OCTOBER 2015 # 12

the Medicine Maker

Finding Fakes

Not all counterfeits are so easy to spot – or so harmless.

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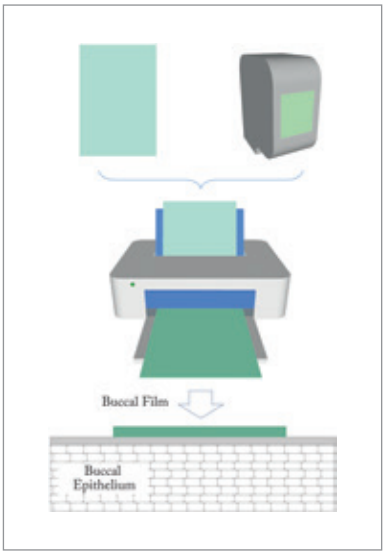

Making Medicines with Inkjet Technology

In our September issue, we explored the potential of 3D printing in drug development and the print theme continues online this month with two mini articles about inkjet printing. Ronan Daly from the University of Cambridge, UK, tells us about his research team's investigations and the six ways in which inkjet technology could benefit pharma manufacturers; and Javier Morales from the University of Chile tells us why he is investigating inkjet printing for the development of buccal films for the delivery of biological drugs.

Read the articles online at:
tmm.txp.to/0915/Daly
tmm.txp.to/0915/Morales

Fighting Fakes

On page 20, we examine the problems of fake medicines that are facing pharma manufacturers. Regulators in the US and Europe are hoping that serialization will help to better protect the supply chain, but other anticounterfeiting technologies are also under development. One innovation that has attracted a lot of media attention recently comes from a small company in Yorkshire, UK. Sofmat is working on a system that can make tiny indentations directly onto a tablet. The indentions can be made at different depths, allowing for billions of unique combinations. We interviewed Phil Harrison at Sofmat to find out more about the technology.

Read the interview online:
tmm.txp.to/0915/Harrison

the Medicine Maker Innovation Awards 2015

The Deadline for Innovation

Nominations for The Medicine Maker inaugural Innovation Awards close on October 30, 2015. The Awards will recognize the top equipment and technological innovations of 2015 that are aiding pharmaceutical manufacturers in their quest to deliver the most cutting-edge medicines. To nominate an innovation, complete the online form at http://tmm.txp.to/0715/innovation or email deputy editor Stephanie Sutton for more information at stephanie.sutton@texerepublishing.com. The winning technologies will be featured in the December issue of The Medicine Maker.

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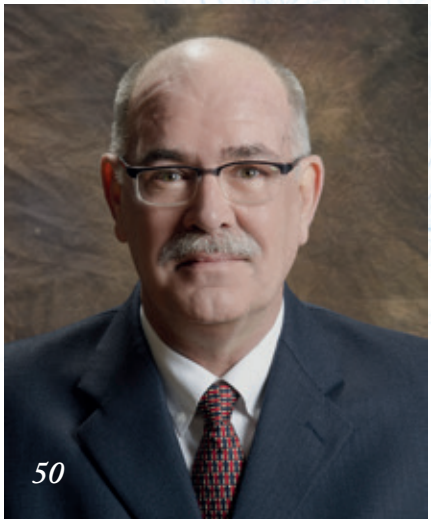

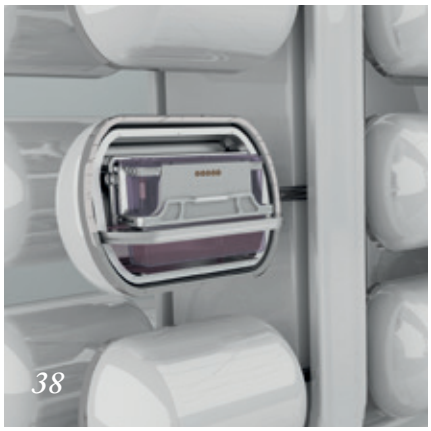

On The Cover

Can you spot the fake? Some counterfeit products are obvious, but others are far more difficult to identify.

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Hiding in Plain Sight

Mislabeled, substandard or falsified medicines are the perfect opportunity for criminals looking for low risks and high rewards.

It is well known in the pharma industry – and among law enforcers – that counterfeit drugs are a growing problem, but Western consumers remain blissfully unaware for the most part. Despite a few high profile cases – for example, fake Avastin given to US cancer patients – the main burden falls on developing countries. Frequent shortages of life-saving drugs force doctors to turn to unofficial 'gray market' sources, while illegal (and potentially dangerous) fakes are sold direct to consumers in markets or on the street. Just this week, the press reported that an INTERPOL swoop in South Africa had seized 150 tons of fake medicines, arrested 550 people and closed 20 pharmacies. The World Health Organization (WHO) estimates that 100,000 deaths a year in Africa are linked to the counterfeit drug trade. That said, counterfeit medicines are not always inactive or dangerous – some are simply generics, mislabeled as brand-name drugs. Critics have argued that pursuing these 'harmless' counterfeits takes resources away from combating the real danger of falsified medicine (1). But it is hard to draw a clear distinction between the two – and is it unlikely that those already engaged in an illegal activity will feel compelled to stick to the stringent quality and safety standards of licensed drug manufacturers.

It's perhaps no surprise that enterprising criminal gangs have turned to counterfeit or falsified medicines – it is big business. And to make the activity even more attractive, penalties for breaking the law are limited. Why take on the risks of dealing in heroin, when fake medicines bring in more money with a much lower chance of jail time?

Currently, there is no large-scale universal, coordinated effort towards stamping out counterfeit drugs, but new serialization initiatives and tracking technologies make the supply chain more secure, and verification services make it easier for consumers to play their part (see page 20). Drug makers have also welcomed the Council of Europe's Medicrime Convention (2).

But perhaps the ultimate solution is hiding in plain sight, just like the counterfeits. Faced with serious illness, most of us would probably choose counterfeit drugs over no medicine at all. And while that choice remains, it will be exploited. Increasing access to drugs in the developing world, by preventing drug shortages and cutting costs, is the only way to reduce demand for fake medicines in the long term.

Charlotte Barker
Editor

Reference

1. *www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html*
2. *www.coe.int/t/DGHL/StandardSetting/MediCrime*

C Contributors:

James Ritchie

James says that he wants to live in a world where the word "cancer" no longer holds any fear, and he has dedicated his professional career to achieving this aim, having been involved in cancer drug discovery and development since 2001. His experience has spanned the entire continuum from early discovery through to pivotal clinical development and he is currently the drug development scientist at Cancer Research UK's Centre for Drug Development. The remit of the CDD is the translation and early clinical development of new anti-cancer agents covering everything from small molecules to immune and cellular based therapies.

On page 16, James explains why attrition is the biggest challenge facing cancer drug development.

Kamal Rashid

Kamal Rashid is the director of the Biomanufacturing Education and Training Center at Worcester Polytechnic Institute, and a research professor in WPI's Biology & Biotechnology Department. He has delivered bioprocessing training programs onsite in numerous countries, including, China, Dominican Republic, Egypt, Indonesia, Iraq, Korea, Malaysia, Philippines, Puerto Rico, Vietnam, Thailand, Taiwan, and Singapore. From 1984 to 2000, he was on the faculty at Pennsylvania State University where he was instrumental in the establishment of Penn State's Biotechnology Institute and Bioprocessing Resource Center programs. Kamal also directed the nationally recognized Summer Symposium in Molecular Biology at Penn State for 10 years.

Kamal discusses how single-use systems can aid biomanufacturing on page 34.

Mark Davison

26 years ago, Mark Davison started his pharma career by donning a white coat and becoming a biochemist at GlaxoSmithKline. Then he donned a suit and tie in business development (at several CROs, two biotechs and two security vendors). And he also discovered lycra – as a keen cyclist and fundraiser for JDRF, a diabetes charity. For the past nine years, he has been helping industry to fight counterfeiting, diversion and fraud. He is expanding the Blue Sphere Health team with consultancy activities based in the US and elsewhere. Mark's work takes him to developing countries around the world and he cautions against complacency. He says, "Fake drugs aren't just an economic nuisance for poor nations, they are a lethal scourge. Millions of children aren't here today because their medicines didn't work. If we can do even a tiny amount to change that then it is job worth doing."

Fighting fake medicines is no easy task but Mark argues that the battle can be won on page 20.

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Upfront

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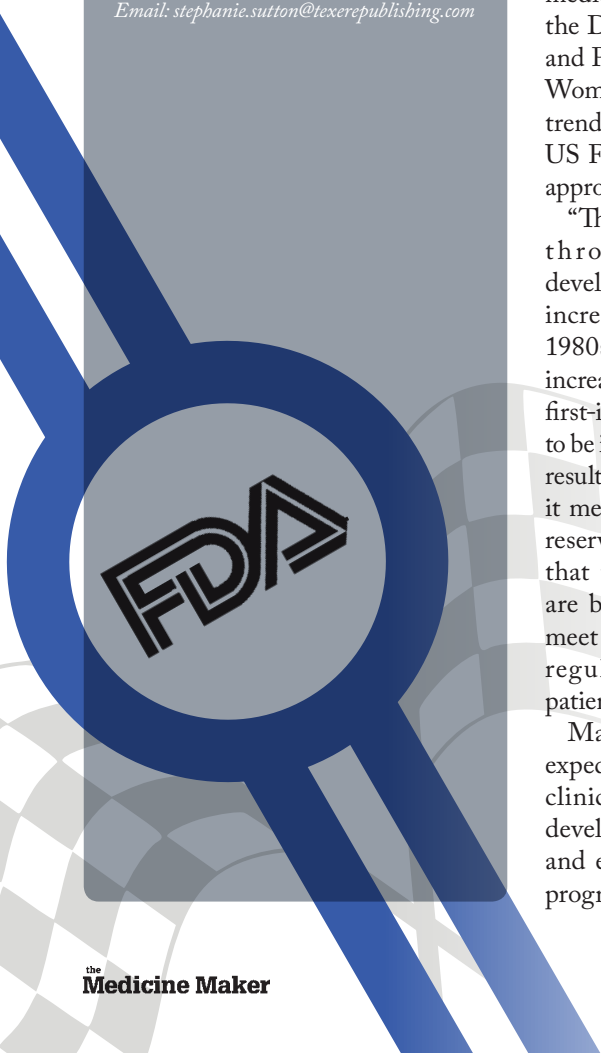

Too Fast and Furious?

Expedited regulatory approvals bring medicines to market faster – but are they the right drugs?

Several drugs regulators across the world have developed specialized administrative pathways designed to accelerate the development and review of innovative new drugs for important unmet medical needs. But is speeding up the approval process always a good thing? Some researchers are not entirely convinced of the benefits. A team led by Aaron Kesselheim, an associate professor of medicine at Harvard Medical School in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham & Women's Hospital, has investigated the trends in the growing utilization of the US FDA's expedited development and approval programs (1).

"The number of new drugs passing through the FDA's expedited development and review programs has increased significantly since the late 1980s, but our study showed that this increase is actually being driven by non-first-in-class drugs, which are less likely to be innovative," says Kesselheim. "These results are potentially concerning because it means that programs intended to be reserved for the most important drugs that treat truly unmet medical needs are being applied to drugs that don't meet these criteria, potentially wasting regulatory resources and exposing patients to increased risk."

Many drugs that benefit from the expedited programs do provide notable clinical advances — but with faster development and review come safety and effectiveness concerns, since such programs usually involve less rigorous clinical testing. With speed comes the risk that a drug's predicted effectiveness or safety profile will be different to what is expected when the therapy is subject to post-approval studies. The reasoning behind fast-track programs is that truly innovative therapies may be worth the slightly increased risk.

"Expedited development and review programs allow drugs to be widely used based on limited data that would otherwise not qualify for drug approval. This is fine in limited circumstances of evolving public health crises — indeed, many of these programs were designed in the context of the early days of the HIV epidemic — but it appears that they're being applied more broadly in situations in which they may not be deserved," says Kesselheim.

Lengthy drug development times due to trials being performed to earn regulatory approval represent a sticking point for the pharma industry and patients alike, so it's no surprise that expedited review pathways and policies are in high demand. As an example, in 2012 US legislators created the 'Breakthrough Therapy' designation, which aims to focus FDA resources and attention on the development of potentially game-changing medicines. The designation was originally intended to apply to only a handful of drugs, but in the first two years the FDA received 250 applications — 68 of which were granted. At least twelve have since been approved; four of which are treatments for chronic lymphocytic leukemia (CLL). However, despite CLL being a very serious condition, Kesselheim questions whether a single disease condition really can be the target of four "true" breakthroughs in such a short time. *SS*

Reference

1. *A.S. Kesselheim et al., "Trends in utilization of FDA expedited drug development and approval programs, 1987–2014: cohort study," BMJ, 351 (2015).*

Digging for Drugs

Genome mining hunts for bacteria micro-chemists that could help develop innovative drugs

Natural products are known to be a promising source of new drugs – particularly antibiotics and antimalarials – but hunting through almost countless possibilities is resource intensive, so many pharma companies long since abandoned the search. Now, University of Illinois chemistry professor William Metcalf and microbiology professor Wilfred van der Donk have used genome mining to rapidly screen thousands of strains of bacteria for a specific gene that they believe is the equivalent of striking gold (1). And, in the process, they've discovered several new compounds with potential, including a pair of antibiotics and an antimalarial.

It's fairly common to use genome mining to find new drugs, but Metcalf and van der Donk have been very specific in their search. "Bacteria are like bad-tempered micro-chemists; they synthesize toxic compounds in tiny amounts to use as a warning sign for others to stay away. One compound produced by actinomycyte bacteria, a phosphonic acid, was found to inhibit cell wall biosynthesis. This is a very good target for an antibiotic because it targets a metabolic pathway that is present in bacteria but absent in humans," says Metcalf. But because bacteria make phosphonic acids in low volumes, they had likely been missed in previous drug-screening programs.

Metcalf knew that the PepM gene was responsible for phosphonic acid biosynthesis – so finding the gene in different strains of bacteria could lead to the discovery of new phosphonic acids. To increase the chances of finding viable strains, Metcalf needed an army of bacteria – and fortunately there was one nearby: "Our university is near the US Department of Agricultural research, who allowed us to use their collection of about 10,000 strains (the largest publically accessible collection of actinobacteria in the US). We screened this collection for the presence of the PepM gene, and we identified 278 PepM-containing strains."

These 278 strains were each responsible for synthesizing about 60 – 80 different potential drug molecules. About seven strains synthesized molecules in sufficient amounts to be easily purified, resulting in the discovery of 13 new natural products so far – including two antibiotics and one antimalarial. One of the compounds identified is potent against three different types of common bacteria: Salmonella typhimurium, Escherichia coli and Staphylococcus aureus.

Metcalf says, "We've focused on antibiotics, but 30-50 percent of all drugs are natural products (many from bacteria) and our approach will apply to all of these molecules too. We could use this approach for anticancer drugs, or even apply it to other fields to develop new herbicides and pesticides. I'm hopeful we could discover every useful natural product out there!" *VB*

Reference

1. *K-S Ju et al., "Discovery of phosphonic acid natural products by mining the genomes of 10,000 actinomycetes," PNAS, 112, 39, 12175–12180 (2015).*

The Medicine Monitor

A digital pill submitted for regulatory approval tells caregivers if you've taken your medicine

A pill incorporating an ingestible sensor – designed to measure medication adherence – has been filed for regulatory approval with the FDA (1). The pill is a new version of the antipsychotic drug Abilify (aripiprazole) and stems from a partnership between the Japanese company Otsuka Pharmaceutical and Proteus Digital Health, a US-based health technology company. The goal is to use the data from the sensor to not only check that the patient has taken their medication, but to get an inside view into the patient's physiological response; the sensor can also measure metrics such as heart rate, body position and activity.

