SEPTEMBER 2015 # 11

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Online this Month

Inkjet Innovation

On page 20, we explore the potential of 3D printing in drug development, but 3D is not the only printing technique that has a place in producing the medicines of tomorrow. Inkjet printing technology has the ability to deposit very precise amounts of drugs and excipients onto suitable substrates. We interviewed Niklas Sandler, Professor of Pharmaceutics at Abo Akademi University in Finland, about his extensive research in printable formulations, from oral film formulations, to enhancing poorly soluble drugs, to printing biomolecules.

Read the interview online:
tmm.txp.to/0815/sandler

the Medicine Maker Innovation Awards 2015

Innovation Awards 2015

The December issue of The Medicine Maker will feature our inaugural Innovation Awards. The Innovation Awards will showcase the top innovations of 2015 that are aiding pharmaceutical manufacturers, from game-changing production equipment and packaging, to new drug delivery technologies, to transformative software. If the innovation was announced in 2015, it is eligible for the 2015 Innovation Awards.

And it's up to you to decide which companies and technologies get nominated.

To nominate an innovation, complete the online form at http://tmm.txp.to/0715/innovation or email deputy editor Stephanie Sutton at Stephanie.sutton@texerepublishing.com.

To be considered, please include:

- Name of innovation
- Brief description (~10 words)
- Detailed description of why you consider the innovation to be groundbreaking (50-150 words)
- The potential impact of the innovation (50-100 words)
- One image (if applicable)

The Process

- The deadline for nominations is Friday October 30, 2015.
- The full list of nominations will be put to an expert panel.
- Under the guidance of the Chair, the panel will decide on the Top Innovations of 2015.
- The panel's decision is final and no correspondence regarding their deliberations or the final list will be entered into.

The Top Innovations will be highlighted in the December 2015 issue of The Medicine Maker, in print, on the iPad app and online. Good luck!

Nominate now:
http://tmm.txp.to/0715/innovation

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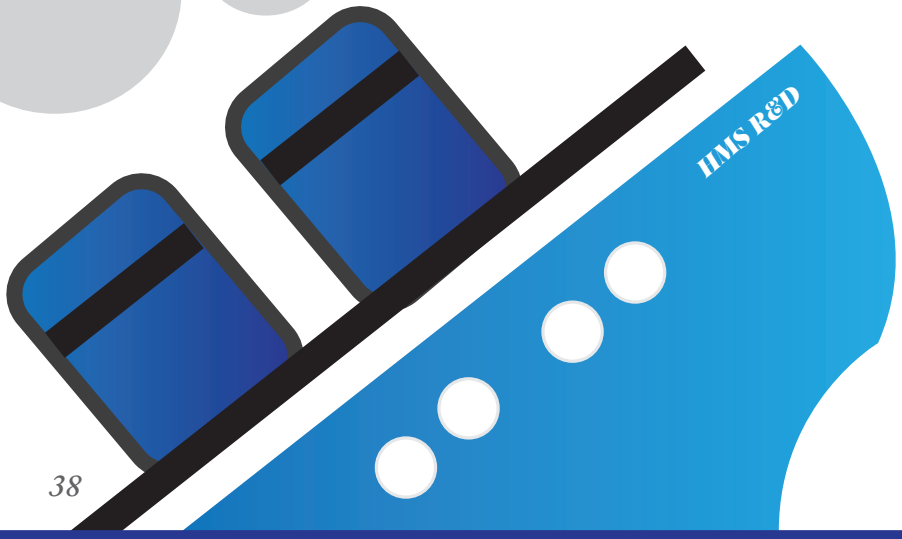

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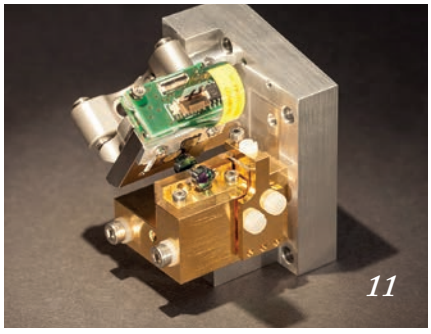
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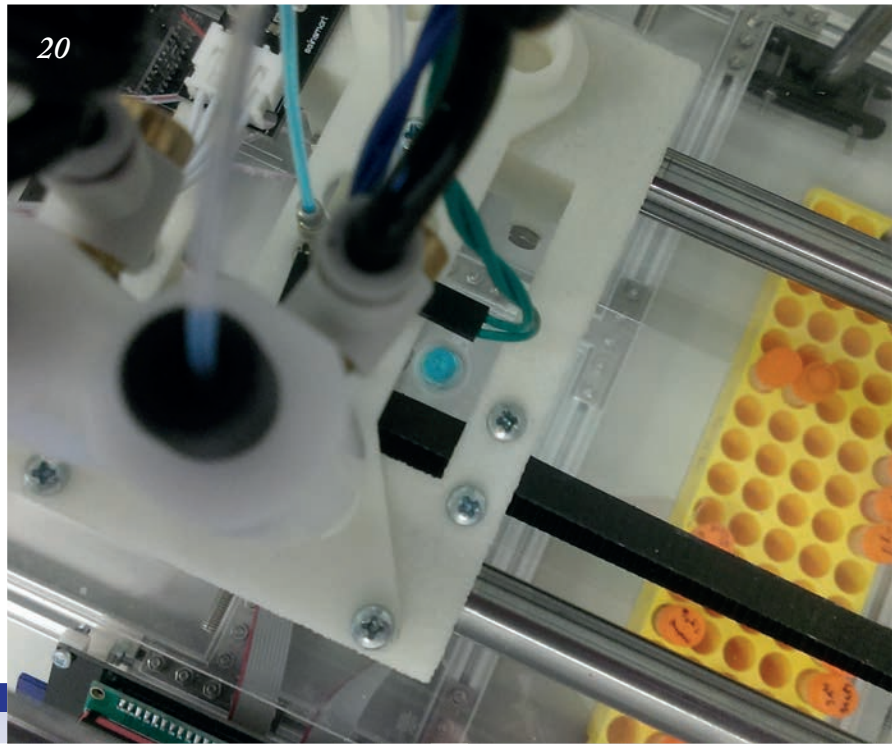
Unlocking new technology to print the medicines of the future.



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Clinical Trial Clarity

Drug makers and regulators are taking steps towards transparency, but is it enough?

Pressure is mounting to expand reporting of clinical trials. The AllTrials initiative (www.alltrials.net) – a coalition of 600-plus publishers, charities and funding bodies – is calling for "all past and present clinical trials to be registered and their full methods and summary results reported." Recently joined by a group of 85 asset managers and pension funds, the initiative is lobbying drug makers to make more data available. New European legislation will make it mandatory to report new trial data in a public database, following the example of clinicaltrials.gov in the US.

Pharma companies are not the only ones guilty of failing to report data – particularly negative data – from clinical trials. A recent study in PLOS One concluded that the number of null results reported in large National Heart Lung, and Blood Institute (NHLBI) funded trials has increased significantly since trials started being registered at clinicaltrials.gov. The authors largely attribute the finding to better reporting (1).

Clinical trials registries are crucial because a significant bias against publication of negative trial results remains in STM journals, with up to half of all clinical trials never published (2). However, AllTrials argue that registries are only useful when their use is enforced, citing a 2012 report revealing that only 22 percent of trials subject to mandatory reporting had submitted the results within 12 months of completion (3). While the FDA has the power to fine organizations for failing to submit data, AllTrials claim they have never done so. They also want to see data from past trials made freely available.

To their credit, pharma companies are themselves getting on board with data transparency. Indeed, with drug makers now publically disclosing details of their research pipeline to reassure investors, it would be hard to conceal failures. GSK spearheaded the development of a website allowing researchers to request detailed study results from 12 drug companies.

It seems that we are heading for a new era of openness in clinical trial reporting, and that can only be good news for science, for patients, and for the hundreds of thousands of people who take part in clinical trials, who especially have the right to know the outcome.

Charlotte Barker
Editor

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Aad van de Leur

Aad van de Leur has been working at Synthon Biopharmaceuticals BV, Nijmegen, the Netherlands, since January 2009. In his role as chief operations officer, he is responsible for all biopharma operational activities, including process development activities from cell line development to formulation and related analytical development, as well as manufacture and supply of clinical material. "Currently, the company's biopharma development activities are directed at New Biological Entities, with a focus on antibody–drug conjugates," explains Aad. Before joining Synthon, Aad worked for over 23 years in different biotechnology departments at Diosynth/Organon, gaining experience in cell culture development, purification process development, technology transfer and more.

Aad describes antibody–drug conjugates as a Trojan horse against cancer on page 34.

Harparkash Kaur

Harparkash always dreamt of being a chemist and started her scientific journey by synthesizing compounds to trap free radicals. Her first water-soluble spin trap was designed to trap the fastest radical known – the hydroxyl radical. This spin trap failed that task but has been found to have other applications, and is now sold by Sigma chemicals. "My HPLC and simple chemical methods are used to test the quality as well as levels of drugs in patient samples, and measure the levels of insecticides on treated materials that are used as the major mode of intervention in the fight against malaria."

When tackling counterfeit medicines, Harparkash urges us not to overlook antibiotics on page 16.

Christoph Herwig

With a degree in process engineering, Christoph Herwig started his career by building continuously operational chemical facilities, but soon realized that it would be higher-value-added products that would secure success. Following a PhD at the ETH Lausanne to develop bioprocesses using novel quantification tools, he made the move back to industry where he worked mainly as a translator between mathematicians, biologists and engineers. "The key success factors for building bioprocesses are interdisciplinarity and sound science," believes Christoph. Since 2008, he has been professor of biochemical engineering at the Vienna University of Technology. At the university's Christian Doppler Laboratory, he focuses on the mission of building safe bioproducts using quality by design principles.

On page 18, Christoph asks how we can change misconceptions about quality by design.

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Upfront

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

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Wasps Versus Cancer

Do Brazilian wasps hold the promise of a new anticancer therapy? The answer is in the sting

Researchers have known for some time that Polybia paulista wasp venom contains an ingredient that selectively kills some cancer cells, but the big mystery is how exactly the agent works. Motivated to investigate the venom further, Paul Beales, a senior research fellow at the University of Leeds, and João Ruggiero Neto, a professor of physics at São Paulo State University, Brazil, believe they have uncovered a molecule with a mechanism of action that is distinct to any current anticancer drug (1). We spoke to Beales to learn more about the science behind the sting.

How did the project get started?
We already knew that a membrane protein called MP1 isolated from wasp venom had anticancer properties, but we did not understand how it worked until now. MP1 is an antimicrobial peptide that selectively disrupts the bacterial cell membrane. The action of MP1 hinges on the composition of two lipids, phosphatidylethanolamine (PE) and phosphatidylserine (PS). These lipids are normally located inside the membrane, but in cancer cells they are often found on the outer membrane where they are "visible" to the cell's environment. We engineered model membranes that contained neither, one, or both lipids to study the MP1's mechanism using an arsenal of biophysical spectroscopic and imaging techniques.

What were the most surprising findings?
Both PS and PE lipids are important for MP1's ability to disrupt membranes. PS increases the binding of MP1 to the membrane, whereas PE makes it easier for MP1 to disrupt it. I think we were most surprised by just how significant the effect of PE was.

What are the potential advantages?
No anticancer drug selectively targets the differences in the membranes of cancer cells, so this would be a completely new mode of action for an anticancer drug and could be useful for combination therapies. What's more, by disrupting the membrane this may also "open the door" for other drugs with intracellular targets inside the cancer cell, giving them easier and faster access to their targets.

Now that we think we understand its mechanism of action, it will be interesting to design modifications to MP1's structure aimed at increasing its selectivity and potency to cancer cells.

How do you see the area of synthetic biology fitting into this research?
Re-engineering cells or creating synthetic biochemical nanoreactors to synthesize and secrete the peptide in situ could provide countless opportunities to develop novel therapies. I like the idea of smart synthetic cells that detect disease biomarkers and respond by synthesizing and releasing appropriate drugs in response. This is a "hot topic" in my research group; it's a bit like science fiction at the minute, but it will be interesting to see how far developments in synthetic biology can take us in that direction.

Reference

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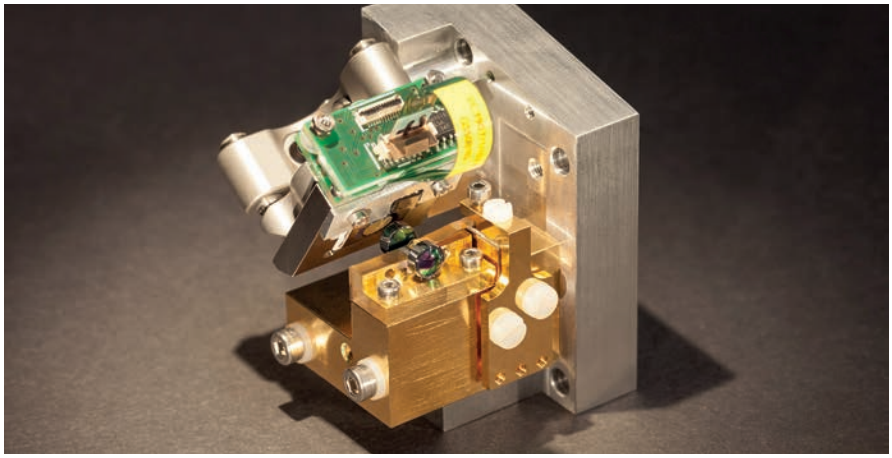


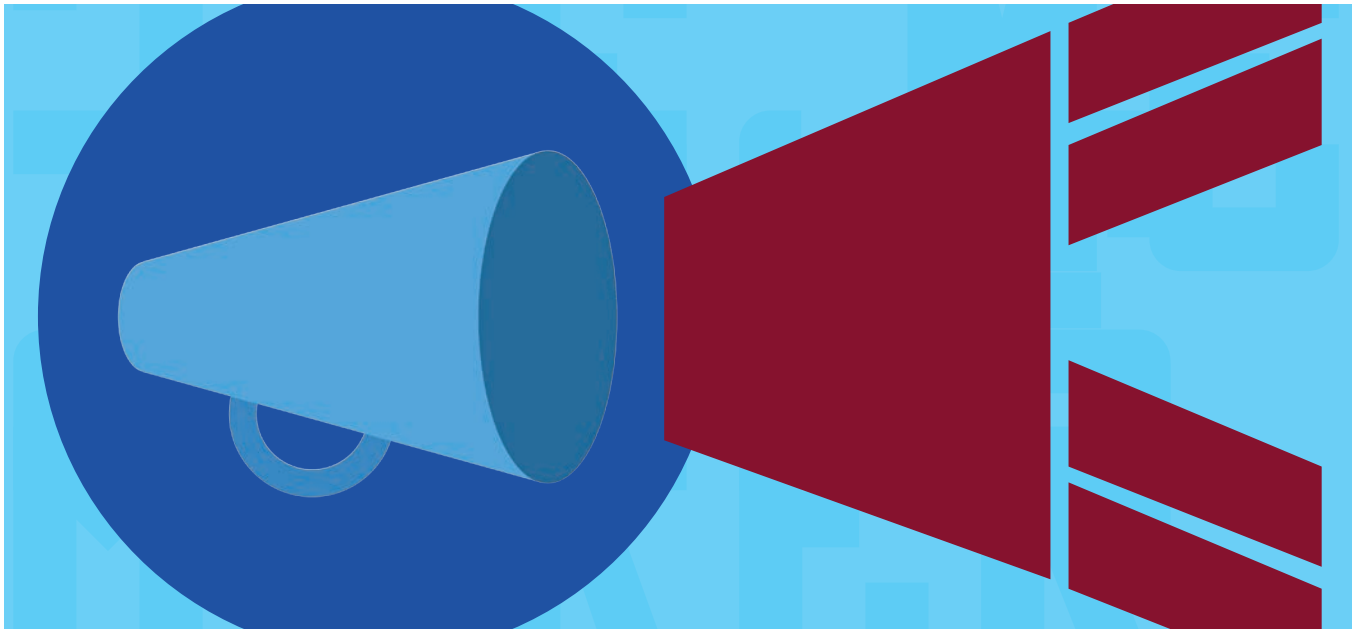
Quantum Leap in Real-time Monitoring?

