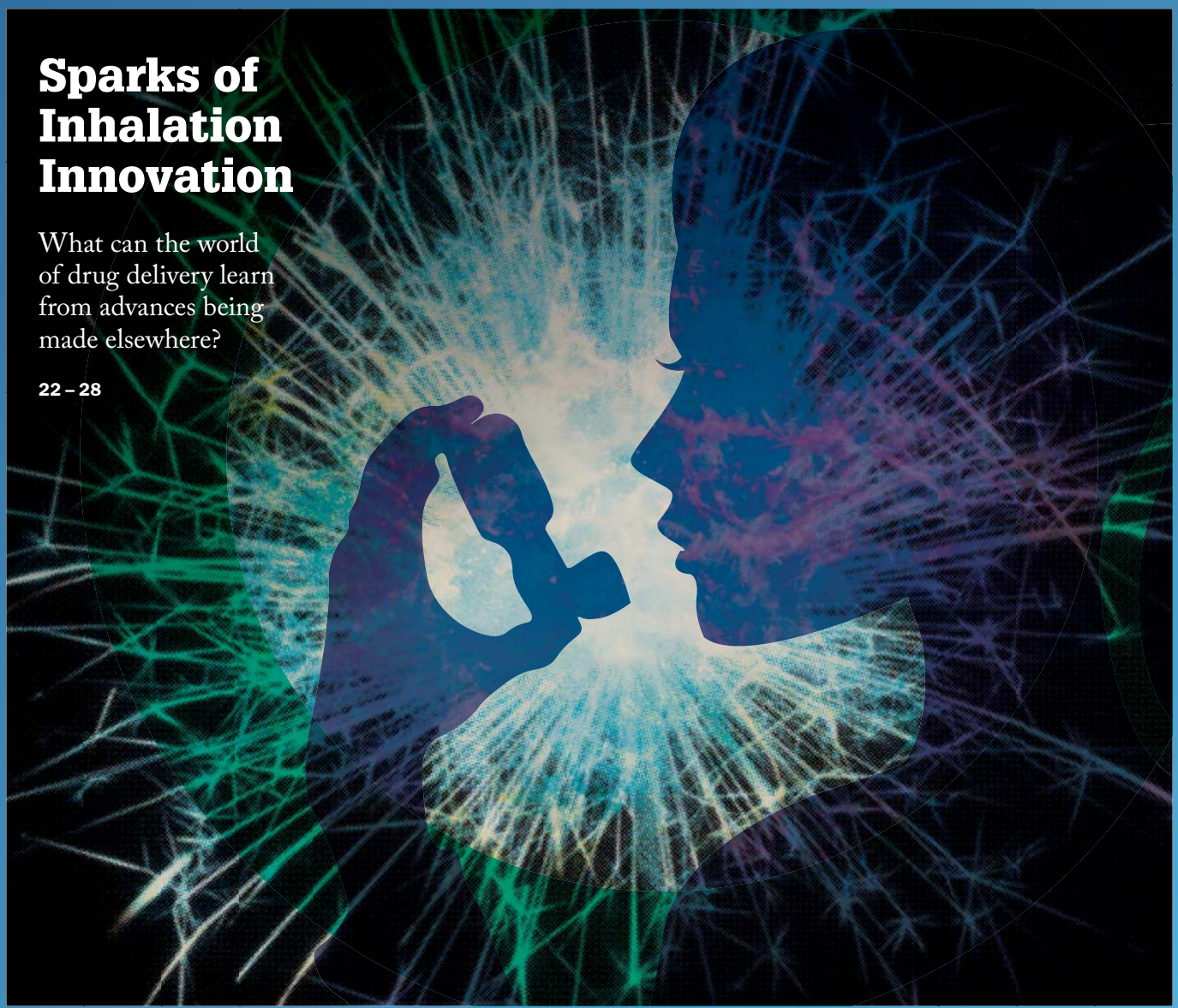
NOVEMBER 2015 # 13

the Medicine Maker



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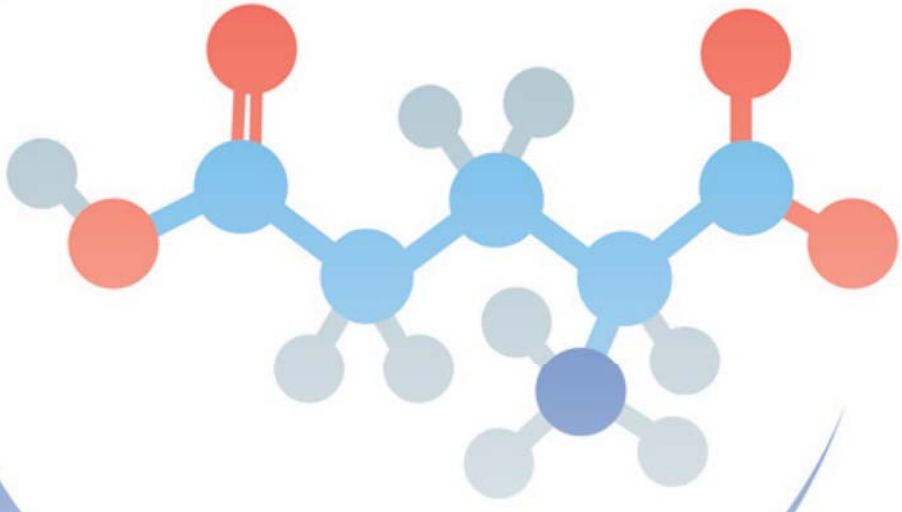

Will You Enter the Humanity in Science Award?

The 2016 Humanity in Science Award will be presented on May 10, 2016, at Analytica 2016, with the winner receiving a grand prize of $25,000.

What is the Humanity in Science Award? The award was launched by our sister publication, The Analytical Scientist (https://theanalyticalscientist.com), in association with Phenomenex, in 2015 to recognize and reward a project involving analytical science that has had a positive impact on people's lives.

The recipients of the 2015 award, Peter H. Seeberger and Andreas Seidel-Morgenstern, directors at Max-Planck Institute, developed a groundbreaking production process for producing low-cost malaria medicines, which we covered in the June issue of The Medicine Maker.

Could medicine be the focus of the 2016 award too? After all, analytical science is essential in the research, development and manufacture of nearly all medicines.

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More details are available at: www.humanityinscienceaward.com

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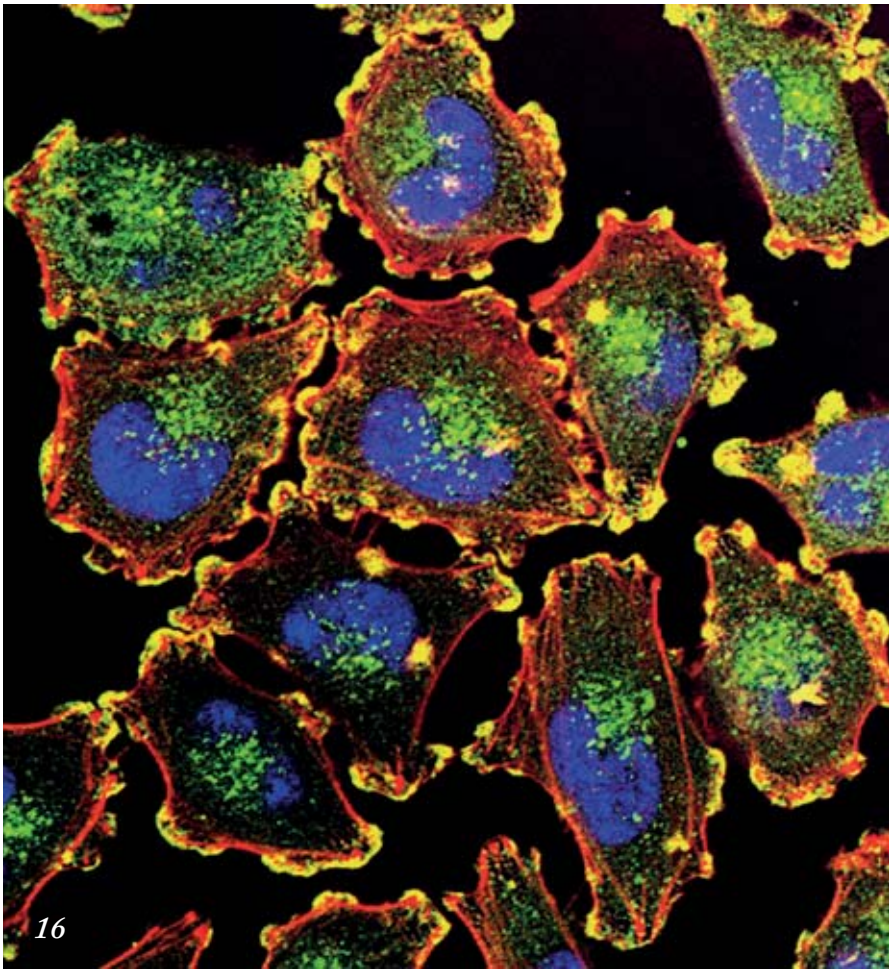

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Round and round she goes, where she stops nobody knows.

Mylan's long-running takeover bid for Perrigo has failed. After a pitched battle – sometimes descending into outright name-calling – Perrigo fended off Mylan for good.

The Mylan-Perrigo story is just a tiny sample of the merger and acquisition (M&A) fever that has gripped the industry over the past few years. Indeed, scores of companies have been racing to secure the best partnerships, hoping to boost growth and fill pipelines. Some companies are pushing for mergers that don't simply add to their businesses, but instead transform them; an obvious example is Allergan (formerly Actavis). Originally a generics maker, its 2014 buyout of Allergan and subsequent divestment of the original Actavis 'legacy' generics business, has enabled its reinvention as a specialty drugs pharmaceutical company. Now there is talk of selling the company to Pfizer in a $100 billion deal...

Where will the M&A juggernaut stop? Will bigger companies swallow up their rivals, until only the strongest – or leanest – survive? Or will falling share prices and tightening tax loopholes eventually dampen enthusiasm amongst investors for corporate mega-mergers? In either case, the current M&A fever will burn out eventually, but what will the outcome be for the industry, its workers and the wider population?

In the short-term, takeover bids are rarely good news for drug company employees. Mylan are downplaying the significance of the bungled Perrigo takeover – and though no one likes to fail, another deal will almost certainly come along soon enough. Meanwhile, celebrations at Perrigo are likely to be short-lived for some, given that the company has pledged to cut 800 jobs in the coming months.

It remains to be seen whether all this M&A will leave the industry better off in the long term. Could it be that by reducing diversity, the industry risks the very thing on which its survival depends – innovation? The increasing trend towards 'buying in' innovation may be necessary to counteract failing pipelines, but if a pharma company is no longer creating new drugs, does it lose something fundamental to its identity? And how will the drug discovery ecosystem cope with that shift? The last round of mega-mergers, at the turn of the millennium, did little to solve big pharma's pipeline woes…will today's newly minted deals fare any better?

Charlotte Barker
Editor

Contributors:

Peter Calcott

A native of the UK, Peter Calcott presently lives and works in Berkeley, California, as a consultant to the pharmaceutical and device industry, with clients worldwide from North America and Europe, to the Far East and South America. To say Peter enjoys traveling is an understatement. He has qualifications from UK universities; he's been a faculty member at McGill University in Canada; and he has worked in various large pharmaceutical companies across the US, including Bayer (Berkeley) and GlaxoSmithKline (Philadelphia). As well as consulting, he publishes articles, presents at international meetings and teaches part time on faculty at the University of California, Berkeley.

Peter explains why you may need a 'Plan B' when it comes to outsourcing on page 36.

Olivier Leclerc

As a Director in the Southern California Office of McKinsey & Company, Olivier Leclerc advises clients in the pharmaceutical, biotech, and medical products industries on strategic and operational improvement issues. "My recent experience includes studies in portfolio prioritization for early stage technologies, product launch strategy, digital strategies, post-merger management and pricing/reimbursement," says Olivier. "I lead the McKinsey Oncology Sub-Practice in the US, as well as the Digital service line for McKinsey Global Pharmaceutical and Biotech Practice."

Digital health is a buzz word and Olivier is at hand with advice in this area on page 47.

Suyoung Lim

Suyoung Lim started her career as a research associate, but later moved into regulatory affairs at a pharmaceutical company in Korea. she says, "I realized that as much as the company wanted to penetrate the global market, they seemed to know very little about global regulatory affairs and regulations. So I continued my education in the same field at Johns Hopkins University in Bioscience Regulatory Affairs." Today, Suyoung works for LG Life Science in Korea as a regulatory affairs and late-stage project leader. Her regulatory affairs experience is not limited to Korea, but also includes all major markets.

Suyoung summarizes her research work on biopharmaceuticals on page 18.

Rasmus Hother le Fevre

Today, Rasmus Hother le Fevre is Managing Director and Corporate Vice President at Novo Nordisk Pharmatech A/S, but interestingly he started out with an MSc in Forestry from the University of Copenhagen before studying Executive Training, General Sales, Merchandising and Related Marketing Operations at Wharton Business School. He joined Novo Nordisk A/S in January 2000 as a Production Planner and held various roles within the company before rising to his current position in 2012.

On page 19, Rasmus talks us through the challenges of rebranding a company.

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Upfront

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

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

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Plant Protein Potential

Can lettuce really help biopharmaceuticals turn over a new leaf? Researchers who have bioencapsulated blood-clotting factors inside salad leaves as a means to create affordable biologics certainly think so

Many biopharmaceuticals are far too expensive to be used by the majority of the world's population. To that end, the search is on for cheaper and better ways of making drugs. And the answer could lie in plants. Henry Daniell, along with colleagues from the University of Pennsylvania School of Dental Medicine in the US, have demonstrated that it is possible to produce a protein drug bioencapsulated in lettuce leaves that can be taken orally by patients (1).

Using plants as an abundant source of medicine is certainly nothing new – mankind has been benefiting from nature's arsenal since ancient times. In fact, plants are at the heart of Peter Seeberger and Andreas Seidel-Morgenstern's low-cost antimalarials – work that received the 2015 Humanity in Science Award (2). However, the use of plant-based manufacturing platforms for biologics is a relatively new and exciting area. Daniell, who has been working in the field for some time, previously focused on tobacco plants, which are not suitable for human consumption. More recently, he turned to something more edible: lettuce.

We spoke to Daniell to find out how lettuce can potentially help with hemophilia.

You appear to be driven by the need for low-cost biopharmaceuticals...

Absolutely. Most protein drugs on the market today are not affordable for the vast majority (>90 percent) of the global population. One third of the global population earns less than $2 per day and the market capital of biotechnology companies was $1.25 trillion in 2014. The sale of protein drugs, which equated to $130 billion in 2013 exceeds the GDP of most countries. Insulin is necessary for treating the global diabetes epidemic and has been around for over 50 years. But we don't do R&D for insulin anymore even though it remains so expensive that most of the world's population can't afford it. I wanted to do something about this and develop a way of making protein drugs more affordable.

The current production costs of protein drugs are mainly dictated by the operation and daily maintenance of sterile fermentation facilities that cost hundreds of millions of dollars. With traditional biopharmaceutical manufacturing, you also need to purify host cells using columns (which also costs millions of dollars), and then you need a reliable cold chain for storage and transportation. Most biopharmaceuticals also require sterile injectable delivery and also have a relatively short shelf life. Plants can help to eliminate these costs. Protein drugs made in plants can be stored in lyophilized cells and orally delivered without the need for purification, cold chain or sterile injections.

Could you share some examples of your work?

