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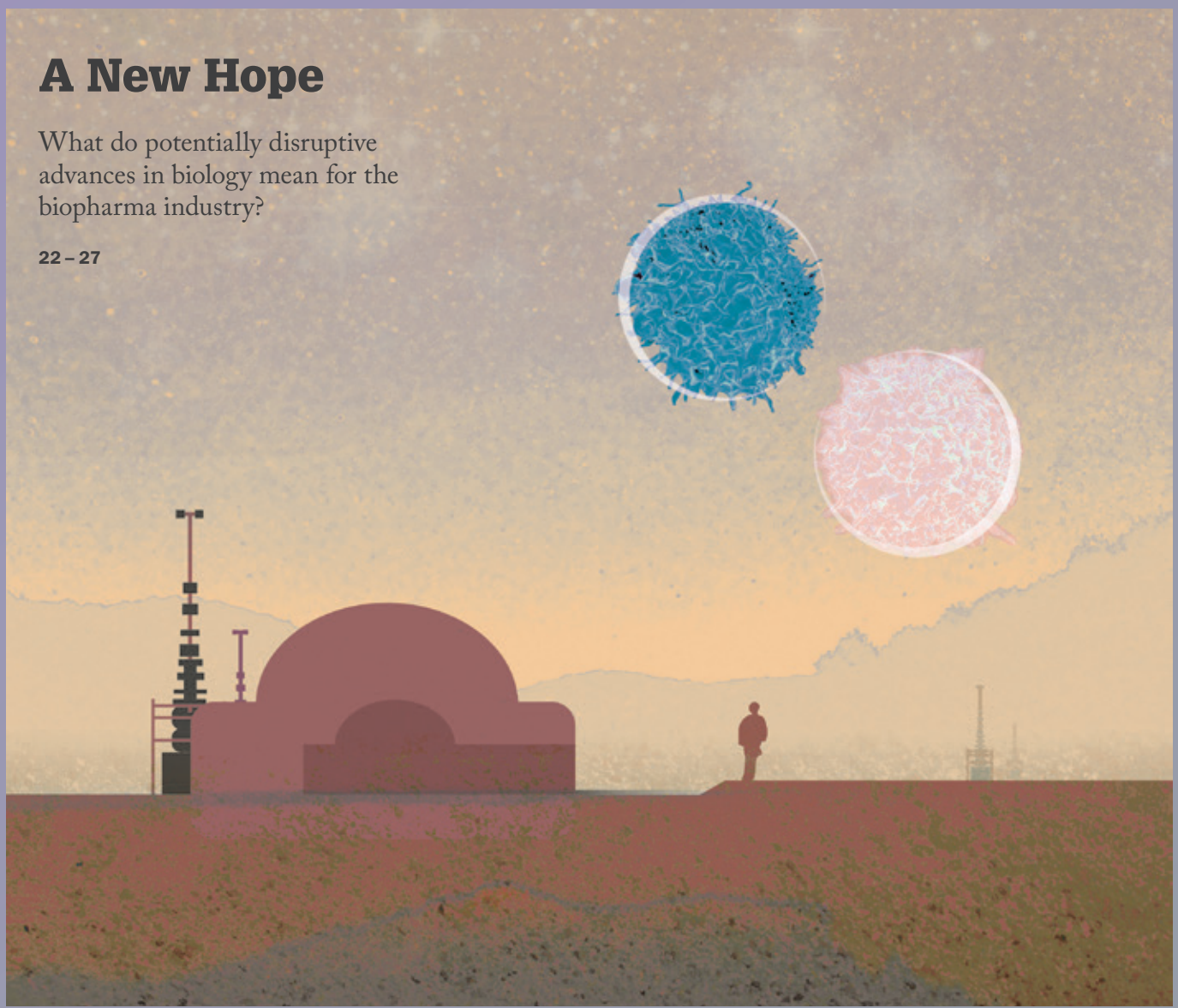

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Online this Month

The Power List Strikes Back!

The Medicine Maker Power List features the Top 100 most influential individuals in the pharmaceutical manufacturing industry. 2015's list included business gurus, Nobel Prize winners, and thought leaders – and ignited much celebration, discussion and even some controversy.

In April 2016, the Power List is back! And as before, it's up to you – our readers – to nominate who should be on it. In 2015, many of you nominated CEOs and executives, but did we miss anyone making significant contributions? Perhaps a prominent scientist whose research you admire or an undervalued colleague whose passion for advancing pharmaceutical manufacturing inspires you greatly?

Nominations are now open. Email: Stephanie.sutton@texerepublishing.com or use the online form at: http://tmm.txp.to/2016-powerlist-nominations

It's quick and easy. Just tell us the name(s) and company/institution(s) of your nominees and, briefly, the reason why.

An independent judging panel will assess the nominations and compile the Top 100.

Who will make it onto The Power List in April 2016? Nominations close on 8 March. You have the power!

Top Ten of 2015

1. Anthony Fauci, National Institute of Allergy and Infectious Diseases

2. Kiran Mazumdar-Shaw, Biocon

3. Sir Andrew Witty, GlaxoSmithKline

4. Arthur D. Levinson, Calico

5. Heather Bresch, Mylan

6. Raman Singh, Mundipharma

7. Peter Seeberger, Free University of Berlin

8. Pascal Soriot, AstraZeneca

9. Robin Robinson, US Department of Health and Human Services

10. Robert A. Bradway, Amgen

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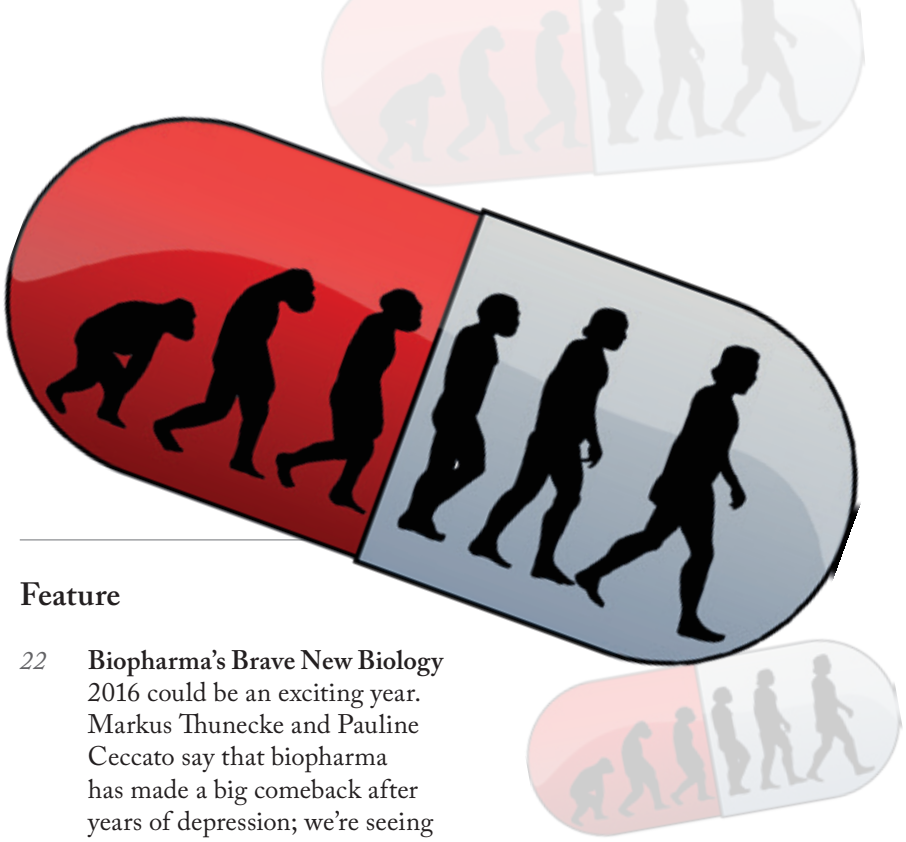

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the Medicine Maker

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innovation loves a guiding hand

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A Brave New Year

How do we move on from a sombre start to 2016?