Continuous monitoring of pharma products with an innovative matchbox-sized laser

Product quality monitoring is essential in pharma and chemical production, but often performed manually. Researchers from two Fraunhofer Institutes (Applied Solid State Physics in Freiburg and Photonics Microsystems in Dresden, Germany) may have found the ultimate solution. The team has developed a matchbox-sized laser module that can be rapidly tuned over a wide spectral range, opening the door to spectroscopic identification and quantification of substances in real time. For pharma manufacturers, this means the ability to trace chemical reactions or to measure product composition continuously.

"At any time, you'll know exactly what is happening, such as what and how much substances are currently involved. This means you can continuously monitor the quality check and be aware if something strange happens. You won't need to take random samples and pass them onto the quality control lab," says Ralf Ostendorf, project manager at the institute in Freiburg."We used a small silicon chip that integrates an optical diffraction grating in a micro-optical-electric mechanical system (MOEMS) scanner and combined this with a quantum cascade laser (QCL) chip. Both chips independently measure only a few millimetres – but the potential seemed enormous," says Ostendorf. The original goal was simply to develop a miniaturized laser source, but the team decided to test the capability of laser-based mid infrared spectroscopy in different applications."We're currently working on our first real-time spectroscopic measurements to demonstrate the capabilities of the technology," says Ostendorf. "The absorption lines of chemical substances are very characteristic and strong in this wavelength range. It's a really sensitive solution that can detect even small traces of chemicals."

Ostendorf expects that the system could easily integrated into pharma settings, and believes its tiny form factor could lend itself to a commercial handheld sensor. It's still early days, but widening the spectral tuning range could open up access to applications outside of pharma and chemical manufacturing. In fact, Ostendorf also has his eye on the clinical sector – perhaps identifying lung disease from breath samples – at which point, the term quantum leap seems entirely justified. *SS*



Fighting for Freedom of Speech

Drug companies claim that off-label drug promotion is protected by freedom of speech

We are all aware of freedom of speech – the right to communicate our opinions without fear of government retaliation and censorship, but how far does this apply when it comes to off-label drug promotion? The FDA has a duty to ensure that drugs are only marketed for their approved indications and frequently rebukes companies for off-label promotion and misbranding. But some companies are fighting back, claiming that preventing them from talking about off-label use is imposing upon their right to freedom of speech, which is protected in the US by the First Amendment. In August, a federal judge in Manhattan ruled that the FDA could not prevent Amarin from promoting Vacepta for unapproved indications, providing that any information disseminated by Amarin was truthful (1). Off-label use of a drug isn't illegal in the US, but it is usually considered illegal to actively promote a drug for off-label use.

Vacepta is approved for patients with very high levels of triglyceride in their blood, which can lead to heart problems. It is also sometimes prescribed off-label for patients with lower triglyceride levels. Amarin conducted a study and sought to officially expand the use of the drug, but was blocked by a Complete Response Letter from the FDA. Unhappy with the outcome, Amarin filed for a lawsuit. Delivering the verdict in August, the judge ruled that Amarin was protected from FDA enforcement providing that the off-label statements are truthful; however, the First Amendment would not offer protection from any false or misleading claims. This isn't the first time that drug promotion has been defended by freedom of speech legislation. In 2012, a court case focused on a sales rep who had been recorded giving a speech promoting off-label use of a narcolepsy drug. The court ruled that providing the sales rep's speech was truthful, it was protected under the First Amendment.

Following on from the Amarin ruling, Pacira Pharmaceuticals filed a lawsuit in early September looking to promote its post-surgery pain relief drug Exparel for a wider range of patients (2). Exparel is approved for pain relief in bunionectomies and hemorrhoidectomies, but the company has been promoting the drug for other kinds of surgeries – and received a warning letter in September 2014 for doing so. In its lawsuit, Pacira contends that all of its marketing claims are actually on-label, but adds that even if they weren't, the Amarin ruling would apply to their case. *SS*

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2. *Pacira Pharmaceuticals, "Pacira Legal Action" (September, 2015). http://phx.corporate-ir.net/*

Antibody Attack

DNA vaccine helps turn patients' own cells into antibody-producing factories

Vaccination against dengue virus is challenging to say the least, but researchers from the University of Pennsylvania believe that synthetic DNA could hold the answer. Specifically, they believe that DNA-encoded monoclonal antibodies could be used as an instant vaccine platform (1). Dengue fever is a mosquito-borne viral infection, but current vaccines do not provide protection against all four strains of the disease. In fact, vaccination against one strain could actually make patients more vulnerable to future infections because of the disease's complex relationship with antibodies.

"Traditional dengue virus vaccines cause the immune system to make antibodies, but dengue virions can use these antibodies at a later stage to more easily enter and replicate in certain immune cells. This "enhancement" of infection (known as antibody-dependent enhancement, or ADE) can occur even in the presence of neutralizing antibodies," says Seleeke Flingai, one of the project researchers.

Given the intricate role that antibodies play in the dengue disease puzzle, Flingai says it was a good target for their work. Their approach has two components: an optimized, synthetically developed DNA plasmid encoding the mAb of choice (DMAb), and an in vivo electroporation (EP) device that delivers the DNA to cells. Unlike traditional antibodies, DMAbs are specially designed not to provoke ADE. Upon intramuscular injection of the DMAb and in vivo EP delivery, the muscle cells engulf the DNA and begin to produce and secrete the desired mAbs into circulation. Essentially, the patient's own muscle cells become antibody factories.

"We believed that DMAb delivery would result in serum-detectable mAbs within some period of time, but we were really surprised by the rapidity of protective immunity; antibodies appeared in the blood of the test animals within a day or two after DMAb delivery," says Flingai.

The next goal will be to increase the antibody levels and improve the consistency of DMAb delivery. Flingai also wants to develop additional anti-dengue DMAbs that target all four strains of the disease, and begin testing the approach in larger animals. *SS*

Reference

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CPhI in Numbers

CPhI Worldwide 2015 in Madrid is just around the corner. Are you ready for showtime?

Break out your smart suit (and comfortable shoes) because CPhI and its co-located events will be back in Madrid, October 13-15 2015, filling 11 halls with tens of thousands of visitors from across the bio/pharma industry. CPhI focuses on the pharma ingredients business, while co-located events ICSE, P-MEC and Innopack cover contract services, equipment and packaging. CPhI will also include the Pharma Forum, which the organizers describe as a "content village" to examine thought leadership from the CPhI Pharma Insights Report. The Innovation Gallery and CPhI Pharma Awards are also located here.

In addition, don't forget the Pre-Connect Congress on October 12th, which is being held at the Novotel Madrid, Campo de las Naciones. Speakers include Clive Badman (GlaxoSmithKline), Jaime Gil Gregorio (Sandoz), Steinar Madsen (Norwegian Medicines Agency) and more.

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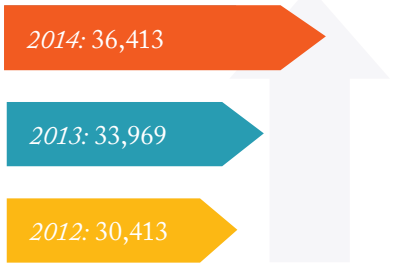

Exhibitors (2014): 2,500+

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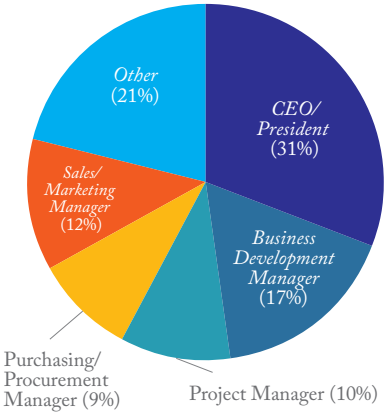
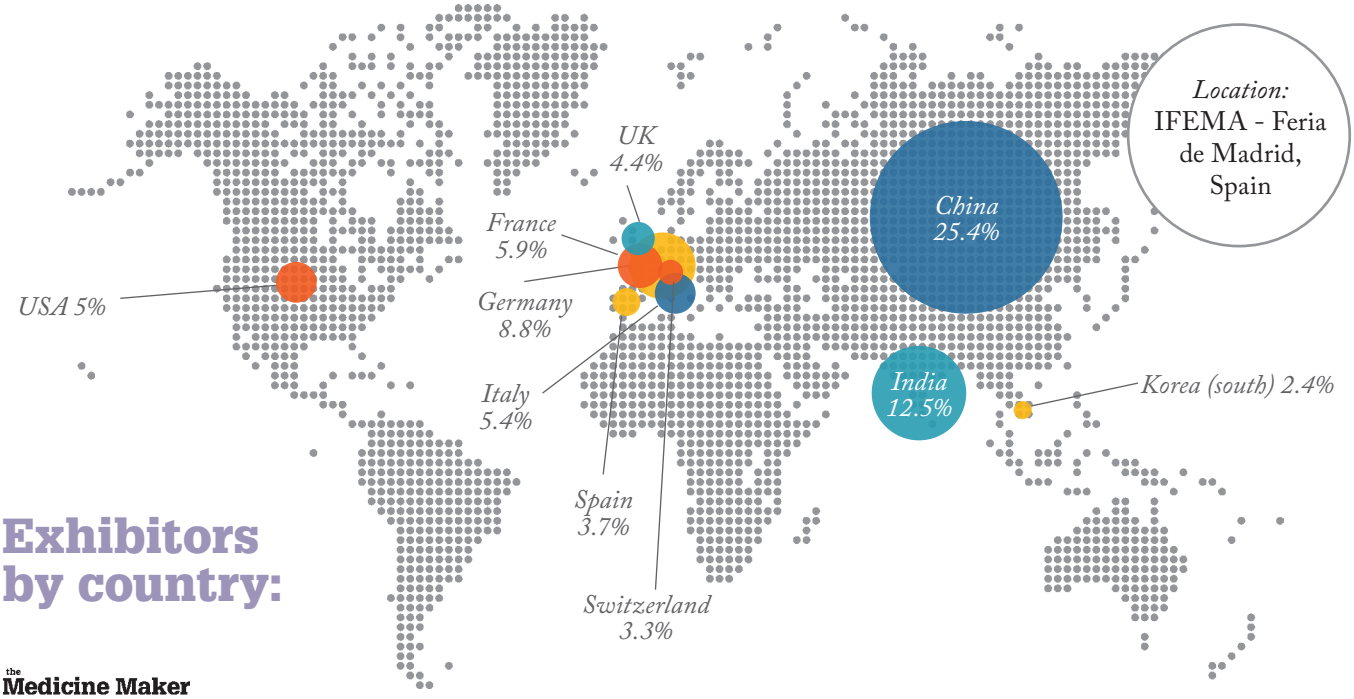


Who attends (2014):

Pharmaceutical Company (generic finished products), 18.1%
Distributors, 11.8%
Pharmaceutical Company (innovator finished products), 8.5%
Other, 5.6%
Consulting, 5.4%
Import/Export, 5.3%
Contract Manufacturing, 4.2%
API Producer, 3.8%
Biopharmaceutical Company, 3.8%
Packaging, 3.5%

Exhibitors by country:



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All Eyes on Antibiotics?

When you think about counterfeit and falsified medicines in developing countries, antimalarials are likely to spring to mind first – but we shouldn't forget that antibiotics are also important targets for fraudsters. In either case, more quality control testing is needed.

By Harparkash Kaur, Lecturer in Pharmacology, London School of Hygiene & Tropical Medicine, London, UK.

As scientists and medicine makers, we all know how crucial antibiotics are; indeed, sulfonamides and beta-lactam antibiotics have saved countless lives since their discovery in the 1930s. However, economic and regulatory challenges have led to disengagement from antibiotic research; though countless numbers of generic antibiotics are being manufactured globally, the number of large multinational pharmaceutical companies actively engaged in antibiotic research has fallen from 18 in 1990 to just four in 2011 – AstraZeneca, Novartis, GlaxoSmithKline and Sanofi-Aventis.

A worrying statistic: in 2011, a total of 262.5 million courses of antibiotics were prescribed in the US – that's 842 per 1000 people (1). Misuse of antibiotics through overprescribing and suboptimal dosing fuels the development of resistance. But superbugs are not the only issue. The sheer volume of antibiotics sold daily and their relatively low production costs makes them vulnerable to counterfeiting and substandard manufacture.

When talking about counterfeit or falsified medicines in developing countries, a great deal of attention has focused on the quality of antimalarial drugs. Indeed, malaria medicine was featured in this magazine back in June (tmm.txp.to/0715/fake_medicine). I've also studied the quality of malaria medicines; our studies of over 10,000 drug samples found substandard formulations (containing less or more of the stated active pharmaceutical ingredients than the specified pharmacopeia limits) in all six of the malaria endemic countries (Cambodia, Ghana, Tanzania, Rwanda and Equatorial Guinea) (2). But substandard or counterfeit antibiotics are also a big problem, particularly in resource-constrained countries, and I believe that a concerted effort is needed to determine the quality of varying antibiotic brands. The threat of superbugs – coupled with the disengagement of pharmaceutical companies – makes the maintenance of good quality antibiotics even more important.

Drug quality monitoring requires effective tools and regulatory systems. Certainly, wherever possible, we need quality control (QC) laboratories equipped with high-performance liquid chromatography-photo diode array detection (HPLC-PDA) and in vitro dissolution testing. HPLC-PDA is seen as the 'gold standard' for drug quality analysis because it offers accuracy, specificity and precision in quantifying the amount of stated active pharmaceutical ingredients detected – or their absence. And in vitro dissolution testing is a valuable predictor of the in vivo bioavailability and bioequivalence of tablets and capsules. Investment in quality assured reference standards is also needed and highly trained staff. Of course, all of these elements are cost-intensive

and not always achievable in resource-poor countries. But even in the absence of well-equipped QC laboratories, the screening of drugs can still be conducted at the point of purchase using portable laboratories. For example, one charitable organization – the Global Pharma Health Fund (GPHF) – has specifically developed the MiniLab as part of its mission to curb counterfeits in developing countries. The GPHF-MiniLab offers "simple drug quality verification in four steps," including thin-layer chromatography (TLC), and though results from the MiniLab should not be relied upon for regulatory purposes, it is able to perform tests simply and inexpensively, without the need for electricity or extensive training (3). Moreover, it provides qualitative data which was found to have low sensitivity for a brand of antibiotic when compared with content analysis with HPLC-PDA plus dissolution testing (4).