I've demonstrated that plant-based biopharmaceuticals could potentially treat metabolic or genetic disorders, including diabetes, hypertension, retinopathy and Alzheimer's disease (3-5). We also recently received the top paper award from the American Heart Association for oral delivery of angiotensin to prevent or treat pulmonary hypertension.

Recently, in collaboration with the Roland Herzog Lab in Florida, we focused on hemophilia. Some protein drugs produce toxic antibodies when they

are injected because the immune system cannot tolerate them. For example, when hemophilia patients are injected with blood clotting factors they can develop inhibitory antibodies. It's a problem that affects a large number of patients and there is no effective treatment to remove these inhibitors other than ITI (International Team for Implantology) protocols, which involves using excessive doses of clotting factors to saturate the immune system. Such a treatment costs more than $1 million per patient, which is clearly not viable for most of the world's population.

We have produced clotting factors in lettuce cells to teach the gut immune system to tolerate this drug. We introduce the therapeutic gene into the lettuce chloroplast genome using the gene gun; coagulation factor IX, or FIX is fused with cholera toxin B subunit to enhance delivery across the gut epithelium. The plants are then grown to maturity, and lyophilized and ground down. The freeze drying step is used to remove water and to protect the drug from any protease activity.

Blood clotting factors expressed in the plant cells (chloroplasts) are protected from acids and enzymes in the stomach because they are bioencapsulated within the plant cell wall. Gut microbes can then digest the plant cell wall and release the clotting factors in the gut lumen, where they are directed to the immune system by specific tags. This method facilitates development of tolerance to specific proteins. We've tested it with repeated injections of clotting factors.

Why lettuce?

Actually, we first developed this oral delivery system in tobacco cells, which are very easy to work with. We did a lot of experiments with mice, but the FDA would not approve protein drugs made in tobacco for oral delivery. So, we developed the lettuce system – and it works better than using tobacco. Our drug was efficacious across at least a 10-fold dose range, and there are also potential benefits in terms of shelf-life. Our work shows that lettuce cells can be stored at room temperature for up to two years, without any negative impact on the efficacy of blood clotting factor expressed.

What were the main challenges?

There were many! Achieving a high level expression of human blood proteins in plant cells was a major challenge and it took at least a decade to develop this system, first in tobacco and then in lettuce. Next, I had to develop a method to get proteins delivered across the gut epithelium into the circulatory system or immune system. And we needed to resolve the challenges associated with delivering the right dose.

The method has been submitted for FDA approval. What are the next steps in your work?

The scale up of our work in a cGMP facility is discussed in our paper (1). I can't disclose names of major pharma companies due to confidentiality agreements, but I can say that things are moving forward rapidly. Based on my experience, the FDA is eager to approve safe and affordable protein drugs and I'm excited by the future prospects.

I am also eager to use this technology to develop vaccines against infectious diseases. The Bill and Melinda Gates Foundation is currently funding our research to develop a polio vaccine that doesn't involve the use of live virus or a cold chain. Many problems are associated with the currently used oral polio vaccine (OPV), which is used in many developing countries that cannot afford the inactivated poliovirus vaccine (which is the one used in wealthier regions). We need to develop alternative methods to reduce dependence on OPVs.

What are your thoughts on the future of plant-based biopharmaceuticals?

Some drugs made using plant-based methods are already on the market. For example, two years ago the FDA approved a new treatment for Gaucher's disease, a lysosomal storage disorder caused by mutations in the gene encoding glucocerebrosidase (GCD). The treatment is an enzyme replacement therapy using recombinant GCD made in carrot cells. Purified protein is administered intravenously twice a month.

It is a major challenge to think outside the box and develop a new technology. For example, the IT revolution changed the way we communicate and this dramatically decreased the cost of communications. I'm sure many international scientists painfully recall the prohibitive cost of phone calls from the US to home countries (costing more than rent) two decades ago... Technological revolutions bring with them incredible benefits. It is now time for us to see a revolution in reducing the cost of protein drugs – and I really think we are well on way to the finish line to making this happen.

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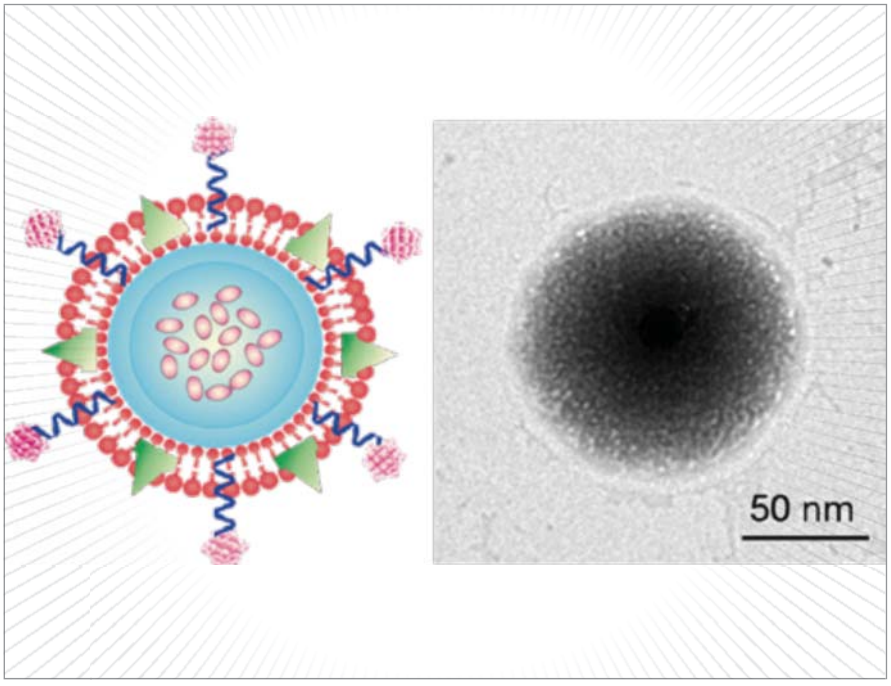
Drugs in Disguise

How to dress drugs to help them survive in the bloodstream



Left: Schematic design of the TRAIL/Dox loaded platelet membrane-coated drug delivery system. Right: A transmission electron microscope image of the drug delivery system; the black part is the synthetic core nanoparticle; the outside shell is the platelet membrane.

A problem with certain cancer drugs is that the body recognizes them as foreign entities and tries to eliminate them, meaning that they don't survive in the body long enough to be effective. One potential solution is to coat the drug with a cell membrane from the patient's own cells so that it remains undetected. Zhen Gu, assistant professor at North Carolina State University, and a collaborating research team at the University of North Carolina at Chapel Hill have developed one such drug delivery system that coats a drug with platelets membranes (1).

"The idea was inspired by the relationship between platelets and tumor cells in the body. When a tumor cell separates from its primary tumor site, it enters the blood vessels and begins circulating in the bloodstream. The platelets stick to cancer cells – aided by a specific ligand-receptor recognition (the P-Selectin proteins on the platelet are recognized by the CD44 receptor on the cancer cell) – and the platelet and cancer cell then travel together to a new site to form the metastatic tumor. The platelet helps the cancer cell survive in the bloodstream," explains Gu.

Recognizing that the platelet interaction could also be exploited to help drugs survive in the body, the team set about creating a platelet-mimicking drug delivery system. "Instead of coating the nanoparticle with multiple proteins expressed on the platelet, we decided that using the whole platelet membrane would be an easy and complete way to generate a platelet-mimicking drug delivery system. We extracted blood from mice, isolated the platelets, then purified and collected the platelet membrane," says Quanyin Hu, lead author of the paper and a PhD student in the universities' joint biomedical engineering program.

Two drugs were selected for the study; tumor necrosis factor inducing ligand (TRAIL), and the small-molecule drug – doxorubicin (Dox), although Hu believes that the approach could be applied to any drug. TRAIL was chemically conjugated on the surface of the platelet membrane and Dox was loaded into the synthetic nanoparticle core to create the platelet-drug system. "The transmission electron microscopy displayed the platelet membrane coating as a core-shell structure," adds Hu. "After being coated with the platelet membrane, the drug can circulate for up to 32 hours, compared to just 6 hours without coating."

After the platelet-drug comes into contact with a cancer cell, the TRAIL drug is well positioned to attack the membrane. Once internalized by the cancer cells, TRAIL enters the lysosome where the acidic environment breaks down the structure, freeing Dox to do its work.

For now, the approach has only been tested in mice. Gu says, "The next step will be scale-up of the platelet membrane-coated drug delivery system and then testing its efficacy on larger animals. Given the important functions of platelets in several physiologic and pathologic processes, we also want to investigate using the platform to treat other diseases, such as vascular-related diseases and inflammation." *VB*

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Breaking Bad Language

Can certain buzzwords really sway public perceptions of a new drug?

Don't call it a breakthrough unless it really is, say US researchers. Lisa Schwartz and Steven Woloshin, from the Dartmouth Institute, and Tamar Krishnamurtia and Baruch Fischhoff from Carnegie Mellon University are concerned that labeling a new medication as a "breakthrough" drug might lead to an exaggerated belief of how well it actually works. The FDA's 'Breakthrough Therapy' designation is an expedited regulatory pathway that was introduced in 2012 to accelerate the development and review of drugs that tick certain boxes; for example, those that treat serious or life-threatening conditions or demonstrate a substantial improvement over available therapies.

"FDA press releases and media reports often refer to these as 'breakthrough drugs,' which implies a major advance. However, the designation is often awarded based on very preliminary evidence, including data from uncontrolled studies," says Woloshin. "Terms like 'breakthrough' or 'promising' are extremely powerful marketing terms, so we think it would be in the public's interest to instead present the cold hard facts about new drugs (for example, what outcomes are affected by the drug and the size of the effect) without using such descriptive language."

Participants involved in an online study were randomly given one of five short descriptions based on an FDA press release for a hypothetical recently approved metastatic lung cancer breakthrough-designated drug (1). One version, a facts-only description, described the drug as meeting the breakthrough criteria, but did not actually use the term "breakthrough." The second and a third description included the words "breakthrough" and "promising," respectively, while a tentative explanation used FDA-required language about accelerated approval drugs for professional labeling. A final description, classified as 'definitive', changed "maybe be contingent" to "is contingent." The participants were then asked to judge the drug's benefit, harm and strength of evidence.

The researchers identified a clear trend, which they call the "breakthrough effect". Compared with a facts-only description, adding the term "breakthrough" increased the percentage of participants who rated the drug as "very" or "completely" effective (from 11 percent to 25 percent), as well as the percentage believing that the evidence supporting the drug was "strong" or "extremely strong" (from 43 percent to 63 percent).

"The 'breakthrough effect' was lessened by explaining the regulatory meaning of accelerated approval (as required in the professional label). Our findings also highlight the importance of communicating the extra uncertainties inherent in drug approval based on preliminary evidence, for example with accelerated approval," adds Woloshin.

Woloshin is keen to stress how this persuasive language should be taken into account by the general media and industry when considering public perception of new drugs. He says, "By using neutral terms, quantifying drug benefits and side effects, and highlighting uncertainties, we can empower consumers to make more informed and accurate judgments about drugs." *VB*

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A Soluble Solution for Drug Delivery

Could an ionic liquid–drug system help solve drug insolubility?

For a drug to work it must readily dissolve in the body, but that's easier said than done. Poor solubility is a common issue in drug development. How can this be overcome? A team of scientists led by Valentine Ananikov, Professor at the Institute of Organic Chemistry, Russian Academy of Sciences, believe that ionic liquids (ILs) could be the way forward. Using salicylic acid as a model drug, the researchers fused it with an ionic liquid (1). The drug retained its activity in the IL form, but dissolved more readily in water compared with the parent drug.

"Ionic liquids consist of cations and anions, and there are a huge number of possible combinations of these ions within an ionic liquid, which allows for the 'fine-tuning' of their physical–chemical properties," says Ksenia Egorova, a research scientist in the Ananikov Lab.

The group tried to obtain non-toxic ionic liquids by incorporating natural molecules, such as amino acids, into them. They found that the amino acid-containing ionic liquids demonstrated higher biological activity than the original imidazolium ionic liquids, motivating the researchers to look at other possible advantages of using ionic liquids in medicine. We spoke to Ananikov to learn more about the work.

What was the aim of your study?

Most drugs are solid substances, but they have to function in solutions. Solid substances tend to form several different

crystal structures (polymorphs), but these can vary in their physical–chemical make up, as well as in their medicinal properties. In addition, their formation is difficult to control. The problems of drug polymorphism are widely recognized in modern pharmaceutics. We could overcome some of the difficulties by using active pharmaceutical ingredients (APIs) in a liquid form, which is why the solubilization of existing APIs is a subject of many active studies. It is known that salts of poorly soluble substances often show better solubility than the original APIs so the idea of transforming insoluble APIs into ionic liquids arose several years ago.

The main goal of our work was to examine whether APIs could retain their activity and acquire improved solubility when incorporated into ionic liquids. The present study involved a model compound (salicylic acid) in order to demonstrate proof of principle. We discovered that there are several ways to combine ionic liquids and APIs, which potentially gives us access to different drug delivery platforms.

What different types of drug delivery platforms did you investigate?

There are three ways to incorporate drugs into ionic liquids: via ionic bond (as an anion or a cation); via covalent bond; and via both ionic and covalent bonds.

We have synthesized ionic liquids containing salicylic acid (SA-IL) of all three types and studied their biological activity in cultures of human fibroblasts and colorectal adenocarcinoma cells. The most interesting and prominent finding was the retention of biological activity by salicylic acid in the ionic liquid form. Pure salicylic acid and SA-ILs demonstrated similar cytotoxic activity, implying that the mechanism of action of salicylic acid was not perturbed. However, SA-ILs possessed significantly higher water solubility than the original drug.

Could your method be applied to other drugs?

We chose salicylic acid due to its relative simplicity, availability and low cost. There is no reason why other drugs cannot be transformed into ionic liquids. Most APIs are complex molecules, and provided there is an appropriate functional group for linking the API to the existing conventional ionic liquid or for combining it with a counter-ion, then the API can become an ionic liquid.

What are the next steps?

We are planning to study ionic liquids containing anticancer drugs in an attempt to create highly active, water-soluble compounds. The numerous possible variations of the chemical structures of ionic liquids will very likely reveal valuable opportunities for target drug delivery into cancer cells.

I also hope that the API-IL concept developed in our study will encourage other researchers to develop new drug delivery platforms. Undoubtedly, the development of new drugs and strategies for treatment of various diseases is one of the most important scientific directions all over the world. To perform this task successfully, researchers must collaborate to explore new possibilities opened up by cutting edge development of modern chemistry. We are open for cooperation and we are looking forward to finding new partners!

How do you see the area of API-IL developing in drug development?

Several studies of ionic liquids bearing various drugs, such as ampicillin and ibuprofen, have been carried out, but data on the medicinal activity of API-ILs are scarce, and none have been approved for clinical trials. However, I believe that API-ILs will attract much attention in biochemistry and medicine as their advantages are explored in more detail.

In addition to practical applications, there is a challenging fundamental problem that remains: to understand spatial organization of molecules in solutions and reveal the influence of this spatial organization on living organisms.