It is traditional to introduce the first issue of a new year with best wishes for success and happiness – and this I most certainly do. And I also have the unusual task of introducing myself as the new editor of The Medicine Maker and wishing my predecessor – Charlotte Barker – all the best in her new role as editor of Texere Publishing's new magazine, The Translational Scientist (www.thetranslationalscientist.com).

And yet, well-wishing and polite introductions seem somewhat out of place given the solemn start to the year. By now, I am sure that everyone is aware of the tragic Phase I clinical trial in Rennes, France, that resulted in the death of one participant and the hospitalization of five others – some of whom may be facing brain damage.

Phase I trial results do not need to be publicly released in Europe or the US, so it is difficult to quantify exactly how many trials fail so dramatically, but clearly, a significant amount of work goes into preclinical development and increasingly strict regulations must be adhered to. A review from 2005 on the risks and benefits of Phase I trials revealed a toxicity death rate of 0.005 percent (1). And some have even suggested that trials are run too conservatively… (2)

Despite the relative safety of clinical trials, recruitment remains difficult, with a lack of volunteers, compounded by ever-expanding inclusion and exclusion criteria. But stated simply, without volunteers for clinical trials, medicine cannot advance – all the more disappointing given the exciting advances being made in cell and gene therapies (some of which are discussed in this month's cover feature on page 22). The publicity of the latest clinical trial tragedy can only have negative consequences on future clinical trial recruitment.

The sad outcome of the trial may be even more concerning to those of us who understand the emphasis on safety in drug development and manufacture, as it highlights the vast amount that we still do not know about complex molecules and their interactions with the human body – or how these interactions may be affected by manufacturing changes or exposure to contaminants.

But rather than speculate on how the French trial went wrong, I would rather pose a question to you all: where does the industry go from here? This incident – much like the disastrous TGN1412 trial in 2006 – will remain in people's consciousness for many years. The industry will need to work hard to earn back people's trust in clinical trial safety – but how?

Stephanie Sutton
Editor

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1. *E. Horstmann et al., "Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002," N. Engl. J. Med. 352, 895–904 (2005).*
2. *R. Kurzrock and R.S. Benjamin, "Risks and benefits of phase 1 oncology trials, revisited," N. Engl. J. Med., 352, 930–2 (2005).*

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

Cross-Country Cancer Cost Comparison

Oncology medication prices can vary significantly between countries – but by how much and why?

It will come as no surprise to many of you that the price of cancer drugs varies from country to country. But the sheer scale of the variance may come as a shock. Researchers from the World Health Organization (WHO) claim to have conducted the first cross-country cancer drug price comparison of its kind in Europe, Australia and New Zealand, and say that prices can vary by as much as 388 percent. You'll see the lowest prices in Portugal, Spain, Greece and the UK, but if you're in Sweden, Switzerland or Germany then prices will be higher – although in most cases the prices impact the state, which reimburses them, more than patients.

We spoke with Sabine Vogler, lead author of the study and a researcher at the WHO's Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies at the Austrian Public Health Institute (GÖG), to find out why prices vary so dramatically and what implications the findings may have for policy makers.

Which findings were most surprising?

Though there is a pattern for some of the countries – for example, Switzerland, Germany and Sweden all rank in the top quarter for at least 70 percent of the drugs surveyed – there is no pattern whatsoever for other countries, such as Australia and New Zealand! Some drugs are priced in the lowest ranks and others in the highest. It was also interesting to see such wide ranging prices when looking at the drugs individually. For instance, the difference between the prices of drugs in the highest and lowest priced countries was 50–100 percent for half of the drugs – and 100–200 percent for three drugs. However, for two drugs, interferon alfa 2b and gemcitabine, the price differences amounted to 223 percent and 388 percent, respectively.

Can you explain the pricing variations?

For two medicines in the sample – gemcitabine and zoledronic acid – generic

alternatives exist in several countries included in our study. The existence of generics can have a strong impact on the prices of originator medicines, but the impact can vary. Originator prices can decrease with the entry of generics, but not always in every country. Gemcitabine, for example, costs €209 per vial in New Zealand and just €43 in Australia.

Variations in price are also linked to the economic situation of a country. Though they are all high-income countries, differences do exist and some countries, such as Greece, have had to undertake austerity measures in the area of pharmaceutical policy (price cuts being one) – zoledronic acid costs €330 per vial in New Zealand but only €128 in Greece. But the economic situation of the countries does not fully explain the differences in price; pharmaceutical policies of the countries apparently also appear to play a major role.

What implications does your research have for policy makers?

Our research offers national policy makers in the surveyed European countries, as well as in Australia and New Zealand, evidence about how prices of oncology medicines of their country rank compared to other countries. It is now up to them to draw conclusions, and to take action, if required.

Independently from these national considerations, data from our research suggest a need for a fundamental discussion about medicine pricing. Such a discussion would address issues such as the current linkage of medicine prices to the patent system, questions of equity among countries and the issue of transparency of prices.

What do you think would make a difference to the pricing system?

In our study, we call for more transparency. A major limitation of our article is that we could only analyze and compare the officially published list prices; in reality, paid prices tend to be lower due to discounts, rebates and similar arrangements concluded in confidential negotiations. This limitation also impacts the pricing system in many countries, as international price comparisons are a key pricing policy. However, authorities also compare to the list prices (since the confidential lower prices are not known), and thus may be at risk of over-paying. We expect that disclosure of discounts and similar price reductions might lead to major savings for public payers.

Reference

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Bio-Butterfingers

Lipoprotein-nanoplatelets leave researchers hungry to explore drug delivery potential

Semiconductor nanocrystals have been used to discover a host of new biomolecular phenomena because of their uniquely bright and stable florescence emission. Recently, a new class of nanocrystal – nanoplatelets – has excited researchers because of a number of potential applications from cellular imaging, to metastatic tracking, and drug delivery.

"Nanoplatelets have an emission band two to four times narrower than most other types of light emitters," says Andrew Smith, assistant professor of Bioengineering at the University of Illinois at Urbana-Champaign, US. "This property could allow us to fluorescently tag two to four times more molecules simultaneously, which is very useful for studying cells and tissues." But only if they are stable within biological solutions; typically, nanoplatelets aggregate in biological media because of the their unusual shape, losing fluorescence in the process.

