the next step is to expand into testing of drugs for non-communicable diseases; for example, cardiovascular, anti-diabetes, and gastrointestinal medicines. Jähnke believes there is room for technical improvement for the Minilab too, such as using a smartphone camera to improve the assay reading, which is currently done by eye. "We want to combine the TLC plate with a final assay reading and interpretation connected to smartphones."

There is also no shortage of countries still in dire need of the Minilab's capabilities. "We would like to focus on regions where there are not enough Minilabs available. I'd like to supply more Minilabs for Congo, Cameroon, Chad, Benin, Togo, and the Ivory Coast. If there's a counterfeit medicine hot spot in the world, it's Francophone West Africa – whenever we go there, we find something. I would also like to supply countries like Libya, Sudan, Djibuti, Syria and Yemen - but currently, it is just too dangerous."

Finally, Jähnke would like local workers to take over

The Humanity in Science Award

The Humanity in Science Award, presented by The Analytical Scientist (a sister publication of The Medicine Maker), in partnership with KNAUER Wissenschaftliche Geräte GmbH, is an international research prize that recognizes and rewards scientific breakthroughs that can substantially benefit human lives.

For his dedication to developing cheap, simple in-the-field tests (sometimes at the risk of his personal safety), Jähnke won the Humanity in Science Award and a $25,000 prize in October 2017. The Award was presented by Texere Publishing Content Director, Rich Whitworth, at industry partner KNAUER's 55th anniversary celebration in Berlin, Germany.

The Humanity in Science Award will be presented again in 2018. Keep an eye on the website for more details.

More information can be found at: www.humanityinscienceaward.com

training on the device. "I have done about 50 training sessions in the past 18 years, and I would love for them to be run independently. I want to empower local people to do the job."

Hold the line

Fighting fake pharma could be regarded as an overwhelming task, but in Jähnke's case, persistence (and by his own admission, a little luck) has paid off. "When I finished my degree, I knew what I wanted to do with my life, but I couldn't gain access to the public health arena. Ten years after my final examination as a pharmacist, I got my chance – and since then, I have followed the Minilab from development to production, to advertisement, to delivery, to training. Twenty years ago, when we were starting the project and talking about counterfeit medicine, not many people wanted to listen. But now it's discussed everywhere."

Considering the innumerable challenges, does he ever feel disheartened? "On the contrary – I am filled with gratitude that I got the opportunity to carry out this task. I've been to big conferences, with legal factions, public affairs, the consumer power groups, and you wonder how anything is moving – they make it so complicated. But I don't get ground down by the scale of the task. If I am blocked in one area – I just pop up somewhere else!"

In 2017, Jähnke was "extremely flattered" to win the Humanity in Science Award for the Minilab. "You work all your life in a lab, hoping that maybe you've made a difference... But an award like this helps you realize you have had some influence. It's another part of the story that has drawn the Minilab from the lab and onto the world stage."

A recent post on Facebook about the GPHF's detection of counterfeit medicine attracted many memorable and heart-warming comments. For Jähnke, one comment in particular struck a chord, when a fellow pharmacist stated, "It's the first time I have been proud to be a pharmacist!"

"That's one of the reasons I do this job," Jähnke explains. "It's not just about counterfeit medicine; it's also about promoting the pharmaceutical profession. It gives us a voice."

Although the battle against counterfeit medicines is far from over, Jähnke feels content. "It's overwhelming to still be working on the Minilab 20 years later, when projects these days can be so short-lived. We have survived the test of time. I've no plans to retire yet, but when I do, I will feel I have made my mark on Earth."

For further information, see www.gphf.org

Joanna Cummings is Deputy Editor, The Analytical Scientist, at Texere Publishing.

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HUMANITY IN SCIENCE AWARD

the Analytical Scientist

In partnership with

KNAUER

Richard Jähnke

Meet the Winner

Richard Jähnke

Richard Jähnke from the Global Pharma Health Fund (GPHF) has received the 2017 Humanity in Science Award for "development and continuous improvement of GPHF Minilab™ (www.gphf.org), which represents a breakthrough for the rapid and inexpensive identification of substandard and falsified medicines in low- and middle income countries in Africa, Asia and Latin America".

Richard received his award at a special jubilee reception in Berlin, Germany on October 2, 2017 hosted by KNAUER to celebrate the company's 55th birthday this year. Richard's work will feature in an upcoming issue of The Analytical Scientist.

Could it be you in 2018?

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

Has your own work had a positive impact on people's health and wellbeing? Details of the 2018 Humanity in Science Award will be announced soon.

@Humanityaward Humanity in Science Award

www.humanityinscienceaward.com

Best Practice

Technology
Quality
Compliance

Prioritizing the Pediatric Dosage Puzzle

How do we fix the course of pediatric medicine to ensure the best treatments for children of all ages?

By Rachel Meyers

People often tell me that it must be incredibly sad and emotional to work in pediatrics. And though it can certainly be distressing at times, kids can be unbelievably tough and their medical journey often finishes with a happy ending. I am always impressed by their resilience and positive attitudes.

I am a Clinical Associate Professor at the Ernest Mario School of Pharmacy at Rutgers University in New Jersey and I also have a practice site at Saint Barnabas Medical Center nearby. As a pharmacist – and from the studies I have been part of, my interactions with children and parents, and my own personal experience as a mother – I think I offer an interesting perspective on the disconnect between drug companies and pediatric patients. There are a few areas that the industry needs to prioritize and improve upon when it comes to pediatric medicines.

When developing any medicine, the priority is obviously the medicine's efficacy and safety, meaning that the actual dosage form can be an afterthought. With a growing emphasis on how patient compliance can be improved, the dosage form is receiving increasing attention, but children's requirements are still overlooked. As an obvious example, many medicines taste bad – especially liquids. Taste may be less important in adult medication – after all, (most) adults can apply reason and overcome the obstacle – but trying to get young children to take a bitter tasting medicine can be a real struggle. The result is non-adherence – few parents want to wrestle with their child every time a dose needs to be administered.

Dosage should not be guesswork

Administering medications to children oftentimes requires manipulating the dosage form, either by crushing or splitting tablets or mixing with water or food. The manufacturers probably don't like us modifying their medicine, but when dealing with kids that require much lower doses, we don't really have a choice, if no appropriate medicines exist for certain age groups. And with rare diseases, pediatric medicines are even scarcer.

A child recently came into our hospital with epilepsy. To help control her condition she was on a ketogenic diet, so we had to rule out liquid dosage forms, as they are often full of carbohydrates. The remaining option was a tablet, but because of her age and weight we calculated that she'd need three quarters of a tablet. Splitting a tablet in half is hard enough, but splitting off a quarter is almost impossible because the tablet begins to crumble; we had to resort to crushing the tablet, mixing in water, then administering three quarters of that.