We used both the MiniLab and HPLC-PDA (plus dissolution tests) to assess the quality of two brands of antibiotics: amoxicillin and co-trimoxazole. The drugs were stated to be manufactured in six countries and purchased in Ghana, Nigeria and England. All samples of amoxicillin complied with US Pharmacopeia tolerance limits, but 60 percent of co-trimoxazole tablets (purchased in Ghana and Nigeria) did not, when tested using HPLC-PDA and dissolution testing. There was also some disparity between results obtained from HPLC-PDA and MiniLab TLC for co-trimoxazole as 13.3 percent samples failed in the MiniLab TLC test, whereas the numbers increased to 60 percent on HPLC-PDA and dissolution testing. The MiniLab is a suitable screening tool in the absence of medicines QC laboratories, but it has been previously reported (5) to only detect grossly substandard or counterfeit drugs as illustrated with the results of our study with co-trimoxazole (4). This highlights the need for further investigation including other brands of antibiotics.

The take home message is that the results emphasize the importance of verifying the quality of antibiotics, particularly in developing countries where antibiotics can be obtained without a prescription. Developing nations must invest in capacity by building and integrating national QC laboratories that use reliable and accurate methods, such as HPLC-PDA and dissolution testing, as part of an integrated drug quality surveillance system.

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The Redeployment Dilemma

Pharma companies often redeploy or sell equipment, but without sufficient expertise it's easy to fall foul of dangerous cargo regulations and other liability risks.

By Tony Parziale, Dale Butler and Peter Harris, EquipNet, MA, USA.

The principal of redeploying production equipment and instrumentation from one facility to another as projects complete, priorities change, or companies merge

is now well established in the pharma industry. The cascade of the remaining surplus equipment into sales or auction channels is now also standard practice and allows companies to recover as much initial investment as possible.

However, just because something is standard practice does not necessarily mean it is straightforward. We can offer a recent example that proves the point. After a local, non-specialist company had packed a consignment of equipment destined for India via airfreight, it was ready for consolidation into our shipment. Fortunately, Peter Harris noticed a problem: one of the items on the documentation had a flammable pressurized cylinder attached, meaning that the package would have to conform to International Air Transport Association regulations and be certified by a Dangerous Air Cargo (DAC) assessor. Essentially, Peter had averted the potential danger of it being placed in a standard passenger aircraft – and we helped the packers quickly get up to speed with regulations. As a direct consequence, the company was made aware that the nitrogen tank in another shipment was also a DAC consignment. Best practice can easily spread.

To achieve the best possible return on

your assets as they are relocated or sold on, there is a requirement for formalized processes, specialist knowledge of the industry and its equipment, and dedicated resources, usually from outside the organization, to provide project management and overall program leadership. Perhaps even more significant, management must implement and abide by a policy that calls for everyone to look for their equipment needs from within the business prior to purchasing new capital assets. Things can get complicated very quickly and we would like to raise awareness of some specific problems.

When developing policy, you first need to consider liability risk. The industry standard is to sell surplus assets "as is/where is", with no warranties expressed or implied. But in practice, companies not only need to have a watertight section in their terms and conditions of sale documentation that covers these aspects, but must also instigate auditable reporting and processes for every aspect of a transaction. Specialist partners can help in this regard since they tend to offer standard terms and conditions that address these areas and meet reporting and auditing needs.

Practices and records of equipment decontamination are a second important area to consider. Though all firms have decontamination processes in place as part of decommissioning assets, many buyers will request proof of decontamination and ask for detailed information on the specific products that have been run on the equipment. Therefore, the seller will need to decide to what extent they are willing to provide product information. In particular, complete decontamination of equipment that has produced certain products, such as antibiotics or beta-lactam, is so costly that, in most cases, it should only be sold to a new owner who is running the same type of product. In all cases, the terms and conditions of sale must be written to protect the selling company. The globalization of the pharma industry can also present challenges. For example, European buyers would want to know whether a surplus analyzer is CE marked. If not, the market demand for the equipment in Europe will be smaller because of the time and costs needed to certify the product.

There are also trade restrictions and embargos – often specific to the individual origin and destination countries – for any given shipment. And these are changing all the time. For example, current embargoes prohibit any equipment that can be used for energy production from being sold and shipped to Russia. Many countries in South America also have very strict import regulations that are driven by commercial sensitivities. These countries often impose very high duties and tariffs on imported goods and, in some cases, will not allow the importation of an item at all if it is readily available in the country from a local manufacturer. When a buyer of equipment from, say an auction in the US, is located in one of these countries, the seller needs not only to be aware of the restrictions but also make the buyer aware of them too, and work with them and their customs broker to ensure there will be no issues with completing the sale.

Given the pitfalls – and the time and resources necessary for successful asset redeployment or sale – it is no surprise that many are seeking the help of specialist companies. We've certainly seen an increase in the number of companies seeking partners to drive and manage their programs, and to ensure compliance with national regulations and local customs. And to be honest, we believe it makes the process much smoother for buyers and sellers alike.

Fixing the Negative Perception of QbD

'Quality by design' has been around for years, but still the benefits are hardly leveraged in medicine manufacture. I firmly believe that knowledge management can help.

By Christoph Herwig, Head of Research Area Biochemical Engineering, Vienna University of Technology, Vienna, Austria.

Quality by design (QbD), which has been with us for decades, is defined by the International Society for Pharmaceutical Engineering (ISPE) as a "systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management". The main principles have been assembled by the International Conference on Harmonization (ICH), as laid down in well-known guidelines.

Today, QbD is interpreted by

"We must understand that QbD is not only about executing risk assessment."

executing systematic multivariate analyses of interactions between process parameters and quality attributes using 'design of experiments' (DoE), as well as risk assessment approaches based on conventional failure mode and effects analysis. But the fact is that many in the industry see QbD as costly, laborious and without the promised benefits of being able to freely act in the design space and do real-time release without regulatory oversight.

As an example, DoEs are currently treated like recipes; there is no real reflection on the actual design and strategic meaning. A lot of data are generated in a systematic way and results are presented in colorful plots with intuitive software. Instead, we should be asking many other questions: why did we initiate this experimental plan? Why did we choose the boundaries of the DoE? How do we document our decisions in process development, technology transfer and scale up? Where can results be used in a lifecycle including continuous improvement?

Very few QbD projects are launched because of economic drivers; instead the main incentive is the regulatory threat, given that only QbD filings are likely to be accepted by the year 2020. Why is QbD so negatively perceived?

In my view, we as an industry must understand that QbD is not only about executing risk assessment (following ICHQ9 – Quality Risk Management (ICH 2005)) and DoEs (following ICHQ8 – Pharmaceutical Development (ICH 2009) – or even ICHQ11 – Development and Manufacture of Drug Substances (ICH 2009)). What we need to understand is that QbD will only work with a clear integrated concept of knowledge management, as encouraged by ICHQ10 – Pharmaceutical Quality System. ICHQ10 introduced the concepts of quality risk management and knowledge management to help achieve the objectives of QbD. There are two steps.

First, we need to generate robust knowledge by analyzing where substantial knowledge can be obtained from the data, and understanding what information can be transferred – as platform knowledge – from process to process, site to site, and product to product. Such an approach results in robust "prior knowledge", which is the ultimate key to any risk assessment and experimental design. We need tools that can convert data into information and knowledge and it is critical to compare experiment through normalization that is independent of initial conditions and scale. It may not be a task that can be automated; it will require an interdisciplinary team of technologists, statisticians and mathematicians – all facilitated by software. University curricula to create such 'knowledge analysts' are urgently required.

Secondly, we need to manage the knowledge we obtain and develop generic workflows that can provide, for example:

- a strong tie-in of risk assessment results with the initiation of experimental plan
- findings/knowledge of experimental results to reassess risk
- knowledge as platform knowledge
- knowledge as prior knowledge for regulatory filings
- sources for lifecycle management, which is targeted by the current development of ICHQ12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.

How do we get there? We need to start with proper representation of knowledge – beyond colorful plots and equations that can only be read by specialists. The difficulty is that technical knowledge (as found in correlations or mechanistic understanding, for example) must be simplified to attain the buy-in of the entire interdisciplinary team.

We hypothesize that the use of semantics and ontology would help to extract and manage knowledge. As an example, we recently analyzed how technical knowledge can be converted into ontological entities – turning a mechanistic model into operator language (1). We believe that ontologies, in turn, can also be used in interviewing team members to extract mechanistic knowledge. Hence, the knowledge of team members is extracted in a structured way and can lead to the construction of mechanistic models.

We strongly believe that the real value of QbD, including economic benefits, can only be leveraged when knowledge is made available in trivialized ontological entities and managed by business processes that follow ICHQ10 and ICHQ12. A benefit of this QbD related approach would be the acceleration of on/off-boarding of team members, which is a very important task in all (pharma) companies independent of QbD.

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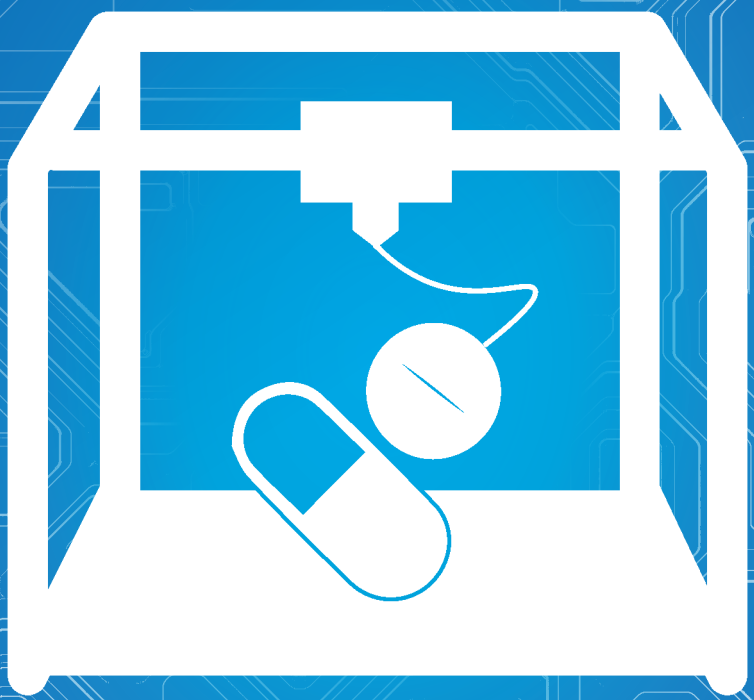

A New Dimension to Medicine Manufacture

Fabricating medicine using a printer may sound like the stuff of science fiction, but the technology exists – and the pharma industry has finally taken the plunge. The FDA approved the first 3D-printed drug in August, and with researchers working on printing everything from tablets to organs, the big question is, will more approvals follow?

By Stephanie Sutton

Watching a 3D printer in action is like magic; it seems as if a solid object is being made from thin air. But if you're into technology, you'll know that 3D printers typically construct objects by layering material from a filament inside the printer. So not quite magic, but impressive nonetheless – it's hardly surprising that it has captured the attention and imagination of people everywhere, from engineers, to researchers, to everyday consumers. Companies are using 3D printing for many applications including printing parts in the automotive and aerospace industries, producing toys, creating food and even printing shoes. The technology can print complex geometries and shapes that might not be possible using traditional manufacturing methods, as well as one-off custom parts, which has made it popular in prototyping.

3D printing has also seen great uptake in healthcare, particularly in medical implants and devices. It has been used to make low-cost medical devices, such as a stethoscope for use in the Gaza Strip (1), prosthetic hands and other artificial limbs, as well as hearing aids, dental implants, bone implants and more (2). So what about the notoriously conservative world of pharmaceutical manufacturing? At the start of August, pharma and 3D printing made media headlines when Aprecia Pharmaceuticals announced that the FDA had approved SPRITAM, an epilepsy drug for treating seizures (3). The drug is made with the company's ZipDose Technology, which uses 3D printing to make formulations more porous. Thanks to the precision enabled by 3D printing, ZipDose allows a very high drug load (up to 1,000 mg) to be given in a single dose. Just one sip of liquid and it disintegrates in less than 10 seconds.

Aprecia is currently the only company that has received an FDA approval for a new drug manufactured, in part, using 3D printing. Compared to other industries, which are routinely hitting headlines with 3D printing-related announcements, pharma's success may seem limited. And on the face of it, 3D printing and pharma does not seem like the perfect match. After all, most applications of 3D printing use plastic and metal as base materials – useful in pharmaceutical tooling and machinery perhaps – but what about the highly-specialized compounds and materials used in medicine manufacture? It's a challenge that the pharma research community has risen to meet, by adapting 3D printing to more specific needs. Here, we take a look at the hot research projects that are shaping pharma's 3D future.

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Big Pharma's 3D Focus

By Clive Roberts, Chair of Pharmaceutical Nanotechnology, Head of School of Pharmacy, the University of Nottingham, UK.

My team at the University of Nottingham started work in the area of printing formulations around 2005, based on conversations within our EPSRC (Engineering and Physical Sciences Research Council) Centre for Doctoral Training in Therapeutics. Our discussions with Morgan Alexander, an expert in developing new materials for medical applications, and Paul Gellert, a leading formulation scientist at AstraZeneca, led to a PhD project where we explored the basics of printing formulations and showed the principal of emulating a commercial formulation. Following this successful project, we nevertheless struggled to attract interest in the idea of printing formulations – not so much from sponsors, but from students wanting to take up such a 'crazy' project! Eventually, an adventurous student, Shaban Khaled, joined us and took up the challenge. And we got a boost when the EPSRC Centre for Innovative Manufacturing in Additive Manufacturing arrived at the university, along with Ricky Wildman, a professor with expertise in modeling and 3D printing.

Shaban had demonstrated that 3D printing based upon extrusion can produce viable solid dosage forms capable of passing regulatory tests (1, 2). These tablets have become increasingly complex, starting as simple bilayer tablets, moving onto osmotic pump release tablets, and recently polypills containing several different drugs, each in a separate compartment and released independently. We continue to partner with AstraZeneca on developing novel inkjet printed solid dosage forms and on pushing the limits of 3D printing towards nanoscale resolution. We are also working extensively with GlaxoSmithKline to explore the wider possibilities in manufacturing.

Working with industrial partners really helps us focus on the key issues that must be resolved if this methodology is going to become commonplace in medicines manufacture. Some people say that pharma companies can be wary of new technology, but in my experience big pharma is always keen to explore promising new technologies and ideas, even if they may seem a bit far-fetched to begin with. 3D printing is an accessible idea; it's an easy concept to 'sell', albeit challenging to deliver.

The main issues preventing widespread adoption are the regulatory view of 3D printing as a manufacturing process (particularly if it is distributed away from a large central facility), a need for new safe materials for formulating the printable 'inks' and viability in fast mass manufacture. The FDA's first approval of a medicine that uses 3D printing will go a long way to addressing the concerns about regulation. The tablets, made by Aprecia, use an aqueous fluid to hold together multiple layers of powder in a reformulation of the anti-epileptic seizure drug levetiracetam. As the tablet is very porous it very quickly disintegrates in liquid. This is a very clever 'niche' product and now there is some real validation of 3D printing in the pharma industry, I expect interest to grow even further.

As to the latter issue of manufacturing speed, the technology of printers is moving at such a breathless pace that it's hard to imagine the speed of manufacture being a long-term issue, especially as, ultimately, 3D printing is likely to be used to produce complex medicines, not to make billions of off-the-shelf tablets.

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From Pharma-Grade Filaments to Capsular Delivery Systems

By Andrea Gazzaniga, Chair of Pharmaceutics, Head of the Pharmaceutical Technology Unit (DISFARM), Università degli Studi di Milano, Italy, President of Interuniversity Consortium TEFARCO Innova.

