NOVEMBER 2017 # 35

the Medicine Maker™

The Far Future

Will pharma's current course lead to dystopia or utopia in the year 2100?

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Online this Month

Visions of the Future

What does the far-distant future hold for healthcare and the pharma industry? A recent sci fi writing competition from Kaleidoscope Health & Care posed this very question. You can find out more about this competition on page 20. The top prize was scooped by Elisabeth Ingram Wallace with her story OPSNIZING Dad, which explores the preservation of human memories.

Why did you choose to focus on memories?

The second I saw the competition on Twitter, I thought of an opening paragraph I had written in the summer. During the Bath Flash Fiction Festival in the UK, I did a workshop with Tania Hershman on using science in writing. The workshop was the catalyst for the story. Tania studied maths and physics, and her first love was science. In her workshop, I read a New Scientist article from three or four years ago, about developments in a new material to store information, a type of glass the article called "Wonder Stuff". I read about lasers, and Hitachi developing a fused quartz. I read about the work Physicist Peter Kazansky was doing at the University of Southampton to record vast quantities of data in glass, by varying the intensity and polarization of lasers. I kept thinking of the physical oddness of that idea, of cramming terabytes of data into a piece of glass the size of a thumbnail.

I put the notebook aside, and got on with other projects until I saw the Kaleidoscope challenge to write about health and care in 80 years' time. I knew immediately I wanted to write about "memory glass" to think more broadly about healthcare, human memory, and loss.

What thoughts do you have about the potential future of healthcare?

I have worries about the future, and glimpses of hope for the future, but not predictions. I love the questions and the ideas that this Kaleidoscope competition raised, but I ultimately agree with what Margaret Atwood says:

"…you can't really predict the future. There isn't any 'the future'. There are many possible futures, but we don't know which one we're going to have. We can guess. We can speculate. But we cannot really predict."

Read more at:
http://tmm.txp.to/1017/wallace

If you are hungry for more views on the future then there's plenty more on our website. Jeff Baur tells us about his career as a futurist, Erik Gatenholm from Cellink delves into the fascinating world of bioprinting, and Gavin Miller from the University of Glasgow offers a 101 on medical humanities and why sci-fi isn't an accurate prediction of the science of the future. Read more at www.themedicinemaker.com.

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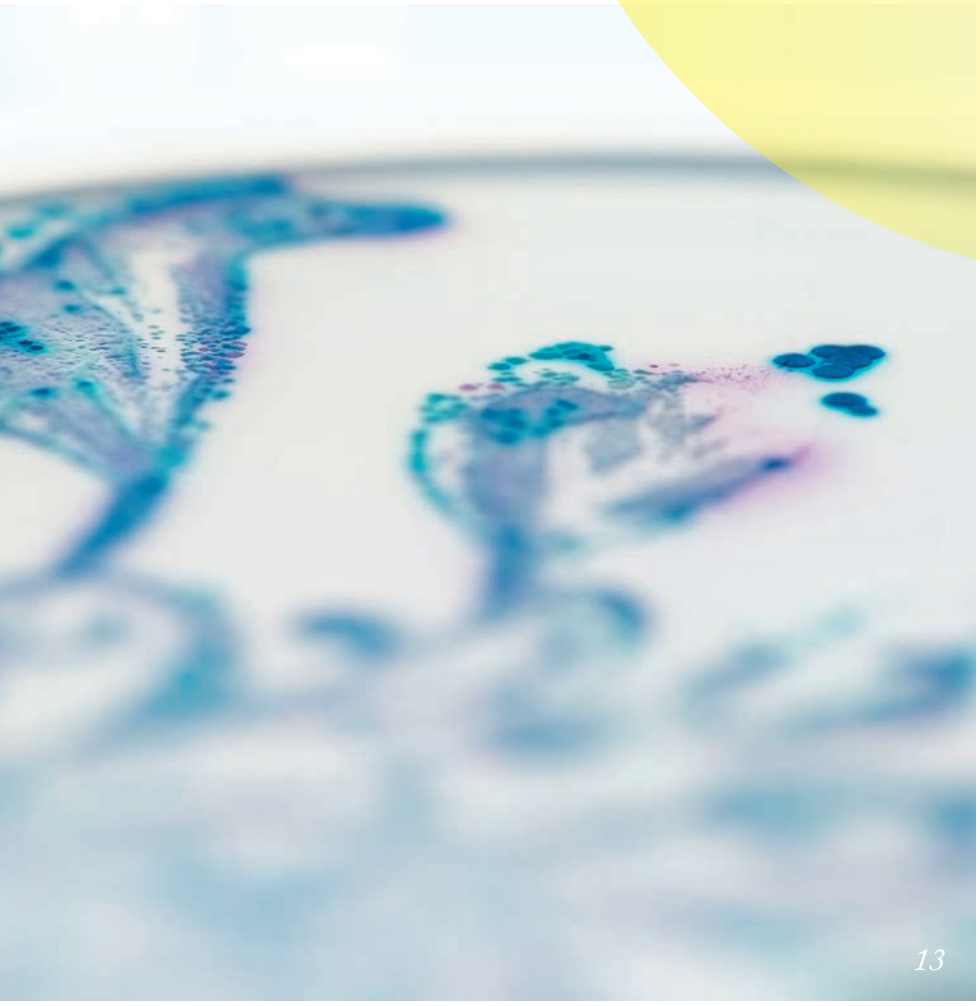

On The Cover

Is the future that awaits pharma utopia or dystopia?

Upfront

In My View

the **Medicine Maker**

ISSUE 35 - NOVEMBER 2017

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Distribution:
The Medicine Maker (ISSN 2055-8201), and The Medicine Maker North America (ISSN 2514-7536), is published monthly by Texere Publishing Ltd and is distributed in the US by UKP Worldwide, 3390 Rand Road, South Plainfield, NJ 07080
Periodicals postage paid at South Plainfield, NJ
POSTMASTER: Send US address changes to The Medicine Maker C/O 3390 Rand Road, South Plainfield NJ 07080.
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Big Brother is Monitoring your Adherence

What does FDA approval of a pill that tracks drug compliance mean for privacy?

Patient non-compliance is a known issue, with some sources touting alarming statistics. In the US, for example, 75 percent of adults do not follow the doctor's orders when it comes to taking medicines, and 125,000 deaths in the US alone are thought to be attributed to nonadherence (1).

The issue needs to be tackled. A variety of factors can influence whether patients take their medicine and much attention has focused on how the color, shape and size of a pill can all play a role (2). Technology is also starting to come to the fore with ingestible sensors that can track when a patient takes their medicine – and report back to health practitioners. In mid-November, the FDA approved a new dosage form of Abilify (aripiprazole; used to treat schizophrenia) (3). Each Abilify MyCite tablet contains a sensor that, when in contact with stomach fluid, sends a message to a wearable patch which in turn connects to a mobile app. Patients can track their adherence on their smartphone and, if permission is given, so can care givers, family members and physicians via a web-based portal. The pill is made by Otsuka Pharmaceutical and the sensor – no larger than a grain of sand – comes from Proteus Digital Health.

The pill was initially rejected by the FDA last year, who requested additional information including data on "the performance of the product under the conditions in which it is likely to be used, and further human factors investigations" (4). The new approval suggests that the FDA's concerns have been addressed, but the pill is likely to open a can of worms around privacy and ethics. Is it right to force patients to use digital pills? And will there be consequences from insurers or payers if patients do not comply? It's worth pointing out that the patch can track more than just pill taking; Proteus' technology can also measure patient activity and rest.

Whether the "Big Brother" pill can actually boost adherence remains to be seen – and the FDA release explicitly states that there hasn't yet been an established association between the new pill and increased adherence. With schizophrenia and other psychotic disorders, adherence can help prevent relapse, but patients can also suffer from paranoia and delusions; would a digital pill induce further paranoia? However, it's clearly useful for physicians and family members to know whether medication is being taken by patients at risk – and a reduction in nonadherence could remove a huge burden from healthcare in general.

It will certainly be interesting to see how real-world use plays out and who benefits most in the end.

Stephanie Sutton
Editor

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2. *RAPS, "FDA Wants to Study if Drug Color, Shape and Size Affect Patient Adherence", (2014). Available at http://bit.ly/1Dfwbhx. Last accessed November 15, 2017.*
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Upfront

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

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

Brexit Update: Calls for Customs Clarity

The EFPIA highlights the risks of disrupting UK–EU medicine supply chains

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has released a survey that highlights the heavily integrated nature of pharma supply chains in the EU and UK. According to the authors, 45 million patient packs are supplied from the UK to other EU/European Economic Area (EEA) countries each month, with over 37 million going the other way. Over 2600 final products have some stage of manufacture based in the UK (1).

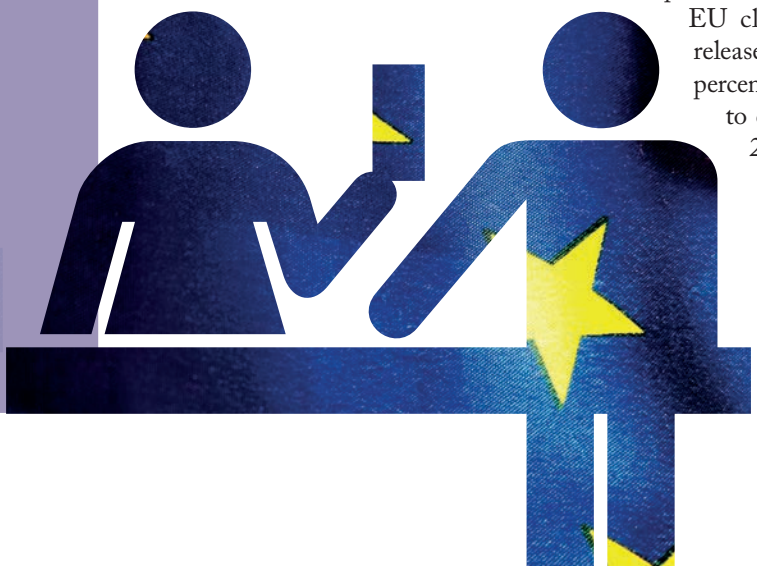
"Companies manufacturing these products will be amongst the most aware of the impact that World Trade Organization (WTO) rules will have on their businesses, particularly in the case of medicines, which are very time-sensitive," says Elizabeth Kuiper, Executive Director of Public Affairs at the EFPIA. "Each company is preparing for Brexit and taking contingency planning extremely seriously."

When the UK leaves the EU, it will become a "third country." And unless the UK remains a member of the EEA, over 12,000 licensed presentations of centrally authorized medicines will require a separate Market Authorization in the UK before they can be prescribed to patients. According to the survey, 17 percent of centralized marketing authorizations are held in the UK.

In the event that the UK and the EU fail to reach an agreement, the UK will revert back to "WTO rules." The US, Canada, Australia, Japan and Switzerland all have Mutual Recognition Agreements (MRAs) – plus other bilateral agreements – with the EU to facilitate trade with the block.

According to EFPIA's survey, 45 percent of EFPIA members expect trade delays if the UK and Europe fall back to WTO rules. "A 'no deal' scenario would result in multiple barriers to frictionless trade, and is likely to disrupt the complex supply chains for medicines," says Kuiper. "We would be concerned that any customs delays may impact on medicines reaching patients. It is essential that the EU and UK put patients first in the Article 50 negotiations, and secure cooperation on medicines regulation and supply."

A "no deal" scenario could also impact ongoing clinical trials. The survey found that 70 percent of investigative medicinal products being used in ongoing EU clinical trials have been released from the UK, with 50 percent of those trials scheduled to continue beyond March 2019 – the end of the Article 50 process.



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Business-in-Brief

Expediting generics, the age of digital manufacture, and coping with API violations… What's new for pharma in business?

Regulation

- The recent furor over drug prices appears to have had an impact in California, with the state's Governor Jerry Brown recently signing legislation into effect that requires drug manufacturers to give California at least 60 days' notice if prices are increased by more than 16 percent in two years. The law has been applied in an effort to offer greater transparency to the general public about changes in drug pricing.
- During a speech about understanding competition in prescription drug markets, FDA Commissioner Scott Gottlieb announced that the US agency is planning to increase the scope of expediting generic drug application reviews, while maintaining safety and efficacy. The FDA has also been in discussions with the US Federal Trade Commission about the move, as the agency believes it may reduce drug costs because of increased competition in the market.
- Amsterdam has been selected as the new host city for the EMA. After hours of deliberation, and votes being tied 13-13 between Milan and Amsterdam, the location was chosen by a coin toss. The agency must take up operations in its new home by March 30, 2019, at the latest.

Manufacture

- Hoping to future proof their manufacturing operations, Sanofi is investing in digital technologies, spanning from virtual reality to collaborative robotics, and plans to develop the next generation of biopharmaceuticals within digital manufacturing plants. They expect their shift towards biologics to result in an investment of approximately €600 million per year by 2020 to boost their capacity.
- Allergan is once again in the spotlight as it faces price-fixing allegations, with investors attempting to sue the company. It is alleged that Allergan colluded with other companies to create artificially inflated prices of propranolol, ursodiol, doxycycline, desonide, tretinoin, glyburide-metformin, and verapamil, between October 2013 and November 2016.
- Janssen Biotech, a subsidiary of J&J, has dropped its lawsuit against Samsung Bioepis with "great prejudice," meaning they cannot re-file the motion. The initial suit was filed regarding a patent on Janssen's Remicade, which Janssen believed was violated by Samsung Bioepis' Renflexis. After the ruling in the Sandoz versus Amgen case, two of Janssen's complaints were rendered moot, as they would have locked Samsung in a "patent dance" (Samsung would have to disclose their ordinarily private application information to Janssen). The landmark Sandoz versus Amgen case saw the US Supreme Court dismiss the patent dance, despite its basis in the Patient Protection and Affordable Care Act.

Warning Letters

- Lupin has been trying for some time to bring its plant in Goa, India, up to scratch but an FDA warning letter suggests that the company is struggling. The letter applies to both the Goa facility and another Indian plant in Indore, and states that the company's improvement efforts so far are not adequate. The FDA also adds that the company is repeating the same mistakes despite earlier direction. Most of the issues raised relate to product testing, with batches of drugs failing to meet specifications.
- Drug manufacturer Guangdong Zhanjiang Jimin Pharmaceuticals has received a warning letter from the FDA about several "significant violations of current good manufacturing practice" after an inspection of the company's manufacturing facility in China. The violations include inadequate quality control – including approving multiple lots of a drug for distribution in the US containing the wrong API – as well as product misbranding, and failure to establish adequate written procedures.

Steady On, Pharma

Pharma's 2022 growth forecast has been reduced for the first time in a decade

EvaluatePharma have published their annual "World Preview," which has – for the first time in the past 10 years – reduced pharma's 2022 drug sales outlook. Last year pharma was forecasted to sell $1.12 trillion's worth of pharmaceuticals in 2022; this year, the report estimates 2022 sales will total $1.06 trillion. The report stated, "This slight retraction is likely due to a number of factors, but the continuing squeeze on pricing is almost certainly a major one" (1). Here are a few key statistics taken from the report.