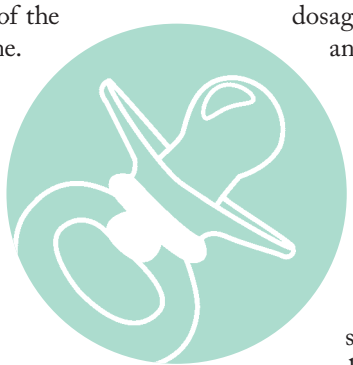
Liquid medications can also be challenging at low dosage. We often have infants who require volumes of 0.1mL or less, and sometimes we resort to diluting medications just to make them more measureable. Each of these manipulations that we resort to in preparing pediatric medications leads to another chance for human error and an increased risk of an adverse event. At the other end of the spectrum, I have seen lots of teenagers who have not learned to swallow pills correctly! One moment, I'll be working with a neonate and struggling to find an appropriate drug concentration and size; the next, I'll be tackling a 14-year old, who is refusing to take a tablet... Pediatric medicines need to come in all shapes and sizes, and we need more attention and research in the area.

Altering dosage forms to fit the patient isn't out of the ordinary for a pharmacist, of course, but it occurs far more with medications for children. Last year, one of our pediatric pharmacy residents led a multi-center study that looked into the manipulation of dosages forms. The study found that we manipulate dosage forms three times more often in children than in adults; the study demonstrates that pediatric patients aren't what drug makers have in mind when developing medications – despite efforts from regulators to encourage innovation.

Another relatively new factor to bear in mind is the issue of pediatric obesity, which raises the question of what exactly dosage is based on (and that goes for adults, too). For many drugs, we do not really know if the pediatric dosage is based on ideal body weight, actual body weight, size, height,

or another variable. The unfortunate truth is that many pediatric dosages are just estimations, as there are very few official guidelines.

Even when pharma manufacturers do give official guidelines for pediatric dosages, they aren't always well thought-out. I had a seven-month old baby on an IV antibiotic at the hospital. When he went home and had to switch to an oral version, his dose was to be 8 mL of liquid three times a day, which is a lot for a baby. Couple the volume with a bad smell and taste, and you can imagine how difficult it was for the parents. I've also worked with a medicine that took the form of a powder packet that needed to be mixed with water. The company had clear measurements for the pediatric dosage. A portion of the water was to be taken into an oral syringe and given to the child, but the amount of water needed was too much for the child to drink in one sitting, so only part of the dose was ingested at a time. In short, it's great to have the dosage information, but I'd really like to see that extended to a dosage form that is easy and reliable for parents to give.



Doing it for the kids

On the upside, 600 new pediatric studies have been conducted (as of August 2017) since the FDA's pediatric legislation was introduced in the early 2000s. But there is still a long way to go before we see real change for children because it takes so long for studies to result in actual labeling changes. We can only hope that those changes will truly take into account children's needs. On the downside, pediatric studies often don't go below the age of 12 years, which leaves a large pediatric demographic unrepresented. In particular, neonates are very difficult to cater for.

At Rutgers, we have been working with the Catalent Applied Drug Delivery Institute to try and address some of the challenges in the area. I first met Ronak Savla, who is now scientific affairs manager at Catalent, when he was a fellow in our Rutgers Pharmaceutical Industry Fellowship Program, which is a collaboration between the School of Pharmacy at Rutgers, and multiple industry partners. Ronak and I had a good conversation about pediatric research needs, and he noticed my interest in dosage forms. Once he joined Catalent, we started talking about how we could work together; Rutgers started doing more research in the area, with a special focus on formulation and dosage form design. A grant from the Catalent Institute has allowed us to survey the work of caregivers to determine, measure and quantify the problems they have in administering medication to children, including patient acceptance, dosage form appropriateness, and easy and accurate dose measuring. I know that I have encountered many problems, but I can't write a research report simply on my experiences. We have surveyed over 1000 caregivers to help us show the industry what is really happening. If "great" products aren't working and aren't great for administration, the industry needs to know about it!

The American Society of Health-System Pharmacists (ASHP) has an initiative called Standardize 4 Safety to create standardized concentrations for medicines, with the aim of improving the quality of treatment and reducing error (1). The initiative has the backing of the FDA, which has given ASHP a three-year contract to develop the standardization. They've already come up with a list for compounded IV medications for adults and compounded oral solutions, and in the future will be working towards standardizing IV concentrations for pediatric patients. In my experience, there is a high risk for error when compounding formulations, so I hope this will make a difference.

Another inspirational project was conducted by Shonna Yin, an associate professor in the Department of Pediatrics at NYU Langone in New York. She published a study in JAMA that examined the top over-the-counter (OTC) pediatric medicines, and found that they were wildly inconsistent in dosage directions and their measuring devices (2). Since its publication in 2010, we've started to see a change in the industry with OTC medicines, but I'd like to see the same change with prescription medications. Yin has also released several studies researching the healthcare literacy of parents and seeing how effective administration instructions are.

All of these initiatives are moving the field in the right direction, but – as always – there's still so much more to do. In an ideal world, we wouldn't have to manipulate dosage forms that were made for adults; we would have access to dosage forms that were easily manipulated and measured.

Rachel Meyers is Clinical Associate Professor in the Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers University, New Jersey, USA, and Pediatric Clinical Pharmacist, Saint Barnabas Medical Center, Livingston, New Jersey.