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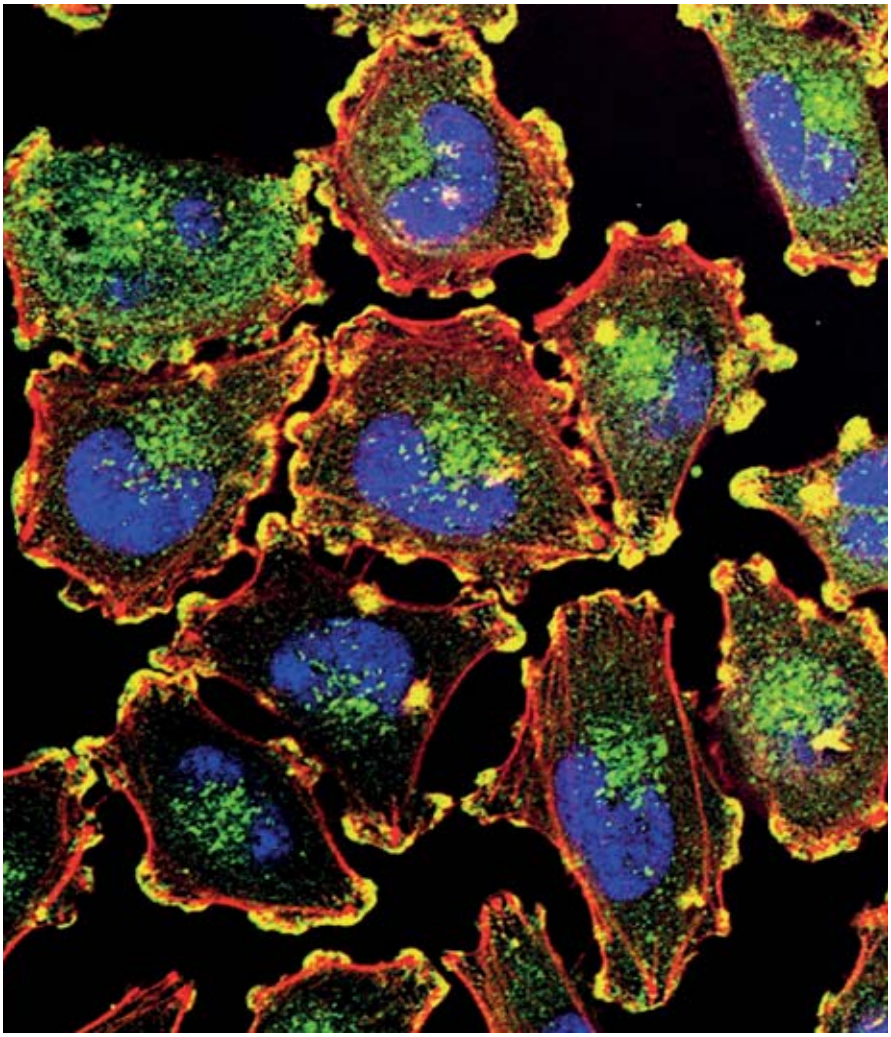
Herpes vs Cancer

A newly approved oncolytic immunotherapy takes on cancer using a live modified herpes virus



A new drug for an aggressive form of skin cancer has been approved by the FDA, and recommended for approval by the EMA. The therapy has caused a bit of a buzz because it's the first of its kind in a drug class known as oncolytic immunotherapies; the drug – Imlygic (talimogene laherparepvec) – is a live oral herpes virus (herpex simplex virus-1) that has been genetically modified to selectively attack cancer cells without harming normal tissue.

The drug originally stems from a spin out from University College London – BioVex, which was purchased by Amgen in 2011. The genetic code for the virus is rumoured to have originally been taken from the cold sore of a BioVex employee... The drug is injected directly into the tumor where it uses the cell's energy to replicate – eventually overwhelming the cell. Once the cell dies, copies of the virus enter the patient's bloodstream to infect more tumor cells. The virus also produces the protein GM-CSF, which helps to stimulate the immune system to join the battle by recognizing and destroying tumor cells. The drug can enter healthy cells too, but it cannot replicate inside them or kill them. Specifically, the drug has been approved for the treatment of adults with skin melanoma that cannot be removed by surgery.

While the science behind oncolytic immunotherapies is intriguing, one challenge that remains is boosting the number of people who respond. A statement from the FDA explains that studies of Imlygic have shown that 16.3 percent of patients experienced a decrease in the size of their skin and lymph node lesions, lasting for a minimum of six months, compared to 2.1 percent of patients receiving a comparator therapy (1). The agency added, "However, Imlygic has not been shown to improve overall survival or to have an effect on melanoma that has spread to the brain, bone, liver, lungs, or other internal organs." The EMA says that the drug has also not been compared with other recently approved medicines for melanoma, such as anti-PD-1 therapies Keytruda and Opdivo.

The Cancer Research Institute believes that there could be advantages in combining several agents that target a different part of the multi-step immune response (2). For example, Imlygic could be used to jumpstart an immune response, with other drugs keeping the response going long enough to wipe out all the cancer cells in the body. *SS*

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Nobel Prize for Noble Causes

The 2015 Nobel Prize in Physiology or Medicine praises advances in parasitic tropical diseases

Tropical diseases have taken the spotlight for this year's Nobel Prize in Physiology or Medicine. Half of the prize went to William C. Campbell and Satoshi Ōmura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites". The second half went to Youyou Tu "for her discoveries concerning a novel therapy against malaria". All three winners are in their eighties, proving that you're never too old to have your scientific work rewarded.

Campbell and Ōmura discovered avermectin, which has been described as having "extraordinary efficacy" against parasitic diseases. The avermectin drug family treat parasitic worms and as well as being used extensively in veterinary medicines, they have radically lowered the incidence of river blindness (onchocerciasis) and lymphatic filariasis (elephantiasis), which are both now on the verge of eradication. Avermectin has also shown efficacy against an expanding number of other parasitic diseases. Its derivative, ivermectin, is used in all parts of the world that are plagued by parasitic diseases – it has limited side effects and is freely available across the globe.

The announcement of Tu as the recipient of the second half of the prize has caused a bit of a stir. Tu is credited with the discovery of artemisinin, which is highly effective against the malaria parasite, and she is the first Chinese woman to win a Nobel Prize. Her scientific discovery was inspired by traditional Chinese medicine and her research was done exclusively in China. In the 1960s, she conducted a large-scale screen of herbal remedies in malaria-infected animals. An interesting candidate was sweet wormwood (Artemisia annua) but the results were inconsistent so Tu turned to ancient Chinese literature on herbal remedies – and eventually discovered how to successfully extract the artemisinin component. *SS*

If your own scientific work has had a humanitarian impact, then why not enter the Humanity in Science Award at: www.humanityinscienceaward.com. It's not quite a Nobel Prize, but the winner will receive $25,000.

In My View

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

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

Contact the editors at edit@texerepublishing.com

Exploring the Product–Process Relationship

What comes first – product innovation or process innovation? For biopharmaceuticals, the two should be inseparable.

By Suyoung Lim, Project Leader, Product Development Department, at LG Life Science, Korea.

The term 'biopharmaceutical' was first introduced in the 1980s, and the market has been growing ever since – and it seems safe to assume that biopharmaceutical development will remain a focal point for the pharma industry. And that's a good thing – because it's a fascinating area to research from where I'm standing.

We all know that there are significant distinctions between biopharmaceuticals and traditional small-molecule drugs due to fundamental differences in their syntheses and structures. The complexity of biopharmaceutical molecules poses numerous manufacturing challenges that are not seen with conventional chemical small molecules. And I am not just talking about the physical manufacturing steps, but the entire relationship between product and process innovation.

In a recent study, Minsuk Suh, Professor at Hanyang University in Korea, and I examined how biopharmaceutical R&D processes – and the product–process relationship – have evolved to become so distinct from small-molecule drugs. We did this by tracking, categorizing, and comparing patented pharmaceutical and biopharmaceutical technologies in development cycles (1).

Our findings are important because an understanding of the product–process relationship can lead to more efficient lifecycle management. I also think our work is interesting for simple curiosity's sake – for example, by answering questions, such as at what stage of drug development do you see the highest number of patent registrations? For small molecules, it's right at the last moment – just before the regulatory approval stage. For biopharmaceuticals, patent registrations are more spread out.

To understand the patterns of innovations, we began with Abernathy and Utterback's product lifecycle model of innovation, which addresses changes in patterns of product and process innovations at each development stage (2). Utterback showed that the rate of product innovation exceeds the rate of process innovation at the initial stage. Basically, this means that firms invest in new processes only after products are developed. You generally see this in the development of small-molecule drugs.

But isn't science – and the pharma industry – supposed to be a process-enabling industry where fast, efficient, and high-quality process development has a direct impact on finished product development? This is a familiar concept in the pharma industry thanks to the implementation of Quality by Design (QbD) (3). The key outcome of the QbD conceptual framework is that quality should be built into a product via a thorough understanding of both the product and process. The quality of a biopharmaceutical is comprehensively determined by both process and process conditions, which should be carefully managed throughout the entire development and manufacturing procedures. In other words, process innovation cannot be separated from the biopharma product's lifecycle.

"The findings of our study are valuable when it comes to decision making in biopharmaceutical drug development."

And indeed, the results of our study show that patents related to biopharmaceutical products show stronger relationships with process innovations than those related to traditional chemical pharmaceuticals. Chemical pharmaceuticals show an asymmetric pattern in innovations, where there is a significant portion of R&D conducted just prior to the commercial launch phase. For example, there is a tendency not to focus on the process too much until promising outcomes can be expected from Phase III trials. Such a strategy has emerged because process development for the production of chemical drugs is generally well defined and focused primarily on production scaling to meet commercial volume requirements.

For biopharmaceuticals, our study showed that product and process innovation activities are more evenly distributed throughout development. This is because biopharmaceutical product and process development activities are inseparable throughout the R&D cycle. Both the product and process innovations for biopharmaceuticals are initiated very early – right at the discovery stage – to establish a fundamental technological basis applicable to commercial production scales.

In my view, the findings of our study are valuable when it comes to decision making in biopharmaceutical drug development. For biopharmaceuticals, you must be prepared to make decisions about in-house manufacturing and investment in human resources much earlier in the development cycle compared with small-molecule drugs. You may also have to revisit decisions after a product is approved for the market, since commercial-scale production must be explored both before and after approval. Moreover, the integrated nature of biopharmaceutical innovations should be reflected differently in knowledge management strategies and capital allocations.

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What's in a Name?

Whether you are a global corporation or a tiny biotech, changing your company name is more than updating your letterheads and putting a new sign on the door. Get it wrong and it could be a costly mistake, but get it right and it's an exciting step towards a whole new image.

By Rasmus Hother le Fevre, Managing Director & Corporate Vice President, Novo Nordisk Pharmatech A/S (formerly FeF Chemicals).

Why re-brand? Well in our case, we have spent the past two decades slowly transforming the company from a fine chemical company into a pharma company, discontinuing all non-pharma products. Now we are a fully focused pharma company, the name FeF chemicals didn't really match what we were doing. And since we are owned by Novo Nordisk, it was natural to adopt part of the parent company into our new name – Novo Nordisk Pharmatech.

"A new name is a natural point to review the mission and vision of the company – an exciting process."

In fact, coming up with the name was one of the easier parts of the process for us. That was when the real work began.

"Just when you think you have thought of everything, something new pops up."

It has taken a full year from making a final decision to change the name to the recent official announcement. There are a lot of practical implications, beyond what you see on our website or in our facilities. Hundreds of legal, financial and technical documents have been updated. Just when you think you have thought of everything, something new pops up – IT systems or links to external websites. You have to take a 360 degree view and review every last one of your business processes to identify the impacts.

But it's not all prosaic, practical changes; a new name is a natural point to review the mission and vision of the company – an exciting process! Alongside the name change, we updated our corporate strategy, enterprise resource planning system and facilities, so we had to coordinate all that with the name change too. Making so many changes at once has made for a stressful 12 months. But the name change influences so many different parts of our company systems, going all the way from standard operating procedure, labels to invoices and a hundred other things; so making all the changes at once cuts down on repetition. It's important not to underestimate the size of the task or the amount of hard work involved.

For us, our new name draws a line under our old identity as a chemical manufacturer, and clarifies our pharma focus. The more creative part of the process was finding a way to reflect those changes in our new logo and branding. We asked several creative agencies to pitch, and chose an agency based on their track record on similar projects and the fact that they quickly grasped what we were looking for. We first asked them to speak with stakeholders both within Novo Nordisk, and from our global customers, to get a feel for perceptions of FeF Chemicals. This was a crucial step for us, to make sure that external and internal perceptions of the company were in alignment and reflected in our new branding. Based on that feedback and our own ambition for the future, we gave them the challenge of creating a clear visual and brand identity. In our case, we needed to remain in line with the Novo Nordisk corporate visual identity, as well as match our future aspirations and past history. We think our final branding is a great mix between being loyal to the corporate brand and forging our own identity.

Of course, it will take some time to get used to the changes. Many of our employees and customers have a 25 or 30-year history with FeF Chemicals – many 'grew up' with the old name and are genuinely proud of it. For them to adopt a new name and learn to fully accept it will naturally take time. To help ease the transition, we arranged a whole series of internal workshops to integrate the new name into our company culture and allowed plenty of time for our customers to get used to it before the final changeover.

The key to a successful brand update is to pay close attention to both stakeholder perceptions of the company and your future commercial strategy. By considering both who you are, and who you want to be, you can create an identity that unites the company and projects a clear image to others.

Treating Before Infection?

Bacterial infection is only treated when we see signs of infection, but what if we could treat earlier and without adding to drug resistance? I'm a believer in the power of endolysins.

By Bjorn Herpers, Clinical Microbiologist, Regional Public Health Laboratory Kennemerland, Haarlem, the Netherlands.

We are sailboats on a bacterial sea; vessels separate from the microbial maelstrom until a crashing wave – infection – brings disease onto our decks. We bail out the infection with antibiotics, and the stability of the sailboat is restored.

Very poetic, but it doesn't quite marry up to reality. We bail out infection with antibiotics but this doesn't always restore the stability of the sailboat – in fact it can make it worse. Drug resistance is a rising tide and we need new options.

Inside the human body, there are ten bacterial cells for every normal cell, and their presence affects us on a daily basis.

Bacteria confer many negative effects, including inflammation associated with eczema, acne and rosacea, and opportunistic infection following surgery due to skin colonization by pathogenic species. But every cloud has a silver lining; bacteria also have positive effects, such as protecting us from infections, synthesizing vitamins and assisting in the digestion of complex carbohydrates. In this very publication, Tim Sandle wrote about the complex relationship between we humans and our bacterial lodgers (1).

When dealing with bacteria, we often donn the silver lining until infection appears. And some will say, "why should we treat something before the negative effects become apparent?" However, I argue that there is room for pre-emptive treatment, before bacteria cause infection. At first, it may seem like a strange concept but there are many stages of bacterial interaction with the human body that eventually lead to infection. I call this the colonization–infection continuum. Every infection is preceded by colonization that may later lead to irritation, inflammation, local infection, and eventually systemic infection and sepsis.

The two major issues that prevent us from using antibiotics early on in this continuum are the fear of resistance, and the fact that antibiotics (particularly broad spectrum medicines) also kill millions of bacteria that do us good. We take this hit to our friendly bacteria when treating an infection because we are very unwell. If we want to treat earlier on a regular basis then we need treatments that are both specific to the target species of bacteria and that do not cause collateral damage to our microbiome. Such treatments open up many new options, such as sustainable prophylactic treatment before surgery or after small wounds, use of targeted-antimicrobials as maintenance therapy in recurrent skin infections like folliculitis and in chronic inflammatory skin conditions where particular species of bacteria are known to play a role (for example, Staphylococcus aureus), and even oral treatments designed to prevent harmful bacteria colonising the gut. Isn't prevention the best treatment? In some cases, we could be hitting bacteria hard as soon as any signs of colonization are detected, such as in the early stages of irritation.

"In some cases, we could be hitting bacteria hard as soon as any signs of colonization are detected."