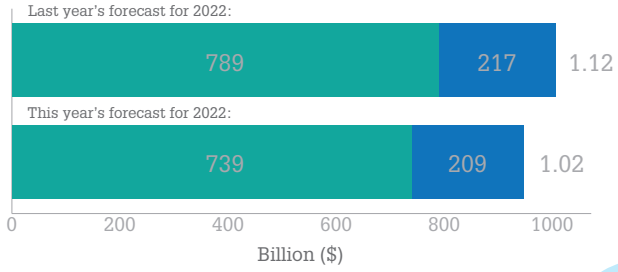
Reference

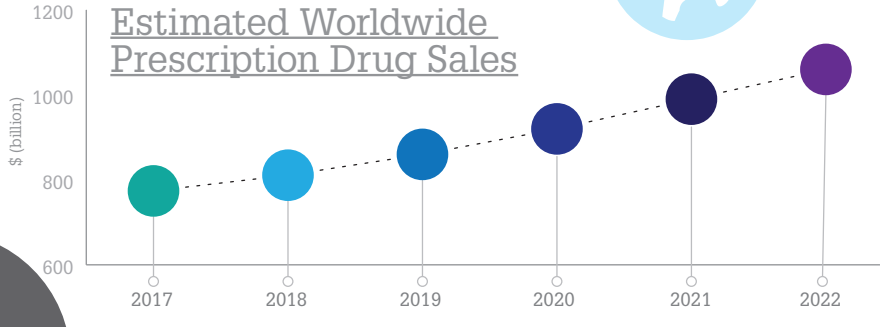
1. *EvaluatePharma, "World Preview 2017, Outlook to 2022", (2017). Last accessed November 11, 2017. Available at: http://bit.ly/2wxzYtd.*

Estimated Top 10 Therapeutic Areas in 2022

- Oncology 192.2
- Anti-diabetics 57.9
- Anti-rheumatics 55.4
- Anti-virals 42.8
- Vaccines 35.3
- Bronchodilators 30.1
- Sensory organs 28.3
- Immunosuppressants 26.3
- Anti-hypertensives 24.4
- Anti-coagulants 23.2

$ (billion)

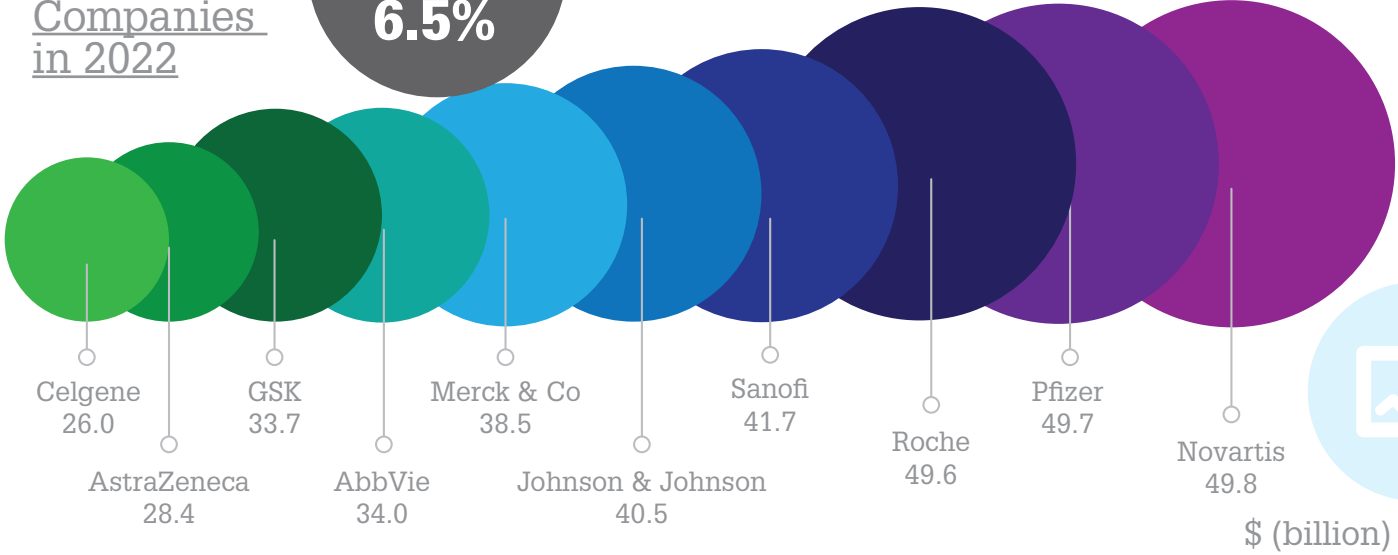




Estimated Drug Sales of Top 10 Companies in 2022

Compound growth between 2017 and 2022:

6.5%



Estimated Top 10 Selling Products in 2022

Product	Company	$ (billion)
Humira (adalimumab)	Abbvie + Eisai	15.9
Revlimid (lenalidomide)	Celgene	14.2
Opdivo (nivolumab)	Bristol-Myers Squibb + Ono Pharmaceutical	9.9
Keytruda (pembrolizumab)	Merck & Co + Otsuka Holdings	9.5
Eliquis (apixaban)	Bristol-Myers Squibb	8.5
Xarelto (rivaroxaban)	Bayer + Johnson & Johnson	8.1
Imbruvica (ibrutinib)	Abbvie + Johnson & Johnson	7.5
Eylea (aflibercept)	Regeneron Pharmaceuticals + Bayer + Santen Pharmaceutical	7.2
Ibrance (palbociclib)	Pfizer	7.1
Januvla/Janumet (sitagliptin phosphate)	Merck & Co + Ono Pharmaceutical + Almirall + Daewoong Pharmaceutical + Merck & Co	6.0

32% of 2022 growth driven by orphan drugs

$522 million Average value of new approvals:(5 years post-launch in US)

Oncology therapies to grow between 2017 and 2022 **13%**

Biologics to comprise 52% of Top 100 product sales in 2022

R&D expenditure to grow from **$158 billion (2017) to $181 billion (2022)**

Mini Mimic

Body-on-a-chip technology aims to streamline drug development and further personalize medicine

Failing to accurately replicate complex human biology and physiology in vitro or in animal studies is one reason for the high failure rate in drug development (also see Learning from Failure on page 12). Anthony Atala, Director of the Wake Forest Institute for Regenerative Medicine, is passionate about an avenue of research that could help: body-on-a-chip technology. By growing a variety of human organoids on a chip, the technology is able to simulate multi-tissue pharmacodynamics. "This approach has the potential to reduce the need for testing in animals, which is expensive and slow," says Atala. "Importantly, the results aren't always applicable to people either."

Atala's lab has developed a platform with three integrated organs – heart, lung, and liver – and also demonstrated multi-tissue interaction (1). Where other organ-on-chip platforms may consist of cell aggregates to mimic an organ's function, Atala's team created 3D organoids that function more like the organs they imitate, including how they interact with each other. For example, propranolol should be metabolized by healthy livers to make it ineffective at blocking cardiac beta-receptors; with cell aggregates, this is not the case, but with 3D organoids, the rule does apply, according to the team.

Atala's lab also aims to create tumor-on-a-chip platforms. "By using a patient's own cancer cells to grow micro-tumors in the lab, we aim to predict how patients will respond to treatment. The model can also help predict where a patient's tumor is likely to spread," says Atala. "This could save patients time and money – but most importantly, aid in personalizing their treatment to make sure it works on their specific tumor."

Reference

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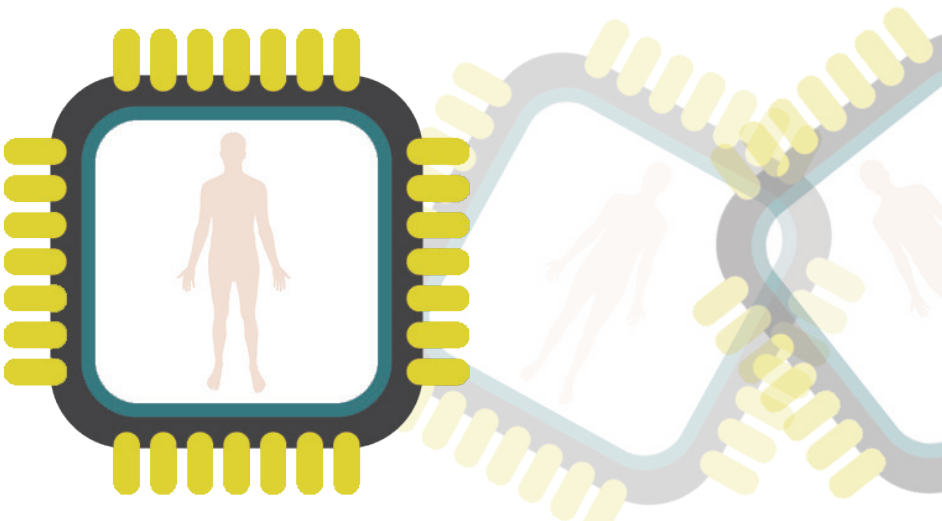
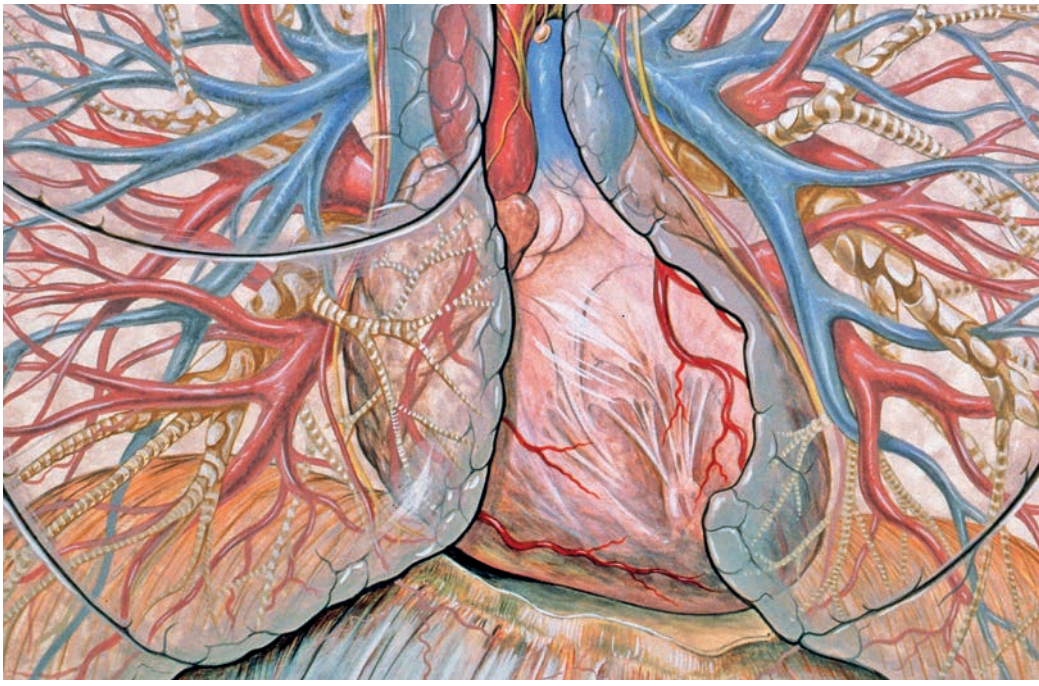


Learning from Failure

Cardiovascular toxicity often hinders success – are companies picking the wrong compounds?



Prolific novelist and academic CS Lewis once said, "Failures are finger posts on the road to achievement." (Given pharma's drug failure rate, the road ahead must truly be paved in gold.)

When it comes to drug safety failure, toxicity – especially to the cardiovascular system – is a major stumbling block. In an effort to learn from past failures and help improve success rates, ApconiX and PhysioStim have teamed up to create a European center of excellence for preclinical cardiovascular safety evaluation. The companies hope to provide high-throughput screening to help pharma companies decide whether their compound is on the right track to pass safety tests. Here, we speak with a spokesperson from ApconiX to learn more.

Why do so many drugs fail in development?

There's a wealth of evidence indicating that drugs fail in development, not because they don't work therapeutically, but because they are toxic. When drug development enters the laboratory, we're dealing with systems in isolation and only two dimensions, which can't match the complexity of the human body – where nothing acts in isolation. New technologies and techniques are helping, but are still topics of research; for example, there have been great strides in mixing cells together and reflecting the structure of a kidney or the brain. We are only just learning to generate tissues in three dimensions and working with different cell types. Looking at one cell type is never going to work very well.

What are the most common toxicity problems?

Cardiovascular toxicity will always be number one, followed by toxicity of the central nervous system, liver, lungs, and kidneys. A lot of work has gone into cardiovascular toxicity testing, especially with ion channel testing. However, the necessary level of understanding and interpretation of safety data is often lacking in projects, which can ultimately lead to project closure. Cardiovascular toxicity is the primary safety-related cause of failure in drug development, which is why our alliance will seek to eliminate potentially toxic compounds at an early stage, while helping companies focus on targets that have greater chances of success. We will focus on a range of cardiac safety studies including automated electrophysiology providing hERG screening and CiPA ion channel assays, manual patch-clamp assays (hERG, hNav1.5, hCav1.2), action potential recordings, Langendorff models and cardiac contractility studies.

Any top tips for choosing the right compounds to take forward?

There is much we can learn from failure. The majority of drug discovery programs fail to get a new drug to market – but do we take full advantage of the learnings? The relevant information is typically difficult to access and remains unpublished, so we don't learn from our mistakes.

My advice is to not bury your head in the sand and ignore toxicology because you believe it's just going to be "bad news". Investigate it earlier, understand the problem and engage with experts. You might be able to get rid of the toxicity and put plans in place to mitigate the risk. If you understand the data then there may be something you can do about it.

Reference

1. *Apconix, "The European Centre of Excellence for preclinical cardiovascular electrophysiology", (2017). Available at http://bit.ly/2zKD4OP. Last accessed November 15, 2017.*

Gut Feeling

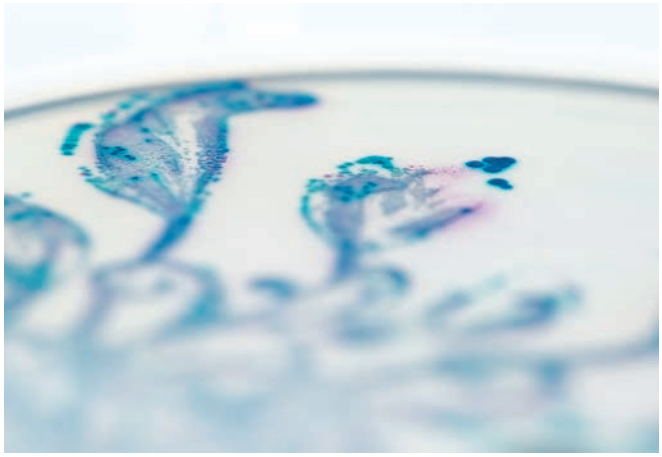
Can the microbiome predict the likelihood of chemotherapy side effects?

Chemotherapy can come with a range of side effects, including severe diarrhoea. Oral antibiotics can be used to reduce toxicity by protecting against infection and increasing the capacity to metabolize dietary substrates, but the indiscriminate depletion of gut microbes can directly impact the effectiveness of the chemotherapy. Libusha Kelly, Assistant Professor in the departments of Systems & Computational Biology, and Microbiology and Immunology at the Albert Einstein College of Medicine in New York, has been studying how the microbiome can influence the likelihood of chemotherapy side effects.

Kelly and coworkers focused on irinotecan (CPT-11), which, in combination with fluorouracil and leucovorin, is one of three first-line treatments for metastatic colorectal cancer. Severe diarrhoea only seems to affect a subset of individuals taking the drugs: 30-40 percent when administered as a single agent, and 11-37 percent when used along with other therapeutics.

"In light of a study demonstrating that CPT-11's toxicity could be alleviated by inhibiting the E. Coli version of a beta-glucuronidase (BG) enzyme in mice (1), we hypothesized that the gut microbiome metabolism would vary between people, and that it might be possible to identify who was likely to be a high versus low metabolizer of the drug based on the expression of certain genes – including BG genes – present in the gut microbiome," explains Kelly.

Using high throughput genomics in combination with metabolomics, the researchers identified gut microbiome-derived metagenomic signatures linked to an individual's ability to convert the inactive form of CPT-11, SN-38G, to the active form, SN-38 (2).



According to Kelly, analyzing the composition of patients' microbiomes before giving CPT-11 might predict whether patients will suffer side effects from the drug. "High throughput sequencing technologies have started to give us a glimpse into the incredible diversity of microbes that live in and on our bodies," says Kelly. "Our work with CPT-11 has implications for the many additional drugs that are glucuronidated via Phase II drug metabolism and excreted to the gut. We anticipate that gut microbes may metabolize many additional glucuronidated drugs, with unknown consequences for patients."

The researchers are now collecting samples from colorectal cancer patients who are on treatment regimens that include CPT-11. "We will track these patients over time to find out whether we can predict, based on a fecal sample, which patients are likely to suffer an adverse response to CPT-11," says Kelly.

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A Media Match Made in Heaven

When it comes to a good cell culture media, biopharma manufacturers desire a chemically defined formula, controlled variance and, increasingly, a specific protein quality profile.

By Bruce Lehr

Cell culture media consistency is crucial when trying to avoid unnecessary introduction of variability in protein production. Over the last five years, customers have been coming to Merck KGaA in the search for chemically-defined cell culture media; they want us, as the manufacturer, to not only understand every chemical within our formulas but also what impact they could have on production processes. It's no small task given that cell culture media has evolved from using serum, cell proteins and hydrolysates – all of which have undefined characteristics that can result in variation.

However, cell culture media have advanced significantly in the last two decades and now, despite the challenges, we at Merck KGaA are reaching a point where we understand every single chemical included in our formulas and where we can control variability within specific ranges.