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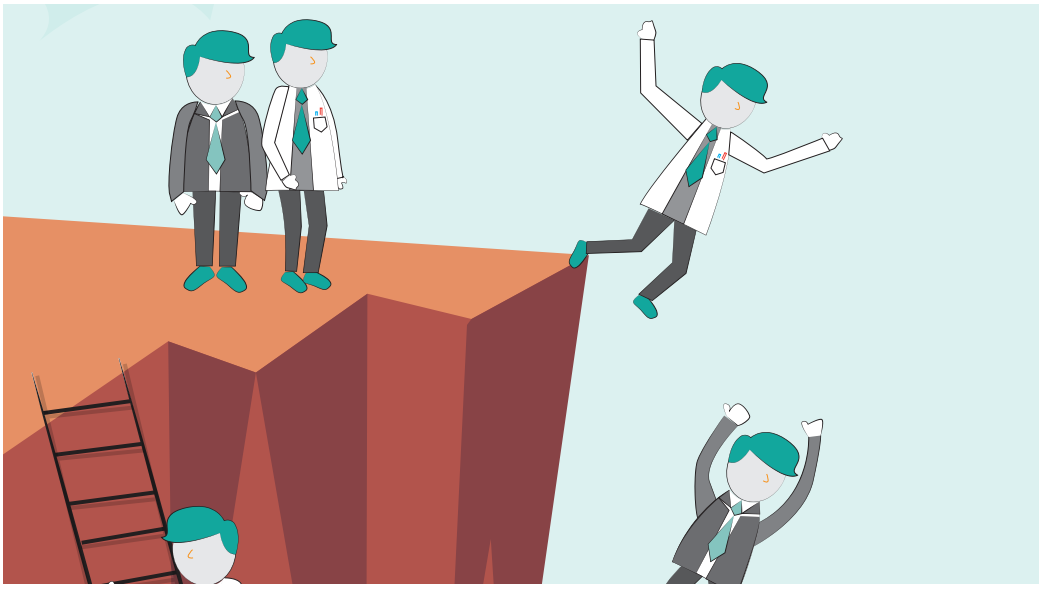


Balancing the Cost of Success and Failure

Publishing negative results might not flatter – but it does matter.

By Ian Catchpole

Late on in my career at GlaxoSmithKline, my colleagues and I published a paper (1). It could have been groundbreaking. In some ways it was. We were seeking a better way to treat wet advanced macular degeneration (AMD) – one that would obviate much of the burden of monthly clinic visits for intravitreal injections of anti-VEGF therapy (anti-vascular endothelial growth factor therapy – used to reduce new blood vessel growth or swelling in the eye) that we see today. Despite solving many problems along the way, ultimately, the project failed – but we should all learn from its failure. Let me tell you my story.

Discovering ophthalmology

It started back in 2007, when I first worked in the field of ophthalmology. GSK's head of research at the time was Tachi Yamada, and he was interested in the gene therapy area. He knew one of the biggest names in that field – Jim Wilson at the University of Pennsylvania – and he enabled GSK to access some of the Wilson group's novel adeno-associated virus (AAV) vectors. We started working with Jim's group and also a number of researchers from the University College London Institute of Ophthalmology in London looking at gene therapy approaches to ocular disease. The opportunities were great – here was an organ where you could actually see the effects of what you were doing! We also started re-profiling existing GSK assets and considering ophthalmic applications for them – this was a therapy area that had great promise! I started going to the meetings of the Association for Research in Visions and Ophthalmology to start trying to understand what kind of problems were out there in ophthalmology: scientifically, clinically, and everything else that we might need to deal with when building an ophthalmic franchise. It was apparent even then (ranibizumab had been approved in the US less than a year before for the treatment of wet AMD) that the large number of clinic visits and intravitreal anti-VEGF injections – one a month, going forward for as long as the drug continued to work – was going to be the big issue, in addition to the hefty cost of the drugs themselves.

Combining drug with delivery platform

Around that time, GSK acquired a company called Domantis that worked on domain antibodies and antibody fragments. As part of that, we acquired certain relatively small anti-VEGF molecules – certainly smaller than ranibizumab. Here was an opportunity to play with drug delivery – i.e. to pack a lot of drug in to a sustained-release vehicle and build a long-acting injectable anti-VEGF. So we presented that idea to the GSK equivalent of Dragon's Den – an internal poster presentation and competition session called the Goldfish Awards. We didn't win – but what we presented generated enough interest within the newly formed GSK Ophthalmology group that they thought it that was a good idea to pick up. We started reviewing drug delivery options, and came across a Dutch company called Octoplus N.V. (now part of the Dr. Reddy's franchise) who had an aqueous hydrogel drug delivery platform (Figure 1) that not only managed to keep the proteins active for a long time, but also released them with pretty much first order kinetics – i.e. with minimal "burst" release – over a long period. They hadn't really performed any studies in the eye, so we moved forward together.

Even then, there were stumbling blocks. Our original candidate molecule just wasn't potent enough, so the big challenge was rebuilding the molecule to make it a more potent VEGF inhibitor. What we ended up making (Figure 2) was at least as potent as the most potent anti-VEGF available on the market today, aflibercept (2). We then had to work to find and evaluate a polymer that could keep the protein intact in the distinctly "wet" environment of the eye and release therapeutic levels of it over a 6–12 month period. That was no easy task: the principal technical challenge was to load enough protein material from the antibody fragment into the microparticle itself – you needed to get liquid protein concentrations up to >200 mg/mL (a huge amount) to enable the release of sufficient quantities to be effective for at least 6 months. But we did it.

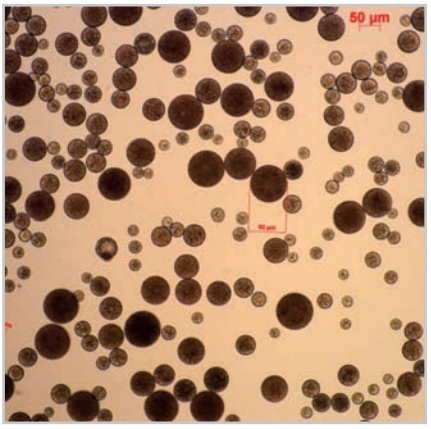


Figure 1. PolyActive hydrogel microparticles. Adapted from (1).

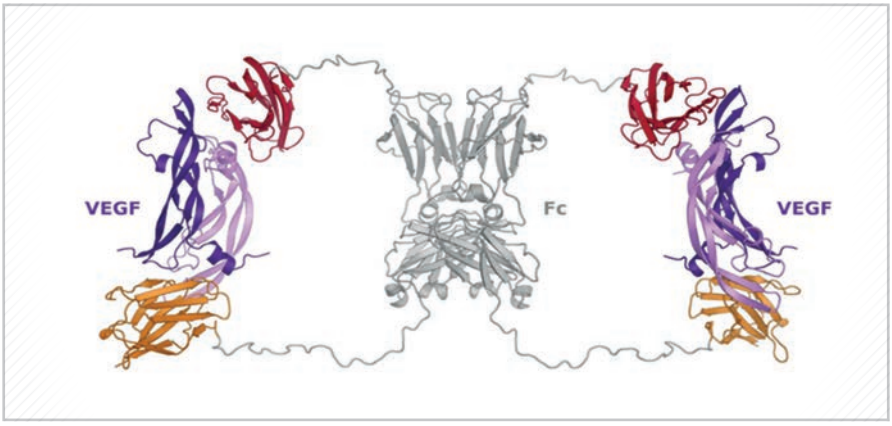


Figure 2. Proposed structure of the dual domain antibody in complex with two VEGF molecules. Adapted from (2).