My day-to-day work involves endolysins. Endolysins are enzymes made by phages (viruses which naturally infect bacteria) and they are an essential part of the reproduction process of phages. Phages can replicate only through a bacterial host. When a bacterial cell is infected, the phage takes over its DNA and starts producing new phages. Many phages use endolysins, which are also produced inside the bacterial cell, to destroy the bacterial cell wall, releasing the new phages and killing the host bacterium.

They have three characteristics that assist in fighting antimicrobial resistance:

1. A working mechanism unrelated to that of antibiotics, meaning even antibiotic-resistant strains of bacteria, such as MRSA, are susceptible.
2. Phages have co-evolved with bacteria over millions of years; therefore, endolysins have naturally been selected to target highly conserved areas of the bacterial cell wall, greatly reducing the likelihood of bacterial adaptation.
3. Endolysins target specific bacterial species; when directed against the culprit pathogens, commensal (beneficial) bacteria are not killed, reducing the chance of opportunistic infection following treatment, as is often seen after courses of antibiotics.

I've been researching the potential that these molecules have in treating bacterial disease and in my view, they are a suitable candidate for using early on in the colonization–infection continuum.

Research is ongoing into the full breadth of potential applications for endolysins, but they have already shown use in the maintenance of treatment for dermatological conditions such as acne, eczema and rosacea, where a bacterium has a role in inducing the inflammation. Also, recurrent infections like folliculitis and furunculosis can be controlled.

We are hopeful that in time, endolysin technology will become established in wound care, and eventually in the treatment of biofilm-related prosthetic joint infection; there is a great deal of exciting research still to be done. A great deal of what we read about the future of treating bacterial disease is very negative and apocalyptic, but I find working with endolysins very exciting. The technology has great potential and it's a refreshing contrast to see a brighter future in microbiology on a daily basis.

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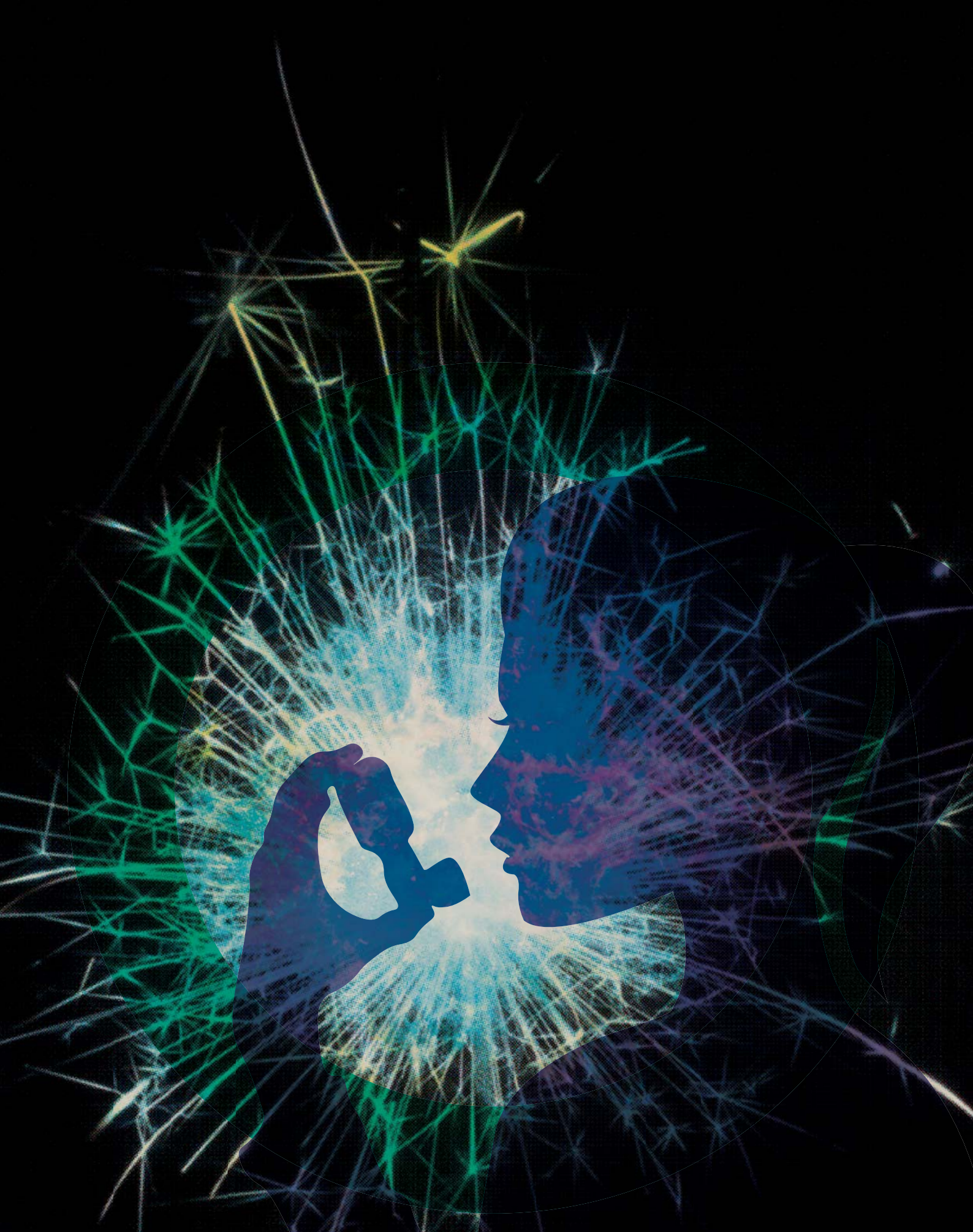
Sparking Innovation in Drug Delivery

In an industry as diverse as pharmaceuticals, there is much that different disciplines can learn from each another. Here, I present a few potential sparks of inspiration by asking if and how the world of drug delivery can benefit from a more holistic use of the innovations occurring all around us – and vice versa.

By Richard N. Dalby

According to the US Department of Commerce (1), the US is the largest medical device market in the world and is expected to be valued at over $130 billion by 2016. The same source reports that there are more than 6,500 medical device companies in the US. I am a co-organizer of the Respiratory Drug Delivery (RDD) meetings and it occurred to me that there is much that my field could teach medical device developers in other areas. For example, could some of the latest advances in inhaler technology be applied to the development of autoinjectors or influence the design of new devices? Conversely, could innovations in other medical devices affect the development of platforms to administer inhaled drugs? Ultimately, combining all of our knowledge and learning could be beneficial to both pharmaceutical development and patients.

Our RDD conferences have traditionally addressed contemporary science issues that affect combination products (hardware and drug-containing formulation packaged together), but the science we cover extends far beyond pulmonary and nasal inhalation products; in part, because the conferences showcase innovations that have applications for other pharmaceutical solid, non-aqueous and aqueous liquids, and dispersed systems – for both small and large molecules. The technologies created in the inhalation industry have enabled developments at many companies making injectors, novel parenteral formulations, biopharmaceuticals and specialty orphan products.



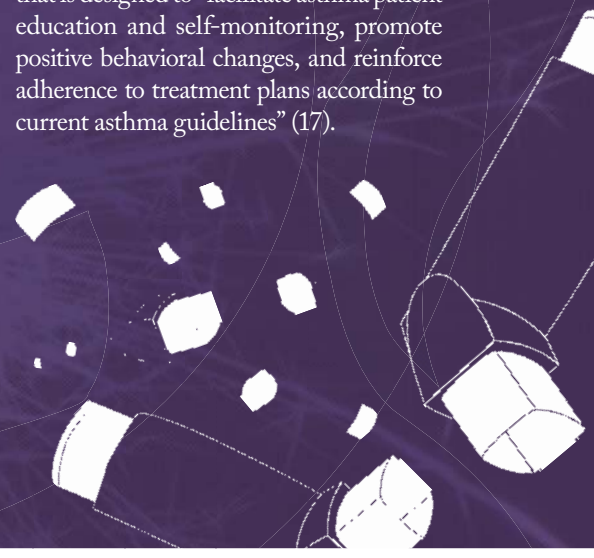
Smarter Inhalers

Electronic monitoring is widely considered to be among the best tools for medication adherence measurement because it provides the ability to record the date and time of medication use. Unfortunately, it is not without additional costs and challenges (15). While electronic monitors have been developed for portable inhalers, including the Doser (Meditrack), SmartTrack and SmartDisk (Nexus6), these technologies have yet to be incorporated (or co-packaged) into a marketed, drug-containing inhaler product, which is probably an essential step to increase their availability and realize their benefits. In contrast, several drug cartridge-containing electronic autoinjectors have been commercialized, including the Easypod platform, which provides visual signals and on-screen feedback, combined with audio cues to guide the patient through the injection process and to provide reassurance that the correct dose has been delivered successfully. To inject a dose, a patient follows a simple three-step process (an increasingly familiar concept for DPI developers).

First, a needle cap containing the needle is inserted into the device; once the needle has been automatically withdrawn into the device, the empty needle cap is removed. When the device is correctly positioned on the skin, as confirmed by a skin sensor, patients can trigger the automated injection by one press of the injection button. Finally the empty needle cap is reinserted into the device to collect the needle for safe disposal. The device features a number of adjustable injection settings that allow patients to control the speed and depth of needle insertion, injection speed and injection time. In addition, the device records an accurate and objective dosing history, including the date, time and dosage of every injection, and the comfort setting used. Innovations such as these make the reed-generated, audible warnings associated with excessively inhaled use of some inhalers seem pretty crude.

Human factors engineering is instrumental in identifying and subsequently reducing or eliminating errors during the use of medical devices (16) – and played a significant role in the design and development of Sanofi's Auvi-Q autoinjector. Auvi-Q is a single-use epinephrine autoinjector that talks a patient or caregiver through the delivery of 0.3 mg (0.3 mL) or 0.15 mg (0.15 mL) of epinephrine during allergic emergencies. Is such technology only warranted on rescue inhalers that are used infrequently? For controller (prophylactic) medications is it acceptable or prudent to design inhalers that communicate through Bluetooth to a smartphone which then does the talking as soon as the mouthpiece is opened? Would innovations such as this expand the range of inhaled drugs in commercial products to naloxone for the treatment of opioid overdose or infrequently dosed biopharmaceuticals that are currently injected?

It certainly seems feasible when you consider that a toothbrush can now deliver real-time feedback on brushing intensity, duration and technique improvements over time. Apple's Research Kit open-source software seems aimed at encouraging companies to move in this direction, and Mount Sinai/LifeMap Solutions have already launched an Asthma Health app that is designed to "facilitate asthma patient education and self-monitoring, promote positive behavioral changes, and reinforce adherence to treatment plans according to current asthma guidelines" (17).



Stephen J. Farr described it this way when Aradigm Corporation acquired Intraject in 2003: "Adding the Intraject project to Aradigm's portfolio extends and leverages Aradigm's core competencies," he stated (2). He went on to describe how both AERx (an inhalation platform) and Intraject (later commercialized as DosePro – a needleless injection system) deliver liquid formulations under pressure through specialized nozzles and involve aseptically filled, single-use drug/device combinations to optimize delivery. These commonalties have also been made apparent by Turanin et al., who have spoken at previous RDD meetings to describe the challenges faced by developers of needleless injectors (3), including bubble formation in the drug-containing cartridge, which can cause glass fracturing. Bubbles are also a problem in mechanical nasal spray pumps where they manifest as under-dosing, so clearly there is a shared interest.

As well as looking at the devices themselves, it is also useful to look at technologies, which are radically altering the way inhalers are conceived and developed. Individual inhaler components can now be designed, manufactured and evaluated in ways that were almost unimaginable back at the first RDD meeting in 1988. For example, rapid prototyping has proliferated

today to allow intricate mechanical components of various materials to be made in a matter of hours. We're also seeing more medical devices, such as heart rate and blood pressure monitors, pulse oximeters, sleep, and exercise monitoring tools, being integrated into ubiquitous personal electronics – and this trend is likely to continue and accelerate. In the inhalation area, this trend will present great opportunities to move away from simple 'apps' that focus on patient education and disease tracking via manually entered data, to sophisticated devices that automatically coach, monitor, report and analyze data through seamless communication with ever-more powerful mobile technologies.

In this article, I'd like to share some ideas and visions that could potentially expand the scope of inhalation technologies, platforms and concepts. I'll focus on three areas – pressurized metered dose inhalers, dry powder inhalers and nebulizers.

Under pressure to perform

The nearly 60-year-old pressurized metered dose inhaler (pMDI) is still with us, and arguably received a scientific and commercial boost after the phase out of the predominant liquefied gas propellant – chlorofluorocarbons – in the 1990s, before which a focus on copying rather than innovating were the dominant themes in pMDI research. Indeed, new intellectual property ownership surrounding hydrofluoroalkane (HFA)-based formulations spurred innovations to address the problems that emerged – primarily, the lack of drug and surfactant solubility, and the subsequent formation of aggregates and adhesion of drug to canister walls.

One approach to the first problem was to simply omit a surfactant and thereby place more responsibility for metering a homogeneous formulation in the hands of the patient – by requiring that they shake the inhaler immediately prior to actuation. Another approach was to add ethanol to aid drug dispersion or dissolution directly, or to facilitate surfactant solubility. Ethanol was well known to increase droplet size when used at high concentrations so HFA-containing formulations sought to minimize the concentration. Safety concerns and negative patient perceptions (intoxication, throat deposition and irritation) also drove down sprayed volumes. Small-volume metering requirements propelled the need for more precision in metering valve design and manufacture, while toxicological concerns led to the development of "clean" (low extractable and leachable content) elastomeric components with exceptional functionality (4). Drug adhesion to container surfaces was addressed not just as a formulation problem, but as an opportunity to explore new canister materials (notably stainless steel) and interior wall treatments (5). Could some of these anti-adherent advances also be applied to implanted pumps, stents and prosthetics, where tube occlusion and tissue interactions can be problematic?

The spray orifice of the pMDI actuator has received much attention because of its ability to modulate the characteristics of the sprayed formulations. A range of orifice shapes and sizes have been studied (6, 7). The use of small orifice diameters in association with a dissolved drug formulation containing a low ethanol concentration and high propellant driving pressure has allowed lower drug doses, as seen in Teva's Qvar inhaler. Could advances in nozzle design be applied to other sprayed formulations, such as sublingual, nasal or topical sprays? Could innovative nozzle design be combined with guided placement within the cross section of the nares to potentiate better coverage of the nasal mucosa or allow some degree of targeting to the olfactory region or sinuses? Could computational fluid dynamic modeling support this effort?

"Although current pMDIs are not sterile products – could they be?"

Spray pattern testing has also advanced for pMDIs; what once took days with TLC plates, drug visualization and crude photographic image analysis is now possible in seconds with highly automated laser imaging. Could precise spray pattern control and innovative actuator designs, combined with accurate dose metering, facilitate development of a near-invisible spray-on patch with a controlled area for drug absorption?

Our industry (and regulators) have been historically reluctant to utilize new excipients, for obvious reasons, but perhaps the formulation toolbox needs to be expanded by first gaining more experience with excipients sprayed on less sensitive targets. Despite concerns, a number of film-forming polymers have made their way into both experimental and commercialized inhaled formulations, such as AstraZeneca's Symbicort, which contains povidone K25 USP (8). This could perhaps pave the way for spray-on patches that adhere to mucus membranes in the mouth, nose and elsewhere.