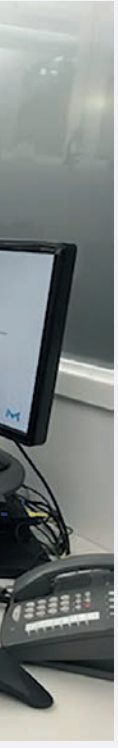
In previous articles in this series (1,2), Chandana Sharma summarized how the raw material characterization team at Merck KGaA was formed to ensure that our raw materials are as pure and as well understood as possible. From my perspective, I need to know that our cell culture media will never be a factor that causes issues with a customer's process. When our cell culture media cause a shift in protein quality, it should not be accidental – we want to elicit the shift by design.

As well as ensuring that trace elements and impurities are controlled in our media, we need to balance the ratio of raw materials so that a given formula has everything the customer needs to produce their protein. I have been working with cell culture at Sigma Aldrich – now part of Merck KGaA – for 26 years. My current role involves working with customers to develop cell culture media formulas that enable them to produce proteins with the right quality profile.

Traditionally, customers have prioritized high protein productivity, but today we find that greater attention is paid to quality, with customers often seeking a particular N-glycan profile, a particular charge, and so on. Meeting a very specific protein profile is particularly crucial for manufacturers of biosimilars, who must copy the innovator product as closely as possible. Depending on what the innovator molecule is, this task could be easy or extremely difficult. But you can probably guess that, as molecules become more complex, we're often working at the "extremely difficult" end of the spectrum. Sometimes there are also intellectual property considerations to contend with; some innovators patent certain methods to perform specific protein quality manipulations.

Success by design

It is impossible for us to supply an effective cell culture medium, if a customer has not identified the endpoints and critical quality attributes, so we target these during development to ensure that we can deliver what the customer actually wants. There is a seemingly unending list of protein modifications that can be inferred by a customized cell culture medium. Whereas finding the right formula was traditionally performed by trial and error, today we use modeling and chemically defined libraries to perform media screens. For example, if we were working to find a medium for a fed-batch process, we would perform



media screens and feed screens, and then use a mathematical approach – multivariate analysis – to draw correlations between single components, formulas, and the responses we want to see in terms of protein quality. In this way, we can see what is positively or negatively affecting a system, and then do more design of experiments to closely look at the ranges of those particular components to achieve the desired protein profile.

It makes much more sense to use a mathematical approach because, at the outset, you may have 70 components in a formula that would otherwise need to be "tweaked" through trial and error, wasting substantial resources. Screening helps identify the main components – let's say 15 – that need to be interrogated further to ensure they don't give any off-target effects.

How the media is put together depends on whether it's a fed-batch or perfusion process. Perfusion systems are being increasingly adopted, but there are not a lot of good scale-down models, which is a challenge. In fed-batch mode, 96 well plates or TPP tubes can be used to perform experiments under many different conditions. There isn't really a comparable system for perfusion right now, although we are reviewing alternatives, and there are still limitations in the number of conditions that can be run. We are looking at even smaller systems, which will ultimately change our workflows. The end goal is to be faster and as scientifically directed as possible.

Sometimes the actual amount of protein that is produced and the quality attributes move in opposite directions – with quality decreasing as productivity increases. In that case, we discuss the options with the customer – and most choose quality over quantity. If all of the customer's requirements cannot be achieved via a nutritional fix, the problem likely stems from the genetics of the cell line, which may not have the range of responses needed. In the unlikely event that we can't meet a customer's requirements, they may be able to further influence protein quality on the process side, using temperature or pH shifts, or a varied feed schedule. In any case, the customer will always end up with a chemically defined medium with controlled variability that is free of animal components.

Improved matchmaking

Our knowledge of cell culture media has led us to launch a number of commercial products. For example, Ex-Cell Glycosylation Adjust (GAL+) is a supplement that allows users to manipulate N-linked glycosylation by increasing sugar attachment. We are also developing a GAL-, which, as the name suggests, does the opposite by decreasing sugar attachment. We are constantly assessing other protein quality parameters and will release new commercial products to help customers whenever we can.

"We are also constantly developing and improving our formulas as our knowledge base grows."

We continue to develop and improve our formulas as our knowledge base grows. For example, tyrosines and cysteines are important nutritional elements, particularly for CHO lines, but can suffer from solubility issues, so we've been developing novel forms with higher solubility characteristics and improved liquid-form stability. Other amino acids and vitamins suffer from similar problems.

Finally, I must say that raw materials will always have some level of variability – the key is to ensure that any variability is well understood and controlled as tightly as possible. With an upward trend in quality, as well as calls for more supply chain transparency, cell culture media consistency will become an increasingly important topic.

Bruce Lehr is Director, Upstream R&D, Cell Culture, at Merck KGaA.

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In My View

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

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

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

Winter is Coming

Cyber attacks are an increasing threat for all industries – so pharma needs to ensure its security measures are up to scratch.

By Florian Pouchet, Head of Cybersecurity and Digital Trust, at Wavestone, UK.

Cybersecurity is still a mysterious area for numerous organizations and is often not taken seriously because it is "just computers" – until you experience a cyber attack. Cybersecurity, also known as information security, focuses on securing assets in the digital world and covers all measures to protect, detect and react to incidents affecting intellectual property, sensitive data or critical IT systems. It is just as important as a lock, CCTV or alarms in the physical world.

Winter is coming for cybersecurity – the threat becomes more tangible (and serious) every day, with new cyber attacks, incidents or major IT vulnerabilities being frequently disclosed. This summer, two malware programs – Wannacry and NotPetya – infiltrated global organizations via Ukrainian subsidiaries, primarily infecting computer networks through a compromised accounting software update. The situation was devastating for Ukraine; more than 1500 companies' business activities were halted, bringing the country to a standstill. But it also spread to the rest of the world. Most infected organizations had no internal network, no email and no core IT systems for more than a week – the irony being that even emergency (continuity) procedures were not accessible. Can you work without IT systems for a week? And with limited systems for weeks after that? Other companies around the world were also hit. For example, Merck, Sharp & Dohme was affected in June, with manufacturing, research and revenue suffering as a result. At the end of October, the company released its Q3 financial results and attributed a $135 million dip in revenue to the attack (1).

In the pharma industry, cyber attacks have a real impact on the physical world in terms of industrial control systems – and subsequently on human lives, when the ability to produce medicines is impaired. Unfortunately, as organizations continue their digital transformation, the potential likelihood of an attack increases. In many cases, a cyber attack is used by criminals to make money, but sometimes the purpose is simply to cause damage and disruption.

Cybersecurity is not going away. Organizations must continue to fight. (And if you haven't started, then you need to join the fight – pronto!) Finding the right level of priority and

"In the pharma industry, cyber attacks have a real impact on the physical world in terms of industrial control systems."

"Cybersecurity is becoming an increasingly challenging issue – and it is unlikely that the problem will disappear."

consideration for the topic, however, is not easy. First of all, remember that tackling the challenge requires a collective effort. No matter your business activity, it is not a task or problem for the chief information security officer alone – no matter the allocated budget or the size of the team. Your security measures must be embedded in your systems, processes, and the behavior of your people. When traveling by car, you have seatbelts, airbags, anti-breaking and anti-collision detection systems all working together to secure your journey – but people must wear their seatbelts and not deactivate other safety features. IT systems also require a seamless integration with multiple elements to ensure security.

To ensure the correct user behavior, and to employ the right processes or technologies, you need to be supported by business lines; it must be part of the company's strategic objective. Knowing the top 10 most business-critical assets is a given for board members – but securing those assets involves everyone – and even includes the actions of the board members themselves. Each and every individual – from top to bottom – within a company has an essential role to play; after all, attacks frequently start with a "human vector," such as a forged email – the target of which may be a privileged user so that access rights can be stolen to infiltrate and navigate the whole network. Most attacks usually start with the unfortunate opening of a attachment, or clicking on an intriguing link leading to a fake or compromised website. The good news is that each individual (both within the professional environment and at home) is part of the solution; weird looking emails with typos or formatting issues, or random requests from other departments (for example, asking to urgently transfer an important amount of money to a third party) should raise suspicion and be double checked before moving forward.

Cybersecurity is becoming an increasingly challenging issue – and it is unlikely that the problem will disappear. I urge organizations to consider the topic at the same level as other fundamental business dimensions, such as financial viability. And whatever your role in your organization, you can definitely contribute to a more secure business environment, if only with "alert" behavior.

Reference

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Believe in RNAi

The gates for gene and cell therapies are open – and RNAi technology could be a serious contender for the therapy of the future.

By Geert Cauwenbergh, President and CEO of RXi Pharmaceuticals, MA, USA.

The discovery of RNA interference (RNAi) was regarded by the scientific community as a crucial advance – evidenced by the selection of RNAi as Science journal's 2002 "Breakthrough of the Year" and the fact that its co-discoverers, Andrew Fire and Craig Mello, were awarded the 2006 Nobel Prize in Medicine. RNAi has high specificity for targeted genes and high potency – and because of its ability to silence genes, RNAi is being investigated as a platform for the development of novel therapies by many researchers, including those in our company (co-founded by Mello).

Much like antibodies transformed medicine, I truly believe that RNAi-based therapeutics will be the next generation of medicine. In fact, I believe that 20 years from now, RNAi-based therapeutics will be at the forefront of approved treatments over antibodies. The exciting aspect of RNAi compounds is that they can potentially be designed to target any one of the thousands of human genes – many of which, such as transcription factors and targets that act by protein-protein interactions, are undruggable by other modalities. The overexpression of certain proteins plays a role in many diseases, so the ability to inhibit gene expression with RNAi is a powerful tool. RNAi drugs also offer key safety advantages in that they can achieve their effects without the need for permanent, and potentially dangerous, gene modifications.

"I truly believe that RNAi-based therapeutics will be the next generation of medicine."

But what is needed to help the field flourish? RNAi is a complex and challenging field of research. Although there has been significant progress in the clinical development of RNAi products, none have yet reached the commercial stage. RNAi needs a "first" to convince the market that previously identified roadblocks for successful RNAi therapy can be resolved. One of the most significant challenges has been the appropriate delivery of RNAi compounds into the cell type of interest. Chemically stabilized small interfering RNAs have been well explored but have demonstrated limited clinical efficacy. Some companies have used encapsulation in a lipid-based particle, such as a liposome, to improve circulation time and cellular uptake, but there are also compounds being developed with built-in delivery properties that do not require a delivery vehicle for local therapeutic applications. Our company is exploring the latter approach as we seek to develop RNAi-based therapeutics.

RXi's first clinical candidate, RXI-109, targets connective tissue growth factor, a critical regulator of fibrosis. A phase II clinical trial is underway to evaluate RXI-109's ability to reduce the formation of hypertrophic scars after revision surgery. An additional clinical trial is evaluating treatment with the same compound in patients with subretinal fibrosis associated with advanced wet age-related macular degeneration.

"I eagerly await the day when the first company – whoever that may be – gets an RNAi product approved."

We have also initiated an immuno-oncology program that will initially focus on cell-based therapies for the treatment of cancer. This approach builds on well-established methodologies of adoptive cell transfer, in which immune cells are isolated, expanded and processed to optimize their anti-tumor activity. We have developed an approach for the ex vivo treatment of adoptively transferred cells to silence immune checkpoint genes, and make the cells more effective in the immunosuppressive tumor microenvironment. We can target multiple immune checkpoints in a single cell-based therapeutic treatment that will hopefully come with fewer of the side effects associated with combination antibody treatments, while potentially providing similar efficacy.

I eagerly await the day when the first company – whoever that may be – gets an RNAi therapeutic approved. Whoever reaches the finish line first will stand in the media spotlight but, more importantly, will signal to the rest of the biomedical community that a new era in drug development has arrived.

Let Data Be Your Guide

Interest in new immunotherapies is increasing, but with complex drugs come complex analytical challenges. SPR-based systems can provide high-quality molecular interaction data to guide biotherapeutic development – from target selection to final QC.

By Fredrik Sundberg

Biopharmaceuticals with immune-mediated effector functions have become increasingly specific and potent when compared with naked monoclonal antibodies. As a result, the commercial interest in antibody drug conjugates (ADCs), bi-specifics, bioconjugates, and fc-fusion-based drugs, has grown in recent years. The latter example involves genetically engineering cells so that the antibodies they produce have an increased or decreased effector function (depending on the desired effect), or a longer serum half-life. The key is being able to understand whether you're making changes that deliver the right properties – and that requires analytics. Indeed, generating high quality data is vital to the development of all of these emerging drugs.

With ADCs, there are several challenges. ADCs are made up of an antibody, which targets the antigen or biomarker of interest, and a linker with a toxic payload attached. The antibody is internalized within the target cell, and releases the drug substance. Finding the right antibody, which tends to be more robust than classical antibodies, means screening for the right physiochemical properties, which affect glycosylation, reactive sites, stability and aggregation. Overall, the process conditions are more challenging for ADCs than for antibodies because you have to consider the antibody–drug conjugation reaction in addition to purification. You also need to control the drug antibody ratio (DAR) – a critical quality attribute for ADCs because it essentially defines the potency. It is also important to check these different properties at the beginning, middle and end of every step in the process.

The right tools in the toolbox

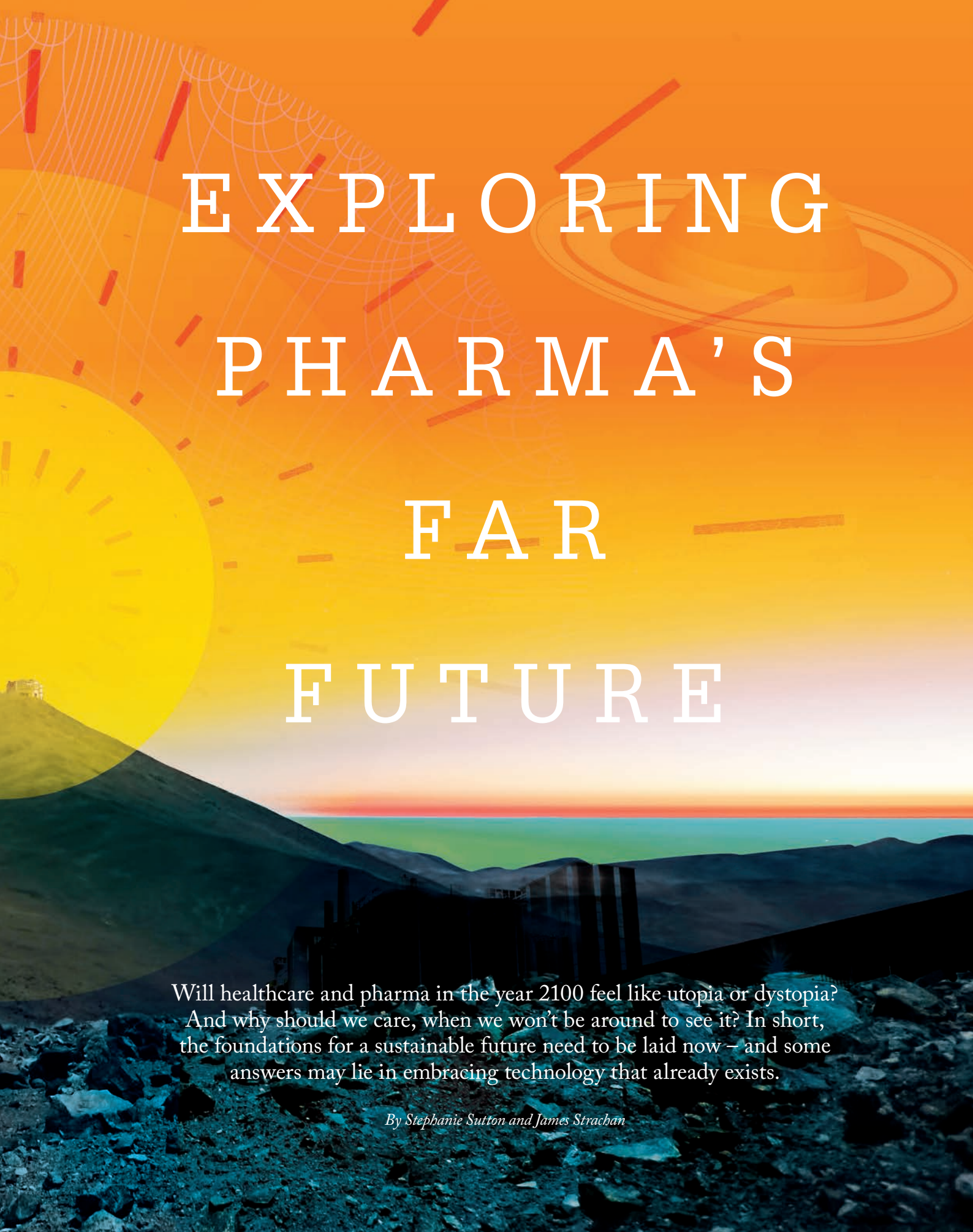
To address all of the above challenges, and when screening for "manufacturability" at an early stage, you need the right analytical tools. Of course, you can use classical chemical techniques, such as RP-HPLC, HIC, analytical IEX, or size exclusion chromatography, when looking at aggregates, DAR, and so on, but there are limitations. Newer techniques, such as surface plasmon resonance (SPR), can provide many benefits such as rapid analysis to address productivity needs and unique insight into binding events. One unique aspect of Biacore's SPR-based platform is the binding information it provides. You can monitor critical binding kinetics and conduct epitope mapping to characterize antibody structure/function throughout the entire workflow, from candidate selection to comparability assessment, to check the effects of, for example, linker on the function of the antibody. You can also ensure each modification made to the molecule doesn't affect binding, and look at ADC binding in lysosomal pH. It's a good starting point before looking at the potency of the molecule in a bioassay.