Progressing through the preclinical steps

The next step was preclinical in vivo experiments. We did our first studies in rabbits, as it is the model of choice for studies of ocular delivery. The use of rabbit eyes are not without issue; though the intravitreal volume is relatively large at 1.3 ml, it is still smaller than man (4.5 ml), but with a huge lens, so you need to make sure that injection avoids the lens – and then there were issues with immune responses. Our antibody fragment was a humanized protein: the rabbit's immune system kicked in and generated anti-drug antibodies (ADA) responses post-dose at high frequency, which blocked detection of the released anti-VEGF and made it challenging to interpret the results. Nevertheless, we gathered together enough data to demonstrate that substantial levels of active anti-VEGF molecule were present in the rabbit vitreous at six months post-dose and to justify progressing to the non-human primate (NHP) model. The cynomologous monkey is far closer than rabbits to humans in terms of ocular anatomy and function – and it also seemed likely that the closer similarity to human would help reduce the negative impact and frequency of ADA responses; enabling simpler detection and interpretation of the pharmacokinetics of the released molecule. It turned out that these successful and very expensive experiments both validated many aspects of the approach but also ended the project…

"The big challenge was rebuilding the molecule to make it a more potent VEGF inhibitor."

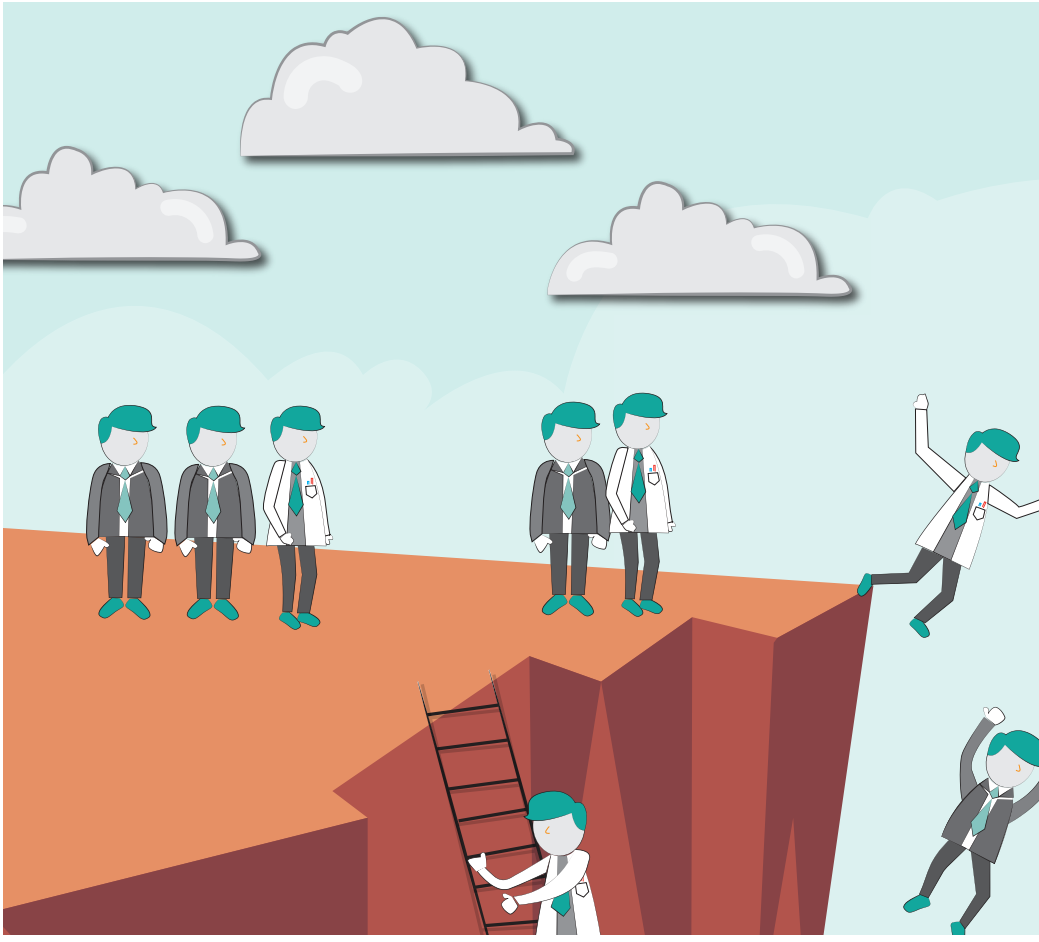
We'd found that in vitro, we could release effective doses of anti-VEGF molecule from the microparticle/ hydrogel, PolyActive, platform over a 12-month period, and in vivo, this translated to at least six months' worth of effective levels of anti-VEGF released in both the rabbit and NHP experiments. We used the NHP laser choroidal neovascularization (CNV) model (the pre-clinical model of wet AMD used to validate ranibizumab prior to the clinic) to test how successfully our therapy managed to suppress the production of laser-induced leaky new blood vessels: we'd dose the eyes, wait 4–6 months, and challenge the eye with the laser – and found that we still got good protection even 6 months out. In that respect, moving forwards to a clinical trial looked promising. But there were three major challenges that prevented us from doing so – and these represent crucial lessons for any other research group that is trying similar intravitreal particle-based drug delivery systems.

Three big challenges

The first hurdle was ocular inflammation: we were seeing it in the NHP eyes, as well as the rabbits. Although both protein and microparticles were prepared at high quality and were shown to have extremely low levels of endotoxin, they were still research-grade materials, i.e., not prepared at GMP grade purity. So it might have been possible to reduce the degree of inflammation by improving the quality of what we were administering, unless the inflammation was solely driven by the particulate nature. But these weren't the only challenges. The second issue was a lack of degradation of the polymer at the same rate as the release of the molecule. The polymer was predicted to last for 6–9 months, based on experiments where similar PolyActive implants had been