I believe that the future of healthcare may rely on personalized medicine. According to the FDA, this means "the tailoring of medical treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up". But today's therapeutic approach is quite the opposite: drugs don't adapt to patients; instead patients have to adapt to mass-produced medications with a fixed dosage and release performance. Our research team has been investigating innovative manufacturing technologies to develop custom drug delivery systems, and one area of interest for us is 3D printing.

For years, we have been looking at capsular devices that act as containers for different types of drugs and formulations, releasing their contents depending on the characteristics of the shell (in terms of composition, shape, wall thickness, presence of openings, slots and internal cavities). These capsules have been prepared by injection molding and, more recently, we decided to see if it was feasible also to use fused deposition modeling (FDM, see sidebar 3D Printing 101 on page 26).

FDM is drawing considerable interest from the pharma

Appreciating the Potential of 3D Printing

Tom West, Project Director, Manager of Intellectual Property at Aprecia Pharmaceuticals, shares the story behind the company's ZipDose Technology.

How did Aprecia become interested in 3D printing?

Aprecia was actually founded in 2003 specifically to focus on – and unlock – the potential of 3D printing for pharmaceutical applications. The technology we use is powder-liquid 3D printing, which we licensed from the Massachusetts Institute of Technology for pharmaceutical applications. The founders of our company had a real appreciation for 3D printing and recognized its potential in pharma. However, the ability to use the technology on a larger scale was missing, so Aprecia's first job was to develop equipment that could fill the big gap.

How did you find your focus?

When looking at all the different things that 3D printing could do for pharma, we tried to focus on what we thought would be a promising first area for commercial applicability. Fairly quickly, we realized that you don't tend to see fast-melt applications for high-dose medicines (over 200 mg), despite all the established and successful technologies – at least not in the US, where the biggest cluster is actually for drugs under 50 mg. Clearly, there was a real opportunity to help patients that are struggling with larger tablets. We did some experiments in the lab and we found that 3D printing with our ZipDose platform can help produce high-dose formulation with rapid disintegration; the dose dissolves in seconds with a sip of liquid. This is the ZipDose formulation.

How does ZipDose Technology work?

First, let's be clear on what is a manufacturing process versus a product platform. 3D printing is a manufacturing process. The ZipDose formulation is a product of the manufacturing platform, which combines formulation science and materials science, with the capabilities of 3D printing to tailor and fine-tune the parameters of the process for certain materials to make a fast-melt formulation.

ZipDose Technology uses powder-liquid based 3D printing, which spreads a powder in thin layers and uses a liquid solution to bind it all together, layer after layer. We use materials that are most appropriate for fast melt and choose a series of printing parameters that, in essence, carefully stitch or bind the materials together. Although we had a lot of familiarity and experience in the area, a lot of the material selection was trial and error, with the main focuses being on things like particle size and the right mouth feel. The materials that we use are all conventionally available – but the way we deploy them is unique.

What are the advantages?

For patients, the main advantage is a medicine that does not need to be swallowed intact. Sometimes there are effective drugs to treat a disease, but without a suitable dosage form for a particular patient. In our application, where we remove the need to swallow the medicine intact, there are many benefits for children, the elderly and other patients with swallowing difficulties.

We don't think of our technology – or 3D printing in general – as something that is analogous to high-speed tableting. We offer a specialized product for specific needs. Of course, it's more expensive than producing the cheapest tablets using the cheapest manufacturing methods, but it is competitive to other advanced techniques, such as freeze drying.

The first FDA approval is a real milestone...

It's a very exciting time for us. And I think a company had to be born to do this. Very early on we were able to really focus on 3D printing, and we put everything we had into building the platform to make it work – and we were deliberately quiet about our endeavors!

Now that we can share our success, the reaction has been really positive – not just from the public and the media, but also in terms of confidential queries from those who are interested in learning more. Our initial focus is on our internally driven products – SPRITAM (levetiracetam) and the rest of our pipeline – but over time, we may start looking at collaborative opportunities to explore the potential of ZipDose Technology in other therapeutic areas. We will likely look at new product platforms in the future as well; after all, powder-liquid 3D printing could also be used for controlled release, multi-phasic release or fixed dose combinations.

industry. One use for FDM is rapid prototyping, which would enable companies to evaluate the design, materials and use of products before their final release. However, a drawback at the moment is that no pharmaceutical-grade filaments are commercially available.

To that end, we decided to develop a pharmaceutical filament that could be used by an existing FDM printing system to create a custom delivery system called the Chronocap, for oral pulsatile and colonic delivery, which we previously manufactured using injection molding. The material used for the filament was hydroxypropyl cellulose (HPC), a swellable/erodible pharma-grade polymer (1).

A commercial 3D printer was used to manufacture hollow bodies that could then be assembled into capsular devices. HPC filaments suitable for feeding the FDM equipment were manufactured using hot-melt extrusion. By introducing minor modifications in both the hardware and software of the printer, we successfully produced both capsule bodies and caps using our HPC filament. In vitro tests demonstrated that the 3D printed devices behaved as pulsatile-delivery containers, showing a satisfactory release performance (lag phase of about 70 min) comparable with that of analogous molded systems with the same composition.

It's an early stage project but the results are exciting – as is the future.

Gazzaniga collaborated on this research with Alice Melocchi, Giulia Loreti, Alessandra Maroni and Lucia Zema (all from Università degli Studi di Milano, Italy) and with Federico Parietti (Massachusetts Institute of Technology, USA).

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Chemical Creations

Lee Cronin, Regius Chair of Chemistry in the Department of Chemistry at the University of Glasgow (UK), is involved in ambitious experiments exploring the assembly and engineering of chemical systems, with the ultimate goal of understanding the origins of life. He openly admits that he aims to challenge conventional thinking with "crazy ideas", and the science behind his work has generated a lot of discussion – and numerous prizes. One important aspect of his work is combining chemistry with 3D printing. We spoke with Cronin to find out how this could impact drug development.

What inspired you to combine chemistry and 3D printing?

My focus is on complex chemical systems, and coming up with technologies or utilizing technologies that allow me to control complexity, or to at least monitor it. Big science questions can be enabled by developments in technology – and basically I see 3D printers as a ubiquitous cheap robotic that could be useful for exploring chemistry.

I first got the idea of using 3D printing in my work about five years ago when I went to an architecture conference and I saw some people 3D printing ping-pong balls and plastic objects. It was really interesting, but plastic is quite limited so I wondered if I could do some sort of chemistry inside the ping-pong ball. That got me thinking about how I could print different compartments and then put different chemicals inside them – the idea for reactionware was born. I came up with the idea of reactionware after realizing that the 3D printer could not only print the test tube for the reaction, but could also be used to modify the test tube architecture and even include catalysts and separators (1, 2). In one of our first publications we even used the 3D printer, not only to fabricate the reactor, but also as a liquid handling robot – initiating the chemical reactions by adding the reagents directly into the reactionware.

What is the main goal of your research group?

Our goal is to understand how life was created and to discover if we can make inorganic life. Some people think this is impossible, but life came from somewhere and the starting point must have been 'inorganic'. Doing chemistry in the traditional wet-lab requires many types of manual operations from preparing starting materials to mixing reagents and initiating reactions. It is possible to automate it, but those automation control systems are extremely inflexible. Given our grand aim, to explore the systems chemistry at the onset of biology, we have been developing a series of automated chemical platforms that together could form a massively parallel chemical engine. We want to see how control of the architecture and control of the process allows us to merge lifelike molecules and systems.

One potential technological spin off of what we're trying to do could be in the area of discovery, from complex materials to drugs. I'm looking at how to make artificial life from the bottom up, but we could use the same system to program new discovery agents for drugs from the top down.

You've also been looking at printing medicines…

We are developing a hybrid liquid-handling robot and 3D printer

system to synthesize simple molecules, and so far it works with one very simple, commercially available drug. We both 3D print the 'test-tube' and use the 3D printer to add the liquids into the printed reaction chamber as a liquid handling robot. It was difficult to get it working, but we did it and we get a reasonable yield of pure material. We hope to publish details soon.

There's a lot of hype in this area, but do people really understand the technology?

3D printing is basically taking a hot plastic filament, screwing it through a nozzle and moving the X, Y and Z axis. But when you start talking about drugs and medicines some people misunderstand. You cannot print a molecule. In my group, we're not printing molecules; we're using a 3D printer to automate the synthesis of the molecule. 3D printing gives you the ability to control the X, Y and Z axes (length, width and height) to perform precise chemical operations. Aprecia Pharmaceuticals' recent announcement has caused a bit of a media frenzy. Personally, I wouldn't call it 3D printing of a drug exactly. They have automated the dosing of a solid form so that they can personalize the dose, which will improve outcomes for patients. It's brilliant and they should be applauded for it. It's not exactly a '3D printed drug' as such, but it's great to see pharma manufacturers getting involved in using this technology.

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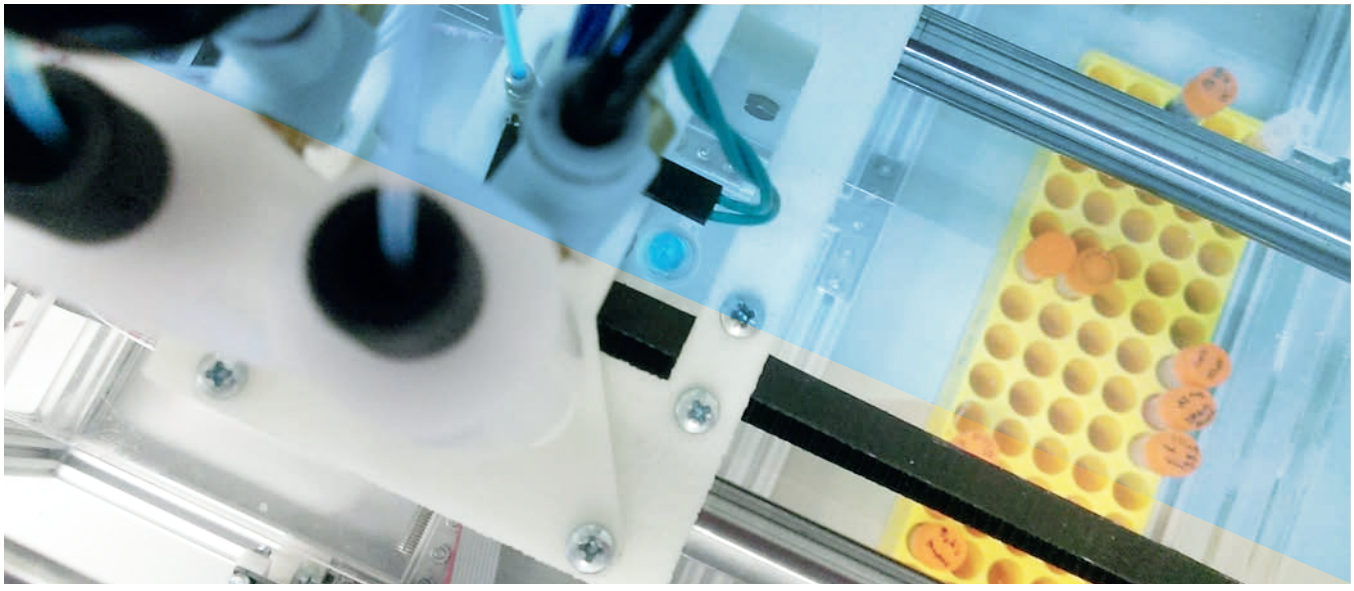

Bioprinting Better Drug Development

By Alan Faulkner-Jones, Research Associate in Bioengineering (Biofabrication), at Heriot-Watt University, UK.

Only a fraction of drug candidates that begin pre-clinical testing are ever approved for human use. The low success rate can be partly attributed to the differences in response between humans and the animal models currently used for testing.

Parallel to the development of 3D printing and additive manufacturing techniques using polymers and metals, another set of novel techniques has been developed that can print living biological cells. By encapsulating cells inside a gel, complex 3D structures can be printed with cells suspended throughout the structure. The cells grow and multiply within the structure, creating their own matrix and forming tissues. By using organ-specific cells generated from pluripotent stem cells, it should be possible to bioprint 3D organ-specific micro-tissues that replicate the response and functions of a human organ, but on a much smaller scale. These could be used for testing the response of human cells to drugs.

The first bioprinter I built was originally designed to quickly and reliably position viable human stem cells into predetermined

3D Printing 101

3D printing – also known as additive manufacturing – is the process of making a 3D object from a digital file. The object is designed on a computer and then printed by laying down or printing successive layers of a material. The most popular material is plastic, but today's 3D printers can also use metal, wood, resin, ceramic, wax and more. The range, however, is still fairly limited, which experts believe is one of the key obstacles preventing more widespread use of 3D printing, alongside issues such as limited speeds and ease of use (1).

A variety of different techniques can be used in 3D printing. The oldest is stereolithography, but the most popular technique used today is fused deposition modelling (FDM). In FDM, the printed part is produced by extruding small beads of material, which harden into layers.

Officially, an American called Chuck Hall is credited with the invention of the 3D printer. Hall received a patent in 1986 for the 'Apparatus for Production of Three-Dimensional Objects by Stereolithography' – which involved making solid, 3D objects by printing thin layers of UV-curable material. Today, Hall is the executive vice president and chief technology officer of 3D Systems, one of the largest producers of 3D printers in the world. However, the first published paper describing 3D printing was published in 1981. The author was Hideo Kodama, a researcher at Nagoya Municipal Industrial Research Institute in Japan. Kodama was inspired after seeing a new printing process – a device that used liquid resin applied to glass to create letters. It was intended for use in newspaper printing; letters made via the technique could be sprayed with ink for printing. To demonstrate the possibilities of layering resin to create 3D shapes, Kodama created a tiny house about the size of a hand – it had rooms, a spiral staircase and a dining table. Despite Kodama's efforts, few people were excited by the technology and he never formally patented it.

According to an article from PricewaterhouseCoopers, the most common application for 3D printing right now is for rapid prototyping (2), but with technology advancing and the costs coming down, the possibilities in industry are expanding. But although 3D printing is taking off for industrial applications, few consumers are buying 3D printers – the cost and usability are still playing catch up to the technology.

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patterns and locations to help study stem cell biology (1). But once it was built, it became apparent that it was capable of far more interesting and complex tasks, ranging from automatically populating microwell plates with greater accuracy and speed than pipetting, all the way to creating complex 3D structures with multiple different types of viable biological cells.

Although at first glance the technology behind bioprinting seems similar to the techniques used in 3D printing, bioprinting is actually more closely related to traditional 2D inkjet and laser printing. The first bioprinting experiments (originally called "cytoscribing") were carried out in the 1980s; roughly the same time as the early additive manufacturing techniques were being invented. Bioprinting and additive manufacturing were developed largely in isolation, although structures created using additive manufacturing techniques have been used as scaffolds for living cells.

It's actually not that difficult to build a bioprinter – if you can build a 3D printer then you could probably build a simple bioprinter. However, if you wanted to use it to create 3D structures with stem cells (which are quite fragile) then you'd have to spend a lot of time determining the correct setup and the make-up of the matrix material to support the cells and ensure it was compatible and printable. We have created several generations of bioprinting platforms that are being used by our collaborating labs around the world. We have validated the bioprinter's capabilities by printing 2D arrays of biomaterials, checking its compatibility with living cells (including stem cells, which were unaffected by the printing process), and creating 3D spheroid aggregates of cells.