Smith and his colleagues set out to overcome this caveat by developing lipoprotein-nanoplatelets (L-NPLs). "L-NPLs are a combination of lipoproteins and nanoplatelets, and are kind of structured like a microscopic Butterfinger candy bar," says Smith. "The crispy peanut butter center is similar to the nanoplatelet – a flat sheet made out of a hard material; whereas surrounding it on all sides – like a chocolate covering – are the soft, organic lipoproteins and lipids." And just like a Butterfinger hides its 270 calories and 11 grams of fat in a relatively innocuous chocolate coating, the lipoproteins disguise nanoplatelets as something that cells would like to eat, which Smith says they do vigorously. Most importantly, the lipoprotein layer allows nanoplatelets to retain their fluorescent properties in vivo.

"It's the first time that anyone has been able to demonstrate the use of nanoplatelets and quantum well-like structures in cells," says Smith. "But perhaps more importantly, we uniquely found that they enter cells rapidly, which sets the stage for their use to optically encode cells and to explore the unknown interactions between flat materials and biology."

The researchers are also confident that L-NPLs could be used to track metastatic cancer cells in the body or deliver drugs to tumor cells. "Their efficiency of entry into cells is really striking, and this could potentially be an efficient way to transport things into cells, such as medicinal compounds, or DNA, that are traditionally hard to deliver," says Smith. *JS*

Reference

1. *S.J Lim et al., "Lipoprotein nanoplatelets: brightly fluorescent, zwitterionic probes with rapid cellular entry," J. Am. Chem. Soc., 138, 64–7 (2015).*

The (FD)A-Team

Are you worried about implementing new manufacturing technology in your plant? Never fear, the FDA's Emerging Technology Team may be able to lend a helping hand

Outdated manufacturing technologies can lead to quality issues and recalls. But implementing the newest technologies isn't easy either since there can be delays while reviewers familiarize themselves with the new technologies and determine whether or not they meet regulatory guidelines. Recognizing that the pharma industry is stuck between a rock and a hard place, the US FDA is looking to help smooth the introduction of new manufacturing methods with a new collaborative program.

In draft guidance titled "Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry," the FDA explains that it is looking for companies to participate in a program where the FDA's Emerging Technology Team (ETT) will work in partnership with pharmaceutical companies to assess and review submissions involving emerging technology (1).

"In order to encourage more advancements in pharmaceutical manufacturing, we recognized the need for a new approach, and established the ETT to work directly with industry to help identify and resolve scientific issues for new technologies," explains a spokesperson for the FDA. "The initiative will encourage the adoption of innovative approaches to pharmaceutical manufacturing by leveraging existing resources within the Agency to facilitate the regulatory review of submissions to the Agency involving manufacturing technologies likely to improve product safety, identity, strength, quality, and purity."

Pharmaceutical companies will be able to engage in early discussions with the ETT regarding manufacturing design and development issues, and obtain FDA's recommendations for regulatory submission content related to new manufacturing technology. In addition, when regulatory submissions involving novel manufacturing technology are received by FDA, the ETT will also work collaboratively with the pharmaceutical quality review offices to ensure timely assessment of the submission. "The continued involvement of ETT from the early technology development to application review will help ensure the consistency, continuity and predictability in the review and inspection of emerging technology," adds the FDA.

Since the guidance document provides recommendations, rather than establishing legally enforceable responsibilities, the FDA adds that the program is voluntary. Participants can apply to get involved by submitting a written request for a meeting with the FDA. Interested parties planning to submit an investigational new drug (IND) or an application for a new drug, biologic or generic that includes specific emerging technology, should send the request electronically to: CDER-ETT@fda.hhs.gov.

"What makes this approach to emerging technology novel is that this dialogue with FDA and industry can occur during early technology development prior to the submission of a drug application to the FDA," says Michael Kopcha, Director for the Center for Drug Evaluation and Research Office of Pharmaceutical Quality at the FDA. "Such early engagement allows the FDA to proactively identify and address potential roadblocks and helps eliminate potential delay in the adoption of promising new technologies." *JS*

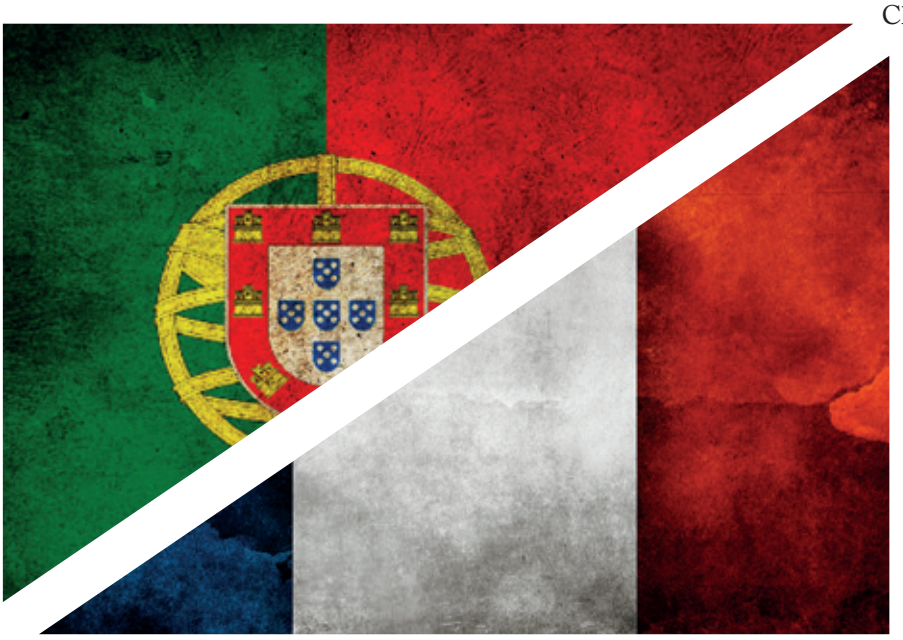
Reference

1. *FDA, Draft Guidance, "Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry," (2015). http://1.usa.gov/1UrbhDP*

Clinical Trial Tragedy

A clinical trial of an FAAH inhibitor in France goes terribly wrong, but whether the compound or manufacturing are to blame remains to be seen

Major problems in early clinical trials are rare, but unfortunately not impossible. In January, one man died and five others were hospitalized – some with potential brain damage – after a phase 1 clinical trial on healthy volunteers went tragically wrong in France. The trial was being conducted in Rennes by a French contract-research organization called Biotrial, on behalf of the Portuguese pharmaceutical company Bial, to test an experimental drug – codenamed BIA 10-2474, which Bial has confirmed is a fatty acid amide hydrolase (FAAH) inhibitor designed to act upon the human endocannabinoid system. It was reportedly in development for treating a range of medical conditions, including chronic pain.



The compound was being tested in an escalating-dose study. Dozens of patients received the drug at low doses, with no apparent problems. The six people hospitalized were the first to receive the drug at high concentrations, but it is not yet known what caused the problems.

"With an oral medicine, as in this case, with up to 90 patients already treated (as been suggested), then an unanticipated critical illness in 6 subjects caused by the medicine is unheard of. This raises the possibility that there were issues with dosing or manufacture, though we will not know until more information emerges," David Webb, president of the British Pharmacological Society, said in a press statement (1).