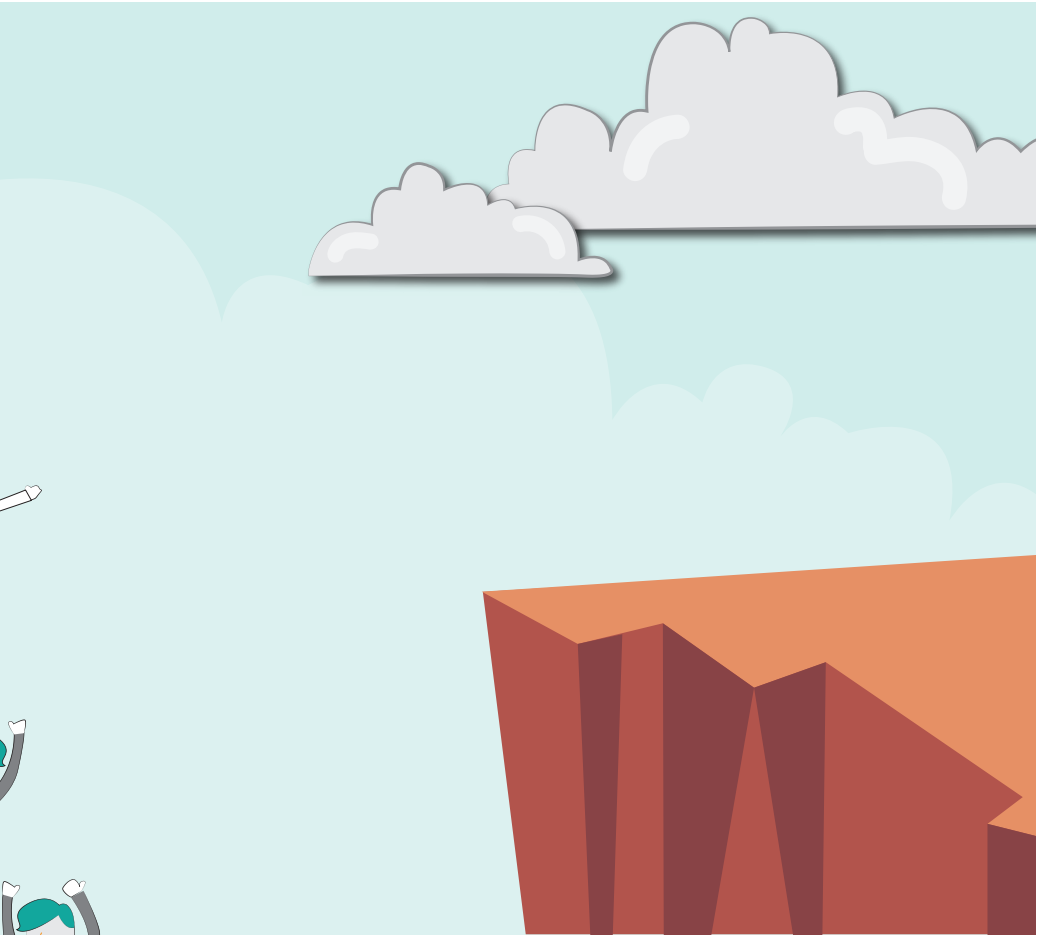
Key Learnings

- Collectively, companies and research institutions have invested millions trying to develop intravitreally administered, extended-release anti-VEGF agents for the treatment of retinal neovascular disease that can act for as long as 6 months.
- GSK, in collaboration with OctoPlus N.V., developed a novel potent anti VEGF molecule and hydrogel microparticle combination that almost fitted the bill – and was close to a clinical trial. Had it worked, it would have been a paradigm changer.
- One of the issues that led to the project's termination was caused by fundamental and poorly understood aspects of primate accommodation, which led to microparticle migration into the anterior chamber.
- The issues highlighted in this research are relevant for others pursuing the use of particulate injectables for intravitreal ocular delivery, some of whom are not easily able to afford the key experiments in the primate eye needed to de-risk likely similar issues in man.



placed subcutaneously in rats – but when we looked at the PolyActive material in the NHP eye, it was still there at 6 months, 9 months… and it was only really 12 months after implantation before we started to see any major en masse reduction and degradation. That meant it would be very difficult to re-dose – the accumulation of material in the eye would start to become a problem after only a few doses. But the third and biggest problem was related to the microparticles themselves. They would travel from the vitreous into the anterior chamber. These three issues combined lead to termination of the project. We were quite surprised by the latter observation – we hadn't seen anything like that in our rabbit studies, and it seemed to be driven by the primate (and presumably human) eye's process of lens accommodation-disaccommodation (3). It seems that ciliary muscle-driven lens movement causes fluid to flow between the vitreous and anterior chamber, and the particles get disturbed and caught up in it. And so, despite some great technical achievements along the way – developing a potent anti-VEGF antibody fragment, and being able to concentrate, load and deliver this biologic

"I hope that others will learn of and from our experience – and not feel the need to cover old ground."



over a long period with a novel drug delivery vehicle – we fell at this last hurdle.

Being open

Why am I talking about our work, both the successes and its ultimate failure? I strongly believe that negative results, especially those that have such a strong bearing on the future of a field should be published (4). Anyone evaluating a similar drug-delivery method needs to be aware of our work – GSK was not alone in working on this approach. There are still biotech companies developing particle-based drug delivery approaches for intravitreal injection who have not performed NHP studies and are either unaware of our findings or are reluctant to accept the full consequences of them, as it might negatively influence their share price. Also, how many biotech companies and academic groups are receiving funding from research councils or companies to fund costly studies – only to repeat our findings? A huge combined investment has likely already been made with this type of approach by GSK, together with other pharma and biotech companies. Although our project didn't work out, there were positive aspects from our study. We clearly demonstrated that hydrogel systems can keep anti-VEGF protein molecules stable and active, and can enable them to be released for over 6 months in the eye at effective doses to treat wet AMD. I hope that others will learn of and from our experience – and not feel the need to cover old ground.

The big questions I'm left with are: how can others build from the positive aspects of our findings and address the remaining issues? Can those working on particulates really take heed of the full message and switch funding and research activities to concentrate on generating similar data to ours with temperature-sensitive solidifying erodible gels? If others with a negative data story are reluctant to share knowledge with the field perhaps they should reconsider and think of what other medical research could have been done with the money others spend repeating their mistakes. The answer to that latter question is the true cost of failure.

Ian Catchpole is a GSK Fellow, Cell & Gene Therapy, and is based in their Stevenage campus in Hertfordshire, UK.