Our current focus is on creating micro versions of human organs from human cells. One stumbling block for the creation of larger tissues is integrating a network of blood vessels to keep the cells supplied with nutrients and remove waste. But it is still early days and in the future, researchers may be able to print whole organs.

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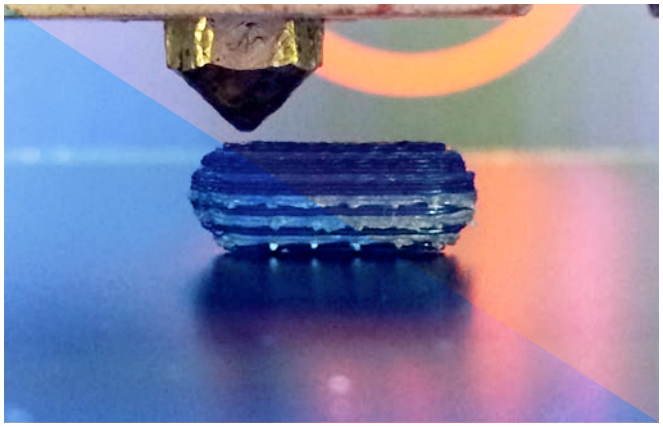
Thinking Outside the Pyramid

Simon Gaisford, Reader in Pharmaceutics and Head of the Department of Pharmaceutics at University College London (UCL) has a keen interest in the concept of 3D printing solid dosage forms. Earlier this year, Gaisford and his team used 3D printing to give tablets a geometric makeover. The group created several shapes that are difficult to produce using traditional



tablet manufacturing techniques, including a cube, pyramid, cylinder, sphere and torus (1) – they even experimented with animal-shaped tablets. But the project wasn't about producing weird and wonderful geometries just for fun; different shaped tablets have different drug release profiles – and could be useful for personalized medicine. The pyramid dissolved the fastest, whereas the cylinder was the slowest – drug release was dependent not on the surface area, but on the surface area-to-volume ratio.

"With 3D printing, it is possible to print tablets of any size and shape – and the minimum production run is one," says Gaisford. "This means we can (i) explore the effect of geometry on drug release rates in a way never possible before, (ii) construct multi-layered or multi-faceted tablets (such as 'poly pills'), and (iii) truly consider the paradigm of personalized medicines where the dose or dose combination can be tailored to the patient."

The group used FDM to fabricate tablets layer-by-layer. Gaisford believes that this type of printing is particularly suited to pharma manufacture because the polymer filaments can be blended with drug(s) using hot-melt extrusion. "Developing printable filaments of pharmaceutically acceptable polymers was one of the challenges," says Gaisford. "3D printers were designed for rapid prototyping and so typically print hard engineering polymers that are not water soluble. Getting the polymer–drug blend extruded was also difficult. It would also be good to print faster (currently it takes 5–10 minutes to fabricate a tablet), and to have in-situ analyses for confirming that no drug degradation has occurred and that the dose is correct. Other than that, the technology is probably already mature enough for commercial use."

At the outset, Gaisford says that the initial area of application for these sorts of tablets will be on drugs with very narrow therapeutic indices, and where there is a real benefit to tailoring doses to patients. Ideally, the printable polymers would be GRAS (generally regarded as safe) approved, and the active will already be on the market – although there would be issues of dose verification at the point of manufacture, as well as safety and efficacy to consider. After that, the focus could turn to formulations for biopharmaceuticals and genomic medicine. The aesthetics of unusually shaped tablets could also have other effects – but Gaisford admits that some shapes might not be useful in practice. "The main advantage is that the release rate of the drug can be 'fine-tuned'. From our initial experiments we see considerable variation in release rates, ranging from 90 percent drug release in under 2 hours to 90 percent drug release in over 10 hours. This is from the same tablet matrix, just a different geometry," he says. "3D printing could be used to design multi-layered tablets that produce controlled or delayed release profiles."

Following on from the project, Gaisford and his group are looking to develop faster-dissolving printable polymers and to explore the stability of the systems. He has founded a company called FabRx to commercialize 3D printing for pharmaceutical manufacture.

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Getting Under the Skin of Extractables and Leachables

There are key benefits to having an industry standard for E&L studies – but a standard is only the beginning. The bigger question is what comes next and how do we dig even deeper into single-use systems?

As Strategic Projects Leader at GE Healthcare, and first Vice Chair on the executive board of the Bio-Process Systems Alliance (BPSA), Jeffrey Carter focuses on the world of single-use manufacturing. He facilitates collaboration, engages with industry stakeholders and fires up discussions to help solve the most critical problems facing users and suppliers of single-use systems. One issue he has focused on recently is the industry's growing uptake of single-use systems and what effect this will have on the way extractables and leachables (E&L) studies are performed.

What is your role at GE Healthcare?

I spend my time trying to identify and understand the most pressing global issues in adopting single-use systems in biomanufacturing – and then investigating how we can help resolve those problems, either within our company or as part of a broader, external industry collaboration.

Single-use technologies are certainly becoming better established, but there are still some issues that users and suppliers must consider, such as addressing particle presence, leak rates, change notifications, and managing the supply chain. One of the most talked about issues is the potential for leachables from single-use material. These leachables could end up as contaminants in drugs and lead to unwanted effects.

What global trends do you see in today's biopharma industry?

Despite the relative youth of the biopharma industry, certain (sometimes inefficient) practices have become engrained. Making drugs, especially specialty biopharmaceuticals, is a notoriously expensive business, and success in today's fast-paced industry often involves bringing down your cost of goods, getting to market more quickly, and managing various forms of risk. To that end, people are trying to figure out how to move away from the 'standard' manufacturing practices (batch unit operations, stainless steel, glass...) and attempting to make their processes more efficient. Two important goals for the industry are to increase the speed and flexibility of manufacturing. Single-use technologies can help in both regards; they are not a silver bullet, but they are very effective at increasing flexibility and can be deployed very rapidly. Conversely, meeting changing needs with a hard-plumbed, stainless steel infrastructure can be difficult.

What does an increase in single-use technology mean in terms of E&L?

E&L is a well-known topic in the industry, as they are a staple tool to evaluate safety aspects to surfaces that are in contact with process fluids or final drug products. People have been talking about E&L for years – and they have been successful in managing it for the most part. That said, E&L have not always been managed in the most efficient way, particularly when it comes to creating datasets.

Today, we're seeing greater uptake of single-use technologies, which means the amount of plastic in the manufacturing line is increasing. Historically in manufacturing, you perhaps had a sterilizing filter that needed E&L testing, which was relatively straightforward. Now, you might need E&L data for the sterilizing filter, in addition to a process bag, a tube set, connectors, and buffer bags. There is also the issue that material changes trigger a new extractables study, which adds to the volume of studies to be managed by both users and suppliers. When you double or quadruple volumes, inefficiencies in the current way of working quickly become apparent. One problem that is significantly adding to the burden is the lack of industry norms when it comes to extractables study designs.

At the moment, end users obtain extractables data from multiple suppliers. But each supplier has their own approach and analytics, so end-users end up with myriad data sets and consequently spend a lot of time, resources and money trying to draw conclusions. From their perspective, it is a frustrating exercise akin to comparing apples to oranges.

Is there enough knowledge in the industry about the importance of E&Ls?

Some people are fully engaged with E&L at a quality level; they understand that E&L study results have intrinsic value in assessing the quality of single-use equipment. Others see it as more of a compliance issue; the work must be done because it is a regulatory expectation, but they are not interested in the gritty details of study design. Others are even more tentative with E&L studies. Indeed, companies sometimes ask for our opinion on how to manage extractables and whether they should be conducting a leachables study. We can help these people by orienting them on how one might design a risk assessment and by providing technical information. Ultimately though, the conclusions and decisions that ensue must be owned by the end-user.

"People have been talking about E&L for years – and they have been successful in managing it for the most part."

How is the industry moving towards standardized E&L studies?

An industry standard for E&L testing, which is being discussed by stakeholders at the moment, would allow everyone to at least read from the same instruction book. We would all know what the study design should look like, and how it's supposed to be executed, meaning that the reports at the end should consequently look very similar. The data would be easier to manage and process, saving time and resources. In reality, a standard would not be a panacea, but it would be a very good start.

And you've been involved in the discussions?

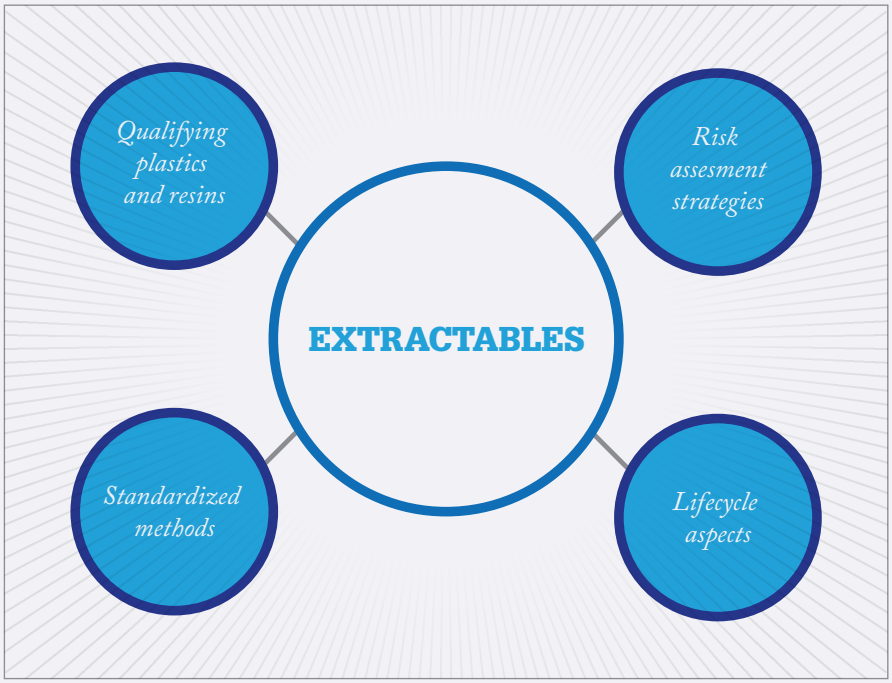
I'm one of the voting members for ASTM's Committee E55 on the Manufacture of Pharmaceutical Products. ASTM is a standards-setting organization, and though it's not the only organization of its type, they do have a very rigorous process for developing and approving international consensus standards. I was on the original committee that was working between the BioPhorum Operations Group and the BPSA to work out a proposal that would be submitted to ASTM. Some of the questions being addressed are:

- what is the correct test article?
- what solvents should be used for the extractables test?
- how long should the extraction be conducted?
- what time points should be used?
- what should the analytics look like?

The big question: what comes after the standard?

It's not clear if or when a standard will appear, but regardless, the standard is just one step. Other topics need to be discussed too. One concern for me is that whenever we test something, there is an element of "testing quality in". In other words, we're assessing whether or not the plastics being used are adequate for the task, but only after the plastic components have already been made. As an industry, we should also be looking to solidify standards that we use to qualify the plastic resins and additives in the first place. In my opinion, this is a good place to practice quality-by-design principles.

We also need to talk about how we use data. Once we have standard datasets, what do we do with them? Those that already know the answer to that question are fully primed to make best use of data. Other companies are not so prepared. When they receive extractables data, they will ask if this is all they need, or if they need to take the next step and



execute a leachables study that is process-specific, rather than relying solely on the supplier's intrinsically generic extractables study. The answer to this question is rooted in process- and product-specific risk assessments. To date, we have seen generalized industry guidance stating that various unit operations are typically seen as high, medium or low risk; however, I wonder if it would be beneficial for the industry to convene a working group to add detail and discuss how risk assessments are conducted.

Finally, we should talk about extractables studies in a lifecycle context. For example, when we consider changes to single-use products, under what circumstances does it make sense to re-do an extractables study? Some argue that in the absence of a change, there is no reason to arbitrarily re-do the study; others argue that processes drift over time and that it would be good practice to re-do the studies at some to-be-determined frequency. These questions are best addressed as an industry collaboration.

"It is interesting to turn the question around and ask how the industry will affect single-use technology."

How else do you think single-use technology will affect the industry?

Clearly, technology is always evolving as suppliers improve the products they offer, but change management practices often prevent users from adopting intrinsically better, more robust, solutions. I am hopeful that we can strike a new balance that can open the change pathway. The concept of "functional equivalence" is one that the industry should explore. At GE, we don't want to "force" changes on our customers; rather we want to share information about what options exist and by doing that help them to make well-informed decisions. The more insights we have and can share, the better the final outcome.

Single-use technology will also mean changes for the supply chain. Adopting single-use manufacturing means that the end-user will relinquish direct control over some quality attributes of their manufacturing equipment and become more dependent on the supply chain. This in turn leads to a need for more information flow from both up and down the supply chain, which will only happen when there is mutual trust. To this point, I think end-users are starting to grapple with the natural tension that exists between wanting to play suppliers off on each other to foster competition, and wanting to develop these more seamless partnerships that are key to managing quality in a single-use equipment environment. It is instructive to ask the following question as we all work our way through our new relationships with our suppliers: are we buying commodity items that can be replaced without skipping a beat, or are we developing security of supply?

The speed and flexibility advantages of single-use equipment are likely to continue to play out, and we will see how the industry adopts this technology on a more wholesale basis in commercial manufacturing, as opposed to process development and clinical batch production. The technology advances are likely to proceed more quickly than the strategies for managing the quality of the technologies and the control of the technologies to assure predictable and reliable performance. From this perspective, it is interesting to turn the question around and ask how the industry will affect single-use technology. I think the more advanced end-users will have a marked influence on not only the technologies that we develop, but also the control strategies that we adopt to support the technologies from a quality perspective.