The sensor is embedded within the pill and upon reaching the stomach begins to be digested by the gastric juices, which powers the sensor by creating a small voltage. The electrical signal is then detected by a skin patch that marks the precise time that the ingestible sensor was taken, relaying the information to an application on a mobile phone or other Bluetooth-enabled device. Patients can monitor the data themselves or give consent for caregivers and clinicians to access the information.

Proteus has been collaborating with the FDA since 2008 to determine a regulatory pathway for the ingestible sensor technology; the US agency approved the device's technology platform in 2012, but the partnership with Otsuka is the first time that the sensor has been manufactured as a complete medication.

Abilify is a treatment for patients with mental health disorders, such as schizophrenia, where it is particularly important to track and report adherence behavior – and given that Otsuka's patent for the drug has just expired (and the fact that the FDA has recently approved generic versions), a digital makeover could be just what the doctor ordered. If approved, the digital drug is likely to be more costly than its generic counterpart, so the payer reaction remains to be seen. But the pharma industry certainly seems keen; there have been reports about a partnership between Proteus and Novartis, and other drug makers have also expressed interest (2) – after all, the ingestible sensor technology could potentially benefit other patients who may forget to take medication, such as those suffering from dementia. Watch this digital space. *VB*

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1. *Proteus Digital Health, "US FDA Accepts First Digital Medicine New Drug Application for Otsuka and Proteus Digital Health," (September 2015). www.proteus.com*
2. *The Financial Times, "US Regulators Accept 'Chip in a Pill' Application (September, 2015). www.ft.com*

Benign by Design

Making drugs greener for our environment and water supply

A wide range of chemicals end up in our water systems, threatening both the environment and our drinking water. And pharmaceuticals are certainly on the hit list. Strategies to prevent APIs entering our water supplies can be expensive but they are not always effective. To that end, Klaus Kümmerer and his team at Leuphana University in Germany are attempting to give medicines a green makeover by redesigning existing pharmaceuticals to be biodegradable (1). Here, Kümmerer tells us more about his 'benign-by-design' strategy.

How big is the problem?

Environmentally non-degradable pharmaceuticals can stay in the environment for a long time. In all countries where measurements have been performed, pharmaceuticals have been detected and it has been shown that at least some of them have effects on wildlife at low concentrations. It's difficult to address the problem because there are so many compounds and environmental processes that often transform the parent compounds into other unknown products, preventing reliable risk assessment. I decided to shift to a more preventative approach – biodegradable drugs.

How do you redesign drugs to be biodegradable?

We use a combination of experimental and computational methods to make small molecular changes to the drug's structure to allow it to be broken down more easily and safely in the environment, crucially while still retaining the therapeutic activity of the parent. Our study focused on the transformation and degradation of ß-blocker class APIs. ß-blocker Propranolol is a frequently used, nonbiodegradable, and highly persistent pharmaceutical. We used non-targeted synthesis using light – photolysis – to generate safer, more innocuous derivatives for the environment. In fact, we identified the products of photolysis and tested them for biodegradability in the environment. We assessed the drug-like properties of the selected biodegradable drugs and ruled out the mutagenic ones.

What were the main challenges?

The majority of pharmaceuticals have been very well researched; any change to the molecule that disrupts the delicate balance of stability and potency could lead you down a dead end. Trying to redesign a molecule is considered somewhat crazy! At least, that's the feedback we get from experts in pharmaceutical industries. But it is possible; chemistry is about reactivity under certain conditions – and you can experiment with the options.

Are any biodegradable drugs already on the market?

Yes – but many of those few do not have a targeted design. And I think that most pharma companies aren't focusing on biodegradable drugs. Nevertheless, those that do exist demonstrate the feasibility of our approach. The new molecules are completely mineralized to innocuous inorganic compounds (e.g., water, carbon dioxide and salts), avoiding the formation of transformation products. There is no need to monitor the byproducts, carry out expensive toxicity studies for them or to follow up with further water treatment – this is at the core of our approach.

Can any drug be made to be biodegradable?

There are many methods that can modify the structures of pharmaceuticals to make them biodegradable so, in principle, there is no limit to how many drugs our approach could be applied to – particularly as we've demonstrated that it works for complex molecules. We are currently looking at redesigning antibiotics and even applying our strategy to improve the mineralization of chemicals such as laundry detergents.

Reference

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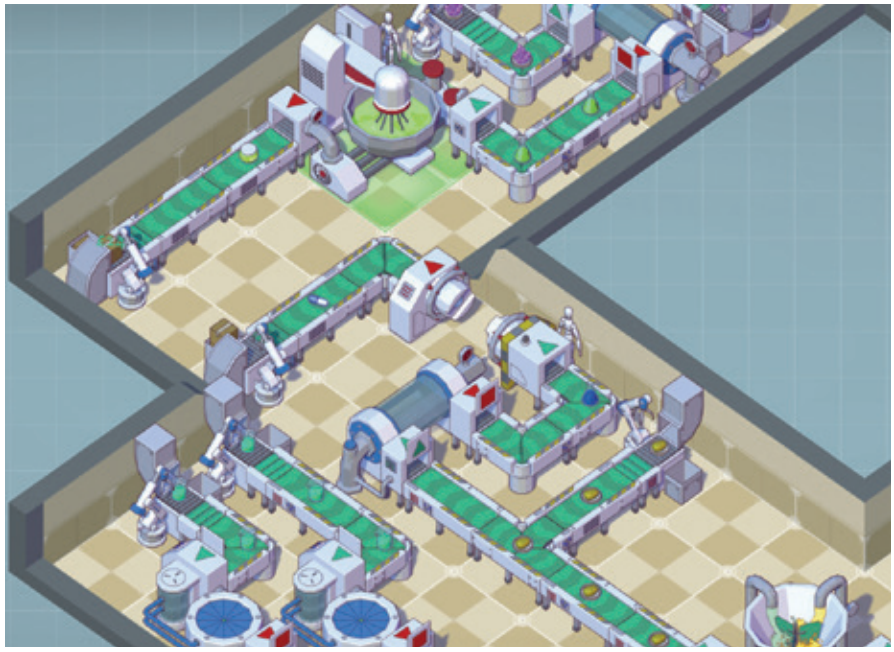

Big Pharma Gets Played

As the industry makes its video game debut, the big question is: will you prioritize patients over profit? Here's our big review.

In October 2014, we reported on the development of Big Pharma, a video game that allows you to take the reins of your own pharmaceutical company (see tas.txp.to/1014/biggame). The aim of the game is simple: rid the world of disease and make a successful business in the process! But is being altruistic the best business plan? Released recently on the PC (an iPad version is being considered), the game is as much about solving puzzles as it is about running a business and making profits – not unlike the real thing.

On launch, there's a detailed tutorial to get you up to speed on how to play the game. In brief, you have a factory floor space where you must install production lines that will manufacture your medicines. The basic gameplay mechanics are not difficult, although at first you might be a little disorientated as you figure out how to lay your conveyor belts effectively and place equipment. There's a lot of freedom in what kind of company you create. For example, some of the medicines come with horrible side effects that you can remove, but doing so may cut into your profits. To make your drug, you must import the necessary ingredient into your factory. Each ingredient has a starting number assigned to it and to activate a particular therapeutic effect, you need to increase or decrease the number by running the ingredient through various pieces of equipment. Once you're reached the right therapeutic number – voila! – your drug is ready to hit the market, and you have the privilege of naming it.

Only basic equipment and a few ingredients are available at first, but you can unlock more as you progress through the game, which allows you to make more complex medicines. You can also upgrade current medicines and remove unwanted side effects, which is where the puzzle element comes in. The main challenge is making best use of your (limited) factory floor space; your production lines can get very long as you try to juggle the numbers and effects needed to make the desired medicine. And it's easy to make a mistake and create a "sugar pill" instead. In addition, your ingredients can only enter your factory through specific entry portals that appear on some of the walls. The production line also needs to finish at a portal before you can export your drug. It sounds simple enough, but when you're building a complex line it always seems to end nowhere near a portal. To be successful, you really need to think and plan ahead. Once again, much like the real deal.

This isn't a game you can pick up and instantly become an expert, and it's probably a bit too complicated for younger children. But it is fun and addictive, particularly if you enjoy puzzles and strategizing. You'll certainly need to have some patience because you're likely to run out of money and fail on your first few attempts... Sound familiar?

The game's creator, Tim Wicksteed, isn't looking to demonize the industry – he merely wanted to make a novel game and was fascinated by the pharma industry because of the moral intricacies of balancing people's health with making a profit. That said, there is certainly an element of dark humor to the game; its website keeps track of how players are doing by clocking up the total amount of revenue generated, the number of seizures averted, and the number of comas caused. The Medicine Maker team hasn't contributed much to revenues, but is pleased to announce that it is has helped to prevent several seizures. Let us know how you get on with your own company – in the game or the real world. *SS*

All Change at the Top

The EMA fights to reinstate its former executive director – and the FDA's new leader is still unconfirmed

The European Medicines Agency (EMA) has nominated Guido Rasi (pictured) as its new executive director and expects him to be appointed following a hearing at the European Parliament. Actually, it's not Rasi's first time in the executive director's seat; he was appointed to the role in 2011 and then forced to step down in November 2014 after a European Union Civil Service Tribunal ruled that he had been improperly selected in 2011. The EMA, which says the decision related to the formalities of the recruiting procedure and was not a reflection of Rasi's abilities, has been fighting to get him back ever since. The agency is trying to implement a new controversial transparency policy for clinical trials, so it's not been a good time to be without a leader.

In a statement, the EMA described the nomination as being the "result of a robust recruitment process" (1) – presumably with the hope of avoiding further tribunals. The original tribunal was initiated by Emil Hristov, who applied for the executive director post but failed to make the shortlist. He believed that there was a conflict of interest during the recruiting process as two members of the EMA's management board were on the European Commission committee that drew up the shortlist.

Meanwhile, the US is still looking for the right candidate to head up the FDA. Margaret Hamburg stepped down from the role of FDA commissioner earlier this year and since then Stephen Ostroff has taken on the role of acting commissioner. In September, President Obama nominated Robert Califf to take the FDA's reins. Califf is a cardiologist and currently the deputy commissioner for medical products and tobacco. At the time of the nomination, no one expected significant opposition to the move. But since then, concerns have been raised over Califf potentially being too close to the industry; Califf has worked with pharma companies both as a consultant and through his research, whereas most FDA commissioners come from a public health background. Nevertheless, the Department of Health and Human Services has stated that Califf has passed a screening process for conflicts of interest. *SS*

Reference

1. *EMA, "European Medicines Agency's Management Board Nominates Guido Rasi as Executive Director," (October, 2015). www.ema. europa.eu*

In My View

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

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

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Cancer Complexity

Clinical development is outmoded; we are witnessing serious attrition in cancer R&D. Perhaps it's time to live and die by the mantra: "no biomarker, no trial".

By James Ritchie, drug development scientist at the Cancer Research UK Centre for Drug Development.

What is the biggest challenge that we face in our mission to bring new, effective medicines to patients? In my view, it's attrition. In 2004, Kola and Landis reported that only one in 20 new chemical entities (NCEs) being developed for cancer make it to the market (1), with other indications faring somewhat better. A more recent analysis from 2014 suggests that this picture hasn't really changed and, if anything, it has become worse (2). The success rate is frankly abysmal. So, what can we do to reduce attrition rates? What are the challenges and how do we overcome them? There is no quick, easy fix. We need a major transformation in the way we develop drugs, spanning preclinical development, how clinical trials are designed, and the way in which drugs are currently approved. It isn't possible to cover every aspect here, but I'll give you a few ideas to get you thinking.

Developing new treatments for cancer can be potentially more challenging than for other indications for numerous reasons. There are more than 200 different cancer types, characterized by inherent heterogeneity both between and within patients. Cancers also rapidly develop drug resistance and can evolve to evade natural immune surveillance. Given such complexity, the high rate of attrition perhaps isn't surprising. Lack of clinical efficacy is the key factor leading to attrition.

To address this, I believe that we need to push vital decision-making points back along the clinical development pathway and base them on a thorough understanding of tumor biology and pharmacology of the experimental agent. Incorporation of robust pharmacodynamic biomarkers to demonstrate target modulation in cancer and/or molecular sub-group specific expansion cohorts need to be applied in the Phase I setting. Only then can we be confident that the agent being tested is doing "what it says on the tin". This strategy should increase the probability of downstream success and rule out agents that have no signs of biological activity or clinical benefit. In other words, we'd be living by the mantra, "no biomarker, no trial".

The development of predictive biomarkers to enable patient stratification can help tackle the inherent heterogeneity of cancer. Initiatives such as the Genomics of Drug Sensitivity in Cancer (www.cancerrxgene.org) are helping to make this a real possibility. Adaptive early phase clinical trial designs that incorporate pre-planned analysis based on biomarker defined sub-groups, such as that of the TOPARP-A study, could also be beneficial (3). Rather worryingly (but perhaps not surprising), an analysis of discontinued oncology drugs from 2013 revealed that none of the agents terminated during pivotal trials incorporated molecular stratification markers (4). The "one size fits all" approach, which served us well during the chemotherapy era, is an outmoded clinical development strategy.

Effective drug combinations can tackle

resistance by increasing the efficacy of cancer drugs, but individual companies usually only have the resources to explore a fraction of the possible drug combinations that have a valid scientific rationale. If we work together, through cross-company and academic–commercial collaborations, then we will be able to accomplish so much more. Indeed, spurred on by the promise of the new generation of immune checkpoint inhibitors, pharma companies are teaming up with other organizations to further optimize these agents with other therapies from either the same or different classes. Cancer Research UK (CRUK) together with the UK Experimental Cancer Medicine Centres are also leading the combination charge, with an initiative that aims to accelerate and broaden the number of rationale combinations being tested in the clinic by bringing together academic experts and cross-company collaborations (www.ecmcnetwork.org.uk/ca).

To tackle attrition head on, we need to raise the bar. Critical decisions need to be made earlier in the drug development process, which is a key aim at the CRUK Centre for Drug Development, and we need drug development "ecosystems" involving industry, academia and the regulatory authorities. One glimmer of hope is the fact that 2014 was a record year for drug approvals by the FDA – only time will tell, but perhaps some of the necessary seeds of change to overcome attrition have already been sown.

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Painting a Better Picture of Quality

When seeking to measure quality across an organization, what is the right approach? We propose to use the synergies of Quality and Operational Excellence programs – and we are sure you will see the benefits.

By Christian Mänder and Thomas Friedli, both researchers at the University of St. Gallen, Switzerland.

The FDA's approach to quality oversight has evolved in recent years, particularly with the establishment of the new Office of Pharmaceutical Quality (OPQ). OPQ exists within the Center for Drug Evaluations and Research (CDER) as a single unit dedicated to product quality with a simple mission: "to assure that quality medicines are available for the American public". In 2013, the FDA announced in the publication of the FDA Administration Safety and Innovation Act (FDASIA) that they intended to examine the use of selected quality metrics (the exact metrics will be decided upon and collected during an FDA quality metrics program) to support their risk-based inspection program. And more recently, the FDA published its draft guidance for industry related to the quality metrics request (1).