There are often multiple pathways that cause disease, and another emerging drug format, bi-specifics, allows two of those pathways to be targeted at once. In fact, blocking two target proteins with one single drug molecule instead of two may be more efficient as it can change the development timeline and, potentially, the dosing requirements. SPR-based assays allow you to assess the binding activity of bi-specific antibodies in a single setup, with either a bridging assay or dual-binding assay. The SPR-based assays are usually superior to other immunoassays in terms of precision, accuracy and specificity. These factors allow for stability studies, for example, to be carried out in real time – instead of hours or even days. They can also indicate function loss in a parallel analysis of both interactions at the same time rather than with two different ELISA-based immunoassays.

The Biacore system can be used as a "platform" technology, from early drug discovery through to quality control, even for more complex drugs. In other words, there is no need to perform any technology transfer between different assay formats, making validation and characterization easier, thus accelerating the time to market.

Newer forms of complex biologics have great promise, but at the expense of added complications, whether the conjugation reactions in ADC production or the need to simultaneously monitor multiple reactions in bi-specifics. There is a clear need to measure critical quality attributes from beginning to end – and how they affect binding. And that's where the SPR-based platform is at its strongest; it can provide molecular interaction data that guides the design of therapeutics with the desired binding properties, all the way from target selection to final quality control.

Fredrik Sundberg is Global Director for Strategic Customer Relations and Market Development at GE Healthcare.



EXPLORING PHARMA'S FAR FUTURE

Will healthcare and pharma in the year 2100 feel like utopia or dystopia? And why should we care, when we won't be around to see it? In short, the foundations for a sustainable future need to be laid now – and some answers may lie in embracing technology that already exists.

By Stephanie Sutton and James Strachan

Incredible advances are already shaping the medicine-making business. Cell and gene therapies are commercial realities; advanced research is revealing new avenues for drug discovery on a daily basis; and, in manufacturing, systems are becoming more flexible, automated and cost-effective. And yet, the challenges have never been so high – unsustainable drug costs, the threat of an antibiotic apocalypse, and calls for pharma to get drugs to patients faster, while retaining safety profiles. What kind of future awaits healthcare and the pharma industry?

Kaleidoscope Health & Care, a not-for-profit company focused on finding new ways of overcoming old barriers to improve health and healthcare, launched a thought-provoking writing competition earlier this year called "Writing the Future." The remit: imagine health and healthcare in the year 2100. Worryingly, nearly all entries had a dystopian vibe, highlighting tremendous concern that the remarkable advances being seen in science might not translate to happier, healthier lives for the many. In the winning story, OPSNIZING Dad, written by Elisabeth Ingram Wallace, long-term data storage makes it possible to preserve memories from family members. The narrator's father is preserved as a robot, but keeping that memory alive costs money – and the narrator is certainly resentful. Meanwhile, Andrew Dana Hudson's Mend and Make Do describes a future shaped by climate change and antibiotic resistance. The Oracle, written by Matthew Warren, tells the tale of an artificial intelligence that tells people what to do to ensure they live healthier, longer lives and how to mitigate the risk of developing illnesses, but the end result is a daughter devoid of human rights and unable to enjoy life. You can read the six shortlisted entries at www.kaleidoscope.healthcare/health2100.html.

The year 2100 may seem too distant for most to consider, but pharma has its role to play in aiming for utopia rather than dystopia. We speak with Richard Taunt, Founder of Kaleidoscope Health & Care, to find out why we need to start thinking and talking about our future.

Tell us about Kaleidoscope's competition...

We asked entrants to write a short science-fiction story of 3000 words or less about health and healthcare in 2100. The aim was to bring new ideas and creative thinking into conversations around health. We had 150 entries – so around 500,000 words in total (about five sci-fi novels worth). Fortunately, the general levels of creativity and quality were fantastic – the judging panel had a tough job narrowing down the entries to a shortlist of six (see The Shortlisted Six).

Why is it so important to think about the long-term future?

Our competition was very creative, but what we are really interested in is the ripple effect and getting conversations started about the future of healthcare – and those conversations could potentially affect what we do today. There are many challenges facing healthcare and medicine and we need to think about the future to ensure that it is sustainable. As part of the project, I spoke with Enrique Ruelas, who, in his work with the Mexican government, was often asked, "Can you modernize our heath service?" His reply was, "Yes, but modernize towards what?" In other words, where are we going? What does a modern healthcare system look like? What does a modern drug development industry look like? What will success look like in the future, and how do we ensure we can lay the right foundations today? We wanted the competition to get people thinking about what they do, and how it actually impacts upon the here and now, rather than some esoteric thing that will be left to future generations to sort out.

83 years may seem too-far a time point to consider, but it is closer than most people realize. Think of this – there is good evidence linking an adverse childhood on lifelong healthcare outcomes. If you undergo particular experiences when young, you will be affected for life. Most babies born today will live over the age of 83, so events today will still be having an impact in 2100. Moreover, the doctors and scientists trained today will train the doctors and scientists working in 83 years' time.

In other words, timescales in healthcare are very long. Often, companies in this sector think about health as a business run year on year, with perhaps a five-year plan or a 10-year plan. If you look at other industries, such as nuclear power, they use a 50 or 60-year timescale. In the UK, the government is building its HS2 high-speed railway line to reap benefits over 40 years. In both cases, it's clear that significant infrastructure needs significant forethought. Why don't we think about health and medicine in a similar way? We want to spark this type of conversation. If people actually start thinking about what healthcare will look like in 2100, then perhaps we can make some changes now that will positively shape the future. Right now, it feels as if we are flying blind – we're too busy firefighting in the present to focus on the future.

Why sci-fi?

In a previous role, I worked closely with Don Goldmann (Chief Medical and Scientific Officer for the Institute for Healthcare Improvement based in Boston, Massachusetts) and we often talked about what we didn't know – and how certain things

"If we are going to have a far greater range of ways to improve health, who actually gains access and what factors determine the equity of the future healthcare system?"

that seem perfectly natural today were unknown to previous generations. When looking back, there's always an air of, "How could they not have known that? It was so obvious!" As one example, consider surgery before anesthesia. Even at the time, it was known that there were substances that reduced pain, so how come it took so long to make the connection? Goldmann and I enjoyed discussing how future generations would look back and laugh at our follies and the obvious connections we had not made. It led to the question of how to crack open a debate about ideas we are not talking about. We concluded that those already working in health and healthcare were probably the worst people to ask, given how immersed we already are in one way of thinking.

At Kaleidoscope, we decided it would be interesting to welcome sci-fi writers into our conversations about the future; to get a handle on different realities. Science fiction is fiction, but it is important to get many ideas on the table to start discussions. Although science fiction is rarely an accurate portrayal of the future, it can certainly offer hints. Think of Alduos Huxley's Brave New World, published in 1931, where the citizens of London are kept sane with mood-altering medicine, and compare it with the use of antidepressants today. The point is not to provide and accurate picture of the future, but to start interesting conversations.

What were the common themes across the entries?

There was a common theme of 2100 being more plentiful in terms of information on your future health state at birth, more technology, a better understanding of medicines, and increased longevity. However, questions were posed about how "plenty" gets divided and what effect it has. If we are going to have a far greater range of ways to improve health, who actually gains access and what factors determine the equity of the future healthcare system? We're already seeing aspects of this today with increasing attention being paid to the cost of healthcare and drugs. Another interesting theme was how medical advances affect the family dynamic, with intriguing questions on parent-child relationships when you have more time at the end of life and greater information at the beginning of life.

IT'S GOOD TO TALK

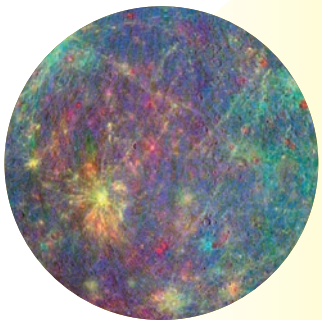
With Richard Taunt

I set up Kaleidoscope Health & Care in 2016. My background lies in working with governments and think tanks, and one concept that has always fascinated me is the great disconnect. Different sects are formed that do not really talk to one another. And when we do say we should talk to one other we often don't apply the same rigor and effort as we do in other activities. Kaleidoscope is about supporting collaborations and releasing knowledge. Even within a single organization, various departments often do not speak, resulting in trapped knowledge.

We have worked with a range of organizations, including Public Health England, NHS trusts, charities and others. We also run Melting Pot Lunches where we bring diverse groups of people together across health and care in energizing locations to talk about key topics. It's not so much about the topics but about getting people to form connections and start talking. If you get people with different perspectives together from management, pharma or healthcare, we hope they may start to see or do things differently.

We're always looking for creative ways to start new conversations and I think it's important to avoid death by PowerPoint. If you want people to have meaningful conversations, they need to feel energized, which is difficult to achieve if people are staring at a screen all day. In think-tank land, it's also common to put out massive masterpiece reports, yet we know few people read these. Our approach is all about face-to-face conversations. We're a not-for-profit and we seek to put as much of our learning as possible into the public domain.

The link between the sci-fi prize and our collaboration work is another energizing approach to start new conversations. We're really interested in working with people on finding new ways to crack open an old problem, and then debate and discuss what's required. If your standard method of discussing a topic is to have a conference, then you might need to find a new way of doing it.



THE SHORTLISTED SIX

Six entries in Writing the Future were shortlisted for the grand prize of £10,000. You can read the full stories at http://bit.ly/2gESZah.

Winner:

Opsnizing Dad, by Elisabeth Ingram Wallace

The winning story imagines a father held together by robotic limbs and LED eye-bulbs who is slowly losing his memory. The narrative deals with the emotional strain associated with having a dependent relative who can't express gratitude, nor remorse for past misgivings. Wallace explores the relationship between human emotional fragility – bitterness and resentment – with technology that may be able to preserve our existence, both in terms of our physical bodies and memories, indefinitely.

Runners up:

Mend And Make Do, by Andrew Dana Hudson

Hudson imagines the Isle of Ely in Cambridgeshire, UK, as an actual island – surrounded by seawater as a result of climate change. This dystopian world also faces an antibiotic apocalypse, with the story centering around a physician carrying out an environmental antibody survey. All hope is not lost, however, as a greater understanding of the relationship between health and ecology arises out of the desperate situation.

The Oracle, by Matthew Warren

In the words of "Genelytics" CEO, Blake Fox, The Oracle can "tell you exactly what you could do throughout your lifetime to ensure that is the longest, healthiest existence possible." Warren's story is a letter from a mother to her daughter, explaining why she put her faith in the Oracle: to reduce her daughter's chance of developing the lethal Fünder's disease. The reader is left wondering, was it all worth it? And when does living the "healthiest existence possible" entail tyrannizing loved ones – or even yourself?

Shortlisted:

Sticking Plaster for the Tin Man's Broken Heart, by Ida Keogh

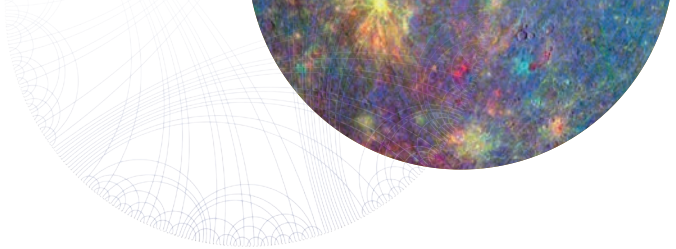
Keogh's story evokes Phillip K. Dick, and deals with inequality and access to healthcare. The protagonist is the prosthetic surgeon, Suki. Suki's young daughter – despite 3D printed limbs becoming widely available 36 years from now – is unable to get a replacement prosthetic leg because, as her dying friend Charlie puts it, "The biotech companies, the insurers, they're all in this together. If you don't have good insurance, you don't get good maintenance."

Project Seahorse, by Hannah Harper

After successive financial crises, an aging population, and a dwindling birth rate, the idea of "Male Motherhood" (MM) gained traction. The story follows the researcher, co-writer and art-director of the MM campaign, "Project Seahorse," and her efforts to build a promotional campaign around footballer Craig Brogan. Harper explores the relationship between pregnancy and parenthood, and paints a picture of a future in which the state and media exert control over pregnant male bodies.

Burnout, by Matthew Castle

Burnout explores the conflicting priorities faced by physicians: the need to diagnose and treat according to stringent targets, while being empathetic and caring, with good bedside manner. Castle's protagonist is an artificially intelligent physician, struggling to maintain meaningful emotional engagements with its patients, while pining for a six-month sabbatical.



"The vast majority of the stories we received were dystopian rather than proposing a rosy vision of where we want to go."

The pharma industry was portrayed quite negatively in some of the entries…

Many of the stories have large corporations playing a very significant role in healthcare of the future – for good or bad. Many views of the future have the state playing a very small role and big corporations having far more power. The upside painted in the stories is that you will have more innovation and technology coming through that will advance health and medicine well beyond where we are today. But there are questions about how some of those organizations use their power; some of it won't make happy reading for those working within the pharma industry! It highlights an interesting tension between the focus on innovation and advancing science, and real fears of social impact with very different standards of healthcare with different groups.

The vast majority of the stories we received were dystopian rather than proposing a rosy vision of where we want to go. The challenge for the industry is that these stories are born out of people and their perception of pharma today. Even looking outside of our competition, there aren't many stories where there's a benevolent role for large organizations. How do you shrug off that typecast and demonstrate that organizations who drive innovation also have a very clear social side? That's something for the pharma industry to address…

What's your view on healthcare in 2100?

I am interested in the sociology of medicine and healthcare. The culture of medicine has not changed fundamentally in a very long time. What I'm really interested to see is how roles for participants in healthcare – from doctors, to nurses, to drug developers – may change. In my optimistic view, we are moving towards a health system that will be far more connected (there is a significant connection between education and health for example), with the overall focus being on how people can live good lives rather than how we fix them when they fall over. Compared with 80 years ago, as a society we are much more aware of the wider determinants of health, which is fantastic. The challenge for the next 80 years is what can we do about it? How can we have a more joined up conversation about health

PRINT POSSIBILITIES

In Ida Keogh's "Sticking Plaster for the Tim Man's Broken Heart", 3D printing takes center stage. 3D printing (also known as additive manufacturing) is already being explored in a variety of ways within the pharma industry – from printing organs, to prosthetic limbs, and also components for biopharma machinery, which could lead to reduced costs.

"At GE Healthcare Life Sciences, we have recently opened a 3D printing lab in Uppsala, Sweden, called the Innovative Design and Advanced Manufacturing Technology Center for Europe. We think it is a very promising technology for engineering," says Andreas Marcstrom, Manager of Additive Engineering at GE Healthcare's Uppsala site. "If you look at the wider business of GE Healthcare, metals are a core part of the business but in life sciences polymers are very common because of single-use systems. We have been investigating the potential of both 3D printed stainless steel and various polymers."

The company hopes to use 3D-printed components in its biopharmaceutical systems. One of the benefits of 3D printing is that a traditionally complex part – perhaps made up of ten or more different parts welded together – can be printed as a single component, leading to faster build times and more reliability. It also opens up the possibility to make parts more configurable and customizable – and Klas Marteleur, Principle Engineer on the additive team, adds that the technology can bring environmental benefits and lower costs.