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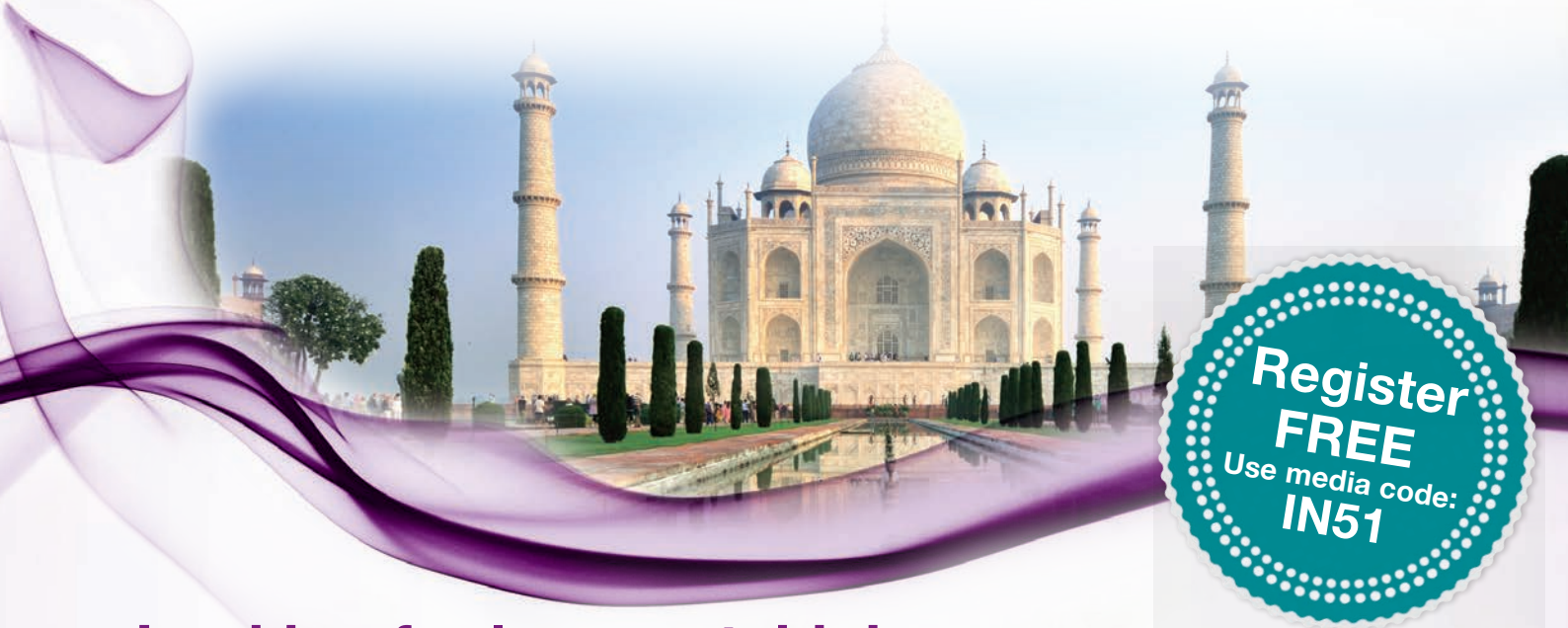

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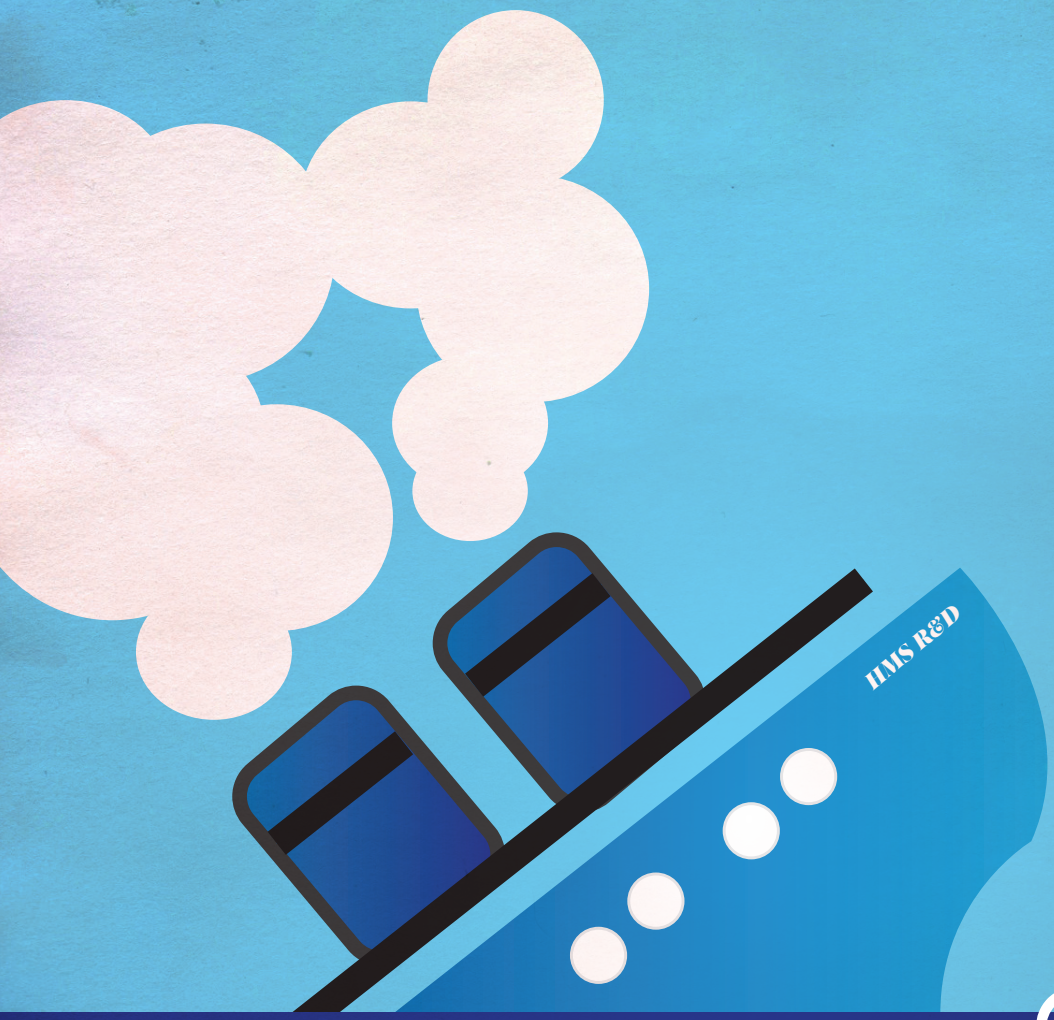

The Trojan ADC Challenge

Often touted as 'magic bullets' against cancer, antibody-drug conjugates (ADCs) aim to combine the effectiveness of chemotherapy with the specificity of antibodies. But the same complexity that imbues them with desirable qualities adds many hurdles to development and manufacturing processes. Fortunately, solutions – and expertise – are on the rise.

By Aad van de Leur

Chemotherapeutics are very effective at killing rapidly dividing tumor cells, but there is a major drawback: they lack specificity and also kill other cells in the body. Over the last decade, targeted anticancer treatments have been developed, including several recombinant monoclonal antibodies (mAbs). The specific binding properties of antibodies allow them to differentiate between cancer cells and healthy cells; however, they are rarely curative in anticancer therapy. Since the approval of the first mAb (Orthoclone) in 1986, only 18 naked mAbs have reached the oncology market. Many fail clinical testing due to lack of efficacy (1).

It is possible to enhance the functionality of mAbs by coupling diverse moieties to the antibody. One subclass of antibody-related therapeutics that is seeing increased interest for oncology applications is antibody-drug conjugates (ADCs). An ADC is a mAb that has been covalently linked to cytotoxic agents, combining the potency of chemotherapy with the specificity of antibodies. The concept is simple: the mAb delivers the cytotoxic payload to the correct location. After being taken up by tumor cells, the drug is released intracellularly, killing the cell in a targeted and effective way.

Next-generation ADCs are further enhancing this concept; for example, by increasing the homogeneity and broadening the linkers that can be used. Efforts are also being made to improve the ADC payload by having the cytotoxin present as an inactive prodrug in the intact ADC molecule. Through internalization of the ADC, the drug enters the cell in its inactive shape and only becomes activated after intracellular processing in the endosomal pathway. It can be thought of as a Trojan horse.

The concept of targeted therapy, selectively delivering a cytotoxic drug to a tumor via a targeting agent was postulated by Paul Ehrlich more than 100 years ago, but it's only fairly recently that they have become valuable therapeutic agents – mainly because of recent advances in linker, drug and antibody technologies. The use of higher drug potency, more stable linkers to prevent early release of the toxin in the blood stream, better control of the amount of toxin per antibody and more selective antibodies lead to more successful treatment (2).

Despite their promise and potential in the fight against cancer, few ADCs have been approved. The first ADC

approved by the FDA was Mylotarg (gemtuzumab ozogamicin) in 2000, but was withdrawn in 2010 after failing a post approval study. It is, however, still available in Japan. At the moment, only two ADCs are marketed in both the US and Europe – Adcetris (brentuximab vedotin) for Hodgkin lymphoma and anaplastic large cell lymphoma, and Kadcyla (ado-trastuzumab emtansine) for breast cancer (the latter has caused some controversy, particularly in the UK, because of its high cost of around £90,000 per patient). But the number of ADCs in clinical trials is growing.

The combined challenges of ADCs

The low number of ADC approvals is testament to their associated development and manufacturing challenges. It's common knowledge that biopharmaceuticals present manufacturing and characterization challenges – and naked mAbs are no exception. MAbs are produced using mammalian cell culture in stainless steel vessels or disposable bags. The product is excreted by the cells and, after removal of the cells, purified to a more than 99-percent pure product – usually using chromatographic techniques. Although mAbs are not the largest molecules produced using recombinant technologies, they have a significant molecular mass (around 145 kDa) and also have complex glycan structures and other post-translational modifications that create additional characterization challenges, demanding a broad spectrum of analytical techniques. Although the manufacture of mAbs is a complex activity, the whole process, including aseptic techniques and purification steps, is relatively well understood.

ADCs are trickier because they are biological products that require chemical transformation. The ADCs currently on the market or in clinical trials are predominantly based on two drug classes. The first comprises auristatins and maytansinoids; both are tubulin binders that block the cell in its progression through mitosis. As a result, only rapidly-dividing cells are attacked. The second drug class is formed by DNA-alkylating drugs, such as duocarmycins, which induce cell death in both dividing and non-dividing cells (3). These drugs are far more cytotoxic than standard chemotherapy methods, with potencies in the picomolar range, and require chemical facilities that are equipped for manufacturing highly potent toxins.

To form an ADC, you need the mAb, a linker and a highly potent cytotoxic drug, followed by the conjugation of all three components to form the final drug substance (DS). Although the mAb and the linker-drug are considered intermediates, they generally have to meet the same level of specifications as if they were a separate DS. As a result, the ADC is considered a biological entity, but both ICH Q6A (Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances) for the linker and drug, and Q6B (Specifications Test Procedures And Acceptance Criteria For Biotechnological/ Biological Products) for the mAb and ADC apply. The DS also needs further sterile filtration, filling, and often lyophilization, to obtain the final drug product for intravenous treatment.

When manufacturing mAbs, Grade D and C cleanroom facilities are needed for cell culture and purification, respectively. A pressure regime is applied to prevent cross-contamination where, in general, a positive pressure to the outside environment is applied to keep any particles and bugs out of the manufacturing areas. For the cytotoxic components used in ADCs, however, the same GMP regulation is applicable, but exposure of highly potent material to the environment needs to be prevented, leading to a negative pressure in the manufacturing area. This dichotomy creates additional challenges to meet GMP in relation to cleanroom contamination – and these should be addressed during the initial facility design.

It is not only exposure to air that must be considered; exposure via wastewater streams and other waste must also be prevented. Cleaning activities often create significant amounts of rinse volumes, but can be eliminated with single-use materials (disposable reactor vessels, filters, chromatographic fluid paths, and so on). Unfortunately, as solvents are applied during the conjugation process, the use of single-

Top Challenges of ADC Manufacture

- Use of highly potent cytotoxic compounds requires additional safety and environmental precautions, demanding complex facilities
- Limited availability of CMOs that have sufficient experience with both cytotoxic compounds, and proteins
- Complex manufacturing process, involving linker, cytotoxic and mAb components and a conjugation process
- Analytical complexity – all components require characterization, including the linker, which makes up a very small part of the molecule
- Complex supply chain, involving multiple suppliers
- Linker-drug technologies are limited in number

use materials could become an issue in relation to leachables. You can also help eliminate the risk for environmental exposure by using a leak-proof floor and the removal of all drains. All waste materials must be packed in closed containers and incinerated, or taken for validated chemical inactivation.

Another important aspect when manufacturing ADCs is characterization and release. The linker drug represents only about 1 percent of the total mass of the ADC, but is the main driver for its potency. Indeed, it can have a significant impact on the behavior of the mAb as some drugs are very hydrophobic, which could result in increased aggregation and increased plasma clearance (4) – a problem that becomes more relevant at higher drug-to-antibody ratios (DAR) as higher DAR will result in higher hydrophobicity of the ADC. Moreover, multiple binding sites for the linker drug results in heterogeneity of the molecule and additional complexity for characterization. DAR is a critical quality attribute and is quantified using UV for lysine conjugation and hydrophobic interaction chromatography or reversed-phase high-performance liquid chromatography for cysteine conjugation. Drug load distribution, the levels of unconjugated mAb and free drug, the charge heterogeneity, aggregation, higher order structures, and potency must all be tested (5). Any structural changes of the mAb or the linker drug caused by the conjugation process demand additional scrutiny.

Overcoming the hurdles

As previously discussed, ADCs require mAbs, linker drug and conjugation manufacturing activities – and these all need their own facilities and technologies. It is not unusual for four different contract manufacturing organizations (CMOs) to be used – a logistical nightmare! In-house manufacturing for all these aspects solves issues relating to supply chain and provides much better control over quality, cost and timelines, but is only appropriate in the case of a robust pipeline since it requires significant investments and expertise. Most companies therefore go down the CMO route.

Many CMOs can deal with either cytotoxic compounds or proteins, but many lack the experience to work with both at the same time, or may lack the required infrastructure and ability to produce ADCs in suitable quantities (multi-kilogram scale). A variety of different linkers and payloads are used in ADCs, which all require sophisticated know-how. Multiple technologies also exist for conjugation. Initially, naturally-occurring lysines or cysteines liberated from interchain disulfides were used for conjugating the linker drug to the mAb. To facilitate manufacturing and create a more homogeneous product, so-called site-directed conjugation is being applied. Site-directed conjugation introduces engineered cysteines or non-natural amino acids into the mAb for use as linker sites, which also has an impact on the design of cell lines used for manufacturing ADCs.

Having so much know-how under one roof is no easy feat, particularly given that the ADC field is relatively new, so when seeking contract manufacturing partners it's wise to look closely at both the manufacturing facilities and expertise on offer. You also need to look at cleaning validation to prevent cross contamination. If the CMO addresses contamination issues by using dedicated equipment, then significant upfront cost and time could be required to qualify the equipment. If single-use equipment is used, then extractable and leachable studies performed by the CMO are also useful. There are also several other questions you need to ask. Is the CMO really capable of developing the conjugation process from scratch, or would you be better off using in-house development and then subsequently transferring the process to the CMO? How well are environmental, health and safety aspects under control? And, of course, you must take into account all standard GMP aspects, as well as cultural fit, financials, conditions and CMO reliability.

To date, we've seen few commercial ADCs, but with increased attention, and more research and technologies pouring into the field, including better understanding of their modes of action, it's likely that we'll be seeing new linker designs and more drugs reaching the market in the near future. Overcoming the manufacturing hurdles, however, should not be underestimated. It takes time and expertise, and timely strategic decisions to successfully develop and manufacture these highly potent biologicals.

Aad van de Leur is Chief Operating Officer at Synthon Biopharmaceuticals BV, the Netherlands.

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Accepting R&D Failure

To file, or not to file – that is the question when it comes to IND applications. Companies don't always make the right choice, but learning when to abandon ship can open the door to potential future gains.

Admitting defeat in pharma R&D and terminating a failing project is a hard decision to make – and sometimes companies file for an Investigational New Drug (IND) application despite unpromising data. Why? A group of researchers recently asked this very question and decided to publish an article on the subject to highlight the issue (1). We spoke to one of the authors, Dennis Lendrem, translational research project manager at the University of Newcastle's Institute of Cellular Medicine, about the problems facing R&D.

What inspired your interest in this area?

In 1990, one beautiful sunny spring morning, I flew down to Heathrow for a meeting at corporate HQ to discuss the fate of our latest, brightest drug candidate.

The question? To file, or not to file, the IND?