This isn't the first time that FAAH inhibitors have featured in clinical trials, but it's the first time that such serious adverse effects have been seen. Whether the trial will impact the whole class of drugs remains to be seen – and will be dependent on what caused the side effects in the Rennes trial. However, Janssen, which is currently conducting two Phase 2 clinical trials of an experimental FAAH inhibitor, is definitely cautious. "As a precaution, Janssen is voluntarily suspending dosing in two Phase 2 clinical studies of an experimental medicine – a FAAH inhibitor – following reports in France," the company said in a press release (2). "Janssen has not received any reports of serious adverse events in our Phase 2 studies with our FAAH inhibitor in patients with social anxiety disorder and in major depressive disorder with anxious distress, or in earlier, Phase 1 safety studies of the drug."

As a whole, the pharma industry has been quick to emphasize that Phase 1 trials are usually very safe. "The 2012 ABPI report stated that the overall incidence of serious adverse events in phase I trials is 0.02 percent," said Sir Munir Pirmohamed, vice president, Clinical, at the British Pharmacological Society.

Whatever caused the tragic consequences in Rennes, there has been a call to make it public. Little information about the drug and its pharmacology has been made available and members of the British Pharmacological Society believe that as much information as possible should be made available to the scientific community so that lessons can be learned to benefit future drug development. *JS*

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1. *British Pharmacological Society, "Members Respond to French Clinical Trial Reports," (January, 2016).*
2. *Janssen, "Janssen Research & Development, LLC Voluntarily Suspends Dosing in Phase 2 Clinical Trials of Experimental Treatment for Mood Disorders" (January, 2016).*

All Eyes on EMA Approvals

From anti-cancer viruses to H3 blocking narcolepsy drugs – we present a year in European drug approvals

The European Medicines Agency (EMA) recently released its "highlights of 2015" in terms of new medicine approvals. All in all, it seems that 2015 was a good year with 93 medicines recommended for marketing authorization, including 39 new active substances. In 2014, on the other hand, just 82 new products were recommended for approval. Our infographic brings you up to speed with some of the key approvals from 2015 that will likely be coming to a European market near you soon.

Cancer Approval Highlights:

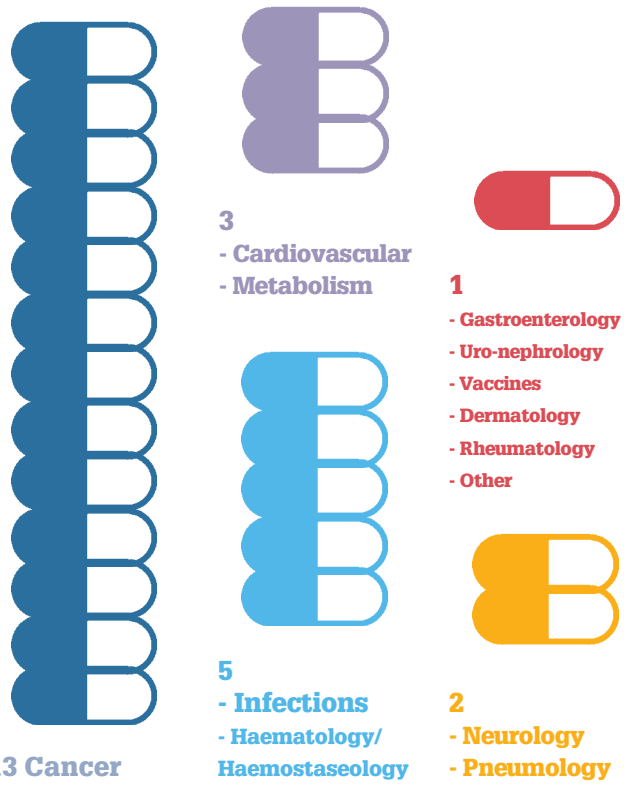
Blincyto - directing the immune system towards cancer cells

Farydak - regulating the activity of genes

Imlygic - using genetically engineered virus to kill cancer cells

Opdivo, Nivolumab BMS and Keytruda - increasing the capacity of the immune system

Medicines with New Active Substances in 2015



New Uses for Existing Medicines: **54**

Bringing Medicines to Patients Faster

Authorizations under exceptional circumstances: 3
Accelerated assessments: 5
Conditional marketing authorizations: 3

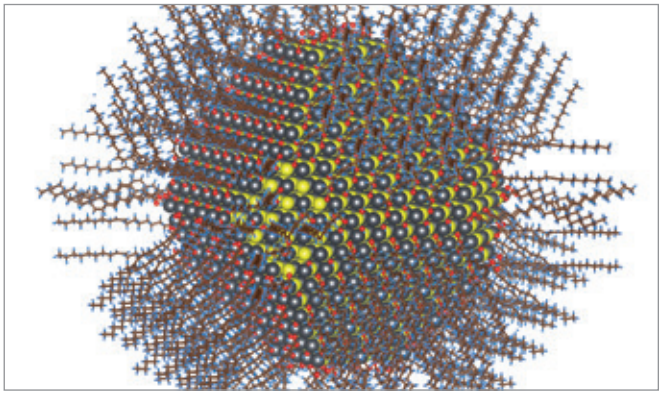
Safety First

Inspections were conducted in 62 countries worldwide
>2,590 GMP inspections. >270 GCP inspections. >190 pharmacovigilance inspections.

New Medicines for Rare Diseases: 18

Highlights:

Blincyto for patients with acute lymphoblastic leukemia
Farydak for patients with multiple myeloma
Hetlioz for blind adults with sleep-wake disorder
Kanuma for patients with lysosomal acid lipase deficiency
Kyprolis for patients with multiple myeloma
Lenvima for patients with thyroid cancer
Strensiq for patients with childhood hypophosphatasia
Unituxin for patients with brain cancer (neuroblastoma)



Three's a Charm

Nanoparticles help to deliver a three-in-one attack on metastatic melanoma cells

Treating melanoma can sometimes feel like a game of whack-a-mole – you inhibit one pathway, the cells upregulate another; you take care of that pathway; and a third pathway pops up. The key to effective treatment is to use three hammers, but delivering a combination of anti-melanoma drugs to the lymphatic system is impossible at therapeutic concentrations without inducing systemic toxicity.

Researchers from the Department of Pharmaceutical Sciences at Oregon State University in the US believe they have developed a nanoscale system capable of delivering three anti-melanoma drugs to the lymphatic system – without toxicity (1). The team prepared and characterized nanoparticles with docetaxel, everolumus and the experimental compound LY294002. According to the researchers, after administering the drugs to mice, they found that the combination treatment was safe and "more potent compared to the individual drugs alone."

"The system is based on a nanostructure platform that can deliver three anticancer drugs to the cancer tissues at the same time," says Adam Alani, assistant professor at pharmaceutics and lead author of the study. "The three drugs inhibit melanoma cell proliferation by three different mechanisms of action and they affect the cancer cells synergistically." Docetaxel acts by stabilizing the microtubules, whereas everolimus and LY294002 together completely inhibit the mTOR pathway – LY294002 is also capable of inhibiting the Phosphoinositide 3-Kinase pathway. "The three-drug delivery system has the ability to target the lymphatic system, which act as a haven for the melanoma cells and is the major path for melanoma metastases to occur," he adds.

To bring the concept of a combined nanoscale drug delivery system to fruition, Alani and his colleagues first had to tailor the nanoparticles to the drugs in question. "While general principles for lymphatic drug delivery are well established, each polymer and drug combination presents its own unique challenges," says Alani. "Finding the nanoparticle with the appropriate surface properties and being able to load clinically relevant drug concentrations was the most time consuming and frustrating part of the work."