Finally, although current pMDIs are not sterile products – could they be? Could we add a microbiological preservative to a sprayed formulation that was intended for delivery into the eyes or ears? The classical advantage of sprayed products is the 'no-

Pre-Filled Challenges

I've noted that pre-filled syringe (PFS) makers are often beset with challenges that inhaler developers and their partners routinely address, including those associated with extractables and leachables in elastomers. MDIs contain metering valves with metal and elastomeric components – and the device industry has developed effective approaches for the quantification of extractables and leachables. These could be beneficial for PFS makers too. Other challenges include:

- the need to better predict human in vivo injection times based on in vitro models
- the need to understand the impact of protein and formulation parameters on tungsten and silicone oil compatibility
- the need to improve the capabilities of analytical methodologies for the characterization of sub-visible and submicron particles in terms of size limitations and particle type discrimination.

Solutions do exist within the inhalation field; for example, there are a range of technologies that can characterize inhaled particle size and determine their chemical nature. Computational fluid dynamic modeling is now a staple at RDD meetings and has a role in the development of needleless injectors (18, 4). We have a lot of experience measuring and reproducing finger forces applied to pMDI and nasal spray pumps that might be transferable to other medical and surgical devices. Furthermore, inhalation scientists are acutely aware of the value of in vitro and in vivo correlations so there is the possibility of shared interest, regulatory overlap and an opportunity for harmonization of registration requirements. Looking in the opposite direction, PFS and autoinjector makers seem to have found ways to incorporate electronics and sophisticated human engineering into their devices, while maintaining commercial viability. In contrast, inhalation devices with onboard electronics and monitoring are rare.

touch drug delivery' to hard-to-reach, oddly shaped surfaces – common situations in ocular and aural applications. Because we have developed low-velocity "soft" plumes in respiratory drug development, why not apply them in other routes of administration? Phospholipid sprays applied to closed eyelids for treatment of dry eyes already exist so perhaps pressurized and aqueous sprays could have an expanded role here too. We are all patients and I'm sure we'd all like to take medicines without head tilting or missing our targets...

Magic powder

And what about dry powder inhalers (DPIs)? DPIs can be seen as the most diverse inhalation platform in terms of device design, but their general method of action tends not to deviate from the traditional three-step mode (open, inhale and close) because otherwise they would likely be too confusing for a patient to use. There are other pharma sectors too that could benefit from standardization, such as autoinjectors. Innovation is all very well, but patients have to be able to use medical devices intuitively and easily, if we want to ensure adherence.

I think there are other lessons that certain pharma fields could learn from the humble DPI. Looking at images of the internal workings of GlaxoSmithKline's Ellipta inhaler (9), I was struck by the elegance with which two strips of powder-containing blisters are stored and opened, and then the way in which the empty cavities neatly recoil within the small device – all achieved just by opening and closing a mouthpiece cover. I contrast this with watching some patients struggle to extract a small tablet from a blister pack… Is it not possible to use this approach to provide a 30-day supply of one or two tablets for patients needing extra convenience? It could also create opportunities for containers that are not only convenient, but also more secure (child resistant) and able to protect their contents from the environment as effectively as individual blister packing without the use of so much plastic and foil laminate. Inhaler manufacturers have, after all, developed expertise in keeping water out of formulations through the creative use of sealing technologies (on valves and blisters) and use of desiccants.

Inhalation expertise in the mechanical handling of plastic strips could be very useful when it comes to transdermal strips (it's often a battle to prevent the patch from adhering to the floor). What about developing something akin to the use of a sticky tape dispenser, which neatly strips away a backing layer as the patch is securely adhered to the skin?

Respiratory drug development experts also have a lot to offer in terms of knowledge regarding particle size, shape, surface morphology and charge – all of these factors play a key role in determining the efficiency with which a drug leaves an inhaler and deposits following inhalation, so there is an in-depth

understanding of how to engineer micron-sized particles with specific and reproducible properties. What other fields could utilize this expertise? Could there be value in using this knowledge base to develop faster dissolving sublingual films and tablets or easier/faster to reconstitute powders in vials for injection?

But DPIs also have much to learn from other pharma sectors and there are a number of areas where I think we could perhaps see device improvements. To ensure effective DPI drug delivery, inhalation profiles are necessary – and this issue has been extensively researched and reported (10). Trainers are also often used to coach patients in achieving desired flow rates. So why then is it necessary to ask some patients to carry a separate peak flow meter to monitor their disease? Aradigm pioneered this concept with its SmartMist product using an electrically operated device. But could training and monitoring be built into DPIs using only mechanical means with a reasonable expectation of better therapeutic outcomes at moderate cost?

We also seem to be solidly in unit dose mode for most locally acting inhaled pharmaceuticals – the prescriber typically has a choice of one or two puffs unless the patient is willing to use a nebulizer and take responsibility for inhaling a partial dose. The packaging insert for Afrezza (insulin human, MannKind) Inhalation Powder makes it clear that fractional dosing is at best crudely practiced (11), but sorely needed if systemically acting biologicals are to have a future via the inhalation route.

Finally, I think that given the increasingly complex nature of DPIs using blister metering of doses, it seems wasteful that they remain single-use devices. Have environmental, economic and regulatory realities altered enough that refillable devices could reasonably be envisioned? Are there sectors that have moved in this direction that we can learn from?

"Respiratory drug development experts also have a lot to offer in terms of knowledge regarding particle size, shape, surface morphology and charge."

Specialized but standardized?

Modern mesh nebulizers are small and efficient, but patient convenience is limited by the use of form–fill–seal ampoules that must be opened and emptied by patients into the reservoir. Other segments of the pharma field have standardized on fittings; for example, the Luer taper is standard for syringes, while more specialized injectors such as Merck Serono's EasyPod autoinjector are designed to deliver a narrower range of medications (12). If we took a similar approach to the Luer Lock on form–fill–seal ampoules, we could fill any nebulizer. That said, newer nebulizers might benefit from filling with less effort or room for error by patients – and it might be possible to make the connection between the nebulizer and the solution for inhalation aseptically, so that unused formulations could be used in subsequent dosing periods.

Staccato (Alexza) seems able to deliver sufficient heat to generate a thermal aerosol from a drug-coated metal foil. We could perhaps explore using analogous technology to heat sterilize the mesh and other potentially contaminable areas of a multiuse ampoule in an ultrasonic nebulizer after each use. This could be made even more realistic if the antimicrobial properties of silver (which are the basis of some preservative-free multiple dose nasal sprays) are combined with heating (13).

There are other areas too where nebulizers could benefit from some standardization. Pressurized inhalers have enjoyed a consistent 'look' for a long time with common operating principles and component vendors standardizing parameters such as canister neck diameters. This has the benefit of making it relatively easy to switch a patient from one product to another. DPI manufacturers seem to be converging on the open–inhale–close approach to simplify patient training. Is it possible to also begin moving nebulizers in this direction to make them as mainstream as the other inhalation platforms?

Boehringer Ingelheim's Respimat utilizes energy stored in a spring under tension to drive an aqueous solution into a nozzle assembly for spray generation. Could this concept be adapted to drive a drug through microneedles being developed for patch systems to yield a needleless injector, or could the high driving pressure attainable by the spring allow use of finer conventional needles than is possible when finger forces alone are used to drive a conventional plunger into the barrel of syringe? Sonophoresis had been combined with microneedle technology to enhance transdermal delivery of large biomolecules (14), so could a nebulizer mesh be modified to become a microneedle-based autoinjector?

"Some developments are inevitable, such as the development of smart inhalers."

Vice versa

Numerous pulmonary and nasal products have been introduced into the world's markets in recent years, and here I've speculated on how learning from these products could inform development of other medical devices and drug products. Of course, learning goes both ways, so why not look at how innovation in other fields might alter the inhalation device landscape? Some developments are inevitable, such as the development of smart inhalers (see sidebar, Smarter Inhalers), but others discussed in this article may seem a little unrealistic... at first. Nevertheless, I feel it's important to push the boundaries of innovation and to explore how innovations from one pharma field can be applied to another.

There are numerous reasons that might spur an organization to look beyond the confines of its own niche for inspiration, including the development of new products with enhanced safety, efficacy or convenience features – and the potential to lower the cost of manufacture of existing products. Electronics and connectivity are likely to play an increasingly important role. Throughout the 25-year history of RDD meetings, reported developments in inhalation products have always reflected the work of a complex amalgam of scientists, clinicians, engineers and entrepreneurs. In the next quarter century of RDD conferences, it looks like we will also need to hear from authorities on human factors engineering, software and electronics experts, and smartphone application specialists. Perhaps it will even make a nice change from my ramblings! I am certainly looking forward to such an exciting future.

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Breaking the Bioprocessing Bottleneck

Battling logjams in downstream processing is a constant challenge, but even when it feels like there's no room for maneuver, small yet clever steps can help gain efficiency. And sometimes a fresh pair of eyes can find new and surprising solutions.

Originally aiming for a career in traditional manufacturing, Madhu Raghunathan obtained an advanced degree in engineering, but later found a passion for the application of innovative technologies. Today, Madhu is Product Strategy Leader at GE Healthcare Life Sciences, where he is tasked with scrutinizing the latest advances in downstream processing operations to help companies identify opportunities for greater efficiency. But the quest for efficient downstream operations is not easy, particularly when you must balance solutions against existing constraints. Fortunately, such problem solving is exactly what Madhu enjoys.

How do you get involved with downstream-processing challenges in your role at GE Healthcare Life Sciences?

My role is to specifically focus on downstream processing. I analyze the market, and study the trends, challenges and constraints facing our customers. From there, I look at how we should evolve our portfolio to ensure that we can address these problems and help make downstream bioprocessing operations more efficient. It's a fascinating area because the solutions and technology applications vary depending on the situation – there is no 'one-size-fits-all' approach. I must look at how innovative technology and a combination of approaches and knowledge can be pieced together to solve real-life problems in a practical way. I'm very interested in process analytical technology, continuous processing, automated unit operations and real-time product release because there are a lot of innovations being seen in those areas. But across the board, whenever GE gets involved with downstream processing, I am happy to join the team to examine areas that can potentially be improved.

Could you provide some examples of technological innovation?

I'm seeing a lot of interest in automating unit operations as recent developments in automation platforms facilitate efficiency and scalability. A lot of companies are also looking at the potential of continuous chromatography and continuous processing; some companies are starting to experiment with continuous chromatography for one purification step, while others are rolling out continuous processing for their entire chromatography operations – or even looking at an end-to-end continuous downstream processing operation. That said, I think that mainstream adoption of these techniques is still a few years away, as they are still novel and the industry is still figuring out how best to implement and use them.

One technology that is becoming

more mainstream, however, is single-use systems. Companies are definitely more aware of – and more at ease with – the challenges and benefits of single-use technology. I've seen a lot of 'hybrid' processing operations that use single-use technology for certain steps, and then traditional stainless steel for other steps, resulting in more economical and functional processes.

What are today's most common downstream bottlenecks?

Historically, resin capacity constraints and column footprint were perceived as the main bioprocessing bottlenecks, but these aren't really a problem in today's industry where binding capacity and downstream productivity tends to be high. This is in part thanks to new developments in downstream processing equipment and materials. However, this doesn't mean that bottlenecks no longer exist; on the contrary, I believe that most bioprocessing companies today face some form of bottleneck in their production processes. This is especially true for companies that have legacy production facilities.

One common bottleneck is inefficient process handling during scale up, such as moving from pilot- to full-scale manufacturing. Many different steps make up downstream processing and all of these need to be scaled up, which can involve hold times for buffers and necessitate new controls to manage things effectively. In addition, once you start scaling up in volume you start to see increased preparation times and higher footprint requirements. If your processes aren't efficient, then delays can occur, which can cause buffers to be held for too long or affect time-critical steps.

Another common bottleneck is column packing. While traditional column packing is a very slow and manual process that requires testing activities, it is still used by many companies. Single-use technology is a third potential bottleneck that companies are not always prepared for. The vision behind the technology is that you 'plug and play' a new component and then move on with your processing. Single-use technology certainly offers many advantages but the implementation can also include challenges. Such challenges are often related to the infrastructure that is already in place. In addition, single-use technology will require additional qualification activity, such as extractables and leachables studies.

Another common bottleneck is cleaning and its validation, which affects many areas of pharma and biopharma manufacturing (interestingly this bottleneck can be mitigated through strategically employing single-use technologies).

"I'm sure we all wish we had a magic wand that could transform everything to a lean, productive process stream – but transformation is never easy."

And do you have any solutions?

When it comes to proper buffer preparation and buffer handling, there are a couple of approaches. One effective solution is to formulate your buffer using concentrated stock solutions at the right point just in time – this is known as in-line conditioning and is really helpful in driving down preparation times, as well as the area and volume required for hold vessels. It makes the process of buffer preparation a lot more efficient by diluting concentrated buffers as and when required in the downstream process.

With regards to column packing, technology can lend a helping hand. Pack in and place technology uses nozzles that somewhat automate the column packing process. Or, even better, there are now columns that employ axial compression technology, and columns that utilize intelligent packing methodology to simplify the packing workflow and help prevent column packs from falling outside of specifications on a consistent basis. Companies can also consider utilizing pre-packed, pre-sanitized, and ready to use columns for pilot scale operations or for campaign use as a means of intensifying their purification process. With the right systems and ancillary products, it's possible to consistently automate most of the operations around column packing.

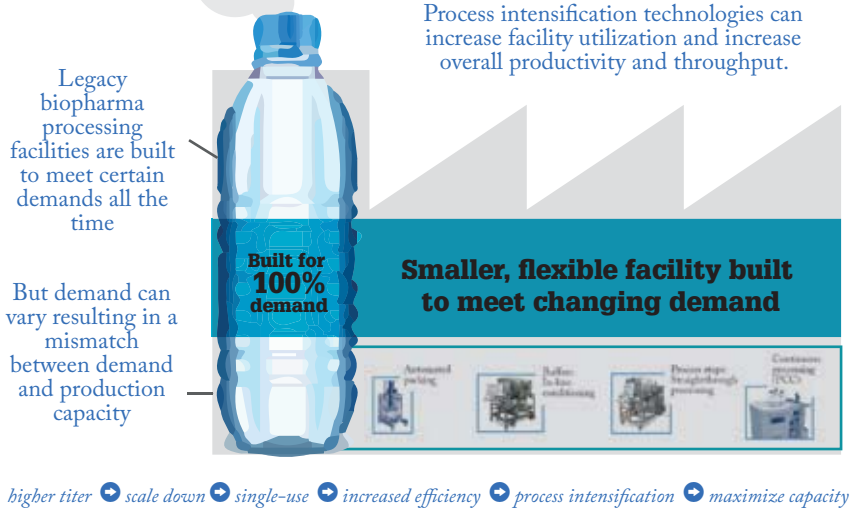
As for single-use technologies, I recommend that you have an upfront discussion with a vendor to see what can be done to facilitate the implementation. You need to introduce the technology in a way that is comfortable for you – and you'll also need to ensure that there is a framework in place for submitting a change control notification in a timely manner. I think that users and vendors should share some of the burden when it comes to rolling out single-use technologies. At GE, we have done a lot of work in ensuring security of supply and building knowledge around integrity testing and single-use qualification. This is essential to allow the industry to reap the benefits.

As for cleaning (and validation) bottlenecks, there are several solutions. As mentioned previously, single-use technology is one. Another approach

Overcoming Production Bottlenecks

Inefficient facility
Production bottlenecks
High COGS

Increasing titers contribute to a decreased COGS but this is not the complete story. Overall process intensification is the key.



higher titer → *scale down* → *single-use* → *increased efficiency* → *process intensification* → *maximize capacity*

is to design your bio-burden control strategy in a very effective way and to leverage recommendations made by the manufacturers with regards to how you clean and validate your equipment. In this instance, the documentation that you get from equipment vendors is useful.

Do you think there is a solution for every bottleneck?