But to paint the entire picture of a site and an organization in terms of quality performance, we must go beyond a limited set of metrics that relate to quality only in a narrow sense. In our view, a more holistic approach to quality must be integrated both into the operation of the manufacturing facility and its underlying quality culture. Fortunately, the tools already exist. Indeed, over the past 10 to 15 years, the pharmaceutical industry has become increasingly aware of formal Operational Excellence (OPEX) programs, where the initial driving forces behind implementation were improvements in operational efficiency – and the associated potential cost savings. But recent developments in more mature OPEX programs have shown that there are other considerable benefits, such as the reduction of variation. The stability of quality management systems of companies with a more mature OPEX program is significantly higher

"OPEX programs help companies to increase the equipment and process stability."

compared to their competitors. OPEX programs help companies to increase their equipment and process stability. Notably, commensurate improvements in quality have also been gained using OPEX programs through measurable stabilization of the organizational systems responsible for equipment and facilities, quality management, inventory control and management oversight.

Based on our experience and in-depth research of the St. Gallen OPEX research team that correlated quality outcomes across the supply chain with available OPEX performance data at a given site (2), we developed a framework to assess:

- Supplier reliability: the service level supplier and the complaint rate related to supply issues.
- Production stability: production related indicators, such as overall equipment effectiveness, unplanned maintenance and right first time, in combination with quality-related measures like rejected batches, scrap rates and deviations per batch, including their closure times.
- Delivery quality: production planning accuracy using the forecast accuracy, the production schedule accuracy and the service level delivery.
- Customer quality: the complaint rate from the customer.
- Quality culture: building the foundation for quality by addressing more than 80 indicators, as well as cultural aspects related to quality, such as management commitment, company culture, preventive activities and continuous improvement.

The framework allows you to examine your whole supply chain with quality-focused eyes, creating a reliable image of robust quality across the organization and its operations. We've been able to prove the potential benefits of OPEX by analyzing 300 data sets from pharmaceutical production sites using an algorithm that combines quality effectiveness and quality efficiency in relation to the OPEX performance of a production site. Sites with a high quality effectiveness and efficiency show a significant higher overall OPEX performance than others. For comparison please refer to our data, at tmm.txp.to/0915/quality.

If you'd like to know more about the approach, you are more than welcome to analyze your own data at http://opexbenchmarking.com. We encourage more companies to overcome the divide of quality and excellence by reaping the benefits of both elements!

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Embracing Rapid Microbiology

Microbiological approaches are faster and more advanced than ever before – so why on earth isn't the pharma industry using them?

By Tim Sandle, head of Microbiology at Bio Products Laboratory Limited, UK.

For the majority of the last one hundred years, microbiology laboratory methods have remained relatively unchanged, with tests being based on culture media and the foundations that were laid down by the pioneers of microbiology: Pasteur and Koch. It's only relatively recently that the fundamental basis of testing has begun to change; as a result, rapid and alternative microbiological methods have emerged.

Unfortunately, uptake in the pharma and healthcare industries has been slow. Companies in the field all appear to be waiting for someone else to make the first move, but the time to move is now. The cost of the technology, validation requirements and time required for implementation may be a hindrance, but one obstacle that has been removed is regulation. Indeed, regulatory bodies like the UK MHRA and the US FDA have expressed a keen desire for the industry to adopt more accurate microbiology systems. New systems are certainly more accurate – and faster (traditional cultural methods can take weeks, rapid systems typically take hours or only a few days) – as well as providing other benefits.

Rapid microbiology methods also overcome the difficulty (and risk) of 'viable but non-culturable' microorganisms. Many bacteria, despite maintaining metabolic activity, are non-culturable due to their physiology, fastidiousness or mechanisms for adaptation to the environment. Such types of microorganisms could exist in a medicinal product but they are not detectable using established culture-based test methods. On the other hand, several rapid methods are not reliant upon growth media and they can detect almost all of the organisms present within a product.

Rapid methods are not only suitable for finished products; they can also be used for screening the raw materials and water that go into making medicinal products; for testing intermediate samples of products as they are being manufactured; and for assessments of environmental monitoring during the manufacturing process. Tantalizingly, we can now have complete confidence in microbiological quality throughout the whole pharmaceutical operation.

Rapid microbiological method technologies aim to provide more sensitive, accurate, precise and reproducible test results when compared with conventional, growth-based methods – and they are simpler and quicker to run. In essence, microbiologists get better results with higher throughput and lower error – all of which should lead to increased medicine safety for patients.

Rapid microbiological methods can be divided into four categories:

1. Qualitative tests for the presence or absence of microorganisms. For example, using DNA probes that screen for the presence of E. Coli in water.
2. Quantitative tests for enumeration of microorganisms. Such methods include those that directly label individual cells with viability stains or fluorescent markers or optical spectroscopy methods that utilize light scattering and other optical techniques to detect, enumerate and identify microorganisms.
3. Quantitative tests for potency or toxicity. An example here is turbidimetric methods for bacterial endotoxin.
4. Identification tests. Methods include looking at regions of microbial DNA and taking genetic fingerprints, which can then be compared to library profiles to identify a microorganism.

Fortunately, the costs of rapid methods are falling as the technologies mature – and as competition between vendors intensifies, which will no doubt make them more attractive to those dragging their heels in pharma industry. Are you really satisfied with ancient methods when regulators and common sense both point to faster and more accurate results? Shouldn't quality and compliance – and the resultant safety of medicines – be a top priority?

When Fakes Attack!

Counterfeit medicines are on the rise. Regulators are driving serialization and tamper-evident packaging initiatives, but is the pharma industry fully primed to defend against fraud and push back the forgeries?

By Mark Davison

Perhaps 10 or 15 years ago, counterfeit medicines were mainly limited to lifestyle drugs, such as Viagra, which people purchased from rather dubious sources on the Internet without a prescription. (No doubt some of you will be thinking, "you get what you deserve (or pay for)," and I think most people actually do understand that prescription medicines should be obtained through legitimate channels and prescribed under the supervision of a doctor.) Sadly today, counterfeit medicines can be found anywhere – including the legitimate supply chain. All classes of drugs – at all price levels – can be affected; we even see counterfeits of extremely cheap drugs that only cost $1 to begin with... The bottom line is that wherever there is any profit to be made, counterfeiters are waiting. It's no longer a problem that only plagues Internet sales and people who should perhaps know better. In general, most of us don't choose where we get our prescription drugs from; rather there is an element of assumption that the medicines we receive from our pharmacies and healthcare professionals will be authentic.

In Europe and North America, I do not believe that counterfeits are flooding the market and reaching patients in any great numbers – those of us who live in these regions are fortunate. But even here, we do see occasional cases that generate a lot of media attention; fortunately, suspect products are usually identified and removed pretty quickly. Invariably, such instances occur when somebody tries to cut corners or attempts to make some extra money on the side (saving or gaining money are big temptations). For example, there have been cases in the US where dispensing doctors have bought drugs on the gray market for a discount, without asking too many questions about the origin. On many occasions, these drugs are not actually counterfeits, but have been diverted from other countries (which is another problem outside the scope of this article)...

"The pharma industry is not standing idly by as counterfeiters run away with their brands. The buzz word is 'traceability'."

If we look at Asia, Africa and some parts of Latin America, there is a much larger problem with counterfeit medicines – and it is very much a daily danger that goes under reported. In some cases, the supply chain itself is controlled by criminals looking to profit from fake medicines – apparently, you can make more money selling counterfeit medication than you can selling heroin. But the penalties if you get caught are tiny in comparison. When viewed from the perspective of pure criminal business evolution, it's clear why the problem is getting worse. In addition, counterfeiters are moving from shanty back street workshops to a more industrial and organized scale. When counterfeits are seized, there are often multiple tonnes of products, which, superficially, appear to be well made with excellent packaging. Clearly, the products themselves will not be up to standard. And though some counterfeits do contain active ingredients, the dosage level will vary considerably – and some of the other ingredients can be downright dangerous.

The ace of trace

The pharma industry is not standing idly by as counterfeiters run away with their brands. The buzz word is 'traceability', and in the last few years drug makers and regulators have been working hard to make the whole supply chain more traceable, so that we know where the drugs were made, whose hands they passed through, and when they were dispensed. In particular, we're seeing this in Europe and the US, as well as in China and some Latin American countries. Eventually, I think most of the world's markets will adopt similar regulations. However, a word of caution: traceability is not a panacea – the 'bad guys' can still find other ways to distribute their fakes – but it does undoubtedly make it more difficult for illegitimate products to be slipped into the mainstream supply chain.

Traceability is being pushed in Europe through the Falsified Medicines Directive and in the US by the Drug Quality and Security Act. The deadline for complying with the European Directive is in 2018, where as the US is looking to roll out a more comprehensive system in various stages by 2023. Broadly speaking, the two systems are reasonably parallel and both involve serialization, which moves beyond the traditional batch-level coding. The batch number tells you if the product was made last Tuesday or the Tuesday before, but now every pack rolling off the production line (sometimes at a rate in excess of 300 packs per minute) will have its own unique ID encoded in a data matrix.

The codes in both the US and European Union serialization systems will be based on a set of standards run by GS1 – a neutral, not-for-profit international organization that specializes in barcode standards. Therefore, countries won't need their own data and frameworks to deal with recording a serial number for each pack, an expiry date, and so on. In Europe, the serialization system will work as an 'in and out' verification system. The manufacturer will inform a central hub which serial numbers and which packs are going to be uploaded into the supply chain, and that information will be shared with regulatory bodies across the EU. When a pharmacist receives one of those packs at the pharmacy, he or she scans the code, which queries the database and (hopefully) authorizes the code as authentic so that the drug can be dispensed. Essentially, the code is checked in by the manufacturer and checked out by the pharmacist. But there won't be 100 percent transactional control at every point in between.

In the US, the end goal is to capture every transaction. The idea is that the manufacturer will make a number of items and record a number of codes. When the items are passed to a distributer, the transaction will be recorded in the database. The distributor may then sell the items to someone else and again the transaction will be recorded. At any point, you should be able to look up the entire history of those items within the supply chain. It's a very ambitious system. But are manufacturers ready for it? In fact, are they ready for either system? Well, it depends on which companies you look at.

When trying to figure out awareness of a particular issue, my rule of thumb is to look at who goes to conferences. Conference attendees are largely from big companies – and many are looking to share their knowledge and learnings, which is great. Most of the big companies are well prepared for serialization and have already made significant investments. Most of them also have small teams focusing solely on serialization and anticounterfeiting. But the people I don't see frequently at conferences are those from medium and small companies, which suggests a lack of awareness (and perhaps even denial). Smaller companies have fewer in-house experts to deal with specialized issues, so there will likely be a big wake-up call when there is a realization that something needs to be done – and quickly – to continue trading.

The deadline for the Falsified Medicines Directive is coming up fast. And though I don't think there is anything in the Directive that is unfeasible for small companies, if they leave it too late then there will be a classic resource crunch; there simply aren't sufficient numbers of people in the world with the expertise or sufficient numbers of equipment suppliers who can be available with a six-week turnaround. The danger of being late to the party is that you may have to get in line for what you need. And it may not be ready in time.

My advice is to start early to avoid the rush and to start senior, so that you can get things moving quickly. In my experience, if brand protection, product integrity or serialization projects are driven by a relatively medium-level technical manager, then there may be delays and difficulties because that manager has to try to persuade multiple department heads to collaborate and spend money. Implementation of an anticounterfeiting strategy is a responsibility that should be given to someone very senior, such as an executive vice president or chief operating officer. The individual driving the campaign must be within earshot of the chief executive, because it means decisions will be made earlier and more easily – and rapid progress can be made. Counterfeit products are a corporate liability issue and a corporate reputation issue. It is something that should concern the board of directors. Certainly, you need the technical managers to pull the project together, but corporate buy-in is critical.

Data, data everywhere

Serialization presents a number of mechanical challenges. You may be printing on a variety of material from cardboard, to labels, to glass vials and it will require changes to packaging lines. The European Directive also calls for tamper-evident features to be added to packaging, which will also necessitate manufacturing changes. But I think the "line-level" hurdles can be overcome relatively easily and there is a lot of know-how in the area.

The biggest challenge is data management. You will need to reconcile all of the numbers on the packs throughout the supply chain. If the code doesn't scan properly in the pharmacy six months later then you, the manufacturer, are going to get that medicine back as a return. You need to have the processes and procedures set up so that you can deal with both the data and physical inventory. Worst-case scenario? You could be out of the market place, if you cannot implement the system correctly and efficiently.

Transactional information is very valuable because it shines a torch into the corners of the supply chain that drug companies usually find quite hard to illuminate. There is a lot of activity in this area; for instance, we're developing easy to use mobile phone tools to enable companies to use their sales representatives to quickly verify serialization codes, take pack shots and report suspect packs. Another question arises as the coded pack makes its way to the patient: who owns the transaction data? At the far end of the supply chain – the interface between pharmacist and patient – there are always sensitivities about information and privacy. Most of the traceability systems being discussed in the US and the EU do not involve any medical information about the patient, so there won't be a direct link to patient records. However, pharmacists may attach value to the transactional information they generate when dispensing. Again, drug companies would probably pay for this sales information – they already do, via IMS Health and others. We could therefore

Crunching Counterfeit Statistics

- Anti-infectives are the most counterfeited therapeutic category (21.1 percent)
- Other highly targeted medicines include genitourinary (14.5 percent), cardiovascular (11.6 percent) and central nervous system (11 percent) drugs
- 77.3 percent of counterfeit medicines are oral dosage formulations; 15.4 percent are injectable biologics
- Around 27.6 percent of counterfeit drugs come from China
- Most counterfeit medicines are reported by external healthcare agencies
- Out of 196 countries, 127 have not reported any incidents of counterfeit medicines

Findings from T. Mackey et al., "Counterfeit Drug Penetration into Global Legitimate Medicine Supply Chains: A Global Assessment," Am. J. Trop. Med. Hyg., 92, Suppl 6, 59–67 (2015).

The Problem of Counting Counterfeits

Tim Mackey is the Director of the Global Health Policy Institute and an assistant professor at UC San Diego – and he has written numerous articles on the subject of counterfeit medicines. Recently, Mackey and his co-authors tried to assess the extent to which counterfeit drugs had penetrated global legitimate supply chains (1). The team used 2009-2011 data from the Pharmaceutical Security Institute Counterfeit Incident System (PSI CIS) database, which is based on both open and non-public data sources, and includes more than 1500 reports. The team encountered many challenges along the way, and the paper calls for more global cooperation between different stakeholders to improve counterfeit drug surveillance.

"The PSI CSI represents the most robust dataset available, but overall the data lacks the necessary detail needed for evidence-based action. First of all, there are only a limited number of countries making incident reports, which makes it difficult to model any potential associations between countries with counterfeits and other important factors such as income level or corruption," says Mackey. "In addition, though the dataset benefits from reporting from a variety of information sources (public and private), there is no harmonization. Companies may operate in silos; only concerned with their own products and can be reluctant to share information."

To make matters even more frustrating, Mackey adds that the international community cannot even agree on a definition for the problem or how to categorize between all the different terms: substandard, spurious, falsely labeled, falsified and counterfeit. This means that some countries will define the problem differently, which leads to a lack of fidelity and comparability of data, depending on the source.

"Though some argue that a definition is needed for law enforcement and prosecution purposes, I think that it's more important to focus on good surveillance," says Mackey. "Surveillance and generation of reliable data on the global counterfeit drug trade drives everything. With good data, we can design anti-counterfeiting partnerships, programs, enforcement activities, and technologies in countries and for drugs that are at the greatest risk, and in the process save more lives. However, such a commitment would require significant partnerships and investments."