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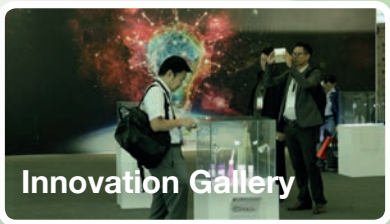

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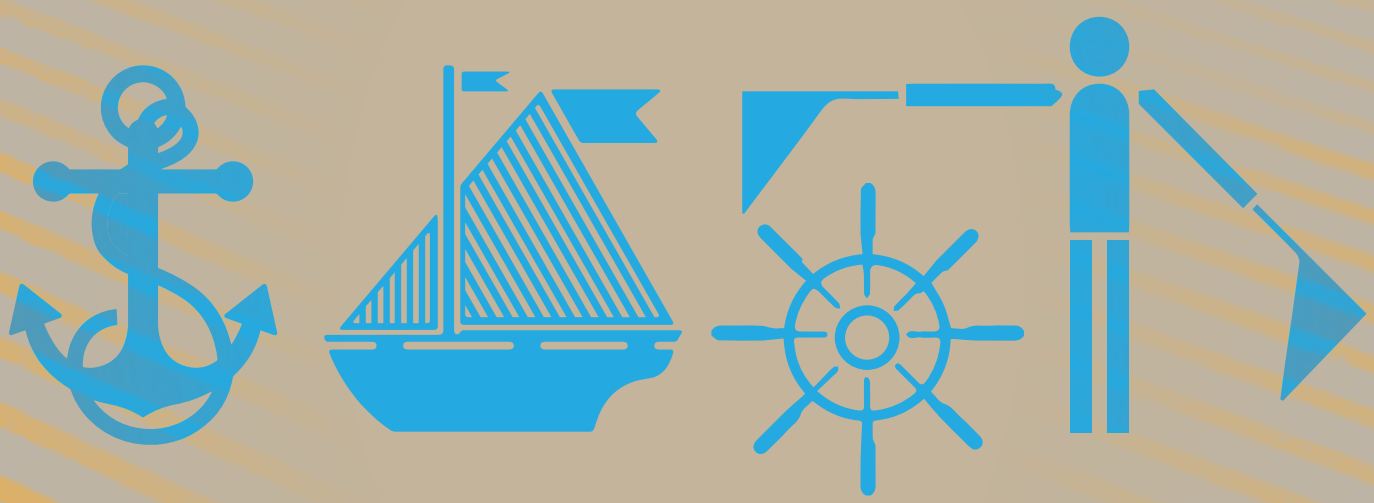

A Second Tour of Duty… Lessons Learned with Annalisa Jenkins

Annalisa Jenkins, new CEO of PlaqueTec, began her first tour of duty with the British Navy as a medical officer, but has since climbed the ranks of pharma to become a CEO and member of numerous boards. Here, she explains how the military gave her an excellent platform to launch a high-level career in pharma.

The battlefield and the boardroom are more similar than you might think

For me, everything started with the military. I was raised in a military family and when I was searching for financial support for my medical studies it seemed a good time to join the British Navy, which had just started to open its doors to women in the medical branch. I served as a medical officer in the British Navy and was part of the Minesweeper Squadron during the Gulf conflict. Ultimately, I rose to the rank of Surgeon Lieutenant Commander, but after my tour of duty I wanted to go back into research, so I trained in cardiovascular medicine. I worked for the National Heart and Lung Institute, where I investigated the role of cholesterol on atheromatous plaques, and in 1997 I was offered the opportunity to join the pharma industry as a cardiovascular medical advisor at Bristol-Myers Squib (BMS), which was an exciting opportunity; in the 1990s, BMS was one of the top cardiovascular companies in the world.

The military turned out to be an excellent precursor for a career as a woman in the pharma industry. Frankly speaking, the pharma industry is very male dominated, but the military is too, so I was used to it. Looking back, I learned many valuable lessons at a young age in the Navy that really helped me to build my business career; in particular when navigating the corporate levels of big pharma. In fact, I have previously given presentations about going from the battlefield to the boardroom. The military taught me the importance of leadership, respecting and valuing each employee equally, and courage and resilience under pressure, as well as being able to cope with a risky, innovative and global environment – all essential skills if you want to succeed in senior roles in the pharma industry.

Pharma does more than simply make medicine

The move to BMS was my opening to the pharma industry – and since then I have traveled all over the world. You might say I did my first global tour of duty in the military, and my second in the pharmaceutical industry! At BMS, I had the opportunity to live and work across 50 countries. I mostly worked in scientific medical affairs and cardiovascular drug development. It was a great step for my career to learn how to develop and register medicines – and seeing drugs that you have helped develop being given to patients is tremendously rewarding. As one example, in 2006 I was asked to chair BMS's steering committee for immune-oncology. We acquired Medrex and ultimately ended up with one of the first immuno-oncology programs in the clinic for patients living with melanoma. I will never forget the days when we started to unlock the phase II data and saw patients with stage II melanoma, who were destined to only live 6-12 months, living beyond 2-5 years – including some young women who went on to have children. Another project I am immensely proud of is the work I did at BMS with HIV. In the Navy, I treated sailors with HIV returning from tours of duty in Africa in the 1980s – essentially it was hospice care for those individuals. Fast forward twenty years later when I was at BMS and a single pill a day could help prevent death from HIV. And it wasn't just the medicine making that helped make a difference; I was also able to get involved in BMS's philanthropic effort in Africa; the Secure the Future Program aimed to prevent mother-to-child HIV transmission and take care of children who either had HIV or had been orphaned by it. The program started a long-term interest in philanthropy and healthcare in Africa – and a few years ago I established a UK charity called You Belong. It looks at new pathways of healthcare and community-based care for people living with mental

"It was a great step for my career to learn how to develop and register medicines – and seeing drugs that you have helped develop being given to patients is tremendously rewarding."

Annalisa's Top Five Career Tips

- Value everyone equally
- Be kind and gracious every day
- Be solutions oriented
- Be inquisitive
- Jump in and take risks
- Be a role model to others every hour of every day

health diseases in Uganda and Sub-Saharan Africa. I really want to be able to make a difference to healthcare – and I am fortunate to have that opportunity.

Embracing the unknown opens new doors

I stayed at BMS for about 14 years, progressing through different roles at the company. There will always be times in your career when you must embrace the unknown if you want to move up – and there will be many times when you need to figure out the way forward by yourself. At one point, I moved to Australia to become BMS's Executive Medical Director across Australia and New Zealand. It was exciting and seemed like a great step up, but nobody hands you a textbook when you land in a new country… Once reality set in, I had to quickly figure out how to create value, build teams and drive progress in a region that was very new to me. The role of a medical director is an important position in a pharma company, centered on market access, pricing and reimbursement. The UK's cost watchdog, NICE, had really just come to the fore in the late 1990s, but the philosophy of paying for medical value had long been established in Australia and Canada. When I landed in Australia, I had to quickly get to grips with how a single payer system allocates resources and conducts analyses in terms of cost effectiveness. It was a tough learning curve, but the rewards were enormous. I was able to take my experience to even more senior roles, such as when I returned to the US to get involved with running the global organization.