I'm sure we all wish we had a magic wand that could transform everything to a lean, productive process stream – but transformation is never easy. Sometimes companies fail to address bottlenecks because they are constrained to doing things a certain way. Biopharma is very regulated and many facilities were built up years ago with legacy infrastructure that can make the incorporation of new technology challenging. It's tricky to balance your constraints with the need to be more efficient, but there are always at least a few steps that you can take.

For example, one area of concern for all companies is resin and slurry wastage. How do you ensure that your resin is effectively transferred from the container into the column – in an aseptic or a near aseptic manner – whilst ensuring minimum or even zero wastage and, at the same time, ensuring that your slurry has been homogenized properly and that the slurry concentration has been measured accurately? There are solutions that help to improve and automate this process to make it more effective – and these solutions can be implemented irrespective of how the facility is set up. As I mentioned earlier, column packing is another common bottleneck and again you can implement new technologies here to bump up efficiency, regardless of facility constraints you may be facing.

There are a wide variety of solutions in the downstream toolbox, from resins, to columns and systems, to consumables – and our toolbox is constantly expanding. When I'm looking at problems, I pick and choose the right tools and solutions depending on the specific situation (and constraints) that I'm dealing with. There is always something. I strongly advise working closely with a vendor because they will have worked on many different projects in many different facilities, which gives them a huge amount of process experience – you may be surprised by the innovative ideas that they can propose.

How can biopharmaceutical companies prepare for future requirements?

Whenever you are looking to build a new facility or revamp an old one, it is crucial to have a good understanding of not only your current requirements, but your future requirements too. Historically, companies have built a large facility and made a huge investment upfront, with the expectation that the demand would come later. But it could take several years to build up a reliable cash flow, which is clearly not the most effective way of building a business. It is far better and more cost effective to keep capacity in line with demand. By designing a facility to be modular, you can meet current demand and build up when necessary.

Part of my role is to make sure that companies have this in mind and I recommend that you think carefully about the scale of operations, throughput and type of facility infrastructure that you may need in place. Are you going to have a controlled environment? What is grade-space? What are your future expectations? Are you going to manufacture a single drug or are you going to manufacture multiple products? Answers to these questions and others all play a big hand in the way a facility is built up. Remember that one size does not fit all! Just because something worked in a specific scenario at a specific scale does not mean that it will work work at any scale or in any production paradigm. We must think carefully and make the right choices. After all, selecting the correct solution is a critical factor in making your operations as efficient as possible.

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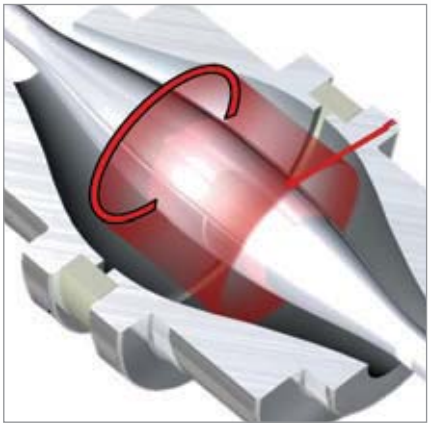

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When Outsourcing Goes Astray

"The best-laid schemes o'mice an' men" often go awry – and that can apply to your outsourcing plans. What do you do if your contractor ends up in the regulators' bad books?

By Peter H. Calcott

Outsourcing is well entrenched in pharma's business models and is a relationship that dates back to the very beginning of the pharma industry. Though some raw materials can be manufactured in house, the vast majority has always been purchased from third parties. And in the last 30 years there has been a surge in the use of outsourcing for all sorts of activities other than ingredients supply. Today, anything and everything can be outsourced including research, development, clinical trials, manufacturing, supply chain, regulatory affairs, business development and more. In fact, I have worked as a consultant at companies where there are barely any permanent staff members. Even the oversight of the contract manufacturing organization (CMO) was outsourced to a third party (me!).

Outsourcing is so common that regulatory bodies have written it into their regulations and guidances (1), and there are conferences and entire magazines dedicated to the topic. I too have spoken and written about outsourcing on numerous occasions. In general, most people focus on the themes of best practice and ensuring success (2-4), and almost all articles assume that if you plan well then everything will go well. But when does life ever go according to plan? As Robert Burns wrote in 'To the Mouse' – "The best laid schemes o'mice an' men, gang aft a-gley", which, when translated and simplified, means that even the best plans often go awry. In other words, you should always assume that something will go wrong – and have a Plan B.

What can go wrong? There are basically two types of outsourcing failures. The first type of failure is choosing the wrong contractor – perhaps incorrect assumptions were made, or

"A change in attention to detail or an unusually slow response to a question is a red flag."

the data collected were incomplete or wrong (see sidebar 'The CMO Checklist'). The second type of failure occurs after the work begins. Usually it is because something changes, such as a loss of expertise from the contractor company due to staff attrition. In other cases, regulatory incidents may occur that change a "good" CMO into a less than stellar one. When something goes wrong in your outsourcing provider, it is usually out of your control – so much so that you may not learn about them until it's too late. The key is to be constantly aware of the situation and to look for telltale signs. With any luck, due diligence activities will flag up warnings and either eliminate the organization from consideration, or at least allow you to put in place a mechanism to prevent those warning signs from becoming a problem. Sometimes everything goes smoothly and it is only later that problems manifest themselves. But with lessons learned, you will be able modify your due diligence system to prevent its recurrence next time.

Learning from mistakes

I've worked in or with a number of organizations and mistakes do happen. For example, I was part of a company that had a very rich pipeline and we wanted to develop more products than we had staff or facilities for, so we decided to outsource the development of one of the products. We performed due diligence with a new player in the space and they impressed in all meetings and presentations. Upper management had clearly done development before and the facilities were new with new staff. The contract was signed and we were off! Within a few months, however, it became clear that the development team at the bench were totally inexperienced. And we were locked into a contract where we were paying them to develop our product – but teaching them how to do it, at our expense. We were lucky that the contract was well written and so after the minimal period we exited. Clearly, the due diligence in the site visit left much to be desired.

In another example, a newly approved product looked like it would take off, but we had limited capacity and needed extra – and fast. We identified a potential CMO and approached them. The "expensive suits" in upper management met with their equivalents at the potential CMO. (Note that no real hands-on technical people were involved – a mistake). The suits returned with a declaration that technology transfer, process validation, manufacturing of qualification batches, amendments to the filing, and an inspection could all be completed, in time for us to get the product onto the market with the second source within 18 months.

"But once they are in the regulatory bad books, it takes a lot of effort to extricate themselves."

Our technical people already knew that the CMO did not run processes the same way that we did and that technology transfer is not that easy (we had already done it from clinical to the commercial facility). The internal estimate was closer to 36 months. Management's response was that we needed to be "Can do" people. We met them half way and became "Can try" people. Eventually, everything was completed in 35 months. In this case, not selecting the right people for the CMO visit and accepting an unrealistic timeline really thwarted our chances of bringing on a second source in the time we needed. As the saying goes, "if it sounds too good to be true, it probably is". But first you have to have the right knowledge to recognize a pipedream.

Beware of change

In my next example, both due diligence and contracts worked well. Many people believe that if due diligence is done well and that contracts and quality agreements are well executed, then nothing can go wrong. But I work with clients who can testify first hand that this is not true.

Sometimes something changes. Perhaps a company is bought out and the staff realize that they have a new owner whose strategy is not aligned. Or the parent company could fall on hard financial times followed by belt tightening. Sometimes, the parent company changes its business model and the CMO is suddenly not the main thrust of the company. What happens then? Firstly, funding decreases, so the company refocuses how they operate. Staff are laid off. And, it is often the "wrong" people that are let go. In many cases "institutional knowledge" disappears overnight and the quality systems and compliance suffer – and the downward spiral ensues. This does not necessarily manifest immediately. It may take several inspections or incidents to surface. But once they are in the regulatory bad books, it takes a lot of effort to extricate themselves.

Earlier in my career, we had outsourced a component of one of our kits and were dependent on a well-known supplier. As a quality professional, I tracked the

The CMO Checklist

1. Technical fit – can the contractor run your technology? You should routinely examine the contractor's physical plant via a visit or technical audit. And unless you take along key players who have practical process knowledge and know how to identify and potentially fix the gaps, you will likely come away with a false sense of fit. You should invest in these technical meetings and audits and ask key technical questions. Each process has peculiarities and unique steps so you should not assume that just because the contractor has run cell culture processes previously that they can run yours.

2. Regulatory record – is the contractor operating under compliance? Have they run afoul of regulators? It is well worth examining the FDA website for recalls and warning letters – and you should also look at their last few inspections (you can get them from the FDA or the company). In the EU, you can go to the EMA website and see if the plant has a GMP certificate – and also if it was ever denied one. Beware the contractor who will not show you their latest inspection. And don't accept the statement, "It contains confidential information". Let them redact it.

3. Quality operation – does an audit indicate that they are operating at the same standards as your own company? During the audit, you are not just assessing their quality systems and operations, but their ability to articulate their systems and principles. Nagging doubts after the audit must be addressed.

4. Expertise – are they capable of technically operating independently without handholding? During the visit, it is critical to examine their labs and manufacturing facilities, and you should talk to staff on the shop floor or at the lab bench. They are the people that are doing the work. Are you confident in handing over your future to them?

5. Timelines – Creating a realistic timeline that has a chance of success, or at least recognizing riskiness, is critical. A timeline is only as good as the assumptions that it is based upon. Often, I see overly optimistic timelines that tell you what you want to hear rather than being realistic and laying out the risks.

6. Business model – Does the contractor operate in a manner that is compatible with your operations and within the right range of costing? Remember that the cost in the contract they quote you is only a small part of the overall costs. If you have to add in more oversight then it is you who absorbs the costs. The cheapest player on paper is not usually the cheapest in reality.

performance of the CMO routinely. Everything was going well until I called my counterpart at the plant only to find that the phone had been disconnected. I tried the plant manager and found the same thing. I was immediately concerned. Such reorganization is often symptomatic of a major issue in the company. And I was right – the CMO had been subjected to a long inspection by the FDA and it had not gone well. Although our Quality Agreement called for notification in the case of an inspection, we were not notified. The inspection resulted in a severe warning letter that took a few years to lift. And we were thankful that we had a second supplier.

Damage control

How can we prevent such problems from happening – or at least control the damage? In most cases, the deviation of a contractor is not, contrary to belief, something that happens overnight. It takes time to get into regulators' bad books. It can seem to happen abruptly but that usually because subtle warning signs have been missed.

The key to success in outsourcing is to be attentive to the status of your contractor. Your CMO may be a standalone company or a division of a bigger one. You need to keep tabs on the owner and look for signs of change throughout the company, such as not meeting financial quarterly targets, failure to get approval of a new drug, excessive recalls (even from other divisions) and bad inspections at other sites. In other words, look for the stability and health of the parent and all the siblings. You should also look for changes in business direction that may signal a change in focus or divestiture of assets.

At the more local level, your ongoing communication with the CMO can tell you a lot. A change in attention to detail or an unusually slow response to a question is a red flag. And changes in heads of quality or manufacturing may

"If you don't have a second source then it's worth qualifying one fast, just in case."

signal some issues at the plant – these people are usually the first to go when a significant issue occurs.

Of course, the obvious place to look for signs of potential problems in your contractor is the results of the routine annual GMP audit. Most people know to look at the audit – and it can certainly bring previously unnoticed issues to light, such as a rash of repeat deviations, or a higher than normal lot rejection rate. However, many problems are easily recognized and can be picked up much sooner than waiting for the annual audit by tracking company performance using key performance indicators.

Plan B

When outsourcing does go awry, you'll be pleased that you've already carefully considered Plan B, such as a second source to fall back on. If you don't have a second source then it's worth qualifying one fast, just in case. One of my main tasks with clients is to line up a second source. To this end, networking and sharing experience is very important, while of course respecting confidentiality. When one of my clients has a problem with a CMO, I routinely ask colleagues in my LinkedIn network for their recommendations for replacement CMOs. And I also ask who we should stay away from. In most cases, my client is not the only person working with that particular CMO and I do sometimes find our CMO on a "not recommended" list. Mostly, I choose safely by going for the regular players on the "recommended" list, but sometimes a new player emerges. But you should remember that these lists can be rapidly changeable and what is recommended today may not be recommended tomorrow.

If you do run into trouble, you should try to work with your CMO to resolve the issue, but you also need to be realistic. How much can you pressure a CMO to change their ways? If you command 50 percent or more of their work or revenue, then you might be able to influence the outcome. But if you are a small player with 10 percent then your chances are small. Remember that the contractor is caught between a rock and a hard place since they will have many clients. But all is not lost. If you know some of the other clients, you might be able to work together to leverage your combined influence. And ultimately this should benefit the CMO too by keeping them out of regulators' bad books. But don't forget to plan for a plan B.

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A New Era of E&L Analysis

Extractables and leachables testing is essential for small molecule and biopharmaceutical products alike, but it can be challenging, especially for companies with less experience. Are you making the most of technological advances that can make analysis easier – and your drugs safer?

Kyle D'Silva

Andrew Feilden

Most professionals in the pharma industry will have at least a working understanding of extractables and leachables (E&L) – but fewer are so confident on the regulatory requirements with regards to analysis. In simple terms, E&L testing focuses on identifying chemical species that can enter drugs from manufacturing components, packaging and drug delivery systems – but the reality is more complex, particularly when it comes to identifying exactly what limits of detection must be met and what data needs to be provided.

According to Andrew Feilden (Chemistry Operations Director at Smithers Rapra, a consultancy agency focused on rubber and plastics) at its heart, E&L testing is about making products safer. "Some people understand the topic well and are doing a lot in terms of risk assessments and choosing the right materials upfront. Other people don't understand what is actually needed – and they are in danger of potentially large delays in delivering their product to market. Regulators expect sound E&L data."

And the devil, says Feilden, is in the details: "Experiments must be designed such that they can detect complex chemical species at the levels at which they are deemed to be toxic or increase risk. To do that effectively, you need to consider a variety of factors, including instrument capability and sensitivity, the dosing regime, and the amount of material. You also need to consider your choice of solvents for the extraction process."

Needle in a haystack

More companies are focusing on biologics and increasing amounts of plastics (with their inherent potential for leachables) are entering pharma's manufacturing chain thanks to the rise of single-use technologies – and that means the workload of E&L tests is rising. Fortunately, the analytical world is keeping pace by developing new, faster technologies that allow for lower limits of detection, while at the same time simplifying the identification process with software and shared libraries. The end result? Greater confidence in the safety of a drug product – and the right data to appease regulators.

Kyle D'Silva from Thermo Fisher Scientific believes that analytical technology has seen advances in three key areas: performance, confidence and usability. "Leachables are varied and complex chemical species. Being able to identify a potential problem – the needle in the haystack – has demanded analytical advances," he says.

Feilden points to a particular challenge that impacts limits of detection – the differences in potential dose depending on medication. "At one end of the scale, you may have an asthma inhaler that delivers a dose of 50 microliters three or four times, right up to dialysis where the biggest dose I've ever heard of is 75 liters. That's a huge difference in dose," says Feilden. "And from an analytical point of view, that represents a challenge. Can you use the same methodologies and instrumentation for asthma inhalers and dialysis bags? And for inhalers, do we have sufficient analytical capability? Instrumentation is rapidly advancing in this area. But identification of the chemical species is another question altogether."

D'Silva has one answer: "Modern instrumentation allows users to both identify and quantify complex chemical species at very low levels. With Orbitrap-based high

resolution accurate mass (HRAM) mass spectrometry instruments, such as the new Thermo Scientific™ Q Exactive™ GC system, we are able to remove interfering background noise for exceptionally clean spectra and routinely gain mass accuracies of one part per million (ppm). Such a high level of mass accuracy has a real advantage when you're faced with unknown peaks because it increases the confidence in compound identification. Perhaps equally importantly, the systems themselves are also considerably easier to use than they were back in my university days."