The data did not look great. The debate that day hinged around whether we needed additional toxicity data to submit. The argument for immediate submission was that additional toxicity data would delay the IND and might even yield further negative data. In my mind, it was a no-brainer. We might not need the additional toxicity data to submit, but we needed to know whether we were storing up trouble later down the line. We should either drop the project right there and then, or run the additional toxicity study. Whether we met our IND quota for the year was irrelevant. Truth-seeking is more important than progression-seeking – at least in my opinion…

Why is it hard to terminate failing projects?

It isn't. It requires brutal, pathologically objective, rational decision making. But decision makers are human and there are powerful cognitive biases at work here – hindsight bias, confirmation bias, optimism bias and narrative bias. These, coupled with the simple heuristics shaped by our evolutionary history, mean we are dominated by loss aversion. This gives rise to problems such as the "sunk-costs" fallacy, where we fail to terminate projects in order to avoid losing monies already lost.

"The argument for immediate submission was that additional toxicity data would delay the IND and might even yield further negative data."

There are strategies to avoid such biases. These strategies can be learned. But they must first be taught.

Are we facing a crisis in R&D productivity?

R&D productivity is low; late-stage attrition is high, and drug development is costly. Much of the development costs are those associated with unmarketable drugs. For most drug candidates, the ultimate customer is the wastebasket. If we accept that most drugs in our portfolio are unlikely to see the light of day – and that most will end up in that wastebasket – it allows us to focus on terminating faltering projects as quickly and efficiently as possible. By terminating unmarketable drugs fast, we free up resources to develop more promising candidates.

How has the problem escalated?

Some analysts believe the industry has turned the corner and is on the comeback trail, but these analyses are deeply flawed (2). The problem escalated rapidly between 1990 and 2010. During this period, 'development speed' initiatives inadvertently sub-optimized the entire drug development process. At the time, development-speed thinking seemed attractive. If you want to increase R&D productivity, then reduce cycle time. What could be simpler? The industry set about re-engineering its development processes to maximize development speed. And the industry was remarkably good at doing this. By carrying out development tasks in parallel, we were able to rapidly speed up the development of these successful drugs. And by 2010 the cycle time for successful drugs had halved.

But we forgot that most drugs are not successful and never make it to market… so in reality we became really slick at delivering late-stage failures to the marketplace. And by placing tasks in parallel, we simply increased the burn rate of R&D. The cost of terminating drug candidates increased drastically. That cost must be borne by those drugs that do make it to market.

The Seven-Point Plan

Are the industry's 'quick-kill' R&D strategies efficient?

There is no question that 'quick-kill' is more efficient than traditional strategies. Quick-kill is about building opportunities to terminate candidates earlier in the development process. Sometimes this involves a profound understanding of the operating characteristics of existing tests. Sometimes it involves the introduction of assays that may (or may not) be part of a regulatory submission. So there are technical challenges in developing these assays and understanding their performance. However, in working with organizations, we found that the real challenge is the cultural and organizational attitudes to quick-kill. Hence, we've developed a Seven-Point Plan. For me, the key is to capture and communicate the opportunity costs of progression-seeking behaviour – and to reframe termination decisions as prospective future gains.

As you've researched this area, what are the most worrying findings?

Complacency. Complacency will be the death of many large, pharmaceutical companies. Many do not accept the need for change. The larger and more successful the corporation, the greater the denialism – and the greater the inertia to make changes to ensure their future.

The current draconian efforts to stem rising R&D costs are unlikely to lead to sustainable R&D productivity improvements. Meanwhile, we flail around grasping for quick fixes to problems that we don't have. We are rearranging chairs on the deck of the Titanic.

I guess it's easy for us here in Newcastle, UK, because we are sitting on industry estimates of the false positive and false negative rates at each stage in the drug development process. These estimates will be published before the end of the year. Once in the public domain, they will allow pharmaceutical executives to estimate the opportunity costs of progression bias and late stage attrition in R&D. And the industry is in for a shock…

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The Cautious Comeback of Oral Peptides

After the initial hype and subsequent clinical failure of oral peptide formulations in the 1990s, pharma took a step back. Today, select oral peptides are yielding positive data in advanced clinical trials. But what is the real potential of the field?

By David J. Brayden

Converting approved injectable peptides and proteins into non-injected formats would represent a major advance for both the biopharma industry and patients alike. Taking insulin (molecular weight of approximately 6000 Da and 50 amino acids) as the upper limit of the molecular definition of a peptide, there were over 100 injectable peptides in pharma's clinical pipelines in 2013 (1) – with a market estimated at $23.5 billion by 2020.

Therapeutic peptides have highly specific targets on cell surfaces, exhibit high potency and efficacy, and tend to have fewer side effects than traditional organic small molecules. However, almost all of the currently available agents are designed for injection. Why? Following costly but unyielding investment in the 1990s, few companies seem prepared to take on the financial and scientific risk of developing a new peptide and a non-injected route of delivery in the same formulation. Drug makers are much more likely to consider a non-injected formulation for an established marketed peptide or protein only (2). A consequence of this approach is that it has limited oral peptide formulation scientists to working with just a handful of established marketed peptides – those which were originally designed by medicinal chemists for injection. Important examples include insulin- and glucagon-like peptide-1 (GLP-1)-analogs to treat diabetes (3). It's a rather poor starting point, with missed opportunities to use novel chemistry to select peptides specifically for oral delivery.

Overcoming oral obstacles

The upper gastrointestinal tract has evolved to degrade and digest proteins and peptides. We can provide the peptide with a safe passage through the stomach using enteric-coated tablets or capsules, so the main challenges lie in managing both the pancreatic and brush-border enzymes (proteases), as well as the permeability of the intestinal epithelial layer. One approach to achieve these two separate goals is to construct a dosage form comprising the peptide of interest, an enzyme inhibitor(s), combined with a permeation enhancer. The aim is to co-release all three components in proximity to the gut wall to achieve high concentration gradients at the actual site of absorption. Examples of such composite formulations are already employed in over a dozen technologies that have reached clinical trials.

A second approach is to develop a nanoparticle-based construct in which the peptide of interest is entrapped, stabilized with a hydrophilic neutral or negatively charged (anionic) coating to permeate mucus overlying the epithelium, thus delivering nanoparticles in close proximity to the absorptive epithelium. These nanoparticles can be delivered in, for example, a polymeric-coated tablet or capsule. Established permeation enhancers, including stable cell-permeating peptides, can also be used as components of nanocarrier systems, but there is no consensus on whether it is best to release the peptide before or after nanocarrier uptake by epithelial cells. Neither is there agreement on whether nanoparticle uptake across the small intestine in vivo is appreciable or sufficient. Although the nanoparticle approach is elegant, it is also complex and most constructs are far from clinical evaluation.

Regardless of the technology, further significant challenges to safe and effective oral delivery of peptides also exist, such as individual patient variation, not only in their underlying disease conditions but also in respect of variability in gastric emptying, dilution, intestinal transit time, regional luminal pH, and formulation interaction with intestinal contents, including mucus.

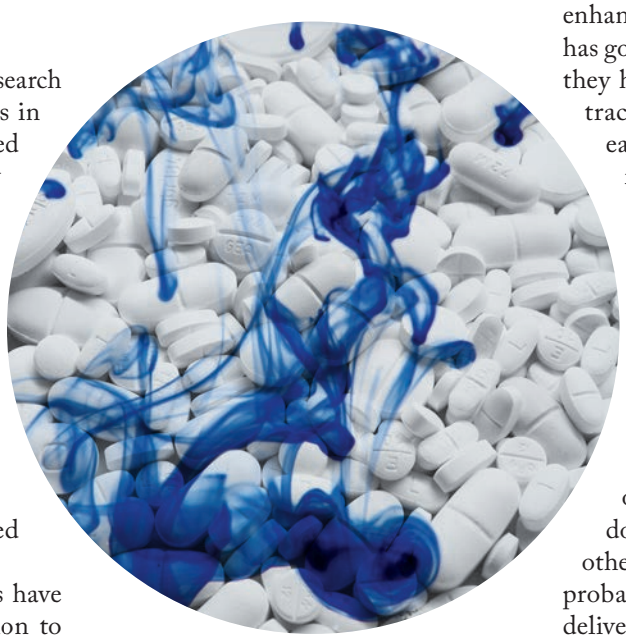
To compound the issues above, pharma companies, at least in their published works, appear to restrict oral peptide studies to a limited range of established formulation components, which is understandable given the regulatory frameworks that exist. Thus, formulation components already classified as non-active ingredients (excipients) or recognized as food-grade materials are highly attractive. In spite of technology improvements in peptide synthesis and design, aversion to creating new chemical entities (NCEs) may be one reason established peptides are used and why the chemical structures of peptides are not normally changed for an oral program. Only in cases where the investment will likely

"The race is on to create oral insulin and GLP-1 analogs."

pay off commercially (for example, for long-acting injectable insulins or GLP-1 analogs) are the additional clinical trial and regulatory costs worth the risk. Encouragingly, new, more lipophilic and stable peptide analogues with longer half-lives are starting to filter across to the oral programs of big pharma, and some of these have not yet been approved as injectables. One such GLP-1 analog is claimed to have returned positive Phase II data in February 2015 when formulated with a long-established permeation enhancer (4).

Enhanced controversy

For over 50 years there has been research interest in permeation enhancers in oral drug delivery. The most studied include medium-chain fatty acids, bile salts, acyl carnitines, and calcium chelators. Most have a mild detergent-like effect on intestinal epithelial membranes, but their mechanisms vary – and there is a gap in knowledge about what occurs in vivo in the intestinal lumen environment compared with in vitro permeability studies in a well-defined media in closed systems.



Although most of these agents have a history of fairly safe application to humans for other uses, their use for intestinal permeation enhancement typically involves relatively high concentrations with attendant concerns regarding possible toxicity. For example, bile salts, the medium chain fatty acids, and salicylic acid derivatives all damage the epithelium to some extent. We and others have investigated the damage–repair cycle in the intestine and found that the disturbance to the epithelium caused by sodium caprate is similar to the reaction to many foodstuffs. Transient changes to epithelial cells resolve within 30–60 minutes (5) and the mucosa completely regenerates within 4–5 days. These results are encouraging but they are not a reason for complacency; repeat-dose studies in man may still reveal problems in using these types of agents. In clinical trials, enhancers used to promote the absorption of relatively low-molecular-weight peptides (< 6000 Da) also appear to have a limited effect on promoting systemic circulation access of microorganisms from the intestine (6). However, recent research suggests that even low-grade damage to the epithelium, such as that which accompanies acute binges of alcohol, can promote the permeability of other bystander molecules, including bacterial exo- and endotoxins such as lipopolysaccharides (7).

Doubts regarding the safety of enhancers in drug delivery science have encouraged academic research into NCEs. It is understandable, but a little ironic, that some of these were originally derived from bacterial toxin motifs with precisely targeted effects on specific tight junction proteins (for example, claudin-4) (8). Others are attempting to mimic nature by creating viral-like cell-penetrating peptide analogue NCEs based on a poly-arginine motif to influence the transcellular pathway when co-administered with insulin (9).

Many of these NCEs may have toxicology issues of their own. Those which act by opening tight junctions may be unstable, and there is little evidence in animal models to date that either type of NCE are any more effective than 'traditional' non-specific surfactant-like enhancers. So far, none of these NCEs has gone beyond preclinical studies and they have had some difficulty gaining traction with industry due to the early stage of research and the high risks involved. To date, the many clinical trials involving early-generation enhancers have not flagged any particular safety issues associated with such formulations. In fact, the most common issues emerging from the trials are the bug-bears of relatively low bioavailability and high intra-subject variability – in other words, the danger of under-dosing some patients or over-dosing others. In fact, insulin is, prima facie, probably a poor candidate for oral delivery given the necessarily complex plasma profile required to match post-absorptive metabolism of nutrients. The high doses required could lead to hypoglycaemia in some patients, while low bioavailability could allow hyperglycaemia in others. Consequently, it may make better sense to select an oral peptide candidate that is potent and efficacious, and has a wide safety margin in order to generate proof of principle for a therapeutically useful peptide in a large patient cohort.

Success at last?

In recent years, two Phase III oral

"No matter what the approach, patient variation poses further challenges."

peptide clinical trials achieved their primary end points, sparking renewed interest in the field. The first was reported in 2012 by Tarsa Therapeutics (USA) with a daily-administered oral formulation of salmon calcitonin (sCT, MW 3420 Da) in postmenopausal osteoporotic women for 48 weeks (10). In a controlled study, patients received enteric-coated tablets containing 0.2mg recombinant sCT, plus several hundred mg of citric acid in the core to prevent attack by serine proteases. The key pharmacodynamic data from the ORACAL trial was a rather weak 1.5-percent increase in bone mineral density over the period, accompanied by reductions in serum cartilage breakdown biomarkers. Importantly, this data still compared well against 33 µg doses of an approved nasal sCT product and was well tolerated by patients. No pharmacokinetic analysis has yet been published, but because the nasal products have an absolute bioavailability of 1 percent, and have no permeation enhancers, we can reasonably assume a similar pharmacokinetic profile to that of the nasal comparator. Whether this oral peptide formulation (OSTORA) will eventually be approved is hard to say; recent regulatory concerns in the US and EU about a possible cancer risk associated with long-term use of marketed sCT in post-menopausal women, makes the benefit–risk for a new oral formulation of sCT debatable.

The second technology for which positive data emerged from a Phase III trial was an oral formulation of the somatostatin peptide analogue, octreotide (MW 1019 Da), from Chiasma (Israel). Octreotide is administered monthly by a painful, long-acting intramuscular injection to patients with acromegaly, an orphan disease caused by overproduction of growth hormone by the pituitary gland. The oral technology is based on the company's "Transient Permeability Enhancer (TPE)" system and the formulation contains an oily suspension of hydrophilic particles containing sodium caprylate, polyvinyl pyrrolidone, and octreotide, entrapped in an enteric-coated capsule. In the Phase III study, approximately 150 patients responding to injectable somatostatin were then switched to oral octreotide in a complex protocol. The read-outs for the oral daily formulation were reductions in the biomarkers of insulin growth factor and growth hormone over a period of up to 13 months in some cases (11). Chiasma's oral octreotide formulation was submitted as a New Drug Application to the FDA in June 2015 using the 505(b)(2) regulatory pathway, a route that benefits from previous approvals of individual components and actives therein. However, when comparing the plasma octreotide level achieved in Phase I studies of a 0.1 mg sub-cutaneous injection of octreotide with those seen using a 20 mg octreotide tablet, the relative oral bioavailability was just 0.5 percent by comparison with injection of the much lower dose (12). This result is still promising because the pharmacodynamics end-points were acceptable. Octreotide can be made relatively cheaply, so the loss of over 99 percent of material in the gut might be commercially-viable, in addition to achieving a currently unmet clinical need for patients receiving a highly painful injection.

The uncertain road ahead

The oral peptide field has gone through several cycles. In the 1990s, companies anticipated clinically-useful delivery of even large proteins, such as erythropoietin, using platform technologies. But they failed to deliver commercial products in clinical trials. As a result, big pharma exited the field, but scientists are now revisiting the development of oral formulations for established, highly potent, low-molecular-weight peptides. However, even the most advanced oral clinical trials report consistently low bioavailability (~1 percent).

Few prototype candidates are available and so the race is on to create oral insulin and GLP-1 analogs. Insulin has a narrow therapeutic index, so proposed platforms would need to address patient variability issues to avoid potential risk to the patient. But on a more optimistic note, discovery programs are yielding many interesting and potent peptide molecules for pain, cancer, and cardiovascular disease management. Several are cyclic, low-molecular-weight compounds, and therefore already have more oral delivery potential than many established injectable peptides. Some of these do not require sustained pharmacokinetic profiles – perhaps needing only a short period of peak plasma concentration.