Some countries do not have the funds to engage in surveillance or to make it a priority. And Mackey believes that another issue is the lack of partnership between all the stakeholders involved. For example, drug manufacturers often have the resources needed to detect counterfeit versions of their medicines – and may already do sample buys of their own products in certain markets to help detect counterfeits – but it is actually the drug regulators, law enforcement, and customs officials who are in the best position to protect patient safety and educate the public about the dangers of counterfeit medicines. Mackey adds, "There are some success stories, but I also think that there has not been sufficient action at the international level, particularly with WHO giving up on the IMPACT public-private partnership cooperation mechanism and moving to the member state only mechanism that is embroiled in international politics on the issue."

Some key findings from Mackey's assessment can be seen on page 23.

Reference

1. *T. Mackey et al., "Counterfeit Drug Penetration into Global Legitimate Medicine Supply Chains: A Global Assessment," Am. J. Trop. Med. Hyg., 92, Suppl 6, 59-67 (2015).*

see a shift in how companies monitor, map and optimize their supply chains.

Avoiding an arms race

Beyond serialization, another way to fight fakes is to incorporate security features into the packaging; for example, by making the packaging tamper-evident or by adding visible features, such as holograms. However, such features are often more suited to over-the-counter-medicines rather than prescription medicines (which have plain packaging). Indeed, many of the features pharma companies choose to incorporate are actually deliberately invisible, such as covert security inks, chemical tracers and even DNA markers. Each drug company will understand what every mark on their packaging means and will be able to tell if a product is genuine or fake. Of course, the reasoning behind covert features is that anything visible will be seen by counterfeiters – who will probably be able to make rough copies that can fool the general consumer within a matter of days. Using visible features quickly leads to an arms race, which can get expensive as you explore ever more distinctive features.

If you have to explain how to interpret a complex visible feature with a leaflet or a newspaper campaign, then it's probably not going to work very well; the general public will be easily fooled by something that looks superficially and even remotely similar – and most consumers don't spend too long assessing which pack of medicine to buy. It's another good reason why the majority of pharma companies use solutions that are invisible to the general public.

However, methods that involve patient interaction can have some success. For example, in Nigeria, there have been initiatives using scratch off labels on medicine packs. Beneath the label is a unique number that you text to an SMS service to check that the medicine is authentic. There are still holes in the system, but the Nigerian drug regulators believe it has had beneficial effects in reducing the incidence of fake products.

In India, one of our customers has printed visible alpha-numeric codes onto packs as part of a tuberculosis adherence program. One of the problems with TB medication is that the regime is quite complicated so patients can forget to take it. The project involves a medical worker registering the drug with the patient when the medication is prescribed by asking the patient to use their mobile phone to text the printed code on the pack to a verification service. This firstly checks authenticity, and then provides an ongoing follow-up and reminder service to the patient to help them keep up with their medication. The program has been funded by the Gates Foundation and USAID, and has been shown to increase the beneficial outcomes of TB treatment programs. It's a great example of the convergence of security and improving medical outcomes.

No problem?

As I've already mentioned, I don't believe that there is a huge issue with counterfeiting in the Western markets. Though of course, any fake drug is dangerous and the harder you look, the more you may find. We have had customers who have been very surprised to learn that they have a counterfeit issue in a particular country with products that they considered to be low volume and low profile; they always thought that no one would consider copying the product. But suddenly, they realize they have a problem that needs to be fixed.

Globally, counterfeits are an important problem and we can't ignore it because medicine and health are global issues today. Fake medicines don't just pose a danger to patients themselves – they can also harm the effectiveness of existing medicines. One of the issues that I'm concerned about is how fake drugs, particularly fake antibiotics and antimalarials, are exacerbating the drug resistance problems that the pharmaceutical industry is trying to solve.

Most companies view laws such as the EU Falsified Medicines Directive and the US Drug Supply Chain Security Act as a compliance obligation. But beyond the obvious supply chain benefits, I think that intelligently designed anticounterfeiting operations will also allow the industry to make better use of the potential of mobile health. If you have a unique code on a box that can be read automatically by a mobile phone, then you could have the beginnings of a new way to reach patients. I certainly wonder what doors that will open in the future...

Mark Davison is the founder and CEO of the consultancy Blue Sphere Health, based in Cambridge, UK and Philadelphia, USA.

Read All About It

Mark Davison is an international consultant on anti-counterfeiting and serialization. He is the author of "Pharmaceutical Anti-Counterfeiting: Combating the Real Danger from Fake Drugs", published in 2011. Notably, it's not intended as a technical know-how manual – Davison says there's no point as counterfeiters also tend to read around the subject – but it does provide a single volume primer or "eye opener" for general managers who understand that counterfeits are an issue, but aren't sure how to deal with it. It's been popular in the industry, with some companies buying a few hundred companies to give to their staff. Davison is currently working on the second edition, which will be out in 2016.

Fighting Spirit

Grant Lindman is director of Eli Lilly's global anticounterfeiting operations and is passionate about fighting fake medicines. Here, Lindman takes a quick tour of industry success stories and shares Eli Lilly's current initiatives.

What does your role entail?

It's essentially about coordination. We're a large global company and a lot of different functions are involved in developing a global anticounterfeiting strategy. For instance, I work closely with legal, security, brands teams, quality and safety, as well as our authentication lab. I've been working in the company's anti-counterfeiting operations for almost 10 years. Patients depend on medicines to improve their lives – and pharma companies work hard to provide these medicines. Counterfeiters undermine all our hard work. It's very frustrating and it's a problem that really motivates me.

Looking at the company's overall strategy, there's no silver bullet for fighting fakes, so Eli Lilly has adopted a three-pronged approach. We want to secure enhanced integrity of the legitimate supply chain; deter major counterfeiters through legal actions, investigations and use of technology; and then partner with governments, non-government organizations and trade associations to elevate the issue and raise awareness about the threat of counterfeit medicine.

How big is the problem of counterfeit medicines?

It's difficult to really understand the size because counterfeiters are criminals; they don't publish business plans or statistics about their activity! A lot of recent evidence has suggested that criminal organizations, such as narcotics gangs, are getting into the counterfeiting business and these criminals are smart. Estimates floating around the industry value the counterfeit problem at anywhere between $75 billion and $200 billion a year.

I think every big pharma company is seeing counterfeits of their products in various markets, and there's definitely growing awareness of the problem. But although we're seeing reports of more counterfeiting or seized products in a specific market, does that mean there are more counterfeits, or is the industry just identifying it more? I think it's a little bit of both.

When counterfeit medicines started to appear, the counterfeiters mainly targeted lifestyle products, such as erectile dysfunction medicines and hair growth products. Now, all kinds of medicines are targeted. It's not just innovative, branded drugs either; we're also seeing counterfeit generic medicines, which is something many people in the industry didn't expect as they are viewed as lower cost products.

Counterfeiters are getting smarter – how do you keep up?

Counterfeiters are all about deceiving people and exploiting someone else's brand, so they need their products to look good. Several years ago, counterfeit products were easier to spot, but recently they've upped their game and the packaging tends to look very professional to the naked eye. Even the fake tablet itself can seem high quality, but it's unlikely to have the correct ingredients. There have been lots of different reports of what can be found in counterfeit medicine – brick dust, lead and boric acid to name just a few. Counterfeiters don't care what's in the medicine. They just need it to look good.

At Eli Lilly, we've set up an authentication lab where we test for counterfeits. If customs or law enforcement seize suspected counterfeit versions of our products then we send samples to our lab for chemical and visual tests. The information is then sent to law enforcement and used in court proceedings and prosecutions.

"We need to work together as an industry to beat the criminal gangs, so we work with governments, non-government organizations and trade associations as well."

How does the problem vary between different regions?

In developed countries, the legitimate supply chain is pretty secure so counterfeiters often try to sell things over the Internet. But in developing countries, the supply chain tends to be a little more porous so there may be opportunities for the counterfeiters to inject their products into that supply chain. Counterfeiters are organized and they usually understand the differences between markets and will take a targeted approach. For example, in developing countries, there is a big problem with counterfeit antimalarials and HIV drugs. In Europe and the US, there have been several reports of counterfeit cancer and heart medication.

What action is Eli Lilly taking to fight fakes?

One of the initiatives that we're focusing on is serialization. Last year, we announced an investment of over $100 million in this area. A lot of countries are passing regulations in this area and it's a good step towards better securing the legitimate supply chain.

We also want to deter counterfeiting in the first place so we partner with law enforcement and we have experts who can testify in court. When counterfeiters are prosecuted, we help to support the effort through legal actions too. We also do training with law-enforcement and customs officials so that they can understand what a legitimate product should look like and who they need to contact at our company if they have a question. And when these questions do come through, we try to get them answered quickly so that they can take action if necessary.

Another important area is partnerships. We need to work together as an industry to beat the criminal gangs, so we work with governments, non-government organizations and trade associations as well. Where you find counterfeits of one company's products you will likely find another company's products too. The Pharmaceutical Security Institute is one organization that does a lot of data capturing on these issues

What recent success stories can you tell us about?

Interpol has something called Operation Pangea, which targets online sales of fake medicines. The operation takes place every year and is a huge partnership that involves the whole supply chain, as well as customs, police, regulators and more. We took part in this operation in 2014. It involved 1200 different investigations, more than 9.4 million fake medicines being seized, removal of more than 19,000 advertisements for elicit pharmaceuticals via social media platforms, and the closure of more than 10,000 websites. It spanned multiple countries, highlighting the global nature of counterfeiting. We took part in the more recent 2015 operation too.

In the area of safe online medicines, there's another organization that we work with called The Alliance for Safe Online Pharmacy. We're supportive of people using the Internet but they need to know if an online pharmacy is safe. The National Association of Boards of Pharmacy has registered the domain name of '.pharmacy', which online pharmacies can apply to use. The application and approval process involves stringent vetting to ensure that the pharmacy is legitimate. When a patient sees an online pharmacy with the right URL, they will know it is reputable.

Finally, regulators are also working hard in this fight. For example, the FDA has partnered with Fight the Fakes (http://fightthefakes.org/), which is a campaign to raise awareness of the dangers of fake medicines. Regulatory agencies are becoming increasingly aware of their role in fighting fake medicine and how they can help to educate the public. After all, patients look to them for advice on all health related matters.

What is the key weapon in the fight against fake medicine?

Partnerships! Operation Pangea shows what we can achieve in collaboration. We also need to work together on securing a legitimate supply chain. There's a big serialization push at the moment, but if all partners in the supply chain do not use the technology, then it doesn't really add value.

And there's still more that must be done. In particular, I think we need tougher penalties for counterfeiting. In the US, for example, the penalties are tougher for running a narcotics business than they are for counterfeiting medicine.

Bringing Vaccines into the 21st Century

Medicine manufacturing has benefited from countless advances in technology over the last few decades, and yet many vaccines are still being produced with decade-old processes. Change is never easy, but is falling behind really an option?

Mats Lundgren has an intense interest in the field of vaccines, with an academic and professional background to match. Dr. Lundgren's passion is understandable; vaccines have helped conquer numerous healthcare challenges and no doubt have a great deal to offer in the future. Despite their value, many vaccines are still being manufactured using legacy technology such as eggs or animal tissues. Today, Lundgren works as Customer Applications Director at GE Healthcare, where he helps companies with implementing modern processes. The end goal? More efficient production and higher vaccine quality.

What was your route into GE Healthcare?

I've worked for several biotech companies over the years, but the reason I joined GE Healthcare in 2008 was because I wanted to be more applications-focused and to work more on the technologies used in the biomanufacture of monoclonal antibodies and vaccines. Vaccines are a really interesting area for me. Not only do they have a major impact on health worldwide (it is thanks to vaccines that we were able to eradicate smallpox) but they are also interesting from a technology point of view. We have seen lots of advances in this area, particularly in terms of single-use technology. At GE, I support our customers with application knowledge, such as how to use innovative products and how to implement new processes.

What are the global trends in the vaccine industry?

Consolidation is one big trend right now. It's being seen across the developed pharma and biopharma industries because of cost pressures and the need to be more efficient. In the vaccines area, we've seen major deals such as GlaxoSmithKline's acquisition of Novartis' global vaccines business, which took place earlier this year. Large vaccine manufacturers based in Europe and North America are also seeing increased competition from developing markets. More and more companies, mainly in Asia but also in Latin America, are setting up their own domestic vaccine production. In some cases, this is for their own market, but many companies are starting to export. For example, The Serum Institute of India is a huge exporter of vaccines to UNICEF.

Importantly, I think we're also seeing a greater appreciation of the value of

vaccines. In the 70s to 90s, vaccines were to some extent considered low-profit products, but now decades of research is starting to come to fruition with the development of more advanced vaccines. Some vaccines could have the potential to even treat disease, such as cancer vaccines. I believe these advances have renewed interest in the vaccine field.

What are the main problems with traditional vaccine production methods?

Some vaccines on the market are produced using egg-based processes and technologies that were developed decades ago. Egg-based vaccine manufacturing is a lengthy process and companies have to predict demand ahead of time. Production can't be accelerated or ramped up in case of a pandemic, and sometimes there may even be situations where eggs cannot be secured in the correct numbers, such as during an avian flu outbreak. Other processes may include a lot of manual handling (for example, with open flasks during expansion of adherent cells), which can be a quality risk. Moreover, the demand for human resources makes production costs high. And it's not only the technology that is behind the times; the industry still uses a lot of animal-derived raw materials, which can carry the risk of contamination.

These drawbacks are being increasingly recognized by the vaccine industry, particularly in light of increased competition in the field. Vaccine manufacture needs to be faster and more efficient – subsequently, companies are starting to look at how they can bring processes into the 21st century. If you're wondering why it's taken so long to come to this realization, you need to consider that vaccines haven't traditionally turned big profits, which didn't match the fact that modernization requires investment. In addition, vaccines tend to be used in healthy individuals (and many children) and must not give rise to unwanted side effects. Thus, there was a mentality that if the old processes work then why should they be changed? And what if changing a process brought about a new side effect? Costly clinical trials might be required to show that the new processes indeed can produce safe and efficacious vaccines. In my experience, updating processes improves product quality, especially as that usually means using the most modern systems, which have been specifically designed to improve manufacturing. Change, of course, always involves an expense, but this can be balanced by a better process economy (and lower production costs) in the long term.

"These drawbacks are being increasingly recognized by the vaccine industry, particularly in light of increased competition in the field."

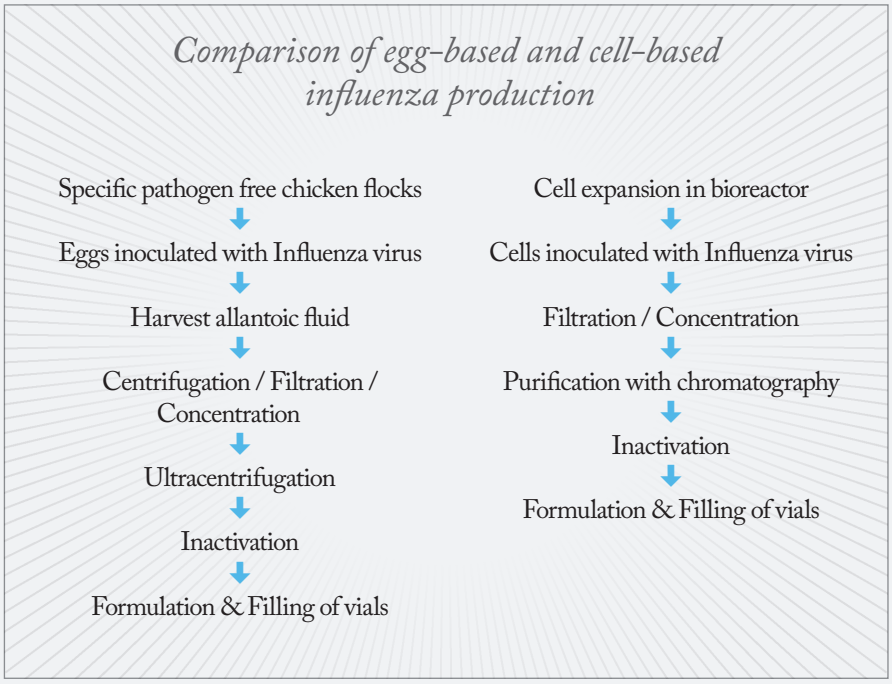
What changes are being made?