In addition to advances in instrumentation, software is also evolving to help interpret data faster, using comprehensive libraries that allow users to cross check data. Currently, libraries tend to be proprietary, but D'Silva expects to see more shared cloud-based libraries in the future, which could simplify E&L analysis. He says, "Tests are being done in labs all over the world all the time – and I think these libraries should be freely available."

Previously, labs tended to be secretive about their findings, but Feilden, who sits on the boards of several industry groups, says that more information is being shared using cloud-based services. Although sharing doesn't eliminate any of the laboratory work – all pharma companies must perform E&L studies – it can at least aid in faster compound identification, so that risks can be eliminated more quickly. D'Silva adds, "I really believe that cloud-based libraries are the future. And we already have some resources available, for example, mzCloud.org, which features a freely searchable collection of high resolution/accurate mass spectra. The database includes several thousand compounds and several hundred E&L leachable impurities. We hope there will be even more in the future."

Knowledge versus ignorance

Perhaps one of the reasons why some people have shown a lack of interest in E&L is that, despite the effort involved in the studies, it doesn't appear to make a 'better' product – instead, says Feilden, "The work leads to a safer product for the patient. All of the work is solely to understand and then reduce risk to an acceptable level."

You might think that all manufacturers want to minimize product risk, but according to D'Silva you'd be surprised at how many companies are reluctant to delve too deeply. "When we demonstrate technology that can confidently identify peaks in a way that wasn't possible before, some people express disappointment because they assume more identified peaks means extra work! We understand (but don't condone) this point of view. However, thanks to advances in software – it actually doesn't mean more work from an analytical perspective. Admittedly, there may be more to do from a risk assessment perspective, but this information is important and will allow for better product understanding and decision making," he explains. "For example, you may see a peak at a very low level in a drug that's been on the shelf for three months, but it could be a dominant peak once the drug has been on the shelf for years. Surely, it's better to be aware of that than to be blissfully ignorant of a potential safety problem?"

"From my point of view, advanced mass spectrometry is becoming essential rather than just 'nice to have'," says Feilden. "The cost of today's new technology has come down to routine level. Sometimes you may look at a price list and think it's too expensive, but when you look at the total cost of analysis, coupled with extra capability and confidence, new systems come out on top. I would go as far as saying that companies that perform E&L testing without the latest equipment may not be around in a few years – after all, it's a competitive market."

"All of that said, there's no silver bullet," he adds. "Even with the best technology and vetted libraries of contributed compounds, no single technique can detect and identify everything."

"Being able to identify a potential problem – the needle in the haystack – has demanded analytical advances."

D'Silva agrees, "E&L (much like any other contaminant analysis) tends to require a multi-faceted approach. Liquid chromatography, gas chromatography, ion chromatography, and a number of different detection platforms might be needed to detect the whole range of potential E&L chemicals. But while I realize there is no single system for all E&L testing, advanced tools that offer increased sensitivity or accuracy or reliability can remove some of the question marks."

Nevertheless, the pharma industry has been slow to adopt such advances. And although legacy instrumentation can 'get the job done', D'Silva says that each E&L peak is associated with a degree of identification uncertainty. "In some ways, it all comes down to how much uncertainty you are willing to accept. If you look at mass spectral libraries that have been on the market since the 1970s, you'll find a few compounds that were misidentified," says D'Silva. "The analysis would have been performed by a very qualified lab, but the technology at the time simply wasn't advanced enough. Today's technology can re-identify those compounds – with greater confidence."

Feilden concludes, "Deciding whether to use the latest available tools really comes down to balancing investment versus the risks associated with potentially dangerous chemical compounds being present – but unseen."

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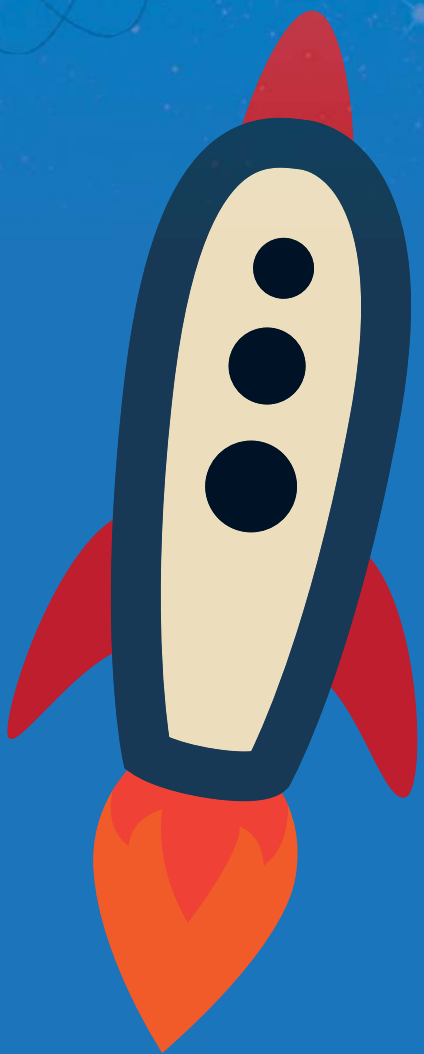
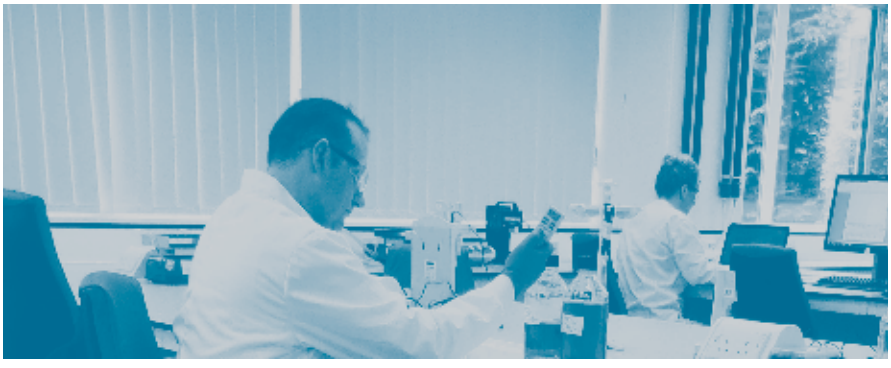


The Journey from Chemist to Entrepreneur

Starting my own bioanalytical research company after many years working for Big Pharma has been daunting, but also satisfying, and I wouldn't have missed it for the world. Here, I describe my journey from naïve beginnings to fully functional lab and the steep learning curve that led the way.

By Elizabeth Thomas



"Why don't we set up our own bioanalytical contract research organization?" That was the simple question that I posed to a group of close colleagues in 2004, back when I was an associate director of bioanalysis at AstraZeneca. It's fair to say that the response lacked enthusiasm. After all, why would my coworkers want to give up well-paid, secure jobs to do something much riskier and more demanding?

Fast-forward to July 2013 and I was asked the same question, and this time things were different, for at least three reasons. One, an established service provider, ICON Bioanalytical labs in Manchester, UK, was closing, leaving a real gap in the market. Two, skilled people would soon be made redundant both at ICON and at AstraZeneca who announced that it was moving research and development from Cheshire to Cambridge. And three, the BioHub was to open at AstraZeneca's Alderley Park facility, adding a tempting location to the mix. Yes indeed, times really had changed since that first conversation in 2004. Entrepreneurial urges had been fueled.

Setting the wheels in motion

After a few phone calls to exchange ideas and concerns, I got together with three recent former colleagues from ICON and AstraZeneca to seriously consider the possibility of launching our own bioanalytical contract research organization (CRO). For the early confabs we met up every Wednesday evening in the "Didsbury office", otherwise known as a pub called The Slug and Lettuce. After a couple of discussions we added a second weekly get-together, on Sunday afternoons in my kitchen. Little by little, our business plan began to take shape and all four of us agreed that we should go for it: we were going to set up our own bespoke bioanalytical CRO.

Reality soon started to set in. We began on several parallel activities, including a search for appropriate lab and office space (as we did not wish to limit options to the

BioHub), investigating the possibility of start-up grants, and getting access to training, advice and business support. Some government-run training courses were useful, although they seemed to be aimed at single individuals setting up small businesses: ours was definitely at the more ambitious end of the spectrum. It is strange what sticks in my mind from these courses; one was when the advisor on the bookkeeping course recommended keeping invoices in a shoe box(!) and the second was the absolute horror on people's faces when, after a show of hands in the social media course, I was identified as the only person in the room not on Facebook. "Is that really a problem?" I asked.

Training was also available via the BioHub in the form of a business Bootcamp event. This was very useful and really made me challenge whether we had a viable business idea. It also drummed into me the importance of managing the business – as opposed to being 'in' the business – and the need to focus on 'sales, sales, sales'.

All four of us had spent the majority of our careers in large pharmaceutical companies and CROs, so we were used to the corporate world and everything that it entails. Suddenly, we were way out of our comfort zone. The difference between working in – or even managing – a business unit and running your own company is immense, and I found my time taken up by a multitude of issues that I had never needed to consider before: "How do I do a VAT return? How do I run a payroll? What exactly is Corporation Tax?" Unfortunately, 3am seemed to be the time when I worried about these things the most. And yet, we kept working and progressing.

Let the science begin?

By January 2014, we had registered the company, becoming the proud owners of Alderley Analytical. We had a logo, our website was up and running, and we had reserved the lab and office space we needed to get started at the BioHub. This felt like a good start, but there was still equipment, rent, accounting, legal issues, insurance, finance and, of course, 'sales, sales, sales' (and marketing) to consider. There was still a very long way to go.

While conducting market research with potential customers and ex-colleagues, a number of them told me I was "brave" to set out on my journey. If I'm being honest, I could have substituted the word brave with many others (some of them good and others simply not publishable) depending on the challenges and hurdles I was trying to negotiate at the time. In those more difficult moments, I was very pleased to have colleagues who I knew well. Without others to share worries and concerns, things would have certainly been much more difficult – even impossible.

By the end of February, we had

Five Top Tips to Get You Started

- Be thorough with your market research. What problem are you solving? Is your business idea viable?
- Get your website up and running as soon as possible.
- Don't be scared to ask for advice business, legal, accounting). You will be surprised how much free advice is available.
- Look at Government websites – they can often guide you to small business advisors and free training.
- Get out of the building. It is essential to get your business known and to grow your network.

Five Pitfalls to Avoid

- Try not to spend too much time 'in' the business instead of managing it.
- Don't get stuck in your comfort zone. You will need to take on a diverse range of tasks and challenges.
- Don't pay full price for goods or services. Negotiate everything and try to get as much free stuff as possible!
- Don't forget about Business Development and sales, sales, sales. No customers means no business.
- Don't get disheartened. Find a colleague or mentor to help you meet the challenges.

"I can honestly say that I still don't consider myself to be an entrepreneur. Perhaps that is because I am still a scientist at heart and always will be."

signed the lease for the lab and office, purchased general lab equipment from the closing ICON lab and acquired a liquid chromatography-tandem mass spectrometry system. Although it was perched on the bench awaiting direction, when I surveyed my new environment, I felt satisfied that we had arrived – we had a fully functional lab. Let the science begin, I thought.

Alas, such thoughts were a little premature. We still had to prepare for Good Laboratory Practice (GLP) accreditation and there were many standard operating procedures (SOPs) to write and forms to design; we had to validate the LC-MS/MS system and the temperature-monitoring system for our fridges and freezers; we had to write company and health and safety policies and procedures. And still the list grew... We had to set up our accounting software, our customer relation management system and our IT infrastructure; we had to get our business cards printed, finalize the website and develop the marketing brochure. And grew… We had to sort out our business banking accounts and banking software, legalize the company, the decision-making, and the shareholdings.

There were the slightly disturbing 'what if' scenarios to consider, those things that 'could in theory' occur in the future and affect the stability of the company. What if one of us died? What if we all died? What if we couldn't work together anymore? What if one person wasn't pulling their weight? Oh – and, of course, we couldn't forget about 'sales, sales, sales.' The next topic to raise its head was 'investment'. Did we need it now, in the future, or at all? On several occasions, we were asked "What is your exit strategy?" That question left us a little bamboozled. Exit strategy? Let us get started first.

Current status

And get started we have. Alderley Analytical is now doing real bioanalytical science for real customers and we have a positive emerging pipeline – and genuine smiles on our faces! In November 2014, we won the East Cheshire Council's 'Start up of the Year' business award because of our potential for growth. We've grown from four to six people and we've also expanded on the equipment side with another LCMS/MS system and a laboratory information management system – so overall we have more capability and more capacity. In our early days, many potential customers told us we were too small and financially unstable, but now we've managed to secure investment, including £200,000 (around $300,000) from Alderley Park Ventures, which ironically was set up by AstraZeneca – right where we started! We've also received further funding from a venture capitalist company called Spark Impact, which funds businesses in the North West of the UK. Getting investment changes a lot of things. We were originally a team of four making all of our own decisions, but now we have a more formal board structure and a board Chairman – Mark Clement – so there's a lot more business expertise and rather than being asked about an exit strategy we're being asked to think about our next round of funding. We're always looking forward (and we're still focused on 'sales, sales, sales') and in 2016 we'll be looking to move to a larger lab space and to add new service offerings. Right now, we're focused on small-molecule bioanalysis, but we also want to expand this to large molecules too. Jump forward to the end of 2018, and we hope to have approximately 50 staff, six LC-MS/MS systems, and several large molecule analyzers, with a matching increase in lab/office space from 1,500 square feet to 7,000 square feet.

And whatever happens, I will never regret starting on my journey. I have learned so much and met so many great people along the way. I wouldn't have been able to get this far without a great deal of support, help and advice.

I still can't get used to being called an entrepreneur, despite the fact that people have already used it to describe me. When I think of entrepreneurs I imagine Richard Branson and Alan Sugar but perhaps that's a generational (and British) perception. If I was younger (and American), I guess my first thoughts might turn to Mark Zuckerberg or Larry Page. Either way, I can honestly say that I still don't consider myself to be an entrepreneur. Perhaps that is because I am still a scientist at heart and always will be. However, life has definitely changed. I was looking at LinkedIn recently and realized that many of my new connections weren't scientists; they were accountants, solicitors, corporate finance people and – you've guessed it – entrepreneurs.

Last week, I had coffee with an acquaintance who is thinking about setting up their own scientific business. The very first question asked was "where do I start?" The answer to that is neither short nor easy – but I gave that my best shot, too.

Elizabeth Thomas is CEO and founder of Alderley Analytical, Cheshire, UK.

The Realities of a Digital World

Advanced digital technologies are sweeping through the world and changing the way we live our lives and do business. And although change is often disruptive, digital technology is allowing pharma to reap the benefits of advanced analytics like never before.

Mobile communications, the Internet of things, the cloud, advanced analytics… digital technology is advancing rapidly and changing the world around us. Significant transformations have already been witnessed in a number of industries, including retail and media – will healthcare and pharmaceuticals be immune? Olivier Leclerc, senior partner at McKinsey & Company, believes that the digital revolution of the pharma industry has already begun. In 2014, $6.5 billion was invested in digital health, a 125 percent increase compared with 2013 (1). The traditional models of the pharma industry are changing as patients begin to take healthcare into their own hands by seeking information online or tracking their health through mobile apps. This provides an unprecedented transparency into outcomes, and pharmaceutical companies need to adapt by becoming solutions companies. Many digital technologies are available to enable this shift, but how do companies harness them? A recent white paper co-authored by Leclerc sought to bring structure and clarity to this issue (2). Two outcomes seem certain: i) there will be disruption, ii) there will be opportunities for business growth and innovation. We spoke with Leclerc to find out more.