Alani also stresses that the development of new drug delivery systems is limited by the complexity of the disease state itself. "We are still uncovering genes that are affected and determining molecular targets for proteins regulated by these genes," he explains. "As our understanding of the disease state improves, drug delivery can become more refined and newer approaches can be explored." *JS*

Reference

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From Brick Dust to Blockbuster?

Many drug candidates are as poorly soluble as "brick dust", making oral delivery a significant challenge. Fortunately, self-emulsifying lipids – and other innovative solubilizers and polymers – have risen to the challenge of the insolubility dilemma in drug delivery.

Shaukat Ali has spent most of his professional life immersed in lipids. After obtaining a PhD from the City University of New York in lipid-chemistry and the post-doc from the University of Minnesota and Cornell University in the physical biochemistry of lipids, he joined The Liposome Company (Princeton, NJ), where he developed methods to reduce drug toxicity by formulation in liposomes. Now, as Technical Support Manager for Pharma Ingredients & Services at BASF, Ali promotes BASF's range of solubilizers and polymers for drug formulation, including a selection of lipid-based drug delivery systems (LBDDSs). "The bioavailability challenge is enormous," Ali says. "There is no one-size-fits-all approach, but it's immensely satisfying to determine the best formulation for a given molecule."

The insolubility solution

Water-insoluble drugs usually dissolve in non-aqueous solvents, such as ethanol, but will rapidly precipitate once that solution is introduced to an aqueous medium, such as which is found in the stomach. Oral delivery of these drugs, however, is not impossible. Ali says the key, is to add other components or solubilizers to the non-aqueous drug solution so when the solution is mixed with an aqueous medium, it emulsifies to form tiny droplets that contain the drug and protect it from exposure to water. Ideally, the droplets both prevent drug precipitation and are readily absorbed. The magic ingredients that promote emulsification are surfactants – molecules that have both hydrophobic and hydrophilic regions, providing them with the convenient ability to interact with both aqueous and non-aqueous media. "In practice, this means that the solution of drug dissolved in the non-aqueous solvent is distributed in the aqueous medium as a suspension of microdroplets – a microemulsion – each bound by a layer of surfactants in which the hydrophobic tails of the surfactant are oriented to the interior of the micelle, and the hydrophilic headgroups oriented to the exterior," explains Ali.

Ali's expertise lies in the precise choice of surfactants. Getting the lipid based surfactants right is crucial because all surfactants have different chemistries and every drug is unique. "It's a case of matching the correct surfactant to a given drug in the context of that drug's delivery requirements. The aim is to identify a surfactant which can not only emulsify the drug as outlined above, but also ensure that the drug remains encapsulated in the interior core during gastro-intestinal transit, ultimately getting efficiently absorbed," says Ali.

Fat benefits

When it comes to micro-emulsion stability, Ali points out that drugs need to remain in solution for extended periods – perhaps 3-5 hours – as they move through the stomach to the absorptive region of the gut. A drug may seem perfectly stable in a given LBDDS at first, but if it starts precipitating after only 30 minutes then the formulation will need to be redesigned. Furthermore, given the number and range of pH changes to which the micro-emulsion droplets are exposed as they move from stomach to intestine, it is essential the droplets remain stable over a broad pH range. Ali says, "The ideal surfactant should be non-ionic so it is resistant to pH changes."

However, it is not just gastrointestinal pH fluctuations that can cause problems – what about all the digestive enzymes? If enzymes penetrate the micro-emulsion, they hydrolyze the surfactant fatty acid chains, breaking down the ester linkage between the hydrophilic and hydrophobic parts of the surfactant. Once that happens, the droplets rapidly break down, exposing their drug cargo to aqueous media, which results in drug precipitation. Resistance to digestion therefore is essential; and it too depends on the surfactant's fatty acid composition of the micro-droplets. "The packing of fatty acid chains inside the microemulsion is critical to the stability of the LBDDS formulation," says Ali. "One solution is to use an emulsifying agent (such as BASF's polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40) that has a long, saturated C18 fatty acid chain that goes deep into the droplet core. These features will reinforce the micro-emulsion surface by making it more tightly packed and promoting lateral interactions between fatty acid chains like those found in lipid-cholesterol natural membrane." Such features keep out digestive enzymes, protecting surfactant molecules from ester cleavage, whereas surfactants with short and unsaturated fatty acid chains may provide looser packing and less effective enzyme exclusion, making them less digestion-resistant.

To promote good drug absorption, emulsion droplet size is critical. Droplet size is a function of emulsification rate, which in turn is, again, dependent on the amount of surfactants in the formulation. Ali says that BASF's surfactants routinely provide droplets of 20-150 nm, depending on the precise surfactant and formulation composition. "At that size, they just disappear in an aqueous medium –the solution is completely clear. Nanometre-sized droplets get absorbed very efficiently, which is always a benefit in drug delivery," he says.

"LBDDSs have clear benefits in terms of solubilization, stability and absorption."

In addition, smaller particles are also less likely to suffer from food effects. Ali points to cyclosporine as an instructive example. Novartis first launched cyclosporine as Sandimmune®, but years later it was reformulated and launched under a new name, Neoral®. "The Sandimmune® formulation does not self-emulsify; it forms large emulsion particles that vary in bioavailability, for example between fasted and non-fasted patients," explains Ali, "but food effects aren't seen in Neoral® because it has the right surfactant, so it is self-emulsifying and produces only tiny droplets."

Development decisions

LBDDSs have clear benefits in terms of solubilization, stability and absorption, but in the time-pressured world of drug development, these features aren't always enough. Drug development also has to be fast. "The more you delay, the more chance for a competitor to launch a product ahead of you. It takes so long to synthesize and optimize drugs that you lose 3-5 years just figuring out which molecule to push into drug development," says Ali. "And your patent lifetime is only 17 years."

Ali believes the need for speed persuades many companies to choose softgel LBDDS formulations. He says, "It saves time and cost; you can go straight to a contract manufacturing organization and they're all set up. They can come up with the desired formulation in a few weeks." As an example, he cites Abbvie's Kaletra®. "This HIV drug was launched as a softgel capsule to save time. It was only formulated as a tablet years later. This is typical of industry trends today as well; pharma wants to get to the clinic as soon as possible, especially when there are patients who need the drug."

As oral drugs are easy to administer (and with many patients disliking injections), Ali believes that oral delivery will always be the dominant route. 70 to 90 percent of drug candidates do present solubility issues, but a growing range of solubilization technologies are being designed to tackle the challenges. "At BASF, we're developing and offering a range of lipid-based and polymeric excipients to meet the formulation challenges in the solubilization of APIs and many other formulation needs," says Ali. "Even 'brick dust' can be turned into a potential blockbuster."

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

The CMO Serialization Threat

The serialization deadlines are coming. It may seem an age away, but preparing for serialization is not as straightforward as you may think. Do you really want to get left behind?

By Dirk Hendrik Kneusels, Branch Director, Antares Vision Germany, Bensheim, Germany.

The serialization race has begun. Worldwide, countries are implementing rules for improving the security of medical supplies – and serialization has become the weapon of choice for fighting counterfeiters and fraudsters. Some countries are even going further by aggregating serialization with product traceability to control their medical supply chains. By 2020, we should expect approximately 90 percent of prescribed (Rx) medications worldwide to bear a serial number.