We are seeing a shift away from egg-based to cell-based production, which is a very well-defined process. Changes are also being seen in technology; instead of centrifuges, you can use chromatography to purify vaccines; instead of stainless steel bioreactors that are difficult to clean, you can use single-use bioreactors; instead of growing cells on the surface of (many) flasks you can grow the cells on microcarriers, which are tiny beads inside a stirred bioreactor. There are also newer cell culture products available that help to more efficiently propagate the viruses and bacteria, as well as analytical tools that can control and track what is happening throughout the whole vaccine production process. The key benefits of all of these new technologies is that they are faster, more efficient and take up less space. Most new technologies have also been designed to accommodate the industry's need for more flexible manufacture by being modular and disposable.

How do attitudes to new technology vary among companies?

Overall, I believe that most companies are really keen to use the latest systems available to them, but at the same time they are also cautious. Many established companies have been using the same processes for 50 years or so. Their facilities are well established and often built around these old plumbed-in processes so it's challenging to accommodate changes – both from an infrastructure point of view and a regulatory point of view given that they are working with long-approved products. But this doesn't mean that updating is impossible. I don't think it's very useful to tamper with an established process just because of cost, but if it benefits vaccine quality or purity then the change will be appreciated by regulators because it will result in a better, safer product overall. A complete retrofit of a plant may be difficult but smaller steps can be taken; for example, getting rid of tissue culture flasks and moving to disposable bioreactors. This change can easily be justified because of the quality benefits.

The big opportunity for change for established manufacturers comes when they are developing a process for a new vaccine, expanding production or building a new plant. There is an opportunity here to employ modern



technologies, gaining the benefits right from the outset. I see a lot of companies – even large, experienced ones – that try to work with processes that were originally developed for lab-scale work rather than commercial manufacturing. Scale up in this instance can be a frustrating experience. Working with modular, scalable technologies right at the beginning saves a lot of time.

Companies new to vaccine manufacturing are perhaps more able to implement the latest technologies because they are designing their processes and plants from scratch, so there is a real opportunity to get a competitive edge on established companies by employing modern, efficient manufacturing technologies. Some of these new manufacturers are located in areas where the regulatory framework might not be as well developed as perhaps Europe and the US. However, these countries are catching up very rapidly and, as mentioned earlier, companies in developing markets are keen to export and will be looking at technologies that can facilitate the consistent production of products in line with global quality requirements. Not all companies are aware of the complexities of establishing a new vaccine plant, particularly one that aims to export. And this isn't just a problem in developing countries – any company anywhere in the world can encounter production difficulties and trouble with scale up, but this is where we come in with our advice and support. It's not just about selling technology – it's important to offer support and knowledge too. And this increases trust between the vendor and customer – and means that our products are used in the best possible way.

How can companies overcome the challenges of change?

Knowledge is crucial. First of all, you need to have a solid understanding of your processes and product to understand where the opportunities for change and an increase in product quality and production efficiency lie. Next, you need a good grounding in the latest production equipment and single-use systems so that you can see how these will fit into your processes – or how they can be used to create a new process from scratch. Finally, you need regulatory knowledge so that you can understand current requirements.

At GE, we've tried to raise awareness of the problems facing vaccine manufacture and of the benefits of new technology. We speak with our customers frequently to understand their problems, we speak at conferences and we are also starting to work with industry organizations, such as DCVMN – the Developing Countries Vaccine Manufacturers Network. This is a powerful organization where manufacturers in developing countries can share their knowledge of new production technologies, as well as regulatory and quality aspects.

What are the real risks of being left behind?

A big part of my role is to visit companies and to talk about the different technologies and how they can be implemented in different processes. I always propose changes that will impact the final vaccine product in a positive way. Companies that don't embrace the potential benefits of modernization could become obsolete. More and more companies are keen to enter the industry and this growing competition means you can easily become outdated. That may sound a bit dramatic, and I don't expect to see companies immediately dropping out of the market, but to secure a long-term future, I think you need to examine the benefits of updating your production processes. It's very tempting in the pharma business to stay with the same old technology that you know and trust, but it's an attitude that can come back to bite you sooner or later. We are firmly in the 21st century. Do we really want to be producing life-saving products with legacy systems?

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Disposing of the Past and Embracing Single-Use Technology

Single-use technology is ready to lend a helping hand to biomanufacturing, but is the industry ready to turn away from stainless steel? A hybrid manufacturing model could benefit from the best of both worlds.

Recently, we spoke with Kamal Rashid, director of the Biomanufacturing Education and Training Center (BETC) at Worcester Polytechnic Institute in Massachusetts, US, about the emerging impact of single-use technologies. Rashid specializes in developing and delivering biotechnology and biomanufacturing training programs and has also been honored with awards for his academic services. BETC combines classroom instruction with hands-on training in a fully functional pilot-scale biomanufacturing facility – which includes single-use technologies. After all, single-use systems could be the future of biomanufacturing so it's important to train end users how to deploy them effectively.

There is a lot of hype about the potential of biotherapeutics…

The sheer amount of biopharmaceuticals in company pipelines and the amount of bio-related discoveries being made in R&D laboratories worldwide are testament to the fact that we are on the cusp of an exponential growth surge in biomanufacturing. In particular, a lot of promising work is coming from academic labs, which are in a great position to form new 'spin-off' firms based on their discoveries or to partner with existing companies to commercialize new products. And there is much more to come: we have only scraped the surface of the potential of biotherapeutics in healthcare.

In 2000, the Human Genome Project announced they'd found more than 30,000 human genes, but we're still guessing at the function of most of the proteins they encode. And of the proteins that are understood only a small minority have been developed into healthcare products. Parallel to all of the discovery in bioresearch, equipment suppliers have been forging their own path of innovation.

This has resulted in game-changing instrumentation and technologies, as well as more efficient media and other materials – all designed to improve biomanufacturing.

It's amazing how far we've come in terms of bioprocess technology. Thinking back to the beginning of my career, when I was working at Penn State University in the 1980s, we had bioreactors that were really quite unsophisticated because the industry was in its infancy at that time. Now, everyone has computer-controlled bioreactors that help manage the processes and are designed to help minimize contamination. These reactors can be cleaned in place and sterilized in place. Many other technical advances have helped the industry, and the latest is the growth of single-use products. I think that this is a really important advance and will play a big part in the industry's future. But this doesn't necessarily mean that you need to throw out your stainless steel equipment. There is room for both technologies.

What are the challenges of working with biologics?

Biologics, by definition, are made from cells, but growing a viable population of cells is a tricky business because living entities are infamously temperamental. For new companies, before you can even think about your biomanufacturing facility and bringing in single-use equipment, you need to perform optimization studies with the cell lines that you're going to be using to ensure you'll get the amount of cells that you need for the required product output. These tiny cells are the factories that will be producing your product so you must look after them and ensure that the environment is optimized for their growth and duplication.

A lot of variables come into bioproduction and you need to be aware of the potential for contamination throughout the whole manufacturing line – from starting the cell line, to introducing it to the bioreactor, to adding the medium – problems can occur at any time. Process optimization is crucial because it minimizes the possibility of batch failure. And that's important, because batch failures can cost you a lot of money! It takes about a month to get a seed culture ready to put into a 10,000 L bioreactor, so if you get contamination at that stage, it's a huge amount of wasted product and resources.

"Single use is a great option for new facilities and for new entrants to the field."

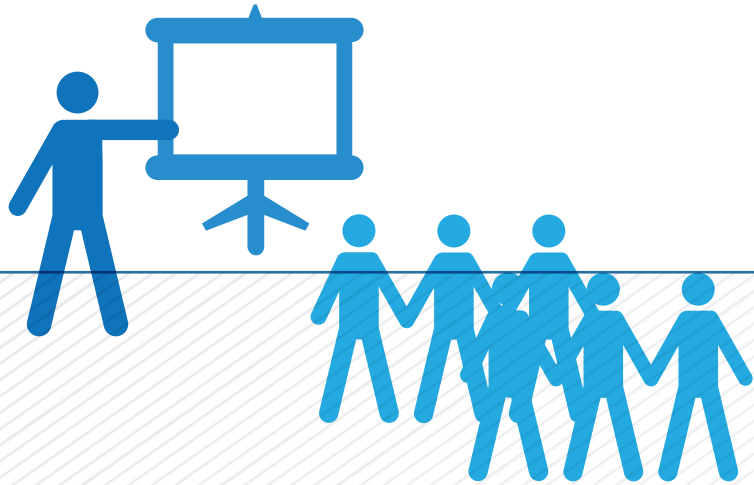
And unfortunately it remains a problem in the industry, although efforts are being made to minimize it. But no one is perfect. Batch failure can happen due to several factors; for example, the operator may make a mistake, there may be a defect in the cell media, or the equipment could fail and cause the pH level to rise. It can be a very frustrating experience when you see the pH level rising and you can't control it!

So it makes sense to incorporate the most effective and reliable technologies into your biomanufacturing process. And single-use systems can certainly lend a hand in this area. And training employees to understand the risks and troubleshoot potential problems is an important step to guard against batch failure.

How have single-use technologies advanced over the years?

While single use is growing dramatically today, the history of single-use technology dates back several decades. First, single-use bags began to be used for storing media and became quite popular in hospitals; for example, bags containing intravenous fluids. And then scientists began asking, what if the bag could be used as a bioreactor? And so, eventually, the first single-use bioreactor was born – the Wave bioreactor. This was a simple, bench-scale system where you put your cells and medium in a bag, which was placed on a platform that moved to create a wave-like motion. Mammalian cells are fragile so the mixing has to be very gentle, which is doable in a bag system. The mixing lets the cells pick up oxygen as they grow. And people then began thinking about the bag in a larger sense, and whether they could develop a whole single-use stir-tank bioreactor with control systems and other features. At first, these new plastic bioreactors were mainly used for mammalian cell processes, but we've come a long way since then and now you can even get 500-L single-use bioreactors suitable for microbial systems.

Whether using stainless steel or single-use systems, the goal is the same: cell growth and protein production. The protocols and procedures for both processes are almost the same, but single-use systems have several advantages. Importantly, you don't need to clean or sterilize your single-use equipment; once you're done with the single-use bags you dispose of them and use a new bag. To operate with single-use technologies means lower energy requirements (no cleaning or sterilization requirements, so far less water and heat are used) and lower capital costs for set-up. Because of the financial and operational benefits, single use has become an attractive option for developing countries that are just starting to form their own biopharmaceutical facilities. Single use can be incorporated in both upstream and downstream processes.



Training for the future

Many readers may have noticed a skills shortage in the biopharma industry. This is because most university graduates today are not prepped for immediate employment in the biomanufacturing industry. They may have had several courses in biology or biochemistry, but they have not developed the hands-on skills that companies need in biomanufacturing, such as cGMP, following SOPs, regulatory compliance and validation. This is starting to change and some academic institutions are offering more specialized courses on, for example, animal cell culture technologies. Still, for the most part new hires who are recent graduates still tend to need a lot of in-house training.

Seeing this need, Worcester Polytechnic Institute (WPI) built a new model for training partnerships with companies. At our center, we bring biomanufacturing companies together with suppliers and equipment manufacturers in an academic environment to deliver short, intensive, industry-based hands-on training programs. It's highly effective to be able to train employees on real equipment, using real processes, but in an environment where the company's products are not at risk.

Training on single-use technologies is embedded in most of our programing, so our emerging collaboration with the Bio-Process Systems Alliance (BPSA) is a good fit. The BPSA was established in 2005 with the intent to help encourage the adoption of single-use systems in biomanufacturing. And of course, the best way to encourage people to use something is to offer proper training so people can experience the benefits.

In July 2015, WPI announced a partnership with the BPSA to help develop a standardized certificate programme for single-use systems. We're in the early stages of this initiative, and we are working closely with peer institutions, including North Carolina State University and Texas A&M, which have also established biomanufacturing training progams.

Stainless steel has been around for a long time, so to help foster the adoption of single use, the BPSA wants to promulgate effective training methods for single-use systems. Now, our working group is emerging to discuss what a standardized single-use technology education program should include, and how academic institutions can respond to the training needs of the industry. Some institutes are already offering some form of training in single use. But what we really need is a standard training programme so that end users all over the world have access to high-quality training.

And this training should not be limited to getting new hires familiar with hands-on manufacturing; what about existing employees? I remind you that the FDA requires all biomanufacturing companies to have a record of employees being trained. Training is not a luxury, but a requirement. New technologies are going to continue to appear and employees need to learn about them. And that includes single-use systems.

In fact, the entire manufacturing line can use plastic components.

Single-use technologies can also, ultimately, help patients by bringing a wider array of biologic drugs to the clinic. Importantly, patients can also benefit from the flexibility that single use and other advanced manufacturing technologies provide. By making it feasible to produce smaller batches of many different drugs, single-use systems support development of so-called "orphan drugs" for diseases and conditions that affect smaller numbers of people. More flexible, cost-efficient biomanufacturing operations could also be helpful for delivering much-needed vaccines to areas of the developing world.

Are single-use technologies a viable alternative to stainless steel in every situation?

Single use is a great option for new facilities and for new entrants to the field, but it's a different story for already established biomanufacturers. Many companies have long-standing, validated processes that are producing important biotherapeuitcs and there is no reason to disrupt that. Take Amgen as just one example. When Amgen first started making Epogen (epoetin alfa), they made it in roller bottles. Today, many years later, while they have continually improved elements of the process through automation and other practices, I believe they are still making it in roller bottles. Of course, Amgen also uses state-of the-art technologies, bioreactors and newer systems for many of its products, but Epogen is a well-established and effective drug. If Amgen were to change Epogen's manufacturing process now, it would require major change control procedures and the company would have to re-validate the whole manufacturing process. That would be expensive and disruptive. So you can understand people asking, if an old process is still going smoothly, why should it be changed?

This is a very common attitude in the

biopharma industry and it's perfectly understandable. Companies that already have big facilities full of stainless steel are not going to suddenly exchange all of their equipment for single-use systems. It would be madness! But these big companies still appreciate the benefits of single use, and so we are starting to see a move to a hybrid manufacturing model, which makes use of both stainless steel and single-use technologies. For example, you may decide to keep stainless steel for products A, B and C, but implement single use for your new D, E and F products so that the single-use manufacturing technologies can be validated at the very start of a new process. The result is that your facility will include both stainless steel and single-use systems. At our training center, we are working with several big companies that have chosen this hybrid model.

Single-use technologies are still relatively new – what are the challenges?

New technologies inevitably bring new challenges. With single-use systems, the main concerns relate to extractables, leachables and waste management. These issues, however, can perhaps be referred to as 'work in progress' because suppliers and end users are collaborating to resolve them.

"With single-use systems, the main concerns relate to extractables, leachables and waste management."