One thing is clear: if we are to fully explore the potential of new peptide structures for oral delivery, we must re-examine the default mind-set of trying to convert an already-marketed injectable peptide to an oral form – and be prepared to create more peptides with structures more amenable for oral delivery as a starting point. While this would involve both scientific and commercial risk, the pay-off could eventually be worth it.

David J. Brayden is Professor of Advanced Drug Delivery at University College Dublin's (UCD's) School of Veterinary Medicine and is a Fellow of UCD's Conway Institute of Biotechnology.

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How to Ace Interviews

Is it time to update your resume and fine-tune your interview skills? Biopharma is seeing an unprecedented jobs boom and your dream role could be just around the corner.

By Megan Driscoll

We are living in the age of biopharmaceutical innovation – and movement. Although the big biotech and pharma industries have seen swathes of job cuts over the past decade, we are now on the cusp of a huge growth period. The number of openings my agency has been asked to work on has increased significantly over the last 12 months and the projections for 2016 are looking even better. A company that was previously hiring two people a month is now hiring fifteen people a month; a company that was typically hiring 50 people a month is now hiring 80 people a month. I've been recruiting within the biopharma industry for almost 20 years – first as an individual recruiter, then as an owner of my own company established in 2004, and I have never seen hiring at this rate. It means more opportunities for all, particularly for those with strong technical, leadership and management skills. In essence, the world is your oyster! Here, I give my advice on how to get through the interview process and land that dream job.

On top of the world

In the US, it's customary to find a new job every three to five years. If you stay at a company for close to 10 years then other firms start to perceive you as being stale and less able to see things from a different perspective. In Europe, however, there is a very different attitude and it's common to see people staying with the same company for 10 years or more. In fact, employers may even be wary of a resume with too many job changes. In the future, I think the European trend will change; the US influences every market in the world and it will eventually influence attitudes towards movement. One thing's for sure, when jobs are plentiful and diverse, you don't need to be trapped in an unrewarding position.

Indeed, if you're unhappy in your current role and feel that you need a new job, then you have waited too long because your work productivity has likely suffered and you won't be giving it 100 percent. It's better to start looking for a new job as soon as you notice a decline in your interest and success in your role. It's even better to start when you're on top because your excitement, enthusiasm and success will speak for itself. You'll be able to go to an interview and honestly say that you're happy and doing great – but that you're really interested in the advertised position and what the company has to offer. You become a commodity worth having.

Before you apply, one of the first steps is to check that your resume is clear, legible and up to date. It's common for people who have been at one company for a long time to state on their resume: 2001 – 2014, Director, Process Development. But it's probably not true – more than likely they had a path of progression. It's important to include all of your roles; for example, senior engineer, then manager of engineering, then an associate director of process engineering... Prospective employers are interested in the progression of your success and want to know that you are ambitious. Make sure you also state the skills and expertise you have gained and use active verbs like 'led' and 'managed' to describe those skills. You need to show that you are more than a 'doer' – you are a leader. At any level within an organization, a company wants to hire people with leadership skills. Regardless of whether or not you have managed people or projects, they will still assess those skills.

"Although a resume is certainly important, I think far too much emphasis is placed on making sure it looks a certain way."

Although a resume is certainly important, I think far too much emphasis is placed on making sure it looks a certain way. Today, most people get jobs either through referrals or by recruiters, and only around 10 to 15 percent are placed through submission via a job advertisement. Using your network is crucial, so a profile on LinkedIn can be very helpful because it's where most recruiters and peers will find prospective candidates. Your LinkedIn profile should have the same amount of detail as your resume, whether you are looking for a job or not.

Falling in love

The interview is really all about the company. Everything you say should relate to how you can improve the company: What skills can you bring? How does your experience match the responsibilities involved? You really need to sell yourself because you want them to feel like they can't live without you. Once the company decides that you're 'the one', the offer process can be all about you. But you'll never get an

opportunity to consider an offer if they haven't fallen in love with you first.

Most interviewees show up on the day looking good and feeling good (those who don't are anomalies), so it's hard to be unique in that regard. The most important key to cupid's arrow is consistently framing your answers and preparing positive responses beforehand. For example, you shouldn't say, "I dislike my new boss," – instead try, "I want to work in a collaborative environment."

The real you

Throughout the process, the interviewer will try to uncover things about the 'real' you. They only have a few hours to figure out whether or not you're going to make a great addition to the team, and usually they use behavioral-based questions to do this. They will ask how you behaved in a certain setting in the past and will ask follow-up questions to dig deeper. Most people do not spend enough time preparing for these questions. Give me an example of when you've been in a situation of conflict and how you handled it. Give me an example of when you failed to complete a project and what you did about it. Give me an example of when you told someone an answer and then later learned it was wrong… the list goes on.

My greatest piece of advice is to look up behavioral-based questions online and practice giving positive answers. Everybody has been in a conflict before and everybody has made the wrong choice. But if you're not prepared for the question, the first thing you will think of (and probably divulge) are the one or two extreme examples where you may have acted out of character, as opposed to the hundred other occasions where you made the right choice. Focus on a less extreme situation and frame the response around a positive approach and outcome.

Embrace the learning curve

Most people don't want to hear why they failed to get the job they wanted – they just want to shut the door and pretend it never happened. But you should try to get a candid answer as to what went wrong. If you know anyone at the organization that can speak to you off the record, then consider approaching them. You may find out what you did to influence the decision (in a good or bad way) – and that will help you to avoid repeating mistakes. It's a really hard thing to ask, but you'll be surprised at how many people will share the real deal with you.

You can also look for indicators yourself. If you're getting a lot of phone interviews but no follow up face-to-face interviews then it's an indicator that you're doing something wrong during the call. It can be hard to be objective about your own answers, so set up a mock call; a close friend or colleague may be able to spot a problem instantly. If you get plenty of face-to-face interviews but you don't get any offers then consider the way you present yourself (appropriate dress code) or even your handshake.

In my experience, interview catastrophes don't happen often; this year, my firm has placed around 300 people and set up over 1200 interviews and there has been less than a handful of candidates that truly bombed. Catastrophes do happen, but they probably never should.

We're not just living in the age of biopharma growth – it is also the age of global movement. In the next few years, we will see more people switching organizations and even countries to seize new and exciting opportunities. Candidates are now in a strong position to grab the job of their dreams, including roles that seemed implausible five years ago – and these jobs may not come around again. Happy hunting!

Megan Driscoll is the founder and president of PharmaLogics Recruiting.

Top Job Hunting Tips

Start looking for a new job as soon as you notice a decline in your enthusiasm and productivity

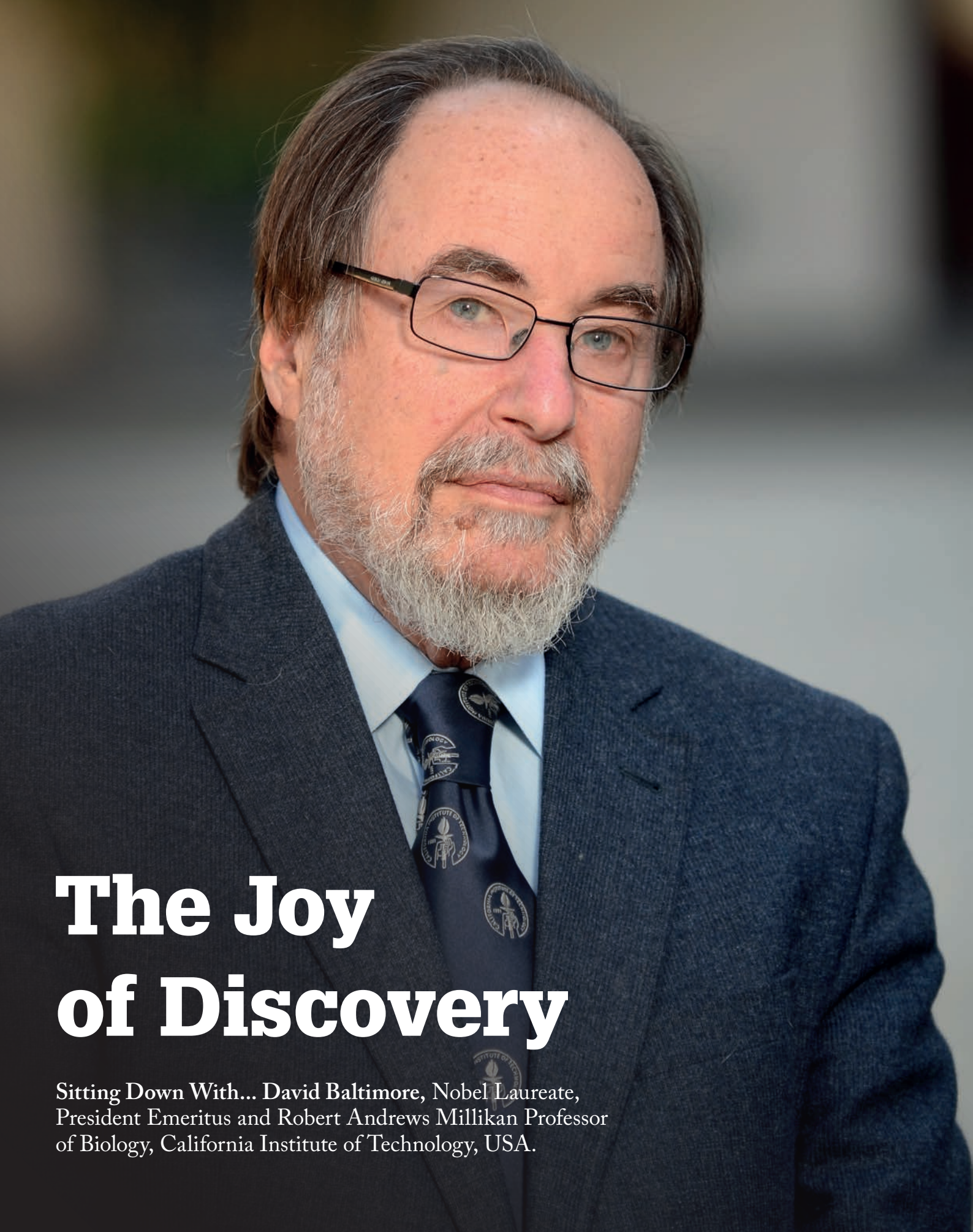
Make sure your resume lists all your previous roles, including multiple roles within the same company, and lists your skills and expertise

Don't agree to job interviews if you already know you won't accept the job

Make sure your LinkedIn profile has the same amount of detail as your resume

Before an interview, research behavioral-based questions and practice giving positive responses

If you don't get the job, try to find out why to make sure you do not repeat the same mistakes



The Joy of Discovery

Sitting Down With... David Baltimore, Nobel Laureate, President Emeritus and Robert Andrews Millikan Professor of Biology, California Institute of Technology, USA.

Going back to the beginning, why experimental science?

Growing up, you often question yourself about what you're good at. And it became clear to me as I progressed through high school that I was good at science and mathematics. In 1955, I had the opportunity to spend a summer at The Jackson Laboratory (www.jax.org) and it introduced me to the huge potential of experimental science. It was very inspirational and essentially determined the rest of my life.

When I went to graduate school (Massachusetts Institute of Technology) back in 1960, I looked at what people were doing in experimental science; the most interesting work was being done with viruses, particularly ones that grow in bacteria. But I thought that the field was very limiting. I wanted to see if viruses could be used as a probe for the behavior of animal and human cells. I left MIT to go to Rockefeller University because there was a professor there – Richard Franklin – whose work was very closely aligned with my aspirations.

Later on, I met with Renato Dulbecco – one of the people bringing animal virology into the late 20th century – and he invited me to join him at the Salk Institute in La Jolla. I moved there in 1965, where I spent two and a half years before moving back to MIT.

You achieved a great deal at MIT. What are your highlights?

The discovery of reverse transcriptase in 1970 was the biggest; nothing beats that. But we did move into cancer research where we discovered that the Abelson virus made an oncoprotein that phosphorylated tyrosine. It stays with me as a great moment because we had found a new kind of protein modification that was linked to cancer. It eventually led to the "miracle drug" Gleevec.

Next, I decided to move the laboratory into immunology. A highlight there was our discovery of RAG genes, which encode the proteins that recombine DNA and give the immune system its variability – and ability – to react. And we also unearthed the NF-kappa B transcription factor – plus a whole host of other transcription factors that control immune function. It was a period of incredible and important protein discovery on the part of the post-doctoral group I was working with. And there is no higher high than a discovery.

But you won a joint Nobel Prize in 1975 for "discoveries concerning the interaction between tumor viruses and the genetic material of the cell" – that must have been a high point...

The main highlight there was that the call came from my wife! She was at a scientific meeting in Europe and heard before the official announcement, and she called me – woke me up, in fact. Going to Sweden for the ceremony was like entering fairyland. I was treated like nobility and given the Prize by the King of Sweden.

Did your research focus change after receiving the prize?

The prize was coincident with my movement into immunology, but it wasn't the reason for the move. I had already made the decision based on the rise of recombinant DNA methods. Indeed, the new ability to use recombinant DNA methods to understand mammalian cell biology was very real in 1975. And at that point I decided to enjoy myself and take advantage of the new methodology to work on the adaptive immune system.

What are you focusing on right now?

After stepping down as president of the California Institute of Technology in 2005, I decided to try something a little different. I wanted to see if we could translate some of our findings from the laboratory into humans – either as therapeutics or prevention. In particular, I focused on gene therapy methods. We've been doing that now for the last 10 years and we have several projects in clinical development; cancer and HIV are major focuses.

As gene technologies advance, what are the major concerns?

One concern of mine dates back to my early experience with recombinant DNA methods. Indeed, when they were developed, I was part of the group that produced the Asilomar Meeting in 1975 to address the potential dangers that might arise from this new technology. Now that genome-editing technologies have appeared, the concern is a reality rather than a theoretical concern. I was also part of a group that called on the National Academy to take some action to limit the use of these technologies until we could at least come to a consensus about what's right, what's appropriate and what's inappropriate. That of course is always a judgement in the context of technology. The National Academy is now actively evaluating the technology and the larger societal concerns that surround gene editing.

What advice would you give to today's scientists?

Science today is such a different world than it was when I started out. But in retrospect, I think I made some pretty good decisions back in the 1960s; I found the right places to work, and the right people to work with. The most important consideration should be your scientific environment and the people around you.

Today, I think that science has been so 'professionalized' that some of the joy of discovery is lost. Anything we can do to give young scientists an opportunity to be independent and to express their own particular notions about science and creativity is positive for the forward movement of science.

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Programmable drug placement enables more uniform attachment of the conjugate at a specific site for improved ADC product consistency and better regulatory compliance.

M **MODIFIABLE**
Precise location control maximizes ADC performance. Placement flexibility results in more homogeneous ADCs, optimized PK, and improved efficacy and safety.

A **ALDEHYDE**
Combination of novel aldehyde tagging technology and naturally-occurring amino acid sequence (leveraging enzyme modification) delivers enhanced efficacy.

R **RECOMBINANT**
Used with recombinant antibodies, the technology works with any cell line expression system—resulting in simplified analytics and efficient, scalable processing.

T **TAG**
Ability to incorporate multiple tags enables more potent payloads. Optimization of linker-toxin combinations for specific targets increases efficacy.

Every molecule has a challenge.
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