Serialization poses challenges to all stakeholders in the medicines supply chain, but I believe that there are some unique challenges for contract packers in particular. They will need to be equipped with adequate solutions to meet international requirements, but must also be flexible enough to meet all of the (very) different requirements of their customers.

Looking at the current situation in Europe and the US, with serialization deadlines fast approaching, I believe the majority of contract manufacturing organizations (CMOs) are not ready. When discussing the situation with CMOs, they often tell me that they have asked their customers for their serialization requirements, but are not getting sufficient feedback. Additionally, they think that modifications to their machines and infrastructure can be completed within just a few months!

Are CMOs using the lack of feedback and general ignorance from customers of what needs to be done as an excuse to not think too deeply on the issue or do they honestly believe that the challenge isn't that great? A significant percentage of Rx medicine production is covered by CMOs. And the deadline for serialization is well known. CMOs – and their customers – need to prepare now.

If I sit and try to think like a CMO, I can see a few choices before me...

i. Invite my customers to help plan a joint strategy, define budgets and set milestones.
ii. Invest in a track-and-trace system – and hope that I have made the right choice and that some of my customers will pay for it.
iii. Give up working in the pharma industry!

Serialization will add cost to the bottom line – a fact that must be accepted. Perhaps through optimizing the system, some of the costs will decrease later, but that is another subject for another day. If CMOs and their customers are caught between two stools over when they should make a move, they need to be aware that time is critical and they really need to get moving – or both will suffer the consequences of being late starters.

My appeal to CMOs is for them to ensure that they remain in the game as deadlines approach. They must get in

"My appeal to CMOs is for them to ensure that they remain in the game as deadlines approach."

touch with their customers and assess potential track-and-trace vendors. Make sure that you treat this as a priority and not just a sideline project; it requires a dedicated full-time team to run a serialization project and to exploit serialization as a competitive opportunity.

I also have an appeal for pharmaceutical companies: you must provide the necessary support early enough by ensuring that your CMO partners understand the needs of the legislation – and that you meet your own specific needs too. As the deadline approaches, it is likely that the CMO market will consolidate as unprepared CMOs end up pushed out of the market. And by then, it will be too late for pharma companies to register their products with another CMO. For that reason, it is in the core interest of the pharma industry to support their CMOs in defining the right strategy.

As the author Douglas Adams is reported to have said, "I love deadlines. I like the whooshing sound they make as they fly by". Don't let that whooshing sound be the last thing your company hears...

The Adverse Event Data Advantage

A personal experience led us to examine how adverse drug events data can be used to benefit the industry.

By Brian Overstreet, President at Advera Health Analytics, Santa Rosa, California, US.

Towards the end of 2011, my business partner's wife became sick from an adverse drug event. We did what most people would probably do in the same situation – we turned to Google. But even with a million hits, we still didn't have clear explanations as to why it had happened.

Here in the US, we see drug advertisements all the time, and although they list possible side effects they do not answer the key questions. What are the odds that I will experience that side effect? What happens if I do experience that side effect? How quickly will I get better? Will I die? Patients need this information. And yet little attention has focused on this area. At the time of the illness, my business partner (Bob Kyle) and I discovered that the FDA had a massive data set on adverse drug events. Unfortunately, it wasn't making that data easily accessible or allowing people to run queries against it.

In my view, there are tremendous benefits to cleaning this type of data up – not just for patients, but also for pharma companies, hospitals and insurers – so that's what we did. Bob and I have a lot of experience in healthcare data and research reports. We are the founders of Sagient Research and, at the time of the illness, we were in the process of selling the company to Informa. Because of our background, we thought that some research into adverse drug events would be a nice little side project – the aim was to quickly throw the project together and put up a website. How ignorant our thinking was at the outset! We quickly realized the importance of adverse drug event data and the project ballooned.

"If pharma companies get involved in digging through this data they will discover a number of benefits."

We formed a company called Adverse Events (although we changed the name in 2015 to Advera Health Analytics). It took us over 18 months to dig through the FDA's adverse event database and we managed (with a lot of hard work) to create a clean data set against which we could run queries against. We also developed an algorithm that maintains the cleanliness as we bring new data in. At the start, we were just using the FDA database but now we're also incorporating other data too.

Most people don't like to think too deeply about adverse events – and I think that pharma companies would prefer that all the negative information

"When we attended trade shows, people would come to the booth, stop, tell us that they weren't allowed to talk to us and walk away!"

about their drugs was not known at all (for obvious marketing reasons). Indeed, when our company was called Adverse Events, we soon found that some companies were scared by the name alone! When we attended trade shows, people would come to the booth, stop, tell us that they weren't allowed to talk to us and walk away! There were bigger reasons for the name change too – most importantly, our business has since expanded to cover much more than adverse events data.

But when it comes to adverse drug events, the data is already publicly available. At times it can be difficult to find, but it is there and if pharma companies get involved in digging through this data they will discover a number of benefits. For example, a company can conduct concert studies or reviews on the data to compare the safety of their new drug with drugs that are already on the market. They could also do the inverse. Such studies produce verifiable and validated results that can be published or taken to a conference and presented as a poster. It's also possible to use adverse events analytics to predict FDA alerts on drugs – we predict correctly about 70 percent of the time. And though companies may not want to deeply consider such facts, it's better to have a heads up on any potential changes. Although our journey started with a patient, I believe analytics actually benefit patients the most through a top-down approach, so pharma companies, hospitals and insurers need to get stuck in.

Layer by Layer

Does the fabrication of nanoparticles and nanocapules sound complex? Don't worry – layer by layer technology allows for simple fabrication of complicated stuff.

By Omar Sakr, Olivier Jordan and Gerrit Borchard, from the Laboratory of Pharmaceutics and Biopharmaceutics, University of Geneva, Switzerland.

The fabrication of nanoparticles sounds complex enough by itself, so what about when we try to be even more adventurous, such as fabricating hollow nanocapsules? How would you feel about fabricating nanoreactors or designing small nanoparticles with two distinct chambers? Innovative ideas are sometimes very complicated, but luckily handy tools are out there to help. In particular, we strongly believe that the sequential deposition of molecular layers, widely known as Layer-by-Layer (LbL) technology holds great potential. Since its introduction by Decher and colleages in 1992 (1), coating flat surfaces, as well as micro- and nanoparticles, using LbL technology has become an active area of research that has many potential applications.

In its simplest form, LbL is based on alternating the deposition of oppositely charged polyelectrolytes on a charged surface. For example, a negatively charged surface is coated with a positively charged polyelectrolyte. Polyelectrolytes are polymers with charged repeating units; when they are adsorbed by electrostatic attraction, some charges will be neutralized and some will remain free, to which a second layer of negatively charged polyelectrolyte is adsorbed. This process can be repeated as much as needed to build up a layered system of tunable characteristics. Interestingly, LbL assembly can be done using other types of interaction as well, such as hydrogen bonding, coordination bonding, and hydrophobic interactions. As a result, a diverse range of components is at hand to build LbL structures, including – but not limited to – synthetic and natural polymers, proteins, nucleic acids, dyes and dendrimers (2).