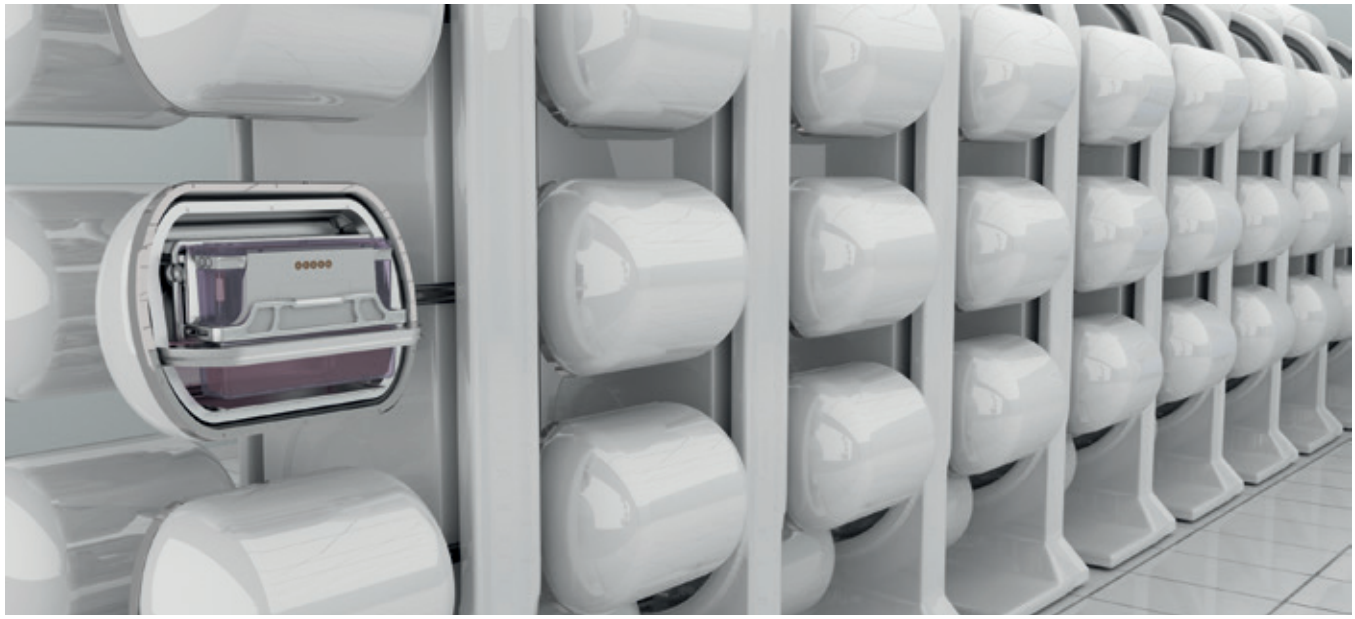
Extractables and leachables (E&L) issues – meaning the potential for particles to migrate from the plastics into the biomanufacturing process – are broadly recognised in the industry. Several groups, including the BioPhorum Operations Group (BPOG) and the BioProcess Systems Alliance (BPSA) are leading the discussion on these issues and pushing for standards. Companies should support those efforts, and also use supply chain management best practices for the sourcing of all single-use technologies. They should work closely with suppliers and industry groups to insure that rigorous studies are done and that real data are available to understand any potential incompatibilities.

In terms of waste management, some concerns have been raised about the amount of disposable plastic in the biopharma manufacturing chain. According to the BPSA, the human race disposes of around 300 million tonnes of plastic every year. Of that amount, only about 2,200 tonnes (or about .00007 percent) is made up of single-use biopharma equipment. This is an insignificant amount of the total, yet the biopharma industry takes disposal very seriously and wants to do even better. So there is a lot of ongoing research about how the plastic can be re-used in other ways, to prevent it going into landfills.

What are your thoughts on the future of biopharmaceutical manufacturing?

Biomanufacturing is advancing rapidly and professionals in the industry are constantly challenged to stay up to date. The best way to get up to speed is to learn the ropes through training courses. I've been involved in biotechnology training programmes for more than 25 years, and it's an area I'm very passionate about (see sidebar Training for the Future). Effective training should be hands-on, which is the best way to learn the potential of any new technologies, including single use. Eventually, I think that single use will play a major role in most biopharmaceutical facilities as concerns around E&L and waste management are alleviated. Training courses covering these new systems are helping to grow a base of expertise in their use, which will have a positive impact on the industry. I think there's no reason why all new products in the future can't be made in single-use systems, providing that the conditions are optimized.

Kamal Rashid is the director of the Biomanufacturing Education & Training Center at the Worcester Polytechnic Institute in Massachusetts, US.



The Hype, Hope and Reality of Personalization

Personalized cell-based therapies have been hyped as the future of medicine, but are current manufacturing technologies up to the task?

By Behzad Mahdavi, Uwe Gottschalk, Nuala Trainor and Tim Smith

Cell-based therapies have been celebrated as a new approach to healthcare because of their potential to treat a wide variety of unmet clinical needs – from cancer to arthritis to spinal cord injury. Cell therapy involves administering living cells to a patient with the aim of replacing missing or damaged cell types, potentially treating the underlying cause of a disease. Some cell therapies have already been approved by regulators and with further research taking place, we can expect to see many more in the future.

The big question is, how do we ensure that these therapies, especially personal cell-based therapies (PCBT), can be commercially manufactured to Good Manufacturing Practices standards at an acceptable cost and quality – and in the right quantities? After all, PCBTs are radically different to both classic small-molecule drugs and even biopharmaceuticals.

Cell-based products require expansion or manipulation in the lab using advanced cell culture and tissue engineering platforms. Cell therapies can be segmented into two groups: autologous and allogeneic, depending on the sourcing of the cells. Autologous cell therapy products are produced from the patient's own cells, whereas donor cells are used for allogeneic cell therapy. Partly because of the sourcing differences, autologous and allogeneic cell therapies face different manufacturing challenges, and therefore require different strategies to enable translation into commercially accessible and affordable medicines. The major advantage of the autologous approach is immunological compatibility; using a patient's own cells obviously eliminates immune-rejection.

A subset of allogeneic therapies are "patient-matched," which means that, although donor cells are used, the final product is custom made for one specific patient at a time – in very small batches. From a manufacturing perspective, this means that each patient requires their own batch. In this article, we focus on PCBT, which includes both autologous and patient-matched allogeneic therapies (see Figure 1) for more than 'minimally manipulated' cells – an FDA term.

The ideal long-term solution, of course, would be a universal allogeneic approach where we could create perfectly matched therapies with no danger of immune-rejection, but the majority of candidates in clinical pipelines at the moment – and most likely to hit the market in the near future – are PCBTs. In the following sections, we offer an overview of PCBT manufacturing and operational obstacles and the manufacturing strategy to overcome these challenges.

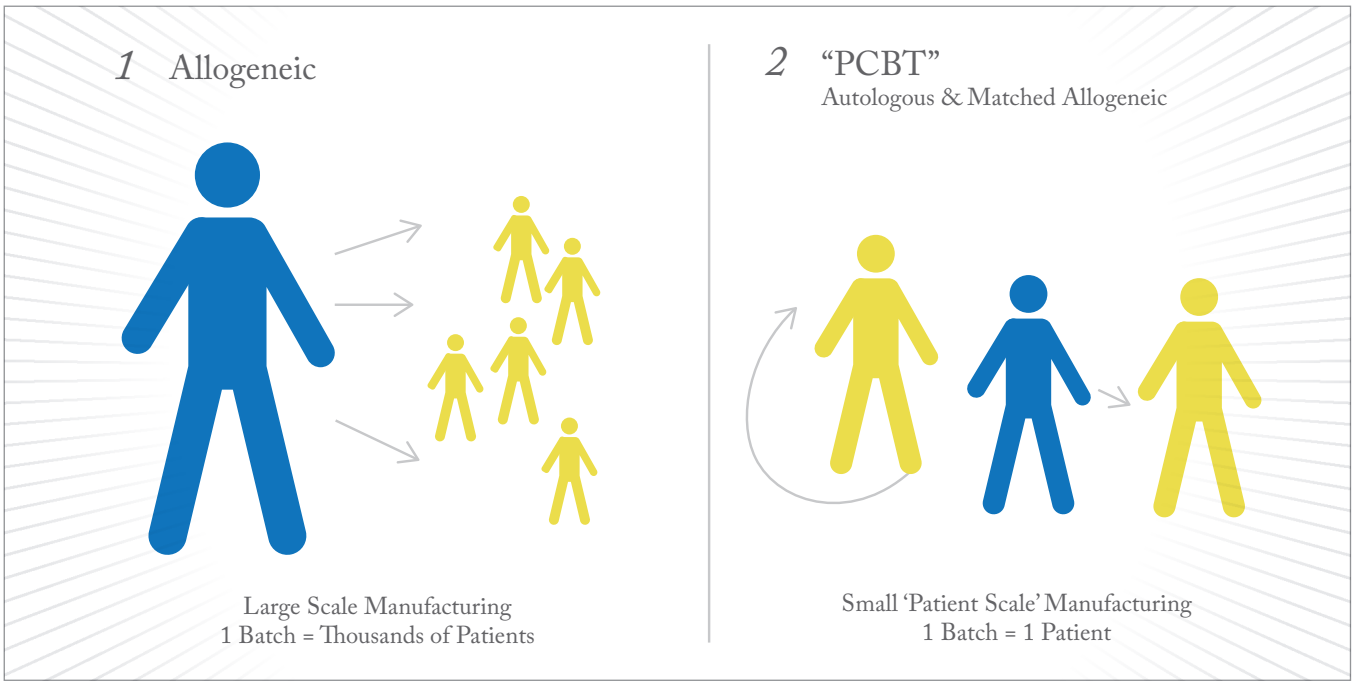


Figure 1. Patient-scale manufacturing.

The product is the process

When working with PCBTs – or any cell-based therapies – the process and the product cannot be dissociated. As with the early stage of development for recombinant proteins and monoclonal antibodies, cell therapy products are defined by their manufacturing processes and equipment, as well as the facility in which these products are made.

The 'source material' of autologous cell therapies is one challenge as the patient can be considered as one of the raw materials. The wide range of ages and physical conditions of cell donors introduces highly variable inputs to the manufacturing process in terms of a healthy number of cells to start the expansion, as well as their proliferation capacity. For example, in T cell expansion, the rate of growth of specific populations may be influenced by the disease state or age of the patient. To help ensure the consistency and quality of the final product, you can use automated systems

"Personalized cell-based therapies are an exciting alternative to small molecule drugs and biologics."

that have built in reactive biofeedback. Reactive biofeedback uses real-time monitoring (for pH, O2, glucose etc.) and software with pre-defined protocols that can adjust and keep critical parameters influencing cell growth within certain predefined ranges to help ensure that the end product has narrower release criteria.

Systems like this are available, but they cannot all work with variable source material or different units of operations. When investing in new equipment you should consider systems that have been specifically designed for cell therapy work and able to scale out to commercial production. In this regard, there is a need to employ automated systems that are flexible and able to accommodate different processes with different cell types and cell culture methods if you want to develop a universal manufacturing platform for PCBT. In other words, the system should be adaptable to fit and reflect the details of the process, rather than require that the process be adapted to fit to the system. Such a characteristic preserves the uniqueness of each process/product, which in turn is useful for preserving the intellectual property component of the therapy (which we all know is an incentive for developers).

Because the manufacture of PCBTs involves many small batches, large processing equipment is not suitable. Instead, many small-scale systems and

Top Tips for Commercial Cell-Therapy Manufacture

Systems should be automated and space efficient.

Employ automation systems in the early stages of new therapeutic development to facilitate scale out later on.

Systems should be flexible and capable of being customized to suit the process; you shouldn't modify your process to fit to systems.

Each batch should use a personalized bioreactor.

Single-use technology solves cleaning validation issues and reduces risk.

All pathways and fluid circulation should take place in a closed system.

Use intelligent software and reactive biofeedback to boost automation and to accommodate for natural variations in the starting patient's cell.

Automated processing should be able to generate comprehensive electronic batch records that can be merged with production management software.

bioreactors are needed – which can become expensive. Many see automation as the ultimate solution for manufacture of PCBT as, in general, it helps to bring costs under control and facilitates the operations. However, the cost structure of the manufacture of PCBTs is complex. The main costs are associated with labor, which can be handled by automation, but there is also the cost of the clean room space, which is defined by the overall footprint of the equipment and process. Each batch of a PCBT requires its own cleanroom space, which is something that many manufacturers forget to consider when investing in commercial, automated cell therapy systems. Automation can certainly minimize the number of manual cell-handling tasks to provide greater reproducibility, traceability and overall specification compliance, but it does not always offer overall space efficiency. Instead, a preferred economical solution would be to select systems that have been specifically designed to be compact – and preferably stackable. Stackability cannot be exploited if each batch requires its own cleanroom space, but there is another solution: a closed manufacturing solution. With more cell-based therapies receiving greater attention in industry, equipment more suited for the commercial manufacture of PCBTs is coming onto the market, including fully automated, stackable and closed systems where you can fit eight closed systems (translating to eight batches of product) in one square meter. The closed system is a very important feature as it minimizes and eliminates the potential risk of contamination between different unit operations. A closed system also allows for manufacturing to occur in a lower class room with less requirements for environmental monitoring and control.

Contamination control

When discussing cell therapies – or any biological medicines – the potential for contamination is always a concern. For PCBTs, contamination could come from the improper handling of cells during splitting, seeding and changing media – or from any mistake during processing. Cells are very sensitive and you can never be too careful. As it is not possible to sterilize the output of a cell manufacturing process in ways similar to other medical devices, comprehensive cleaning and handling protocols are required to minimize the risk of contamination. Furthermore, in-depth quality control tests must be performed to verify that no contamination occurred. Whatever the cause of contamination, the most important consequence is that the batch will be a loss. In most cases, a lost batch of a biological drug means lost profits, but the consequences are far worse for PCBTs because production is not easy to restart because of the length of time required; in many cases, the patients receiving PCBTs are very sick and cannot afford to wait or restart a process.