It is early days for the center – and 3D printing as a whole in biopharma. However, GE is already working with Amgen to test a 3D-printed, custom-designed chromatography column. "Right now, we are only just scratching the surface of additive manufacturing and how it will be used in the future," says Marteleur. "The biggest limitation is the minds of today's engineers. 3D printing is limitless in terms of the complex designs you can achieve, but today's engineers are trained in old-school techniques. It will take time for us to really understand what we can do with 3D printing. It won't replace all other techniques, such as injection moulding, but it's a good addition to the toolbox."

"It is a very exciting technology – and I can't imagine where it will go in the next 10 years, let alone 100 years! Certainly, we hope to see increasing use at GE Healthcare in Life Sciences," adds Marcstrom. "But 3D printing is not just limited to biopharma machines – I find the advances in the bioprinting of organs very fascinating. 3D printed ovaries have allowed infertile mice to give birth so we know it works and has potential. It will be a reality for humans one day."

But will it be affordable? Despite the dystopian vision presented in Writing the Future, Marcstrom and Marteleur are optimistic: "3D printing is generally very cost effective and the more the technology is used, the more the prices will come down. Overall, I would say this is a positive technology and I hope it will lead to positive things," says Marcstrom.

"The dystopian elements of the stories in Writing the Future stem from a system that does not support the outcomes we want."

and healthcare? And what else do we need to concentrate on beyond scientific and medical advances? I'm an optimist; I think we can get there, but changes will be needed in how people and organizations perceive their role, and how they relate to the wider economy – and this will take a long time.

The dystopian elements of the stories in Writing the Future stem from a system that does not support the outcomes we want. Rather than trying to think about who are the bad guys, we need to think about how we steer systems so that organizations and individuals are operating in a way that maximizes health and happiness for all, rather than mass inequality.

What happens next?

We are running events on the back of this competition, including a live reading of the stories at Europe's oldest operating theatre on December 5. We are also working with the Global Health Institute at Imperial College London. We want people to take the stories from our competition and to diffuse the information wherever they might be, using them as way to frame some of the challenges today. At Kaleidoscope, we also talk to organizations about the future – and we now have a rich treasure trove of visions of the future that we are able to analyze and delve further into. The six shortlisted stories are really just the tip of the iceberg in terms of the wonderful array of different ideas and visions that came through. We want people to take what we've done, reflect on what it means for them, and think about how they could use it to start discussions for their journey to 2100.

You can find more views on the long-term future of health and medicine at www.themedicinemaker.com. We'd also love to hear your ideas on how healthcare and the pharma industry could look in 2100 to kick start the discussion. Get in touch at Stephanie.sutton@texerepublishing.com.

TECHNOLOGICAL DISRUPTION

In a recent conversation, Daniel Kraft, Chair, Medicine & Neuroscience, Singularity University, California, explained to The Medicine Maker that it can seem as if the industry is stuck in the past. In some cases, blockbuster drugs only work for 25 percent of the population, for example, and precision medicine is not regularly practiced. But because healthcare has so many challenges, from health and prevention, to diagnostics, to therapy, to clinical trials, there are many opportunities to reimagine medicine with the tools that are exploding around us, such as AI and machine learning, machine printing, robotics, drones, and nanotechnology. Some of these are not new technologies but they are becoming increasingly powerful.

However, implementing new technologies is difficult when people are busy with their day-to-day work. Kraft believes that we don't need anymore new technologies per se, but that we need to connect the dots on the ones we already have. How could technologies like Amazon Echo or a Google Home help patients to understand their disease more and stay on top of their medication, for example? These tools are already being used to help people track their medication or make doctors' appointments. The connected home will likely become increasingly important to healthcare – and these changes are likely to be highly disruptive to the traditional biopharma industry. Perhaps it is time that biopharma looks beyond the pill – perhaps focusing on a digital wrapper that can help track or coach the patient through their disease by reminding them to take the medication.

There will always be a dark side to new technology – often explored in fiction. Today, advances in genetic modification, CRISPR and embryo modification are happening fast, and certainly, there are dystopian elements, such as the "Big Brother" element of having health tracked 24/7. In the next decade or so, Kraft hopes that we can make medicine smarter, more proactive and personalized, where an understanding of genomics and risk factors guide smarter, proactive health. Statins are already given to people with high cholesterol risk, or at high risk for cardiovascular disease, and perhaps one day there will be medicines suitable for those at risk of Alzheimer's disease. Could we even hope for an era where disease is treated at stage 0 so that it never presents clinically?

INTELLIGENT DRUG DISCOVERY

One technology likely to play a role in pharma's future – and that frequently came up in Writing the Future entries – is AI. Artificial intelligence is already being explored as a means towards making better informed decisions, generating new hypotheses and repurposing failed drug candidates.

With Jackie Hunter

Pharma must be the only industry on the planet with a 98 percent failure rate. One recent study found that 52 percent of drugs terminated at phase II or III were because of a lack of efficacy (1), which tells me we're either not getting the right molecules or not getting the right targets – I believe the latter is more likely. Worryingly, the study also found that 25 percent of terminations were due to strategic or commercial reasons, which suggests the industry is also not very good at making key decisions.

Having spent most of my career in the pharma industry – working for GSK and running a center of excellence for drug discovery, – I've seen first-hand how decisions are made without having access to all the available evidence, often relying on people's narrow perspectives. Knowledge is incredibly important, yet our ability to mine it is limited.

Artificial intelligence bridges that gap rather well. It can enable the industry to use evidence without bias, enhancing our ability to make good decisions – this is the essence of Benevolent AI.

We have built an AI platform that can crawl through scientific papers, patents, and structure databases, and recognize and ground certain entities. Based on a dictionary we compiled, the platform can recognize, for example, that CB2 is a cannabinoid receptor (and not a postcode in Cambridge, UK!). It then uses natural language processing to look at the sentences and paragraphs to identify a relationship between one entity and another: is this receptor related in any way to a certain enzyme? Does gene X downregulate protein K? The AI can also determine that "AD" in the context of one paper referring to "atopic dermatitis," but in another context referring to "Alzheimer's disease." We take all that known information to build a knowledge graph consisting of over one billion relationships. The idea is to ask, given this known information, what can be inferred about what should be known, but currently isn't. Essentially, the platform is a hypothesis generator, whereby we can link new targets and molecules to different diseases. It also allows us to mine for negative information, which quite often only appears in very obscure journals or meeting abstracts. Once we have a hypothesis, the scientists can see if it makes sense, and then investigate it. It augments the ability of a scientist to come up with new ideas – using information from outside of their limited sphere of knowledge.

Typing a disease into the platform will pull up hundreds of clinical trial results, thousands of related diseases, thousands of molecules, as well as symptoms and potential targets – and this only takes a few minutes. We're currently collaborating with experts to validate some hypotheses, and we're looking to see whether we can repurpose drugs or start our own drug development programs.

Doing things differently

Our platform is just one example of how AI can be used in pharma, but we can't change the industry by ourselves. I think often the issue of being slow to adopt new technology in pharma isn't tech readiness, but people readiness. There are a lot of organizational structures that have been built up within pharma and they must be deconstructed to allow some of these emerging technologies to flourish. I've been through a couple of mergers in pharma and you need strong direction from the top to say, "This is how it's going to be done differently." Without the support of leadership, things stay as they are.

It's always going to be difficult to change things from within and that's why we've created a completely different structure at our company. We have cross-functional teams with drug developers, engineers and data analysists all working together. We like to see ourselves as "discoverers," as opposed to "tech people" or "engineers." Sometimes it's hard for people to get their heads around these latter terms as applied to drug discovery.

Having said that, AI is already an integral part of healthcare. People track and analyze the data generated by wearable tech, and AI is being used to stratify patients for personalized medicine. In addition, pharma companies are increasingly thinking about how they might investigate the data that they generate – especially from previously unsuccessful compounds.

With any new technology there are always people concerns. For example, there is always concern that technology and automation may take people's jobs and livelihoods, but the 98 percent failure rate demonstrates that pharma's current model is unsustainable. The increasing number of mergers we are seeing isn't the solution – we need more innovation. In my view, the only way we're going to become more innovative is to mine and use data more effectively.

Jackie Hunter is CEO at BenovolentBio, the bioscience arm of BenovolentAI.

Reference

1. *RK Harrison, "Phase II and phase III failures: 2013-2015", Nat Rev Drug Discov, 15, 817-818 (2016). PMID 27811931.*

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WHERE ARE WE GOING?

Joe Flower is a healthcare futurist who has built a career around helping companies prepare for the future. Here, he shares where healthcare and pharma should head, if we want to avoid a dystopia.

How did I become a healthcare futurist? I was a failed poet, desperate to make some money, somehow, from my highest skill, which was writing. My wife said, "Why don't you try this?" I said, "I don't know anything about healthcare." She said, "All you have to do is learn the acronyms."

There was definitely a lot more to do than learn acronyms… but the work that bloomed from that dinner table conversation now spans 37 years, half a dozen books, and thousands of articles. Once I got into it, I found it fascinating, from the bloom of new technologies, to the passionate personalities, to the enormous problems. I learned about healthcare by writing and reporting about it, by interviewing thousands of experts, practitioners, executives, and pharmaceutical scientists across the globe.

It was 20 years before I could truly say that I understand how healthcare actually works, and why it works so poorly. Right now, the system is a mess that leads to hundreds of thousands of unnecessary deaths in the US alone, while bankrupting individuals and society at the same time. I began to see that I could, just maybe, make a difference if I could help people inside and outside the industry learn about how healthcare has become so different from what we all hoped for.

How we run healthcare is a life and death issue for every human who owns and operates a human body. Yet we have managed to design our healthcare systems as a strip mine for our individual and private interests – more so in the US than elsewhere, but far from exclusive to us. It is easy to see countless policy, funding and innovation decisions up and down the line that serve the narrow interests of the people making the decisions and outsourcing the cost to society. Look up "corruption" in the dictionary and you will see no daylight between that and much of what goes on in healthcare – all under legitimate legal cover because we built the system that way.

Knowing the future

To paraphrase JBS Haldane, the future will not only be queerer than we suppose, it will be queerer than we can suppose. If you look back at the futures forecast in science fiction and by expert futurists over the last century, you find only one important innovation that really came true: Isaac Asimov's description of communications satellites. Consider the technological innovations that have become mainstays of our lives – like the smartphone I am dictating this into, and Google, which just told me how to spell JBS Haldane – not only did they not exist 20 years ago, they were not even imagined.

Every prediction of the future will likely turn out to be wrong, but what we need is deep, systemic, complexity-based futurism that explores the emerging possibilities in a rigorously flexible framework. If we learn to do this as a normal part of running healthcare, imagining and responding to the systemic consequences of any policy change, invention, or funding shift, then we can imagine a future that is as different from our own as we are today from medieval alchemy. If we don't, then any dystopian future you can imagine is far more likely. I believe that the following points are essential:

- We must know the future. The changes that are coming are larger and of wider scope than we can possibly imagine or prepare for.
- We can't know the future.
- We must anyway. We must gain insight into the future, by building the deep and constant discipline of studying its emerging elements and their interactions, using the insights and methods of complexity science, behavioral economics and other fields.
- Futurism is a craft that can be learned, and should be learned and practiced by anyone who hopes to lead organizations into the future.

The will to change

Certainly, there are a number of key technologies that are almost certain to play a part in shaping the future. I believe that AI will become as ubiquitous, as easy to access, and as taken for granted as electricity is today, and will super-power all medical information gathering and decision-making. Blockchain will also likely drive transaction inefficiency toward zero. However, there are thousands of emerging innovations right now that could produce astonishing outcomes (and it's easy for any futurist to pull some of these shiny things out of their magic bags and wave them around). The real study needs to be how these new technologies work within the system of healthcare. Vaccines are probably the single most effective medical advance ever. Yet we did not eradicate smallpox because a new vaccine had been invented; we eradicated smallpox when we realized that we could do it, set ourselves to doing it, and gathered the global political will, social drive, funding, and army of volunteers to carry it out.

If healthcare and drug development are to be sustainable in the future, then one important change is to economically

"I believe that AI will become as ubiquitous, as easy to access, and as taken for granted as electricity is today, and will super-power all medical information gathering and decision-making."

disconnect the development and patenting of new compounds from the marketing and distribution of drugs. In our current model, compounds are developed, translated, and tested so that they can become big sellers and support a company for years. This means that promising research is often abandoned if it does not seem to immediately produce a compound with a large market. At the same time, life-saving drugs with profound implications for millions (such as the recent cure for Hep C) come with high price tags. This model does not produce pharmaceuticals that are well-matched to the real needs of the society at a price that the society can afford.

Pharmaceuticals are not optional luxury items. They are fundamental to keeping people alive. They are a part of the infrastructure of any modern society, and we should fund them that way. In the US, we did not build the Interstate Highway System by letting private companies decide which would be the most profitable routes and leaving them to get the land rights to build them. The government decided the routes and put together the funding, then hired private firms to build them.

We need an industrial policy for pharmaceuticals. Drug development should be driven by government groups (such as the US NIH or the UK NHS) deciding priorities and picking promising areas of research, then letting large grants for research into promising compounds and approaches. The results of all research should be made public, with the government retaining patents to any discoveries. The government license all comers to market and distribute the resulting drug. The pharmaceutical companies make their money by doing what they do best: the research and development, then marketing and sales. The government does what it does best, allocating resources for the good of society.

Joe Flower is a Healthcare Futurist (www.imaginewhatif.com).

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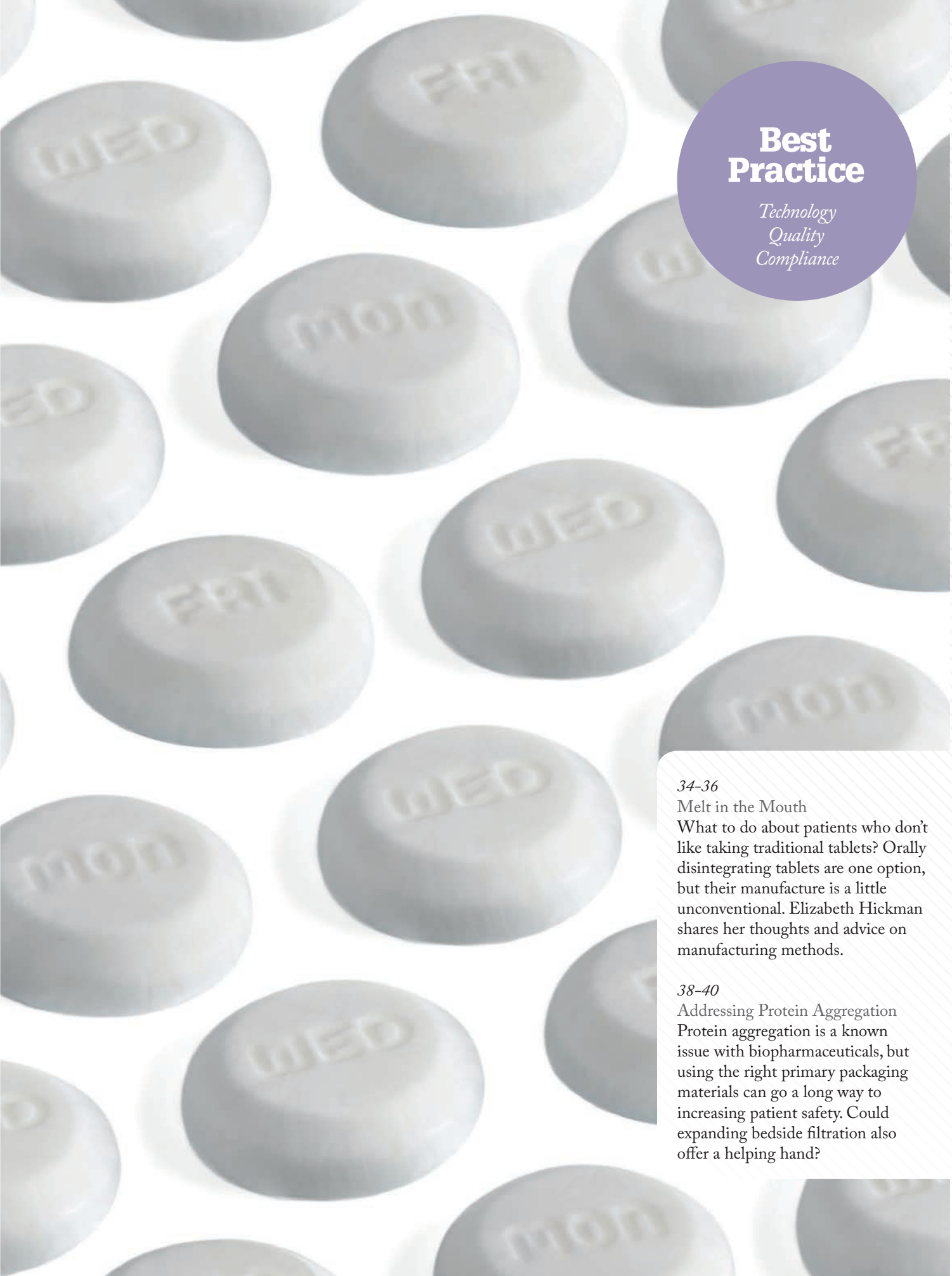


Best Practice

Technology
Quality
Compliance

Melt in the Mouth

Orally disintegrating tablets are winning patients over thanks to ease of use, but manufacture is unconventional, which raises a number of challenges and the need for careful consideration.