Perhaps we have made LbL deposition sound very simple (and, in some ways, it is), but when it comes to creating very complicated, multifunctional structures the magic only happens when the right components are added in the right sequence. Initially, LbL structures were typically flat films coating charged surfaces; for example, surgical stents coated with films that release anti-bacterials to reduce infection-related complications or the immobilization of antibodies to create immunosensors (3, 4). A turning point was the introduction of the "sacrificial core" technique. Let's consider a suspension

of calcium carbonate nanoparticles carrying a negative charge. After coating with several polyelectrolyte layers, cores are destroyed using an EDTA solution, leaving a suspension of hollow nanocapsules. If these layers were assembled on enzyme crystals followed by dissolution of the enzyme crystals, we can obtain high enzyme loading in nano-sized capsules. As small molecules can diffuse through the pores of the LbL shell, we obtain nanoreactors – where substrates can diffuse in, get processed by the enzyme and products diffuse out (5).

Enzymes were also used to design multilayer films that are glucose sensitive, releasing insulin in response to the presence of glucose molecules in the surrounding medium. The design depends on an assembly of alternating layers of glucose oxidase (GOD) and catalase (CAT) on positively charged insulin crystals salted out in an excess of sodium chloride. GOD converts glucose into gluconic acid, releasing molecular oxygen and producing H2O2. The production of gluconic acid lowers the pH value at the surface of the shells and enhances its permeability to release insulin. In addition, the decrease in pH favors higher insulin solubility in water, thus facilitating the release from the system. Nevertheless, GOD activity may suffer decay with time due to peroxide-introduced degradation, leading to low sensitivity to glucose. However, the role of CAT is to convert the aggressive H2O2 into H2O and O2 – most of the oxygen produced is consumed by GOD (6).

Another exciting (but complex) application of LbL technology is the co-delivery of protein and small-molecule drugs via double chambered nanocarriers, with the aim of overcoming the non-uniform distribution of different, simultaneously administered drugs. In an interesting example, liposomes loaded with chemotherapeutic agents were coated with LbL films containing siRNA molecules to attack an aggressive form of breast cancer (7).

LbL is a technology with high potential, and with many research groups in this field, we expect to see a plethora of applications. But we should not forget that technical challenges exist in terms of upscaling the process and the handling of excess volumes of liquids. However, these are challenges that we can overcome together with the pharma industry – with the ultimate goal being to introduce new, innovative and more efficient products.

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Ultra-Engineering UHPLC from Scratch

Incremental improvements to ultra-high performance liquid chromatography (UHPLC) have failed to deliver the tangible advances that researchers really want. Sometimes, a full overhaul by re-engineering from the bottom-up is the only way to innovate and move the field forward.

Graduating with a B.S. in Microbiology, Kevin McCowen confessed that he didn't know a lot about analytical science when he took an interview for an entry level QC chemist role. The company decided that he was a cultural fit and would be worth taking a risk on training. Sixteen years later, he is an associate scientist in analytical development at Ajinomoto Althea in San Diego – and he can't get enough of analytical science, particularly biotherapeutic characterization.

Althea is a biologics contract development and manufacturing organization. The main role of the Analytical Development department is to support its clients' drug programs, but the Analytical Development team also likes to take on independent projects (particularly with partners) that allow them to exercise not only their knowledge of biophysical characterization, but also regulatory requirements. "I am constantly looking for a challenge, so a field like biopharmaceuticals is well suited for my need to expand and explore," says Associate Scientist, Kevin McCowen. "And I get to apply a variety of different techniques. I might start with HPLC, but if I see something interesting I might look at it further using Fourier transform infrared spectroscopy, and then I might do an ELISA for functional characterization. I enjoy thinking about a problem and looking for a solution that is multifaceted."

And although Althea's Analytical Development lab has a number of techniques in its analytical toolbox, UHPLC is one that McCowen is particularly excited about because it removes the need for the HPLC-associated trade-off between sensitivity, speed and resolution.

Putting the ULTRA back into UHPLC

When UHPLC systems were first introduced, they were faster and offered higher throughput than standard HPLC systems, but there were also a number of teething issues, including system robustness, complicated method transfer, and reproducibility concerns. Efforts were made to address these issues, but according to Jeanine Pippitt, Regional Marketing Manager for Thermo Fisher Scientific, the industry mindset tended to veer towards incremental improvements over instrument revolution. However, if you fix one problem at a time, you may cause further (and sometimes new) problems. For example, providing the system with a higher pressure pump can damage the injector; and developing an injector compatible with the new pump may cause column problems. "I think a lot of incremental improvements that we've seen in UHPLC systems were actually more like a series of band-aids," says Pippitt. "We wanted to do better."

The Althea Analytical Development lab recently took delivery of a Thermo Scientific™ Vanquish™ UHPLC System. "When instruments evolve, it's always interesting to see what new challenges the technology will allow us to solve," says McCowen. "We are working on transferring an amino acid method to the Vanquish UHPLC System, and we've been able to achieve faster separations as well as good resolution. As a practical example, we've been able to resolve leucine from isoleucine while decreasing the run time by half – without putting a lot of effort

into method development."

And, despite initial skepticism, Pippitt certainly has no doubts about the capabilities of the system. "When I first saw the data on the Vanquish UHPLC System, I almost didn't believe the chromatography presented in the literature. I thought it was just marketing fluff. It's not."

Analytical advances – engineered

"We didn't want our system to offer an incremental increase above other systems. We designed it from the bottom up and looked for the best technology – from whatever industry – for each UHPLC feature," says Pippitt. "We rejected industry-standard column injectors, and instead developed a device which meters samples with better precision. Similarly, we tried to find the best pumping technology, construct robust valves with diamond-like coatings, use 'fingertight' fittings with zero dead volumes, produce a detector with the highest sensitivity and build in a continuous flow of solvent to wash the needle. Developing a system that delivers uncompromised UHPLC – no trade off in performance, robustness and ease of use."

As a development lab, McCowen's group is expected to work with clients to solve difficult problems related to biotherapeutic characterization, which goes beyond simply analyzing a sample and sending back the data. In many instances, clients are working to tight timelines. "UHPLC instruments such as the Vanquish are helping us to turn around data in a short period of time. I think that the increased speed and resolution have made the biggest impact so far, but it's still a new addition to the lab," says McCowen. "We're still investigating different column temperature control modes and pre-column compression capability – and how they affect separations of larger proteins."

"In a busy lab, systems need to be easy to use and maintain," adds McCowen. "For example, it's easier to track column use and performance. Another factor that's important in labs today is space. Instruments designed to be stackable help address this issue. What I really liked with the Vanquish UHPLC System is that the mechanics can be slid out of the housing on rollers – just like a drawer. As a bonus, it also looks like something NASA might like to use..."

"In a busy lab, systems need to be easy to use and maintain."

"Kevin has also been exploiting the extended sample capacity afforded by the Thermo Scientific™ Vanquish™ Charger module, allowing increased sample analysis capacity while maintaining the samples at the same conditions as the autosampler; the Charger module is integrated into the autosampler as an add-on," says Pippitt. Unlike other systems, the sample extension is aligned well with software and bar code readers so that there's never a sample missed.