To reduce contamination risk, cell manipulation and culture process should be conducted in a fully pre-steriled closed system. When the tissue biopsy or cells are collected from the donor at the clinic, they should be introduced via the hood into the clean system. All subsequent steps of manufacture then take place within the closed system, with one closed-system cell manipulation unit being used for each patient to help eliminate cross-contamination. When dealing with any kind of cell therapy – or any donor biological material – it is standard practice to keep all samples isolated from one another. This actually becomes far more complicated than you might naturally assume when you are in a commercial setting because you could be dealing with more than 10,000 patients per year. When you have that many batches, human error can happen more frequently, particularly if you are managing samples that are not produced in single-use technologies. We also recommend using patient-specific reagents for each cell culture unit, which can be achieved economically and automatically with single-use cell culture units and fluid-contacting

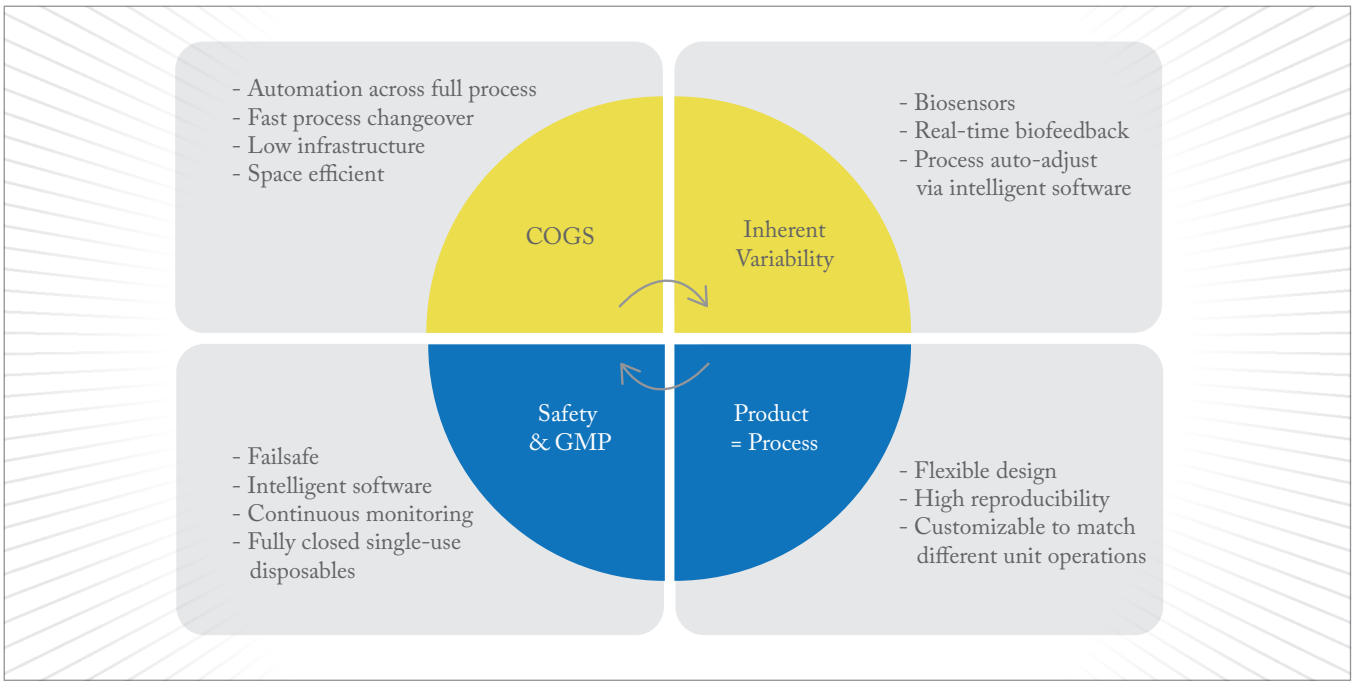


Figure 2. Overcoming the challenges of manufacturing personal cell-based therapies.

components available as a pre-sterilized system that can perform all processing events. Such systems reduce the risk of patient-to-patient contamination to zero – and also avoid validation of cleaning processes for non-disposable equipment (and the associated cleaning costs). With disposable cell culture units, each disposable component can be tagged to a specific patient, which aids in traceability and secures the logistic chain.

Despite best efforts across the industry, most of the current platforms and solutions for the manufacture of PCBTs don't fulfill all the necessary requirements. New technologies, however, are emerging that will enable manufacturers to build safer, more efficient, processes that overcome some of the manufacturing challenges, providing that the manufacturer has a good knowledge of critical process controls. This type of approach can also fit with both centralized and decentralized production models, in the sense that manufacturing production can be centralized in one manufacturing plant in an efficient and economical way, with the products shipped to different point of the care facilities. Or you can use a decentralized model where different smaller manufacturing units are used at the point of care.

Despite the challenges posed, personalized cell-based therapies are an exciting alternative to small molecule and biologics – and really could be the future of medicine. The (bio)pharma industry's perspective on regenerative medicine is maturing and shifting from the cautious role of the observer and venture-capitalist to a more focused approach with active research and clinical development teams. In particular, the industry has seen impressive early clinical results from chimeric antigen receptors (produced by genetically engineering T cells to produce receptors that allow T cells to recognize antigens on tumor cells), which is exciting and also fueling interest. The demand for such therapies could be extraordinary and hopefully new game-changing technologies will help to complete the missing piece of the puzzle for a successful commercial PBCT to meet clinical demand and demonstrate rigorous efficacy.

Manufacturers must learn how to grow cells on a commercial-scale for each patient in a cost effective way, while meeting ever-evolving regulatory and quality requirements. Examining manufacturing strategies and closely evaluating the latest technology is the only way to transform promising products into commercially successful – and affordable – medicines of the future.

Behzad Mahdavi, is VP of Strategic Innovation & Alliances, and Uwe Gottschalks is Chief Technology Officer at Lonza. Nuala Trainor is Director of Biological Programs, and Tim Smith is Chief Executive Officer at Octane Biotech.

Finding Optimal Form

There are many hurdles in drug development, but your chances of success increase significantly if you pay more attention to API optimization from the outset.

The high costs of bringing a new drug to market are notorious and often dominate discussions about the challenges facing today's drug developers. With so much attention focusing on financial aspects, it can be easy to overlook more practical development steps. In fact, formulators face many of the key problems at the very early stages of R&D: how do you optimize the molecule's stability? How do you enhance bioavailability? And how do you select the optimal delivery method? Addressing these issues early – and comprehensively – can lead to less problems down the line, and helps to avoid overly long development times and the associated costs. Long development times, and the selection of the right formulation and delivery platform, have been cited as the top challenges (in addition to cost) for formulators and R&D managers (1).

At the early stage of development, a common problem with the molecule is lack of bioavailability. "70 percent or more of new chemical entities (NCEs) face bioavailability challenges, which often expand beyond solubility and permeability," explains Julien Meissonnier, Vice President of Science & Technology at Catalent "We are also seeing an increasing number of NCEs that, when developed, are not appropriate for their chosen delivery system. Sometimes these compounds eventually reach the market in a sub-optimal form, but they do not realize their true potential, nor meet the expectations and needs of patients. The right delivery technology can make a huge difference."

The early development stage is actually a golden opportunity to make the most critical decisions. During this period, formulators build a huge body of knowledge about the molecule, such as an understanding of its stability, affinities, and particle and bulk attributes, which can be used to dictate and optimize the molecule's future development, final dosage form and manufacturing process. Although there is awareness in the industry that optimization and the use of quality-by-design principles at the early stages of development are directly linked to a product's future success, the big question for many is, how exactly is this achieved – especially when being asked to make formulation decisions quickly.

Knowledge is power

Today's scientists are under significant time pressure. Drug candidates must be screened quickly and, in some cases, the complexity of a candidate is not fully understood when decisions are made. For example, a formulation approach may be chosen too rapidly, resulting in a mismatch with the API. Or perhaps formulation scientists expect one delivery technology to be used, while those further along the development chain are expecting (and preparing) for something very different. It makes great sense for everyone in the development chain to have a single target and a similar outcome in mind; collaborating with experts and connecting the dots between competencies are both important in this regard.

There are many high-throughput salt, crystal-form, and co-crystal techniques, as well as prediction and modeling technologies that can help to optimize drug development. "But there is no one-size-fits-all solution to a drug development problem," says Meissonnier. "At Catalent, our focus is on both applying a structured and science-based methodology, and the best scientific toolkit to accelerate product development. We look at the specific problems that a partner is having with a particular molecule and then assess why these problems are occurring and how they can be solved. We've combined all of our knowledge, expertise and a comprehensive scientific toolkit within Catalent to develop a service that matches viable drug delivery technologies to each molecule and screening programs. We describe it as a solution suite for integrated drug development, and it's called OptiForm. I would say it is the natural evolution of our solutions offering to resolve complex biopharmaceutical limitations."

The preliminary molecule assessment phase of OptiForm Solution Suite was originally developed by GlaxoSmithKline, which used technologies to support its internal screening programs at the candidate stage. It's now been used for more than 700 candidates. Catalent integrated the platform into its service offering in 2010 – and has been building and expanding on the service ever since so that it exists as both a set of tools for assessing candidates, and for selecting the right enhancing formulation to progress in preclinical and clinical studies.

According to Meissonnier, identifying the solution is not just about using the right technology – it's also about the mindset and expertise behind it. It's difficult, however,

to be an expert in every technology. Successful drug development calls on a range of disciplines including analytical science, organic chemistry, physico-chemical properties, materials science, crystal engineering, statistical analysis and biopharmaceutics, all working in concert to reach the optimal, patient driven outcome. Catalent has essentially created networks of experts who understand the correct utilization of each enabling drug-delivery technology.

The path to optimization

The ultimate goal of API optimization is a final drug form and delivery system that makes sense for both the molecule and the patient. Broadly speaking, this optimization process can be divided into three stages. The first stage involves API characterization and salt, crystal-form, and co-crystal screening. Using a solubility limited absorbable dose (SLAD) model in this early stage is also key to building an early formulation screening scenario that will allow you to reach the necessary drug exposure and the ability to escalate the dose.

"We call this the ranking and risk assessment stage – or the 'Assess' stage. High-throughput screening tools applied to solid state analysis, combined with modeling techniques, help to identify the most stable solid-state form," says Meissonnier. The molecule is then ranked according to the Developability Classification System, which as James Butler from GSK notes (2), is an effective way of differentiating drugs based on their developability characteristics, such as their solubility to dose relationship, permeability, and risks such as chemical and physical stability, and processing risks in dose form selection. OptiForm has a variety of automated tools and workflows to support this phase and to assess more accurately the complete dataset earlier and faster.

The second stage 'Enhance,' encompasses the parallel screening of formulation approaches. After the first stage, there should be a good understanding of the molecule and any potential risks that may limit drug exposure. Now is the time to look for more specific formulations and solutions, such as considering particle size reduction or other approaches to enhance solubility and bioavailability. Feasibility studies and rapid prototyping should be used to check for effects on drug exposure and the potential for future dose escalation; all selections should be made with these two critical factors in mind. Evaluating all the available technologies requires experts in each area who can assess the benefits.

The final stage is 'Deliver', which comes after the 12 week screening program. It is at this point that the molecule's true value – and the value of early optimization – will begin to materialize by providing animal PK study materials, a risk ranking of formulation approaches, and a recommended path to first-in-man studies to reach exposure and successful dose escalation.

The recommendations go beyond Phase I. "After the first human study, you will have even greater knowledge of the drug and its potential therapeutic effect. Now you need the complimentary enhancing technology that will optimize the final profile of the drug and help resolve issues such as variability, modulating the release profile to match the therapeutic index, and maintaining exposure without affecting the release profile or product viability," says Meissonnier.

Connecting the dots

High-throughout screening technologies and services have seen tremendous uptake by the industry, but, according to Meissonnier, the real value does not simply lie in identifying promising assets early on, but in being able to connect the asset with an appropriate form of development – and using the knowledge as a science-driven decision tree for the product's entire development. After all, the knowledge generated in early development can also benefit manufacturing later on; it's no use finding the right formulation only to realize that it cannot be commercially scaled.

"We were confident about bringing our service offering to the market and our customers because we were convinced that it was a real industry need. We're proud that our customers have embraced it – to the point that some consider Catalent as an extension of their own R&D lab," says Meissonnier. "It's gratifying to be able to provide something so valuable. Making a difference is what makes us scientists get up in the mornings with a desire to work on the most complex projects."

The Stages of OptiForm

OptiForm Solution Suite can enhance bioavailability in 12 weeks.

ASSESS – By applying proven high throughput screening tools, detailed pre-formulation data are collected to characterize the molecule's potential challenges.

ENHANCE – Scientific advisors determine the feasibility of the proposed drug delivery approaches, select prototype formulations, and collect preliminary stability data.

DELIVER – Within 12 weeks, a technical report will be provided with a recommended path forward, accompanied by animal PK study materials to maximize chances to reach exposure and dose escalation.

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1. *The 3rd annual drug delivery landscape survey was sponsored by Catalent Applied Drug Delivery Institute. For more information, visit www.drugdeliveryinstitute.com*
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Harnessing Emerging Markets

The emerging markets are home to 85 percent of the world's population and represent a potentially massive source of untapped consumption. How can the pharma industry capitalize on this huge, underserved market?

By Ambuj Jain

Regardless of industry, whether it be smart phones or medicines, emerging markets hold enough 'pockets of non-consumption' to be of commercial interest. However, issues such as per capita income and low levels of reimbursement have led some to wonder how deep these pockets are. The aim of our recent workshop at Cambridge Consultants was to bring together senior executives from across the pharma industry to explore the sustainable growth potential in emerging markets, particularly the Indian market, and assess the opportunities and challenges of the next 5–15 years. The findings were published in a recent report (1). Here, I share some of our key discoveries and offer advice on how to make your journey into the emerging markets a successful one.

A rebalancing act

If you single out any multinational pharmaceutical corporation, be it Pfizer, Novartis, GlaxoSmithKline, or Abbot, and look at its annual performance over the last 6-7 years, you will see rather low levels of revenue growth in the US or European markets – maybe 1-4 percent at best. Now consider this: the corresponding figures from emerging markets are in the 15–20 percent range.

How? The trend is part of a global rebalancing away from mature economies. Whereas industries previously saw challenges in the emerging markets, they now see opportunities. And the pharmaceutical industry too is embracing this change; multinationals are setting up local operations, often giving them significant autonomy, and exploring numerous innovative arrangements to access local markets. Indeed, emerging markets should expect to receive 30 percent of global pharmaceutical spend in 2016, which I predict will increase to 35 percent in the next 5 –7 years. Currently, a large organization may have an 80/20 revenue split between developed and emerging markets, but this too is evolving. Soon, I believe these companies may start moving towards a 65/35 split. It's all part of a trend that's occurring in all industry sectors.

We can see the potential for growth in an emerging market if we take an example from another industry: smart phone technology. Four years

ago, Apple India had a revenue of around $250 million and was probably overlooked in boardrooms across the world as contributing only a tiny slither of Apple's total $80 billion pot. But something surprising happened in the last four years – Apple India consistently doubled its yearly revenue and now, in 2015, is chasing two billion dollars (3 percent of the total Apple revenue), a number that is growing exponentially. As Apple India's revenue increases, so too does its influence. I expect the pharmaceutical market to evolve in a similar way, especially given the growing Indian middle class, with its burgeoning spending power. Ultimately, this has to translate into growth in the pharmaceutical market. And it's happening already – look at Abbot Pharma. In the last few years, Abbot has started chasing a billion dollars in revenue in the Indian market alone, and its projected revenue growth rates are 16–20 percent.

However, it would be a mistake to think that all emerging markets are the same, or that any of them will be easy markets to enter. There are still unique challenges to address. When deciding whether to enter a market, an organization has to balance the demand and supply considerations with its own company culture, resources and vision. For example, a company that needs a very quick return on its investment should probably focus on a smaller market, such as Vietnam, where you can get a product to market quicker and start making returns that can then be used to enter bigger markets like South Africa.

Untapped consumption

There is a misconception that emerging markets are only interested in low-cost mass-market products, but it is possible to price the product according to the value you are offering. Each emerging market has its own intricacies and idiosyncrasies, which demands the tailoring of specific commercial and production models orientated around accessibility and affordability to ensure value at the right price. Many emerging markets are characterized by high levels of out-of-pocket expenditure for medications, but we should also consider that over 208 million households have an average income above $10,000 per annum – which is more than the combined income for many of households in the US and EU. There is clearly a significant chunk of the population that can afford some level of healthcare expenditure. In addition, we're also seeing emerging markets starting to converge with the developed markets in some aspects of healthcare dynamics.

"There is a misconception that emerging markets are only interested in low-cost mass-market products."

Like mature markets, emerging markets have many stakeholders in the value chain. But a significant difference between mature and emerging markets always used to be the identity of the payer. In developed markets, the payer is the government (for example, the UK) or an insurance company (for example, the US). In these markets, a patient is entitled to receive medicine or treatment, but someone else funds it. Until a few years ago, people living in emerging markets had to pay out of their own pocket to get their medication, which essentially meant that most people didn't receive treatment. Recently, some governments, such as the Indian government, have been putting more money into public health, with a focus on making healthcare affordable for their population. At the same time, private insurance or social insurance systems are expanding in many countries. The pockets of untapped consumption we spoke of earlier can now be accessed.