Following industry trends leads to new career opportunities

My time at BMS was a fantastic way to learn about the pharma industry – and I remain eternally grateful to all of my mentors who guided my development through the company. But I still had a love for research and wanted to get more involved in that area. The next stage of my career took me to Europe, to work for Merck Serono. I was tasked with completing the merger of Merck KGaA and Serono Development on a global basis, but predominantly to try and rationalize and refocus the pipeline. The company had over 2500 employees and a budget of $1.5 billion a year, but had been struggling to get drugs over the finish line, so I externalized research, doubled down on oncology and immunology, women's reproductive health, and multiple sclerosis. I helped spot a number of opportunities during my time at the company, including accelerating and investing in the PDL 1 Merkel cell tumor to make sure we could catch up with what was going on at Merck Sharp & Dohme, BMS and AstraZeneca. We also refiled cladribine in Europe and launched new phase II studies in osteoarthritis and Lupus. I'm pleased to say all of those programs have made progress since then – and the company has had two very significant drug approvals in the last 24 months.

I'd already been getting interested in biotech at BMS, but my interest intensified during my time at Merck. We did a number of deals with small biotechs; for example, we were the first company to sign a large deal with Beigene – which have gone on to become a multibillion dollar biotech company in Hong Kong. By the time I left Merck, I had decided that I wanted to get on the biotech bandwagon – it was a clear trend for the industry and also tied in with my general love for R&D. I was particularly interested in small companies, but I also wanted to take the next step in my business career. I started getting involved with boards – which is a really rewarding experience. It's fascinating to see lots of different technologies, and good for your career. I was especially interested in women on boards and diversity.

In time, I received a call from PRIME – they had a small company focusing on gene therapy for haemophilia – Dimension Therapeutics. There were around 10 employees and Fidelity was injecting some cash – and they asked if I was interested in becoming Dimension's CEO. I gave the classic female response of, "I've never been a CEO so I'm not sure I can do the job." They told me not to worry; it would be an R&D focused company so I could run it like the other R&D organizations I'd headed in the past. Famous last words! It was similar to when I stepped into Australia and realized that I had a lot to learn. I realized that we needed to expand our portfolio, and I had to learn what it meant to be a biotech CEO – fast! It went really well at first. In 12 months, we raised $146 million, and we took our lead program into the clinic with some of the best gene therapy manufacturing capability in the sector. Unfortunately – as is all too common in biotech – we had to end that program following an incident in a patient during phase I, which led us to terminate the trial. I then had to think about how to fund the rest of the portfolio as a public company. Ultimately, I decided to restructure the company, culminating in a sale to Ultragenyx – one of the

leading rare disease drug development companies out there. I think it was the best option for the company. I was one of the few people who left as a result of the restructuring, but most jobs were saved.

Diagnostics are essential to pharma's future

Rather than going back to big pharma, I wanted to stay with smaller, early-stage companies that could see a major inflection point – either from a scientific or business perspective – on the horizon. I also wanted to return to the UK.

I was still on numerous boards (and still am today), including the board of PlaqueTec – a UK diagnostics company. PlaqueTec is developing a novel approach that can assess an individual's risk for coronary artery disease, so I had a keen interest; it felt as though I was coming full circle in my career. Moreover, it was fascinating to see the field from a new diagnostic angle. I jumped at the chance when they asked if I wanted to be CEO last year. The company's lead technology is the PlaqueTec Liquid Biopsy System – and it's actually the first product approved in the European Union for collecting biomarkers directly associated with plaques within coronary arteries, as a means to assess and potentially resolve residual inflammatory risk. It's a UK invention that emanated from Papworth Hospital, one of the leading global cardiovascular institutions in the world. What makes the technology special is that it is the first that can enter an artery and sample the blood in the direct layer around the plaque, which is where a lot of the inflammatory biomarkers or cytokines reside.

In my research days, I looked at the concept of residual risk – why patients on statins, ace inhibitors or beta-blockers continue to be at very high risk of future acute coronary symptoms. And that made PlaqueTec all the more compelling. There seems to be an increasing interest in the role of inflammation, which can be assessed by paying more attention to some of the unique markers involved. Medical imaging has certainly improved – and it does offer a good static assessment with a focus on structure – but I'm more intrigued at the possibility of looking at dynamic biology in our coronary arteries. Cardiovascular disease is the world's biggest killer and we need new approaches to tackle it.

"Once again, I am leaping into the unknown – it is the first time that I've had a leadership role in a diagnostics company."

Once again, I am leaping into the unknown – it is the first time that I've had a leadership role in a diagnostics company; my previous experience with diagnostics was in pharma, working with companies to develop companion diagnostics to support our therapeutics. It can be difficult to build successful businesses in the diagnostic space because of issues around funding, but I believe there are a number of transformational and disruptive shifts going on in our industry – and one of them is the validation of new biomarkers. The FDA and EMA are also pursuing new pathways for the approval of diagnostics, recognizing that they will be crucial as we move towards personalizing medicine. I can't wait to see what the future holds!

Women can be successful in pharma

Working in pharma is a challenge – it's a risky environment and, as I mentioned earlier, male dominated, which can be difficult for some women. I am fortunate because of my background, but I'd also really like to help inspire more females to enter the industry – and upper business roles. I sit on a number of boards and I think board diversity is incredibly beneficial. Today, I am chair of the boards of Vium, Cocoon and Silence Therapeutics, and I sit on the boards of Cell Medica, Oncimmune, Ardelyx, iOx, Phesi and Thrombolytic Science International. I am also a committee member of the Science Board to the FDA and I am on the Advisory Panel of the Healthcare Businesswomen's Association. Is this all hard to balance? I like to think I have carefully selected my roles to ensure they all fit together like a jigsaw puzzle! They all contribute in some way to each other; for example, many of them involve the same investors. From a career point of view, it's never a bad thing to be well known by investors! The fact that all of my roles involve different platforms also allows me to share knowledge and experience across the board, whether that be from a regulatory, manufacturing or drug development point of view. And when you have lots of interesting roles, it also keeps your mind active and fresh.

Some people believe such a busy career comes at the expense of a personal life. It definitely is a 24/7 commitment, but I do have a life too! I go to the gym, love fashion and I have two wonderful children making their way professionally and a great supportive partner! I really hope that by successfully building, leading and chairing companies I can be a good role model. I want to prove that women can make it to senior management, survive and thrive, and have a fun life with family and friends – and that pharma is a great place for someone who understands the importance of strong value-based leadership.

Spirit of Columbus

Sitting Down With…
Tony van Bijleveld, BU Head of Softgels, Pharma Services Group, Thermo Fisher Scientific, the Netherlands.