By Elizabeth Hickman

Though tablets are the most common dosage form, some people have an aversion to – or even fear of – swallowing them. In the mid-1990s, orally disintegrating or dissolving tablets (ODTs), began to appear on the market. Dissolving rapidly when placed on the tongue, the ODT is a convenient dosage form for many groups of people, particularly those likely to have swallowing difficulties, such as mental health, geriatric or pediatric patients. But they are also good for people who simply do not like taking tablets, for whatever reason.

ODTs typically have very good shelf life and do not require refrigeration, which simplifies transportation and storage. Additionally, as the drug is absorbed via the mucous membrane within the oral cavity, it avoids first pass metabolism in the liver and provides rapid onset of action. For that reason, ODTs are particularly popular for therapeutic categories where very quick relief is preferable, such as painkillers, treatments for gastrointestinal disturbances, and anti-allergy medications.

The ideal ODT should be both physically and chemically stable, and not too large – typically, about 500 mg is the maximum size. The tablet should disintegrate completely within the mouth in no more than 30 seconds, and should give no unpleasant sensations, whether that is an offensive taste, a gritty texture, or a burning sensation in the mouth or throat. To overcome these challenges, formulators generally opt for either a loosely compressed ODT or a lyophilized ODT. With each method, there are some specific considerations to bear in mind.

Loosely compressed

The loose compression process for manufacturing ODTs is not that dissimilar to producing traditional tablets. As well as the active, three main functional ingredients are required for a loosely compressed tablet to impart rapid disintegration: super-disintegrants, effervescent agents and soluble agents. Super-disintegrants, such as sodium starch glycolate, crospovidone or croscarmellose sodium, will either swell or wick up the liquid on contact with the saliva, disrupting the tablet's structure and encouraging dispersion. The effervescent agent is commonly sodium bicarbonate in conjunction with an organic acid – normally citric or tartaric acid. Contact with saliva causes effervescence and, again, affects the structure of the tablet. Soluble agents, such as xylitol or mannitol, should be included to assist with tablet disintegration in the mouth.

Numerous other excipients can also be added to impart specific properties, such as sweeteners, colors and flavoring agents. Excipients that aid in the direct compression process are also beneficial in formulation development, such as fillers, lubricants and binders. However, some additional ingredients, though necessary in certain formulations, can impede disintegration; for example, high levels of lubricant.

The particle size must also be carefully considered; if it is too large the tablet may give a gritty and unpleasant mouthfeel as it disperses. The key processing parameter when manufacturing loosely compressed ODTs is the compression force. ODTs are compressed at much lower forces than traditional tablets. If the force used is low, it may improve the disintegration properties of the final tablet, but it is likely to result in an extremely friable tablet that may fall apart in transit or when handled. At the other end of the scale, if the compression force is too high, the tablet will be more robust, but disintegration could be affected. To that end, choosing the most appropriate compressible excipients to balance the strength and dissolution properties is extremely important.

Recent developments in loosely compressed ODTs include specifically designed highly compressible excipients. Excipient blends formulated to enhance

disintegration are also available from a range of suppliers. Indeed, several providers offer blended excipients in a ready-to-use form for the creation of loosely compressed ODTs, including F-MELT from Fuji Chemical Industries Co., Ltd, which combines inorganic excipients and disintegrants with a carbohydrate complex. Another commercially available mixture, Ludiflash from BASF, is a mix of crospovidone, polyvinyl acetate and mannitol.

To manufacture a loosely compacted ODT, the usual method involves the drug active being blended with the excipient mixture and then moistened with a solvent (usually water or ethanol). This is then molded into a tablet via low compression. A step in which it is treated with heat or air should be carried out to remove excess solvent, and in some cases, promote a solid-state excipient phase transformation, which increases the hardness of the tablet.

Freeze drying

Lyophilized ODTs do not rely on super-disintegrants to provide rapid dispersion; instead, rapid disintegration results from the way in which they are manufactured and the formulation of excipients. For example, an ODT may use gelatin to form the overall tablet polymeric structure, in combination with mannitol, to increase robustness and attractiveness. Both ingredients dissolve readily in saliva, giving a quick-acting, melt-in-the-mouth experience for the patient. The active and excipients are all dissolved, or suspended if they are insoluble in water. The solution (or suspension) is then dosed into blister trays, before being frozen in a liquid nitrogen freeze channel. The blister trays are then lyophilized. Lyophilization involves the sublimation of ice crystals from within the formulation, leaving behind a network of air pockets within the tablet's structure. The porous matrix of gelatin, mannitol and active ingredient that forms the ODT will be left behind.

The porous structure formed during lyophilization is key to achieving rapid disintegration. The highly porous nature of the tablets allows saliva to wick into the tablet and cause disintegration. As with a loosely compressed ODT, a range of other excipients can be incorporated to impart specific properties, including taste masking agents, sweeteners, flavors and pH modifiers. With careful formulation, the creation of a dosage form that is easy and pleasant to take should be possible. The most critical excipients are those that form the porous structure – the gelatin and mannitol. While the freeze drying process is under way, it is important to ensure that all of the mannitol remains crystalline in the finished dosage form, or there will be a risk that it will collapse on storage. Using the optimal conditions for freezing is crucial. If the tablets are frozen too quickly, then small ice crystals are likely to accumulate, which will affect the ODT's porosity.

"Many drugs have an unpleasant taste and taste masking is therefore necessary to obtain a palatable formulation."

One of the key challenges when working with an ODT is taste masking. Many drugs have an unpleasant taste and taste masking is therefore necessary to obtain a palatable formulation. Taste masking can be achieved by three main principles: covering the unpleasant taste sensation with a pleasant one, preventing contact between the trigger molecule and a patient's taste receptors, or by inhibiting the taste receptor response.

Traditionally, taste masking a lyophilized ODT was a challenge due to the resulting particle size formed by the coated particles leading to a larger tablet, but it is now possible to achieve taste masking on tablets up to around 400 mg by coating the outside of micronized API particles in a vessel that is equipped with an acoustic vibrator. These particles can be as small as 100 µm in diameter. Additionally, the process does not require solvent, leading to process improvements. As an alternative, the active ingredients can be held inside cyclodextrin molecules, which prevent them from touching the taste receptors on the tongue.

From jabs to tabs

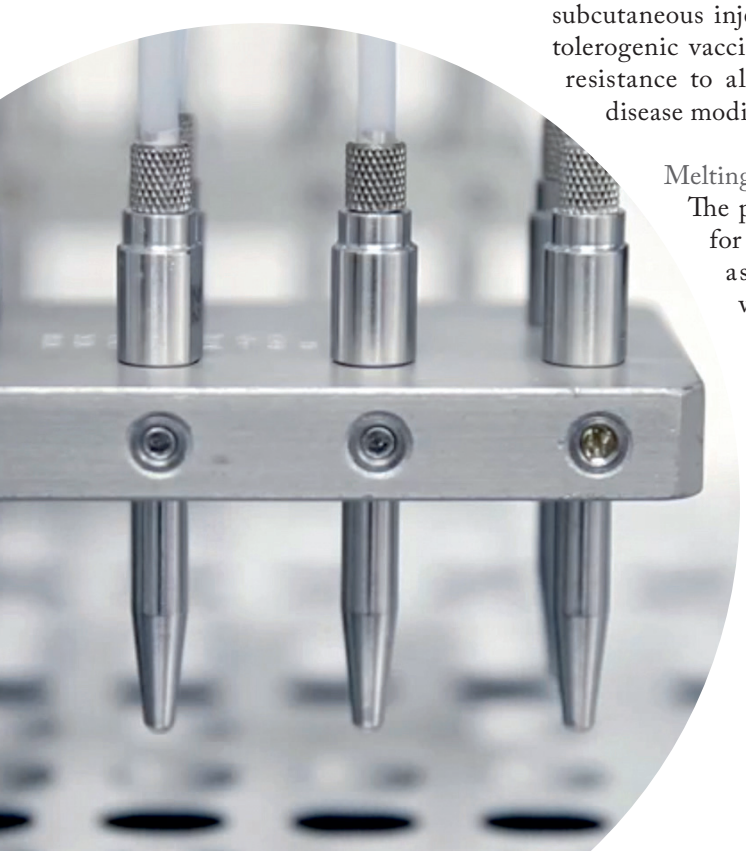
Other recent developments include the ability to create stable oral formulations of vaccines and other protein and peptide drugs, traditionally administered by injection. Moving from an injectable dosage form to an ODT can improve patient compliance, especially for pediatric populations. Additionally, the creation of a stable room temperature dosage form provides cold-chain advantages, especially for developing countries. Some ODT platforms can also enable the sublingual or buccal delivery of biologics, such as peptides, proteins, allergens, and vaccines in an ODT formulation. There are no extreme pH exposure or proteases in the oral cavity and this route avoids the harsh environment of the gastrointestinal tract. For vaccines, this technology offers the potential to eliminate cold-chain storage, and can be beneficial

Manufacturer	*Brand*	*Active Ingredient*	*Indication*
Aptalis/ GlaxoSmithKline	Lamictal ODT	Lamotrigine	Epilepsy and bipolar disorder
AstraZeneca	Zomig ZMT	Zolmitriptan	Migraine
Bayer	Claritin RediTabs	Loratadine	Allergy
Eisai Co.	Aricept ODT	Donepezil	Alzheimer's disease
Eli Lilly & Co	Zyprexa Zydis	Olanzapine	Schizophrenia and bipolar disorder
Ferring Pharmaceuticals	Nocdurna	Desmopressin	Nocturia
GlaxoSmithKline	Zofran ODT	Ondansetron	Nausea and vomiting caused by chemotherapy
Reckitt Benckiser	Nurofen Meltlets	Ibuprofen	Pain
Valeant Pharmaceuticals	Zelapar	Selegiline	Adjunctive therapy for Parkinson's disease

Table 1: Examples of approved ODTs

for mass immunization programs and emergency response. Our platform uses a lyophilization process with low processing temperatures, and there are formulation options to optimize in-process stability such as through matrix component selection or pH adjustment. The dried product has low water activity to ensure long-term stability.

As an example of a marketed biologic ODT, Danish pharmaceutical company ALK-Abelló launched Grazax as a patient-friendly allergen immunotherapy for the treatment of grass pollen-induced allergic rhinitis. Patients previously had to make monthly visits to the clinic for their subcutaneous injections. Grazax is a tolerogenic vaccine, which increases resistance to allergens and can be disease modifying in patients.



Melting innovation

The production processes for ODTs can be seen as costly compared with traditional tablets and capsules, but actually the difference is not so great – especially when considering the advantages of ODTs – ease of use, rapid onset of action, easy dosing properties and wide acceptance by patients. Perhaps the biggest drawback of ODTs right now is their limited ability to incorporate higher concentrations of active drug, but this is improving with research. New manufacturing techniques are also emerging. For example, a new type of ODT was introduced in 2015 based on 3D printing. Antiepileptic levetiracetam, under the brand name Spritam, is manufactured using Aprecia's ZipDose technology. ZipDose "prints" multiple layers of drug powder, tightly packing them together into a porous, water-soluble matrix. The process creates a high dose tablet (up to 1000 mg) that dissolves instantly with just one sip of liquid, which breaks the bonds formed during the printing process. Taste masking technology can also be applied.

Another alternative to ODT is thin film strips – a delivery technology that can be used for both systemic and local action via several routes of administration including oral, buccal, sublingual, and even ocular and transdermal routes. The technology is considered easy to swallow, self-administrable, and fast dissolving. However, application of film strips is somewhat limited as the maximum dose that can be formulated for delivery is in the 20–50 mg range.

ODTs are still relatively new – the FDA approved its first ODT in December 1996 – but with manufacturing costs coming down and increasing calls for more patient centric medicines, we can expect more ODTs in the future. Perhaps one day the industry will soon be able to create ODTs for immunogenic vaccines, helping to reduce reliance on injectables – and representing a significant advance for patients.

Elizabeth Hickman is Strategic Marketing Director, Oral Drug Delivery, at Catalent Pharma Solutions, NJ, USA.

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Addressing Protein Aggregation

The formation of protein aggregates in biopharmaceuticals can be difficult to predict and control. Here's how we can improve patient safety through primary packaging materials and bedside filtration.

By Benjamin Patrick Werner and Gerhard Winter

Biopharmaceuticals possess the capability to treat severe illnesses and can generally be considered as relatively safe, but despite stable formulations resulting in high product quality, the formation of protein aggregates can occur for a number of reasons, including chemical or physical degradation, such as oxidation or denaturation (1). Aggregates can be small and soluble or grow into larger particles. Other factors that contribute to particle generation include light, shearing, shaking or temperature (2-4). The majority of protein drug products will encounter most of the above mentioned factors at some point during their production cycle and shelf life – and the risk associated with these protein aggregates is that they can endanger drug safety and efficacy (5, 6). Immune reactions caused by non-native protein species have been known about since the 1950s (7). Despite many improvements in the generation of recombinant proteins, such as fully humanized proteins or sequence modifications, it is still rather common to detect the formation of anti-drug antibodies in the blood of patients treated with protein drug products because of protein aggregation (8, 9).

In the majority of cases, anti-drug antibodies only have minor clinical relevance, but severe events – anaphylaxis, serum sickness or life-threatening cases like the neutralization of an endogenous protein – can occur (5, 10). Furthermore, beside proteinaceous particles, a protein drug product can contain other particles, such as silicone oil, glass microflakes, rubber, plastic or metal (11-13). Combined particles, such as non-proteinaceous particles covered with native or non-native protein species, can also be formed. Some of these combinations, like protein adsorbed to silicone oil, are known to trigger an immune response (14). However, with the immunogenic potential of each of the possible particle subgroups, one could theoretically encounter in a protein drug product that is not yet known, and unlikely to be clarified in the near future.

Although the correlation between immunogenicity and protein particles is commonly accepted, plenty of other factors, such as the immune status of the patient, dose, dosing frequency or route of administration, also play a role (7, 15-17). Handling, transportation and storage of the drug after the drug product release by the manufacturer can also impact product quality (18).

The problem with packaging

It is important for biopharmaceutical manufacturers to consider how primary packaging materials impact product stability, particularly for sensitive biopharmaceuticals. Protein drug products are generally filled either in vials, syringes or cartridges made of borosilicate glass (18). For glass syringes

and cartridges, silicone oil is necessary to enable smooth gliding and low break-loose forces for injection. The problem with silicone oil is that it can contribute to the particle burden of the product by shedding from the glass barrel and is also a known agent that fosters the formation of protein aggregates (13, 19). Silicone oil microdroplets derived from prefilled syringes can also act as an adjuvant leading to induction of anti-drug antibodies (14). Although multiple techniques, such as baked on or cross-linked siliconization, exist to reduce the amount of free silicone oil in glass syringes (19, 20), interactions still occur between the silicone oil and the protein solution.