Regulatory roadmaps

Before companies start establishing local operations in a particular emerging market, they should invest time and effort in building a close collaboration with the government of that country. Close liaison with policy makers may provide valuable insights into market dynamics and uncover collaboration opportunities that could otherwise be missed. Furthermore, many emerging markets have some elements of protectionism in their industrial policy, and it may be impossible to access the market without going through government channels. Even so, governments will probably try to negotiate a lower price so that you will end up selling at a lower margin, but then you will be able to supply a high volume to that market. In addition, the government may take care of distribution channels, product awareness and making the product available to the patient, which means you can start making revenues much earlier. In some cases, the annual volume and price may be guaranteed over a set period of time, giving the manufacturer a valuable level of certainty. However, nothing is free; in exchange for the above benefits, the government is likely to require significant local investment or technology transfer. Nevertheless, all things considered, I believe that companies would benefit from examining the potential for

"It would be a mistake to think that all emerging markets are the same, or that any of them will be easy markets to enter."

their products to make their mark in emerging market.

Another key parameter that affects the pharma market in an emerging economy is the nature of the regulatory environment. Some countries have rigorous regulatory regimes, while others have none. Markets that don't have regulatory guidelines are often perceived as being unsophisticated. However, a lax regulatory regime can be an advantage, since a market with a lower threshold may be a convenient entry point for an innovative product, allowing it to rapidly gain in-market data and momentum. But it is important to remember that these markets do eventually adopt guidelines from the US or Europe, resulting in good manufacturing practice (GMP) regulations in the long term. And that means that products approved in these markets should also be acceptable to the regulators in mature markets.

The importance of innovation

Investment in innovation is important in a market like India, which has 80 percent branded generic saturation, multiple iterations of the same drugs and a dwindling pipeline of new drugs. Regarding areas of focus for new products, I believe that we can drive innovation through reformulation (e.g., extended release tablets, syrup formulations of unpalatable drugs, or nasal delivery formulations of drugs that are currently given by injection) and novel drug delivery devices. New drug delivery devices will be important because the disease profile is changing in India. Infectious diseases are being replaced by chronic, so-called Western diseases, such as diabetes, cardiovascular disorders, hypertension, chronic respiratory disorders, neurological diseases, and so on. Innovation is investment intensive, so to get an adequate return it may be necessary to 'cluster' countries that can absorb a particularly innovation you are trying to drive, rather than focusing on just one market.

As an example of drug delivery device success, let's look at the Sanofi insulin pen. By outsourcing design to the UK and manufacturing the pen in India, Sanofi was able to create a quality product with lower costs. Product uptake has been very strong, suggesting pent-up demand (although sales have been assisted by a strong marketing and branding campaign). But the main point is that Sanofi was able to offer the right product at the right value, and, as a consequence, many more patients are now able to afford insulin pen therapy. In fact, the product has been so successful over the last two and a half years that it has significantly changed the way emerging markets are looking at insulin therapy.

In brief, a focus on innovation and technology is important, but it has to be well researched, keeping the patient and other stakeholders involved in the overall system – that is how to make a real impact.

Emerging ecosystems

Each emerging market is developing its own ecosystem involving patients, pharmacists, insurance companies and the government. The way in which pharma companies collaborate – and engage – with all of these stakeholders will affect the position and success they achieve in an emerging market. Companies must be aware of the important trends that are manifesting in these markets. For example, patient services are expected to grow significantly in the next 5 to 10 years, driven by the evolution of changing disease profiles. And the increasing incidence of lifelong chronic therapies will drive patient desire for new drug delivery techniques, especially systems that allow patients to self-administer drugs at home.

Another key trend is that of "reverse innovation". An example of this comes from GE Healthcare's Indian innovation center, which developed a lower-priced version of a portable ECG device specifically for the subcontinent. It only has about 80 percent of the features of the standard ECG machine sold in the US, but still works effectively. It has achieved a great deal of success in India and a few other markets, which is why reverse innovation is important: a product that was developed for the Indian market, at the right value and at an appropriate price (so that many more patients were able to afford it), will likely return to the Western market and be successful there too. In other words, by focusing on the needs of emerging markets, multinational pharmaceuticals will also be serving – eventually – the mature markets too.

Ambuj Jain is India general manager at Cambridge Consultants.

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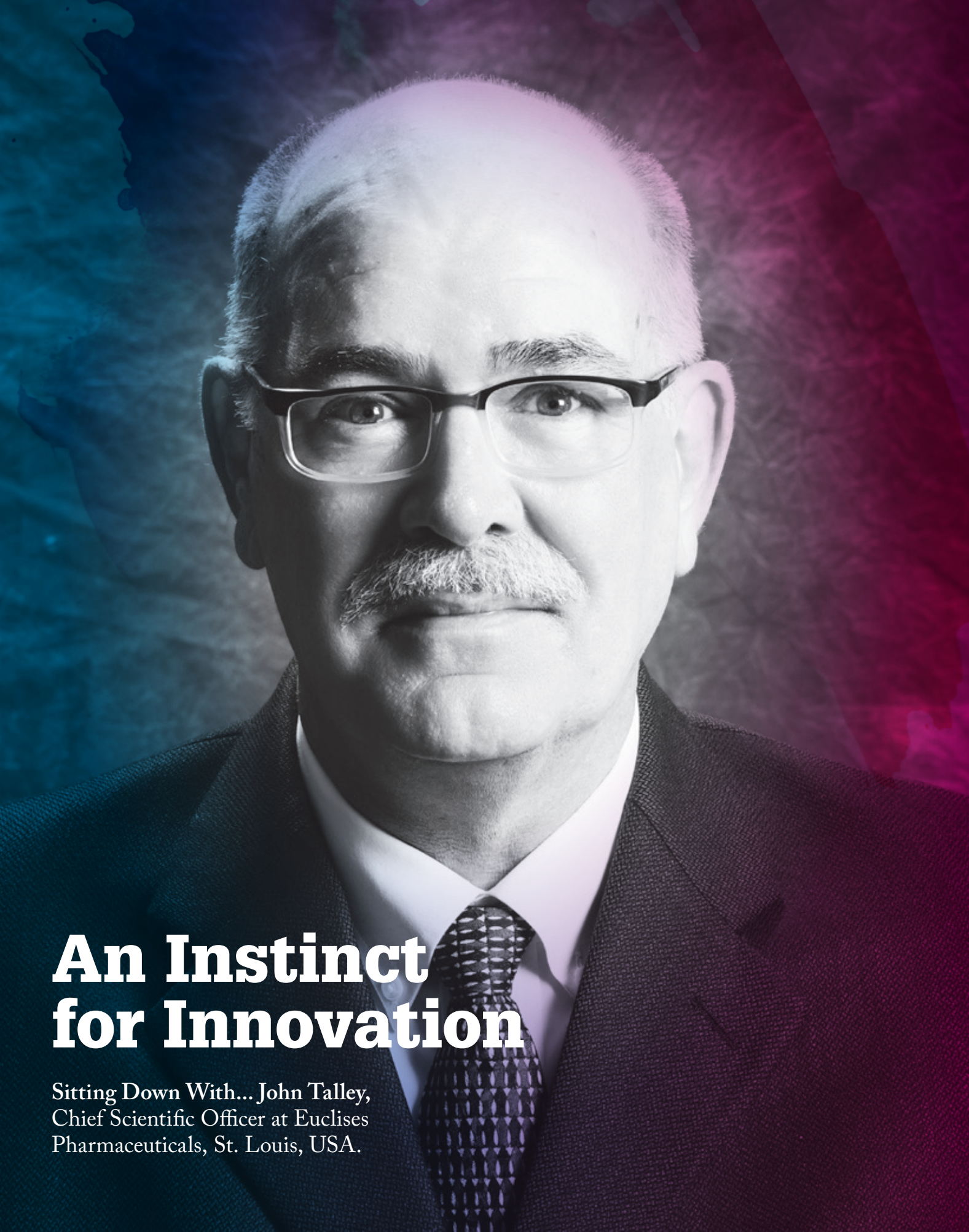

An Instinct for Innovation

Sitting Down With... John Talley, Chief Scientific Officer at Euclises Pharmaceuticals, St. Louis, USA.

You were originally destined for a career in a greenhouse…

My father owned a greenhouse and I thought I would be a business major at university and take over. But after one class, I realized that business was dreadfully boring! I decided to take a mixture of chemistry and biology classes instead, which I liked much more. I graduated with a Bachelor of Arts degree in science, but I lacked focus. During my undergraduate research I'd worked with a guy who had obtained his PhD from Paul Gassman; they conspired to recruit me. I ended up working with Paul at the University of Minnesota. That's when I fell in love with organic chemistry. Over my career, I've had the chance to do lots of interesting research. And I'm glad I'm not running a greenhouse.

Why did you choose industry rather than academia?

I thought about getting a post-doc position and finding an academic job, but I had paid my way through college and I'd been living below the poverty line, so I wanted to get a job. I ended up working for a research lab in New York. It was the golden age of research and it was a very appropriate place for great ideas – Thomas Edison's desk was in the lab. I loved it there, but over time, the company got a new CEO and the environment became much more bureaucratic. Eventually I moved to Monsanto, which had just bought G.D. Searle and was starting to focus on medicinal chemistry and drug discovery.

What was the first commercially successful project you worked on?

Around 1988, we saw a paper published in Nature about a mutation of the HIV virus; the HIV protease was mutated and this rendered the virus particle non-infectious. In the 80s, HIV infection was invariably fatal and this seemed like a potentially good target for treatment. We targeted the pathway that the virus used to reproduce itself and we found some really interesting compounds that were eventually licensed to and commercialized by other companies to become the drugs Agenerase, Lexiva, and Prezista.

How did you get involved in developing COX-2 inhibitors?

In early 1992, while the HIV project was still going on, I was asked to work on a project to identify an inhibitor of the cyclooxygenase-2 (COX-2) enzyme. My main role was to look at structures made by other people and I came up with the idea of making a hybrid structure. By 1993, we had a core structure that had great in vitro and in vivo activity in animal models of inflammation and pain. Ultimately, it led to the development of Celebrex (celecoxib). It was approved by the FDA on the last day of 1998. A lot of people at different facilities in Searle worked on this project – teamwork is one of the most important elements in drug development and discovery.

How do you cope when molecules fail?

When you're in discovery, you never know if a molecule that you advance and nominate for pre-clinical development and clinical development is going to make it, so you just keep on making new analogues! It's really satisfying when something works out but many things don't. I was involved in identifying a drug that unfortunately ended up being pulled from the market because of some severe side effects, which affected a handful of people. It wasn't the kind of thing that you could ever see during the clinical trial; post-marketing surveillance led to its withdrawal. It wasn't a bad decision, but the drug actually helped thousands of people in its lifetime.

How has the process of discovering new molecules changed?

Over the years, some companies have tried to increase the productivity of drug discovery with the idea that if you make lots of compounds then you will probably make a lot of drugs. But I've always felt that finding drugs is not a statistical activity, rather you end up with even more compounds that go nowhere. Today, you could argue that drug discovery has been industrialized with the advent of screening and computational chemistry. But I think there is real value in having people at the bench, looking at the raw data and using their own insights and experience to identify new drug candidates. When I consider all my discoveries, I was in the lab making the compounds and had real intimate knowledge of the chemistry and the physical properties of the molecules.

"It's really satisfying when something works out but many things don't."

What approach to drug discovery does Euclises have?

We try to identify unique chemical structures with some known biological activity and then attempt to fix any shortcomings. Over the years, a lot of people have talked about drug re-purposing, but that's not what we're trying to do. We dig things out of the literature that look interesting, but that don't have the desirable characteristics to be advanced into clinical trials. We're using our experience to try and do more. I'm actually part of the management of Euclises, but in an ideal world I'd be in the lab with a cellphone headset in case somebody wanted to call me!

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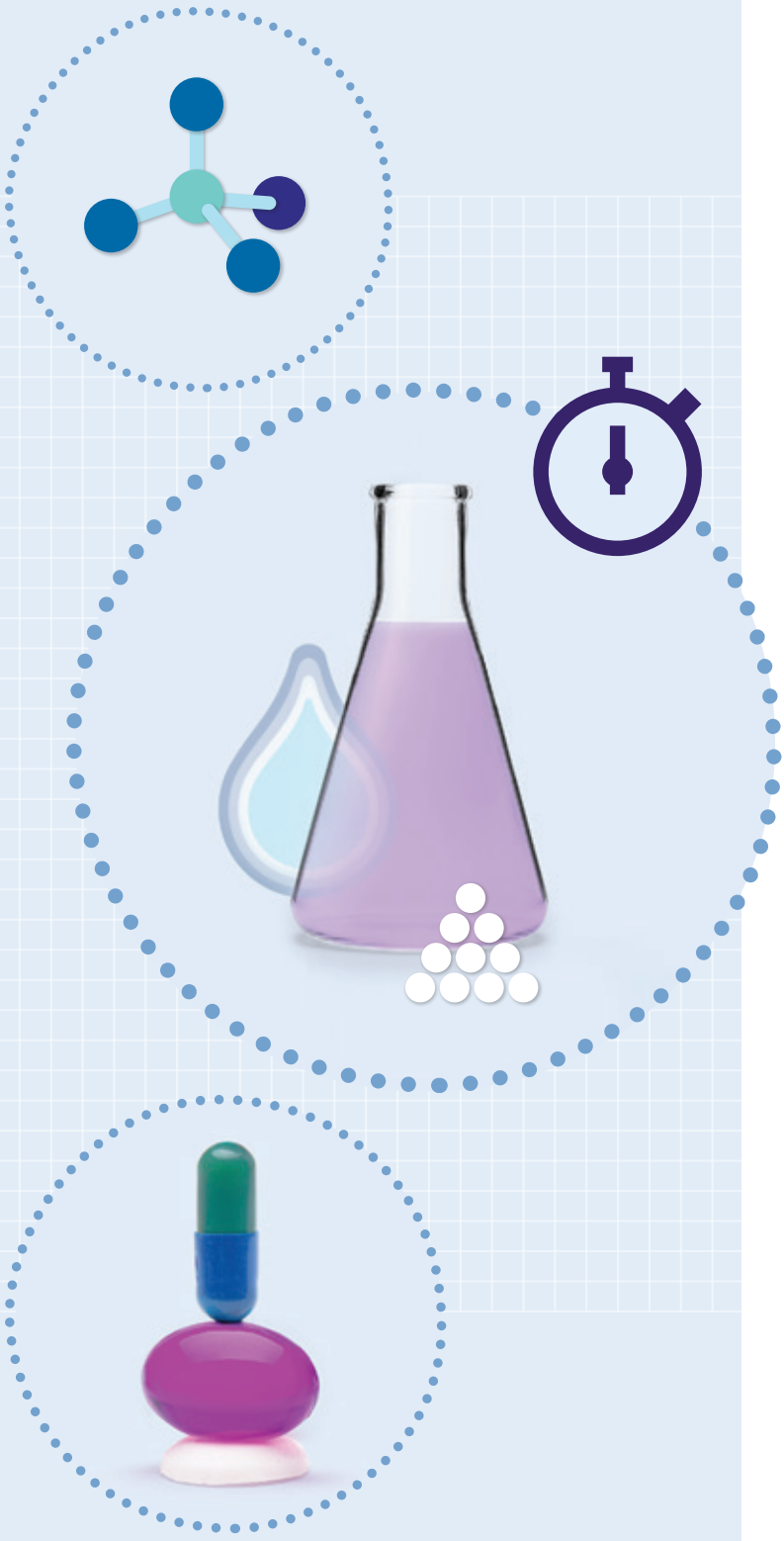

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