You've worked in a number of different countries…

I've lived and worked in Colombia, Venezuela, Argentina, Brazil, Pakistan, Libya, Chile, Russia, France, and the Netherlands – where I'm based today. I've enjoyed experiencing different cultures (some perhaps more than others), but as my wife recently remarked, it's funny how I've never chosen a job because of the geography – the geography always came with the job!

How do you adapt to unfamiliar cultures?

I never expect a new country to adapt to me – that's probably the most important thing I've learned. You can't pick up Amsterdam or London and then move it to Brazil or Russia, so the important thing is to embrace the cultural differences and learn to enjoy them. I've worked in some places that can be pretty dangerous – taking a wrong turn in Sao Paulo could be a serious mistake. So you have to be savvy; bear in mind that as a foreigner you will be associated with wealth and that can make you a target. That being said, as long as you keep a low profile and do what the locals do, you should be fine.

I strongly believe you shouldn't judge a country until you've lived there and properly experienced it. I always say the best captains are the one's standing on the harbour, watching the ships dock. Many times my perception of a country has completely changed after having understood how the people think and what makes them tick.

Did you always want to work in pharma?

Not as such. After my chemistry degree, I joined AkzoNobel's management development program. They had a number of different divisions – chemicals, fibers, salt, and pharma – and I transitioned into the pharma side as part of the program. My first taste of the industry was selling a muscle relaxant drug in Colombia. Following that, the company asked if I would head up the sales team in Venezuela. At that time, Carlos Antonio Perez was president and the whole region was booming – it was great time to be in South America. I moved from Venezuela to Argentina after my boss asked me to expand the company's presence in the country, which I very much enjoyed – kick-starting a trend that would run through my career.

What do you look for when seeking out new opportunities?

If I look back at the jobs I've done over the years, they've all involved starting from scratch or rebuilding something that's fallen apart. It just so happens that the opportunities have arisen in a wide variety of countries across the developing world. I also love a challenge, so after a few years in a job I tend to get the itch to try something new – usually after I've put in the work to grow the organization and steady the ship. I've always been in leadership roles – either sales or general – driving a new organization to do bigger and better things.

What are some of the business challenges in the developing world?

Doing business in parts of the developing world can be very different to doing business in Western Europe and the US. Brazil, for example, thrives on a small number of distributors (local entrepreneurs) who, together with the Ministry of Health in Brazil, determine the landscape for pharmaceutical companies to operate in – and Russia is much the same. In Russia, there's no reimbursement system so everything is paid out of pocket, unless you're a war veteran or you have private insurance. The size of these countries (it can take eight hours to fly from Moscow to Vladivostok) also presents some additional challenges in terms of guaranteeing supply to patients, which makes solid distribution networks a must. In Brazil, the inaccessibility of the outer regions in the Amazon or in the swamps of the south present similar challenges. We can sometimes take for granted the vast transport networks that exist in the US and Europe. As a company, you have to accept that the way you conducted business at head office won't work in these places: there are different stakeholders, people, values and culture – and that means you have to adapt.

"I also love a challenge, so after a few years in a job I tend to get the itch to try something new."

Patheon was recently acquired by Thermo Fisher Scientific… How is the transition going?

The transition is going well! I think there are a lot of cultural similarities between the two companies and we both share the same goal of delivering a healthier, cleaner, safer world. And we're both dedicated to delivering the highest quality medicines to waiting patients. The other thing I see is that the integration is not disrupting the business – and that is essential. Usually what you see with acquisitions is a larger company buying up a smaller one to increase the size of their market share – but this is different because it's about adjacencies. At Patheon, we covered the entire drug supply value chain from early stage development through to drug manufacturing, except clinical trials packaging and distribution. Thermo Fisher Scientific has that clinical trials division; and, in pooling our capabilities, we're able to cover the entire supply chain from API through to the patient. It's a complementary relationship.

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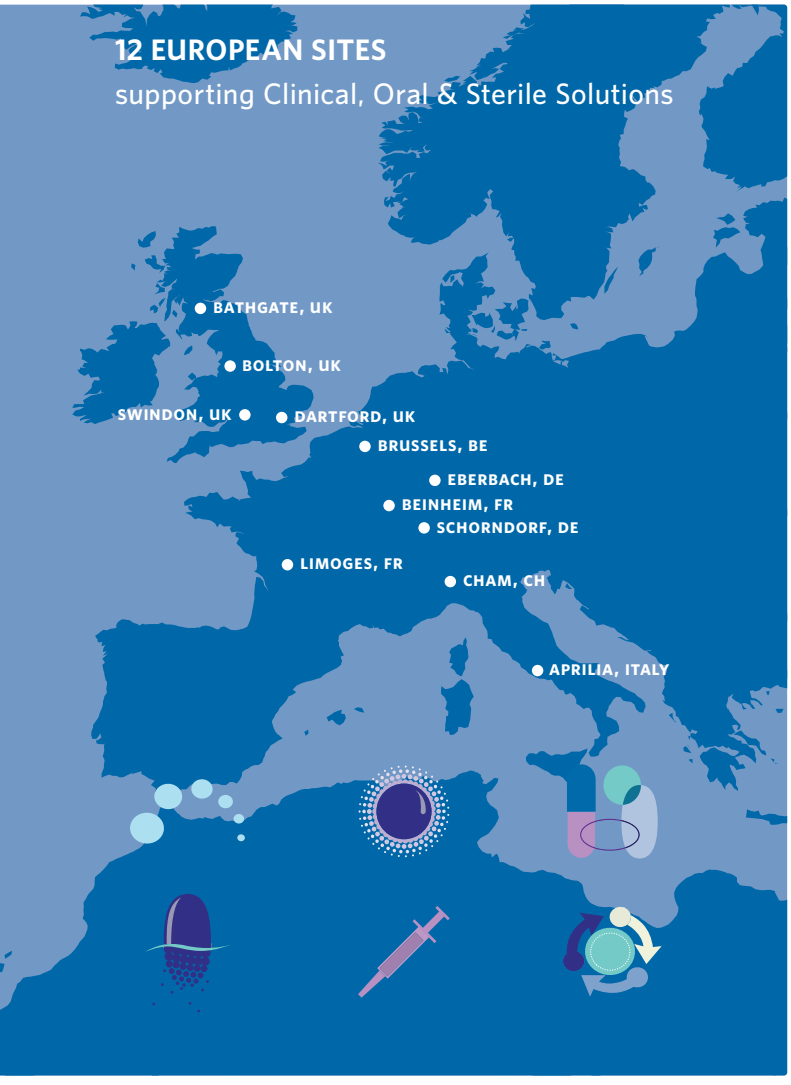

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