Eliminating silicone oil could be seen as beneficial, but alternative materials would be needed. One option is to use plastic syringe barrels made of cyclic olefin (co-) polymers. Several major syringe manufacturers have these polymer-based syringes in their portfolio, but only two systems are completely free of silicone oil (21) – both use new coating technologies for the stoppers that enable functionality without silicone oil. For the storage of biopharmaceuticals, this is a major advantage and it has been shown that the particulate burden of a solution can drastically be reduced in silicone oil free polymer syringes (18). Further, these syringes can be produced without tungsten and glue in the case of staked needles, eliminating other potential complication (22-24). A major shortcoming of these syringes might be their higher oxygen permeability in comparison to glass (25), but simple modifications may overcome the problem; for example, designing syringes with multiple layers that possess higher gas barrier properties. Cheaper solutions include using oxygen-tight labels or sealing the syringe in a gas-tight aluminum bag (26). So far, these syringes have not been evaluated for the long-term storage of oxygen-sensitive biopharmaceuticals, but we are currently investigating this topic. For the moment, we can confirm other reports about lower particle counts in polymer-based syringes. Oxygen permeability is also controllable with easy modifications, as our study has shown.

"Our concept is based on an expansion of already used bedside filtration to a much broader range of products."

Increasing patient safety

Although improvements on the primary packaging side may lead to better products, no one can guarantee that the quality of every single drug container, particularly in regards to the overall particle burden and the nature of the aggregate type, is the same. We would like to propose an approach that should be easy to implement and that has the capability to reduce a potential risk for patients from particulate matter to a minimum.

Our concept is based on an expansion of already used bedside filtration to a much broader range of products. This should provide increased safety to every single container. To support our idea, we carried out a survey analysis on more than 300 marketed protein drug products. We found that 16 percent of them are already filtered during bedside preparation and administration of the drug. Only a handful of drugs had explicit statements not to use filtration (27), so there is great potential to expand bedside filtration. Today, regulatory authorities require greater monitoring of particles in the low micrometer range – and more of the recently approved drugs are filtered. Our analysis also revealed that specific recommendations for filtration are rare and the user is often left alone at this point. If specific instructions were included, polyethersulfone membranes with a pore size of 0.2 µm were the most commonly used (27).

Using a filter with a pore size of 0.2 µm has several benefits. First, these filters are broadly available and commonly used in clinical settings, enabling easy, quick and cheap distribution. Second, these filters remove most particles above 0.2 µm as our data show. Third, another final sterile filtration is carried out. With that, the patient benefits from other effects of bedside filtration, including reduced occurrence of infection, sepsis or thrombi (28).

A change to more frequent usage of bedside filtration will not occur overnight. So, the question of how to establish common routine bedside filtration remains. A start would be to integrate the filtration step into processes where several handling steps are already necessary. For example, the preparation and administration of lyophilisates, include addition of the solvent, swirling the vial until complete dissolution of the powder, inspection of the vial for particulates, aspiration into a syringe, change of the needle, and finally administration. Other applications with several handling steps include multi-dose vials or mono-dose vials where the solution needs to be aspirated into the administration syringe. Also in the case of infusion, a filter proximal to the patient can be easily included (29).

Our work has shown that filtration has huge potential for eliminating protein aggregates for multiple relevant protein drug products, and we have not encountered problems such as protein adsorption or denaturation. Although our data show that filtration is easily

possible, the filtration process has to be further improved with the help of the filter industry. New filter designs with lower hold up volumes and filtration areas are necessary to expand the concept of bedside filtration to smaller volumes. Filter cleanliness has to be assured by the filter manufacturers, which includes not only the particle burden of the filters themselves, but also extractable and leachable profiles, which are partly lacking (30). Based on the generated experimental data, which will be published soon, we believe that bedside filtration can contribute significantly to patient safety.

It is important to emphasize that the quality of today's protein drug products is very high. Our proposal for an expansion of bedside filtration is not an attempt to cover any shortcomings in product development or manufacturing, but an immediate opportunity to further improve the safety and efficacy for patients.

By Benjamin Patrick Werner, and Gerhard Winter Professor, both in the Department of Pharmacy, Pharmaceutical Technology & Biopharmaceutics, Ludwig-Maximilians-University, Munich, Germany.

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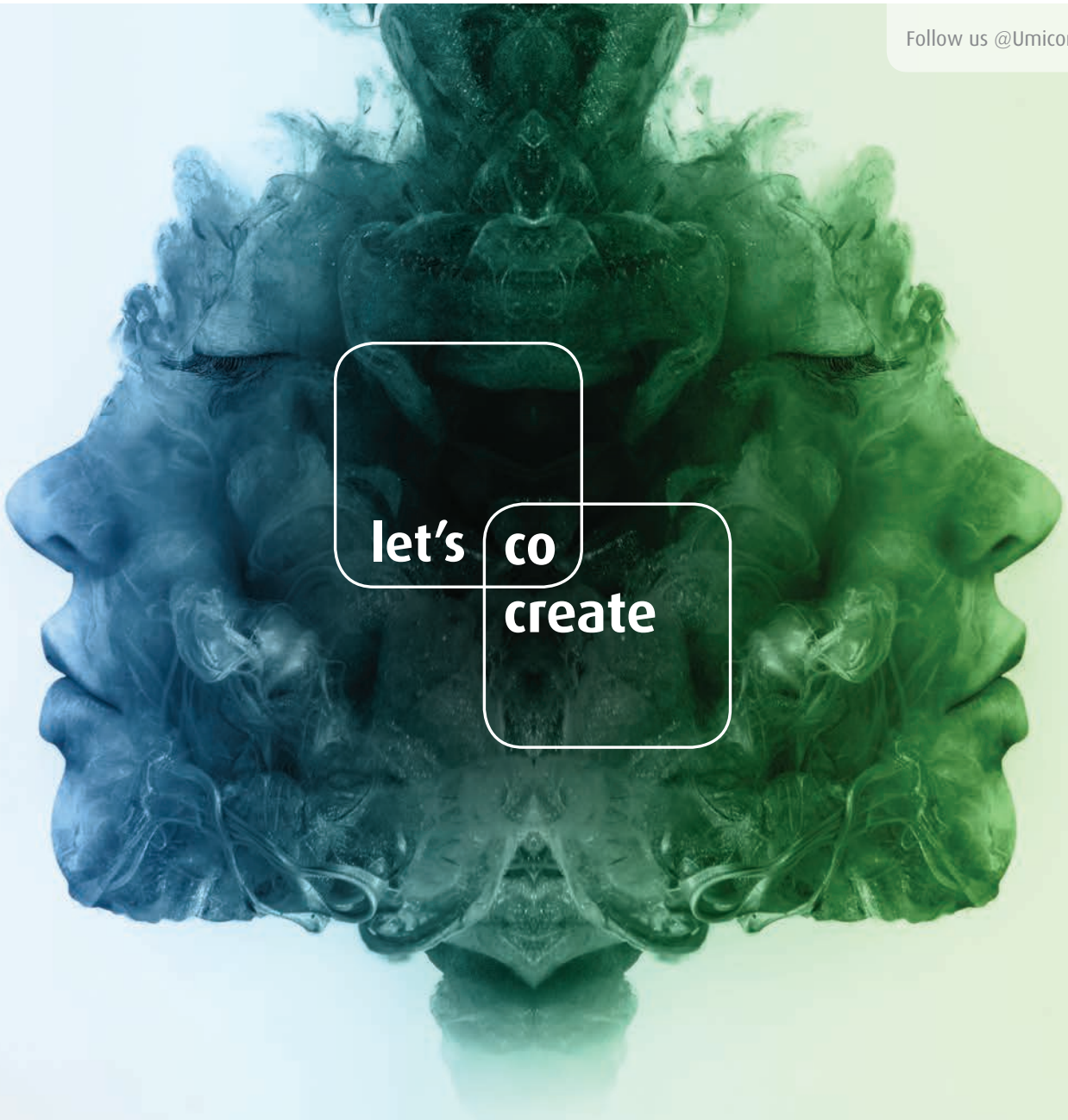

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Coming in From the Cold

Lyophilization has changed little over the last 75 years, and the pharmaceutical industry has struggled to address the known inefficiencies of this old technology. Now, a new consortium has been founded to provide a risk-free environment to help advance lyophilization instruments and processes. Is freeze-drying finally heating up?

By James Strachan and Nick Miller

Lyophilization is an essential pharmaceutical process, but it is considered time-consuming and expensive. The LyoHub consortium, based at Purdue University, Indiana, USA, hopes to change that by advancing the science and technology of freeze-drying. Other members include the University of Connecticut, IMA Life, Pfizer, Janssen, Millrock, Inficon, Baxter, SP Scientific, Allergan, Abbvie, McCrone, Roche, Pfanstiehl, Siemens PLM Software, Fresenius Kabi and Bristol-Myers Squibb. Importantly, LyoHub is not just a talking shop; it has developed a unique demo facility, located in the Birck Nanotechnology Center in Discovery Park, on Purdue University's campus, where consortium members can test new lyophilization processes in a low-risk environment. LyoHub also aims to be an important information depository about lyophilization processes and training. One of their most recent achievements is the publication of the LyoHub Lyophilization Technology Roadmap (1) – which over 100 experts contributed to. The Roadmap aims to identify advances that are needed in lyophilized products, lyophilization processes and equipment, the regulatory interface, and workforce training and education.

To find out more about how freeze drying is entering the 21st century, we talked with two of LyoHub's founders, Alina Alexeenko (a professor in the School of Aeronautics and Astronautics at Purdue) and Elizabeth Topp (a professor of Industrial and Physical Pharmacy at Purdue).

How was LyoHub formed?

Elizabeth Topp: Alina and I are an interesting combination. My background is in engineering, so I have an affection for the process side of things, but my current focus is on the product side, particularly the behavior of lyophilized formulations of proteins. But Alina is a process person – she started out as an aerospace engineer with an interest in computational fluid dynamics. She became interested in lyophilization because its high vacuum/low temperature flow regimes are very similar to those seen in rocket propulsion in outer space. We joke between ourselves that lyophilization really is rocket science! When I came to Purdue, we started collaborating and, soon after, Alina proposed developing a consortium to bring together multiple collaborators and achieve more than we could as individuals. Today, Alina and I lead the consortium, but the leadership team also includes Michael Pikal, a professor of pharmaceutics at the University of Connecticut; and Steve Nail, senior research scientist at Baxter Biopharma Solutions.

Is lyophilization yesterday's technology?

ET: It is yesterday's technology in the sense that the freeze-drying process has hardly changed since the 1930s. The first large-scale application of biological freeze-drying was in World War II. The American Red Cross in Honolulu was collecting a lot of blood plasma that needed to be stored – so they flew in a freeze-drier from Philadelphia. Early lyophilizers were based on the autoclave, and the fundamental design has not changed since. And it's an enormously inefficient design: Alina's calculations show that some production-scale lyophilizers have an energy efficiency of only five percent! It's an old technology and the field is ripe for process improvements.

Alina Alexeenko: That said, though the process of lyophilization has been used for decades, it is still very relevant to today's needs. The number of FDA-approved lyophilized drugs has dramatically increased since the mid-2000s, mainly because of the development of fragile biologics, such as antibodies and antibody drug conjugates. So freeze-drying is becoming more important as time goes on. Although the largest end-product market is lyophilized foods, the greatest compound annual growth rate among lyophilized products is for biologics.

I would also add that there is a lack of education and training around lyophilization. Although young scientists may be familiar with batch lyophilization for isolating chemicals, process lyophilizers work quite differently. I think we're seeing a generational gap appearing, with the older experts moving into retirement without necessarily passing their skills to the younger generation. But lyophilization has expanded from its traditional use in pharma to things like biosimilars, cells, and diagnostic test kits – and the demand for those skills is only set to increase. We need to make sure the younger generation is able to cope. In the 1990s, only around 11 percent of injectable drugs were lyophilized, but now it's over half.

What holds innovation in the field back?

AA: Pharma companies must work under strict regulatory constraints, which makes the risk of innovation higher. For example, when a drug is approved, its manufacturing process is linked to that approval, which historically has resulted in a disincentive to change the process. An unintended effect of that has been to put a dampener on process innovation. To get things

moving, it is important to get people from different industries to work together. We are partnering with people in the food processing sector as well as pharma. The food industry is very different to pharma: "high volume, low value add" as opposed to "low volume, high value add" of the drug industry. Consequently, food sector processes have evolved, and are ahead of pharma processes in some respects. It is a good time to learn from them and make pharma processing better.

How difficult was it to bring different parties together for LyoHub?

AA: The formation of LyoHub involved a great deal of networking and relationship development in the lyophilization community. Part of it happened naturally through collaborations; for example, when Purdue was working with Abbvie, we needed more information about their lyophilizer, so we had to interact with the equipment manufacturer too. Another part came from linking up projects, resulting in discussions of research needs common to equipment manufacturers and pharma companies. Of course, it takes persistence to get competitor companies to openly discuss these things! We had to keep repeating that improving lyophilization doesn't give a competitive advantage to one company or another – it increases the whole market, improving revenues and profitability for all companies.

ET: We also had to be open-minded and accept that our members' research needs might not correspond to the areas that we found most interesting as academics. The consortium consistently asked for the development of a set of common best practices for operational and product qualification. It is not the most exciting research topic, but it's true that standards are lacking in this field. So LyoHub members have been collaborating to produce best practice papers. This will enable them to speak with one voice to the FDA and hence inform regulatory policy.

What other issues need to be addressed?

AA: On the regulatory side, the number one topic for LyoHub members is process instrumentation, particularly for measuring product temperature; for example, the best thermocouples for the lyophilizer environment, optimal thermocouple positioning, and techniques for monitoring the end of primary drying. Another important topic is equipment performance qualification. These issues are common to any lyophilization process, whether for pharmaceuticals or food, large scale production or pilot clinical production.

ET: Lyophilization cycle time is a particular near-term challenge; balancing short cycles with adequate quality can be difficult. Cycle times of several days, together with the capital costs of lyophilizers, cause production bottlenecks, so cycle time reduction could potentially increase production throughput. This is something we are exploring with our members.

If lyophilization is to really join the modern world, we need better sensors. There is interest in continuous process lyophilization, but we need feed-back and feed-forward control, so that the process can run itself based on sensor information. More sophisticated monitoring will also enable us to determine how the lyophilizer conditions vary across a shelf and from vial to vial, and ultimately to design lyophilizers

"Meanwhile in the biologics field, there are increasing cost pressures on both innovator and biosimilar companies."

that make the process more uniform. As a rule, the product temperature is not measured during production, only chamber temperature and shelf temperature. Direct measurement of product temperature would allow the cycle to be optimized in real time during each process. Innovations in this area would also help scale-up – because at present lyophilizer performance is not very reproducible between pilot scale and production scale; the production environment is cleaner than the development environment – there are fewer particulates, which impacts lyophilization because particulates help induce ice nucleation. Once you start to understand the complexities, you can begin to better control nucleation in the production environment.

What led to the Lyophilization Technology Roadmap?

AA: Product innovation helps drive process innovation – technology road-mapping and consortium research has resulted in many innovations, including combination products, prefilled syringes, processes compatible with very small fill volumes, and new diagnostic products. It is a very good time to rethink lyophilization and develop new equipment and new processes – not least continuous processing systems.

Our roadmap brought together over 100 different people – from end users, to equipment or instrument manufacturers – to think about what we need to achieve in the next decade to really move lyophilization forward. The project was funded by the US National Institute of Standards and Technology (NIST) and is published on the USA Manufacturing website. It is a living, breathing document, and it will be updated with new information.

ET: The Roadmap is our process for identifying trends and drivers in lyophilization, to forecast key developments over the next 10 years, as well as issues that may change the field of lyophilization. What if it were possible to lyophilize tissues for transplant therapy? What are the implications of the demand for biologics from the developing world? Could we lyophilize cell-based therapies? Cell therapies could be a game changer for pharma, but the process is tricky. Novartis' new CAR-T is logistically and technically very complicated – where cells are cryopreserved, flown to a manufacturing site, genetically modified, and then flown back to the patient. The whole thing reminds me of well-choreographed ballet, with the cryopreservation steps taking time and requiring specialized equipment to maintain the ultra-low temperatures. Could lyophilization potentially be a faster and cheaper alternative? It is still early days but there is interest from some companies in seeing if lyophilization can replace cryopreservation.

In the biologics field, there are increasing cost pressures on both innovator and biosimilar companies. Improving process efficiency by implementing advanced lyophilization technology will help drive down manufacturing costs. As well as identifying trends and drivers, we have mapped out areas where the consortium should focus its efforts, and projects it should undertake to meet the needs of its members, such as improved analytical methods, new tools for product design, modeling and simulation, better container/closure systems, and new lyophilization processes that can handle cell and gene therapies, and diagnostic agents.

How have industry reacted to the roadmap so far?

AA: With great enthusiasm! The roadmap includes best practices and we have published one of those in AAPS. There is a counter on the AAPS website and we have already passed 2000 downloads, and the lead author of the paper was also invited to the FDA to present the paper – so I think the community has already begun to take notice.