What digital technologies are the ones to watch?

Digital technology is having a growing impact on every level in the pharma enterprise, but many companies in the field are struggling to understand what digital initiatives they should be focusing on. We believe that there are three fundamental technology gaps that should be watched closely.

- Smart phones. Today, almost all consumers are carrying a high-powered computer, which means there is huge potential for using digital tools to connect with them and gather data.
- The cloud. People are only now realizing the implications of the cloud in terms of cost reduction and increased application flexibility. Consider that we can now develop useful applications in six weeks; previously, we would need a system integrator working on it for months. This change alone is triggering a lot of innovation.

- Advance of informatics, enabled by computer power. Not only can you now collect a huge amount of data, but you also have the computer power and analytic techniques to analyze the datasets. Such power will generate many new insights as these big datasets are fully mined. And we're not just talking about genomics data – gigabytes of data can also come from clinical trials, or even tracking technologies.

But given the rate of change, it is no surprise that some executives are struggling to identify and prioritize all of the opportunities.

How do you pick which projects to prioritize?

This is a crucial issue. You need to be able to measure success so that you know which projects are working and worth continuing. Even a medium biopharma company can typically have upwards of 250 digital projects – and large companies have many more. Often, these projects are initially developed to fulfill specific needs from marketing or other functions and tend to grow organically; no one is really tracking their actual impact on the business. So although digital technology already has some momentum in pharma companies, it is not always carefully directed.

The problem for the biopharma industry then is not just how to harness this momentum, but also how to direct it so that it adds the most value. And to direct it effectively, you need an infrastructure and a measurement system that alerts you to failing projects. When we started working in this field, tools were limited and it was difficult to assess which digital projects were creating impact. It's a very different story today.

What practical examples can you give that highlight the benefits of digital?

One of the great benefits of digital is that once you have the right measurement systems collecting the right data, your decision making can be accelerated because the feedback cycle is faster. In other words, you generate the datasets, you analyze them, you derive insights from the analysis, and then you take the appropriate action. For example, if you measure drug response in different patients, and generate insights from that data, you could act upon it by segmenting patients according to predictors of response – and then you could continue collecting data to monitor the effect of that action.

"Tailored treatment is already happening for some diseases, such as cancer, but I expect this to dramatically accelerate in the coming years."

Ten years ago, if you were conducting a trial that incorporated quality of life measures, you would typically rely on patient diaries. Every day, patients would write up how they felt, what they did, what their treatment was, and what the effect was. And you would have to rely exclusively on the patient to record the information accurately over the period of the trial. You would probably also be restricted to a small trial because the approach is costly – and slow. It takes months to gather and analyze the data from all the diaries. Today, you don't need diaries. Instead you use an application, and directly collect patient data using wearable technology that measures vital signs or by using smartphone-based sensors. Data collection is very fast – in real time in some cases. It is this dramatic acceleration in the cycle of data collection, analysis, insight and action – enabled by digital technologies – that is transforming the industry.

Will digital also have a significant impact on R&D activities?

Yes – I believe that the speed of R&D activities can be accelerated thanks to the combination of genomics and digital technology, which together enable the generation and analysis of massive amounts of data – and the derivation of valuable, novel insights. At the same time, we're also seeing the emergence of powerful biotechnology platforms (for example, gene-editing and mRNA), which can generate tailored drug candidates very fast – in a matter of weeks. Not only are you generating novel insights around disease biology – that 'wow' moment when you realize that a gene is involved in a disease – but you also have the ability to quickly develop and test new treatment options. The upshot? Generating hypotheses – and eventually treatments – is much faster than it used to be.

And let us not forget the huge impact at the other end of the spectrum – the patient. Digital technology enables you to gather huge amounts of patient data, such as treatment responses, which leads us ever closer to precision or personalized medicine. Tailored treatment is already happening for some diseases, such as cancer, but I expect this to dramatically accelerate in the coming years simply because we are collecting more and more data on patients. After all, it only takes $150 to sequence a genome...

What are the considerations around data?

To understand what data must be collected and how value can be extracted, you need to have a certain hypothesis. Let's postulate a

nervous system drug, which is efficacious at first but loses efficacy over time, after which the patient needs a higher dose. You want to know when to change the dose, and you want to know as soon as possible. If you only collect data when patients visit their physicians, you could be waiting three or four months between data points. During that time, the patient could have been receiving an ineffective dose for several weeks. You need to think about what kinds of data would be helpful and meaningful in this situation. For example, should you measure tremors in the patient's arms or vital signs? You need to see what is happening to allow timely intervention – and you need to understand what you want to improve. Then it's simple – you gather specific data that will enable you to address your goal.

Another important consideration with data is data transparency. Biotech and pharma companies historically controlled all data pertaining to a given treatment, such as clinical trial data. Today, with data transparency initiatives, more people have access to these data and can use them to make treatment and prescription decisions. Though such data access has advantages, there is a risk that someone else may use different methods to analyze the same data sets, and come to very different conclusions. To that end, you need good, trusted analytic methods backed by a solid methodology. I believe that we will see the emergence of academic or private 'infomediaries', which will become trusted advisors on real world data, as well as partners to the pharma industry. These experts will be able to suggest the best methodology to use when analyzing data.

What steps should pharma companies be taking on the road to digital success and what are the potential hurdles?

First, you must define the specific digital initiatives that will actually make a difference. This is a prioritization process where you focus on value: where is the value for the patients, where is the value for the enterprise, and how do I capture that value?

You'll find that there can be many internal obstacles that should be addressed from the top. Complex projects that cut across multiple functions rarely work well unless you have a mandate from the CEO, which helps to spur the organization into action. One common internal challenge starts with the fact that IT departments are essentially complex, and typically deal with large, cross-functional projects. You need people that understand both digital technology and the pharma environment – and these people are rare. Also, the IT department must be willing to experiment because application development can take several attempts before finding the method that works best for your needs. You'll probably discover that pharma IT departments are culturally inclined to enterprise resource planning (ERP) rather than experimentation. To overcome this, we advise companies to have two-speed IT departments; the 'normal' IT department focuses on ERP, running the core processes and features that are critically important to the supply chain, and so on, while at the same time, you carve out a group of people who are able to work with other groups in the company to make agile computations happen and integrate them into the system. This kind of two-speed IT organization is important if you want to develop digital capability.

Do all companies accept the importance of digital?

Companies' rates of progress vary dramatically, but in general I believe that all pharma companies are committed and accept that digital advances are important for them. The one common question that I hear all the time, however, is: where is the return on investment? The answer to that question is not always straightforward, which is why it is important to have a measuring framework. You may not see the return on investment immediately since it can take time to implement new technologies and understand how best to use them in each company. However, some initiatives should pay off fairly quickly. For example, if you launch an app that measures and improves adherence, you may be able to judge its success within a few months, at which point you can tweak it or kill it. Improving patient outcomes is a longer-term objective and demands a very different measurement system. It will take time and research to define the projects that seem viable – and it will take more time to decide on the appropriate framework and metrics for measuring success. It's better to start with two or three initiatives that are very clearly defined, and associated with very clear metrics. Not all projects will be successful, but it's okay for some to fail – if you're monitoring them. It's a process.

Looking forward, with all the advances in digital technology, I am excited about the future of healthcare. We're on the cusp of a big change and we're seeing a lot more innovation now than we've seen in the last 30 years. Remember that we sequenced our first genome at a cost of a billion dollars, back in 2001, and today, we can see the fruits of that sequencing effort in new cancer research and other areas. I am also very positive about the influence of digital technology on the pharma industry. And it doesn't end with drug discovery and development. Pharmaceutical companies are certainly not the leanest organizations, but digital technology can help manage and control the complex infrastructure at play. After all, in an expanding digital world, the scope is almost limitless…

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The Receptive Regulator

Sitting Down With... Siu Ping Lam, Director of Licensing Division at the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

Did you always envision a career as a regulator?

Not at all. I've got a PhD in pharmaceutical chemistry and I'm a pharmacist by training. I've worked in both retail and hospital pharmacies, and for a while I was a research and teaching fellow at King's College London. I was looking around for new opportunities and I saw a job advertisement at the Medicines Control Agency (MCA, the former Medicines and Healthcare products Regulatory Agency (MHRA)). I liked the idea of being an assessor, and I had research and academic skills that I could bring to the role. Perhaps most importantly, I felt it was an opportunity to really make a difference to public health. I joined the MCA in 1989 and I've been here ever since.

How would you define a regulator's role?

The role of a regulator is very different to what some people think – we are not just there to stop you! Everything we do is for the protection and benefit of public health. Of course, we have to make sure that medicines are high quality, safe and efficacious – but we also want them to be developed and manufactured in the most efficient manner and we want patients to get them as quickly as possible. To that end, we have a very open door policy when it comes to offering regulatory and scientific advice to support organizations to make the best possible products.

And that's what the MHRA's Innovation Office is all about?

In 2011, the Prime Minister's strategy in Growth in Life Sciences highlighted the challenges facing the UK's life sciences sector and the development of healthcare innovation, including new medicines. The establishment of the Innovation Office is one of the MHRA's ways of responding to those challenges. The office was set up in March 2013 and it aims to help organizations that are developing medicines, medical devices or using novel manufacturing processes navigate the regulatory system. The benefits are two-fold; the innovator clearly gains from our expertise, but it also helps us to get closer to what's happening on the ground – and that means we can more easily identify gaps that could be addressed. It's in our interest to work closely with developers and we see early dialogue between innovative organizations and the MHRA as an important step in the process.

What kind of projects does the Innovation Office support?

Essentially, anyone with a novel concept, product, technology, manufacturing process or even just some new ideas can come to us for advice. We try to explain what the regulatory issues for the innovation in question might be at different stages – and what advice we can give to help them. For example, in the case studies that we have published, we've worked with AstraZeneca on plans for a new facility for supplying cancer medicine, and we've been involved with the Jenner Institute at the University of Oxford, who asked for advice with the development of a malaria vaccine that uses viral vectors from chimpanzee virus DNA. We will be publishing more case studies where we have helped organizations, with their agreement.

What has the Innovation Office achieved so far?

The innovative sector has reacted very well; we've had over 230 enquiries since launch – and we've received lots of very interesting and exciting ideas, which make me feel positive about the future of the medicine pipeline. However, given that pharmaceutical development takes many years, we haven't actually seen any of the products we've been involved with make it to market yet, but some of the projects have progressed to clinical trials, which is extremely satisfying.

Something else I'm very proud of is the fact that we've extended the Innovation Office to be a one-stop-shop for advanced therapy medicinal products (ATMP) or regenerative medicines to hopefully ease the development process for these important therapies. Such medicines can be somewhat tricky because you may have to work with different regulators (HTA, HFEA, HRA and MHRA) depending on the stage of development. The Innovation Office acts as a portal and we can pass queries from companies on to the right authority at the right time.

How do you think regulatory processes are perceived?

There are many trends and challenges in the industry, but I think that, from the point of view of the innovator, regulatory processes are probably seen as the biggest challenge. Innovators know how to generate ideas and may have a good understanding of how to turn that idea into a reality, but when they look at our area – the regulations – they see huge complexity. Big pharma companies tend to have large regulatory affairs departments, but for small companies or academic institutions there is often a lack of regulatory knowledge, and the processes can seem daunting. We are very much aware of that perception and we want to ease the process for everyone as much as possible.

What are your hopes for the future?

We need to continue reaching out to innovators, academics and other drug developers to get our message across: regulators are here to help and guide. We are scientists and we all want to bring safe and effective medicines, as early as possible, to patients. I encourage the industry to make use of the scientific knowledge and advice that regulators offer. There is no need to see us as the barrier to successful innovation.

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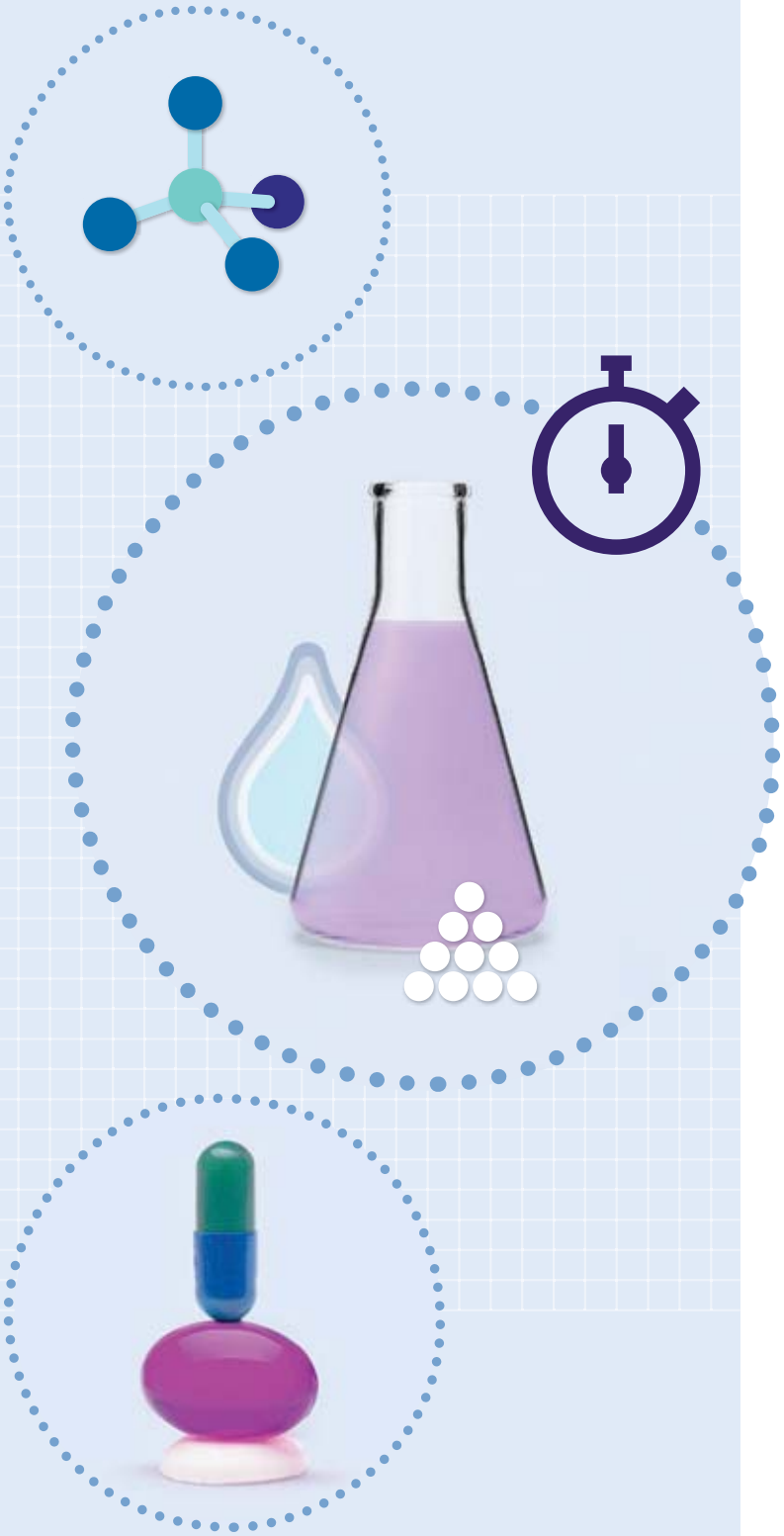

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