What is LyoHub focusing on now?

AA: We are very focused on our lyophilization demo facility. We see this as a unique "open playground" where different perspectives and capabilities come together to benefit from access to specialized equipment. We hope by next year to see the commercial application of some of the sensor technology that is now being tested in the facility, and to make a start on continuous process lyophilization.

ET: It is very difficult to change a production process once it has been GMP-certified, but a demo facility like ours enables companies to experiment with processes in a risk-free environment. You can't go drilling holes in a production lyophilizer to insert mass spectrometry sensors for monitoring individual vials, but we can do that in our demo facility. In the near future, I hope we will see direct benefits from this resource, such as the commercial adoption of the temperature sensors that are now being tested in the facility, and generation of data to support best practice documents for the entire community, not just our members.

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Single-Use That's Ready When You Are

Biopharma has embraced the benefits of single-use, but with a growing number of available components and highly customized assemblies, the supply chain becomes quite complex. Merck KGaA has designed a new program offering customized single-use assemblies with reduced lead times, and an enhanced level of supply security.

Sara Bell is fortunate to have been on both sides of the fence, spending 11 years in operations at Amgen before joining Merck KGaA, where she is now Senior Marketing Manager of their single-use portfolio. Sara knows full well the challenges faced in biopharma manufacturing – and why single-use is seeing increased uptake. Here, we talk to Sara about trends in single-use systems and why supply security of these products is critical to drug manufacturers.

What are the pros of single-use?

I would highlight four key benefits. The first is flexibility, which is really beneficial to multi-product facilities and contract manufacturing organizations (CMOs) that need to produce a variety of different products at different scales. Demand for those products can change rapidly, so being able to adapt quickly – which single-use allows – is a huge advantage. Secondly, single-use helps lower costs by reducing plant footprints and upfront capital spend. For emerging markets looking to get into the biopharmaceutical market, single-use is a great option because it requires less investment than a traditional stainless steel plant. The third benefit is speed. It's often faster to get a product to market using single-use. There is no need for clean-in-place or steam-in-place, and no need for validation of these operations, which greatly reduces the time it takes to get a facility up and running. Finally, single-use reduces your risk profile in terms of contamination. As the name suggests, once you use the product you throw it away and install a brand new sterilized assembly, so the risk of product carry-over is completely eliminated. In addition, due to the closed nature of single-use, you have better biological and viral contamination control.

And the cons?

There are risks and considerations to evaluate when implementing single-use, but I firmly believe that the benefits outweigh the risks. So, what is keeping drug manufacturers up at night when it comes to single-use? One of their biggest concerns is supply security. With traditional stainless steel manufacturing, the amount of consumables needed to run a process is limited to cell culture media, process chemicals, resins and filter elements. Additionally, production plans are primarily driven by turn-around time, or the time it takes to clean and sterilize vessels between batches. With single-use, the amount of consumables needed to run the process significantly increases, which makes the supply chain, especially procurement and inventory management, much more complex.

Many single-use suppliers use proprietary components, such as films, connectors and tubing – as well as their own technologies and assemblies for bioreactors, mixers and automated systems. Such non-uniformity means that it can be very challenging for end-users to dual source the consumables needed to run their processes. Therefore, they are forced to manage the risk by holding large quantities of safety stock, or performing tests to justify that two different products are "like for like". Varying supplier lead times and delivery delays can also impact production plans. These are challenges that we have sought to address through the Mobius® MyWay program.

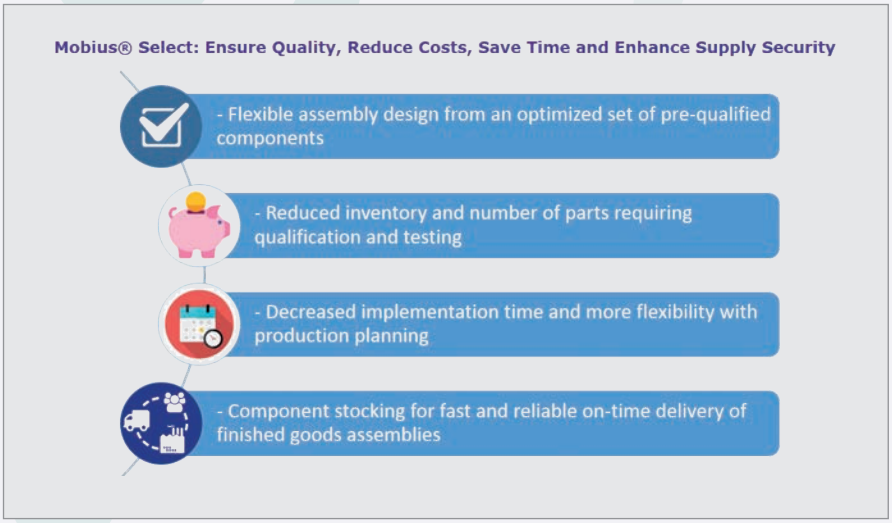
What's the story behind the Mobius® MyWay Program?

The single-use market has seen significant growth over the past 10 years, and is predicted to continue to grow at a double-digit rate through 2025. Like many other single-use suppliers, we began to run into capacity challenges and it was important for us to define a scalable manufacturing model that met or exceeded end user expectations in terms of lead times, delivery, quality and supply security. The Mobius® MyWay program, which launched in January 2017, came into being to meet those end user expectations. Essentially, the program offers three options for customized single-use assemblies.

The first option is Mobius® Stock, which covers catalog items and high-volume repeat custom assemblies. With this option, we maintain stock of the assembly part number on our shelf and deliver when needed, which allows end users to maintain less inventory.

Option two, Mobius® Select, allows end users to design configured assemblies from an optimized component library, and receive them within six weeks. We maintain safety stock of every component in this library, thus enabling fast and reliable delivery with an enhanced level of supply security. The third option is Mobius® Choice, which allows end users to design customized single-use assemblies using our full Mobius® component library, and receive them with a traditional lead-time of 12–14 weeks.

Many single-use suppliers have chosen to address capacity challenges and custom business complexities using a different approach, by defining pre-configured standard assemblies. They offer solutions that they think end users will want. From our experience, no matter what you expect the end user to want, they will always want something slightly different! The Mobius® MyWay Program allows end users the flexibility to design a custom assembly and decide when they want to receive it.



Mobius® Select has been particularly popular…

Yes – and for good reason I think. If you look at the global market today, there are many dynamics impacting the biopharma industry. To remain competitive, drug manufacturers must examine how to cut costs, as well as how to increase flexibility and productivity. Biosimilars, emerging markets, novel therapies and next generation processing are just a few of the variables driving greater adoption of single-use. Many users are designing customized assemblies, using different components, from a variety of suppliers. It's gotten quite complex for end user networks to manage, so many are now looking to standardize and harmonize their single-use assemblies, by defining a set of preferred components – essentially a design space that they use to develop new assemblies. The Mobius® Select library provides them with just that; an optimized design space of pre-qualified components backed with supporting quality documentation and a growing dataset of extractables, tested per the BioPhorum Operations Group (BPOG) protocol. This significantly reduces the amount of testing required by the end user, and enables them to implement single-use faster. The six-week lead time allows end-users to hold less inventory and be more nimble with their production planning. And the biggest benefit with Mobius® Select is that it still gives end users the flexibility to customize their assembly, across a broad range of applications, to meet their specific processing needs and requirements.

How has the industry reacted to the new offering?

We saw adoption pick up significantly mid-2017. We find that once an end user experiences the entire process from the design of their assembly through to order receipt, they realize the value that Mobius® Select can provide – not only in terms of delivery time, but also in terms of quality assurance, reduced inventory costs, time savings, flexibility, and security of supply. These benefits drive the creation of new Mobius® Select assemblies and have also prompted end users to reach out to us with specific requests; for example, "I have X number of existing assemblies from Merck KGaA or a competitor. Can you help me transition these to a Mobius® Select design? What components would I need to tweak to make this Mobius® Select compliant?" For common applications like mixing, storage, transfer and filtration, typically only minor component or tubing length changes are needed to make a design Mobius® Select compliant.

The program has proved to be very successful for both us and end users. The aim of the Mobius® MyWay Program was to meet drug manufacturers needs in terms of fast and reliable delivery, easing the implementation of single-use, and increasing the level of quality and documentation that they receive with the product. But the solution we came up with also enabled us to scale our manufacturing operations to ensure we can support the continuing growth of single-use through 2025 and beyond.

We are going to continue to enhance the program and evolve the library based on market needs. Towards the end of November, we are launching a web-based interactive tool that will allow end users to see which components are available in the Mobius® Select library. For more information on the program, or to request the help of a single-use specialist, I encourage readers to visit merckmillipore.com/singleuse-myway. To directly link to the Mobius® Select tool, you may visit mobiustool.com

On a (Public Health) Mission

Sitting Down With… Margaret Hamburg, President-elect, American Association for the Advancement of Science (AAAS); and Foreign Secretary, National Academy of Medicine.

Did you always want to work in public health?

My career has turned out very differently to the one I had in mind. Originally, I wanted to be an academic physician: teaching, taking care of patients, and doing research. But as the AIDS epidemic unfolded during my time as a medical student, I witnessed its devastating impact on individuals and on public health. This, combined with a new appreciation of the broader set of social, legal, ethical and economic issues involved, led me to switch over to public health and health policy. Since then, I've been committed to figuring out how to best serve those in need by bringing the best science to bear on public health problems.

I've been lucky enough to continue on my mission in a number of fascinating roles: Assistant Director of the National Institute of Allergies and Infectious Diseases at the NIH; Health Commissioner in New York City; Assistant Secretary for Planning and Evaluation at the US Department of Health and Human Services; I also had a brief stint in the world of philanthropy, working on biological terrorism and naturally occurring biological threats; and of course, FDA Commissioner.

Was it an easy decision to take the FDA job?

Becoming FDA Commissioner was never on my bucket list of things to do – and I never thought I would be in consideration! At that time, I was actually planning to work in another part of the administration: the Office of Science and Technology Policy in the White House. When I got the FDA call, I was a little taken aback because I hadn't formally discussed the job with anyone – and if you were reading the papers at the time my name wasn't being mentioned. The FDA is such an essential component of what the government can and should do to serve its people, so I felt it was an opportunity of a lifetime that I simply couldn't pass up.

How do you look back on your role as FDA Commissioner?

I'm very proud of the work I did at the FDA. And once I started, I found it to be quite a good fit with my background interests, as well as the concerns I had at that time. I think I arrived at a critical moment for the agency. Back then, the FDA was under fire from the media and congress over food and drug safety issues. In a sense, the agency had circled the wagons somewhat with people worried about how to do their jobs in an increasingly hostile environment. I think I was able to provide some new leadership and perspectives.

It was also a time when the agency really needed to reposition itself for the challenges of the 21st century, which meant opening up and working in partnership with critical stakeholders, being more transparent, and trying to be as responsive and innovative as possible. It was also a critical time for advancing regulatory science – which has been underappreciated and undervalued – to support biomedical product research, product development and review. We also had to modernize our regulatory review systems, and make sure we were equipped to work in an increasingly globalized word.

I believe I was able to both renew the sense of the public health mission, which underpins the work of the FDA, and also to support the FDA's extraordinary workforce; I was so impressed by the people who devote their lives to the FDA and its efforts.

What are the main challenges facing regulators today?

Being able to continue advancing and innovating in an environment that is, in many ways, increasingly anti-government and anti-regulation is just one grand challenge faced by regulators. They also have to deal with increasingly complex products – from both a scientific and technological standpoint – as well as the challenges of globalization. The demands on regulators are enormous and growing. Regulatory leaders must make the case for the work they do, which is so critical for the safety of citizens of every country in the world.

"The AAAS can be a voice for science and a voice for making sure the public and policy makers really understand what science is about."

What are your objectives as Head of the American Association for the Advancement of Science (AAAS)?

I think it's an important moment for the AAAS. The AAAS can be a voice for science and a voice for making sure the public and policy makers really understand what science is about, and why it's important to continue to support science.

We are living in a world where science is increasingly devalued and the role of expertise is often dismissed. But so much of what we do is underpinned by science – whether we recognize it or not. Be it climate change, the environment, energy, preventing pandemics or the challenges of living in urban environments, investment in science has the potential to improve lives.

I also think it's important to develop our interdisciplinary and cross-sectoral scientific efforts. We'll get the most bang for our buck by making best use of the minds and resources we have, wherever we can find them. And while it is the American Association for the Advancement of Science, we must recognize that science is a global enterprise. Enhanced international engagement and collaboration must be a priority as well.

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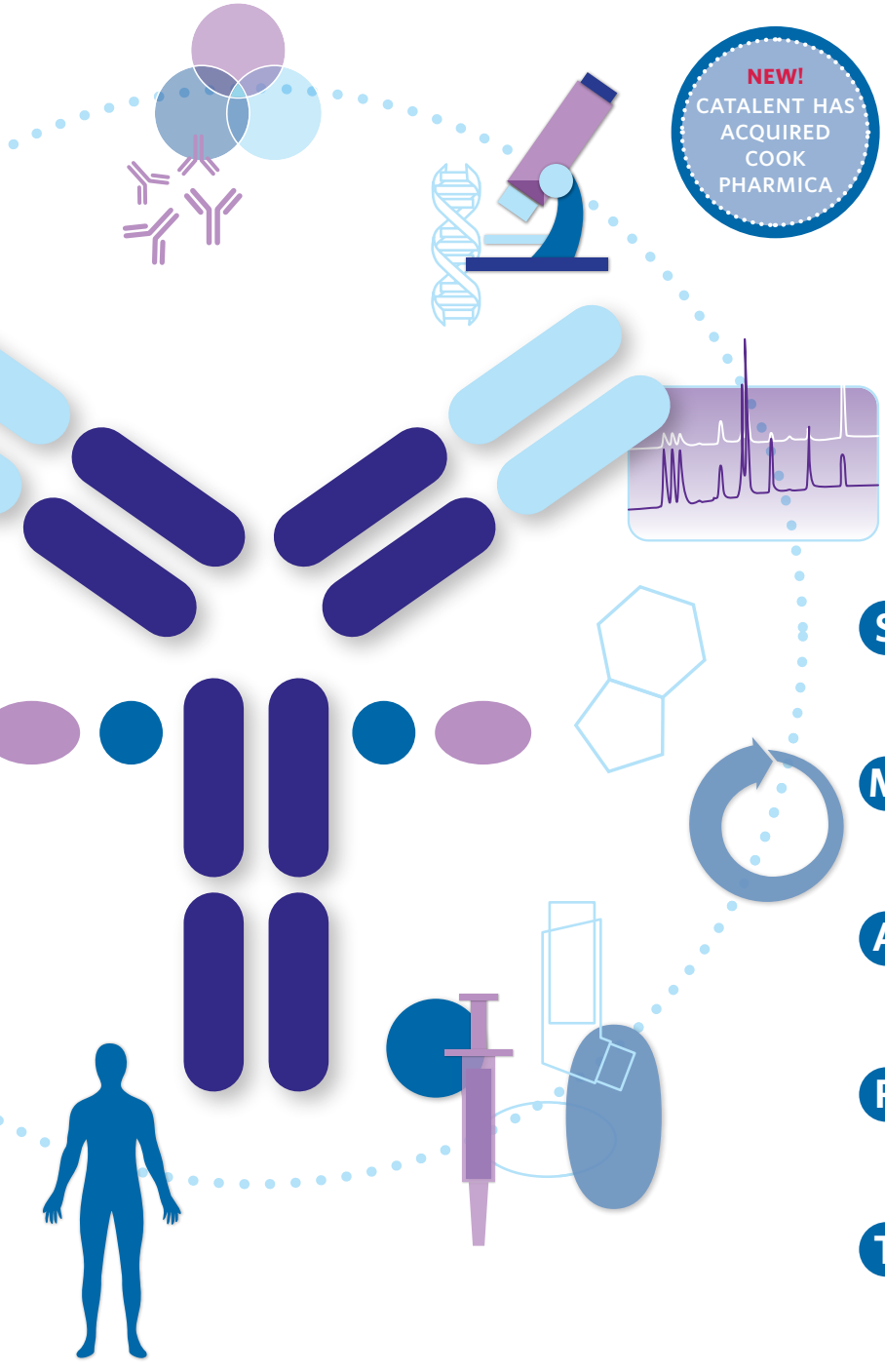

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