Since the Vanquish UHPLC System is a relatively recent addition to the Althea Analytical Development lab, the team is still experimenting with its potential and investigating how certain features (such as the two different methods of temperature control and the pre-column compression) can affect separations. "We've already started working on some projects that we hope to publish. I can't give too many details away, but I will say that we're planning to take full advantage of all of the column heating mechanisms and detector capabilities to do that work," says McCowen. "And we've been using the Thermo Scientific™ Dionex™ Chromeleon™ Chromatography Data System to help us keep things in order – and ensure that our data are meeting compliance guidelines."

Analytical crystal ball gazing

What does the future of biotherapeutic characterization and instrumentation hold? McCowen and Pippitt are unsure of how accurately the future can be predicted. McCowen says, "If you'd asked me about the future 15 years ago, I would have given you the wrong answer. I never would have imagined that a mass spectrometer that fits on a bench top could rival the data coming out of the system I was using back then, which had a magnet so large that a room had to be built around it!"

"Speed, sensitivity and specificity will always be crucial aspects – so I can definitely say that they will continue to advance in both LC and MS technology," says Pippitt. "But right now, the Vanquish UHPLC System is pushing those limits of sensitivity, speed, resolution and retention time precision. In fact, when I demo our system side-by-side with a lab's existing set-up and their application, some customers ask us to leave the demo machines with them..."

Overall, McCowen believes that the move to UHPLC has significantly increased his lab's analytical capability. "The trend towards more automation is also changing how we work. But the most important thing is that technology should evolve for the right reasons. Incremental changes aren't always what researchers want. Real evolution should build on what we already know – it shouldn't be like having a dial on a guitar amplifier that goes to 11, even though we can't really make 11 any louder..."

Biopharma's Brave New Biology

We live in exciting times for the biopharma industry. The 100-year-old promise of cancer immunotherapy turning cancer into a chronic (if not curable) disease seems within reach in selected indications. Complex cellular and gene therapies are starting to deliver significant benefits to patients; we now have a well-tolerated cure for Hepatitis C virus; and more broadly, new players like Google are bringing a fresh approach to biopharma innovation, with big data fueling R&D and clinical decision-making.

By Markus Thunecke and Pauline Ceccato

If we look at the market appreciation of the last three years (see Figure 1), it's clear that biopharma has made a big comeback from a long period of relative depression. The industry climate has dramatically shifted; after years of dreary discussions concentrating on patent cliffs and poor R&D productivity, the focus today is more positive – leaning towards the technologies and drugs that can make a real difference to patients.

But at the same time there are concerns that this new trend will not live up to its promise – memories of the last bull market around the 'genomics hype' of 2000, which ended in a crash and a decade of depression and R&D productivity crisis for biopharma, come to mind. In addition, growing arguments around drug pricing and reimbursement have generated a general nervousness in the industry, especially when these concerns become a topic of political debate (biopharma share prices tumbled after Hillary Clinton tweeted a promise to tackle drug costs). With unprecedented clinical advances on one hand, and growing sustainability questions on the other, what is the outlook for biopharma? Can we believe that we will not once again fall into a 'post-2000-style' depression?

The path forward is certainly not clear. But unlike 2000, when immature science and the hype of genomics drove up valuations, today we are seeing new products and medicines that truly address unmet medical needs – in some cases, offering cures where there were previously none. Many of the developers of these products have turned into fully integrated biopharma powerhouses, such as Gilead, Celgene, Biogen and Regeneron, reaching a size and stability that was unthinkable back in 2000. Behind these products and companies lie exciting advances in applied science – which is becoming known as 'The New Biology'. The following sections highlight a number of exciting advances.

Immuno-oncology keeping cancer in check

Immuno-oncology is starting to fulfill its promise of turning cancer into a chronic, if not curable condition. For instance, the arrival of treatments such as Bristol-Myers Squibb's ipilimumab (Yervoy) in 2011, followed by nivolumab (Opdivo; also from BMS) and Merck's pembrolizumab (Keytruda) in 2015, have dramatically improved the survival rate of certain subsets of patients with melanoma and non-small cell lung cancer, both of which are known for poor outcomes. The success of these immune checkpoint inhibitors is paving the way for an array of cancer therapies that harness similar mechanisms. Over 20 disease-relevant immune checkpoints have been identified and are currently being explored as therapeutic targets. Moving forward, combinations of different checkpoint therapeutics are expected to improve survival even more radically – and in a larger number of patients, as seen with the combination of ipilimumab and nivolumab in advanced melanoma.

However, the downside of harnessing the immune system is the risk of pushing it into overdrive, which can lead to serious autoimmune reactions. As a range of checkpoint therapeutics reach the clinic, combination regimens will have to be carefully designed and monitored to avoid excessive toxicities. But this revolution initiated by checkpoint inhibitors is now opening a window for a broader range of immunotherapies. Once an exciting field, cancer vaccines have been plagued by multiple failures in the clinic due to weak efficacy; in the near future, combinations with

Figure 1. Compared relative evolution of the NASDAQ Composite and the NASDAQ Biotech Index. After the depression of the 2000s, market appreciation of biotech stocks has been climbing up to unprecedented heights since 2011, coinciding with promising scientific and medical advances on multiple fronts. The recent drop illustrates growing concerns regarding the sustainability of this trend, amidst an uncertain pricing and reimbursement climate (source: Yahoo Finance).

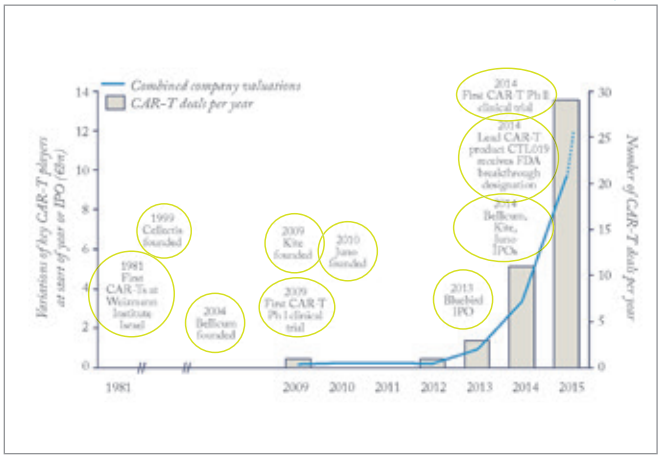

Figure 2. Bars: number of deals (strategic alliances, licenses, or company acquisitions) involving CAR-Ts. The upward trend over the past three years reflects the soaring interest for the technology (source: Global Data). Line: combined market capitalizations of key companies focusing on CAR-Ts (Bellicum, Juno, Kite, Cellectis, Bluebird Bio) in € billion, at the start of each year or time of IPO. The dotted line represents these combined valuations, as of November 2015. (source: Yahoo Finance). Bubbles: key CAR-T events.

checkpoint inhibitors may be able to lift the brakes off the immune system and allow vaccines to finally deliver on their promise.

Overall, immuno-oncology is triggering an unprecedented seismic shift that is poised to far surpass the advances we have seen with the advent of targeted therapies. Reflecting this, analysts are forecasting the immune-oncology market to grow to over €20 billion by 2025.

The key to curing cancer: cell therapies

Another recent breakthrough in immuno-oncology is the advent of complex cell-based therapies, such as T-cells engineered with CARs (chimeric antigen receptors) and eTCRs (engineered T-Cell receptors) to selectively kill tumor cells. In early trials, treatment with CAR-Ts has produced previously unseen rates of clinical responses, including complete remissions (80-90 percent) in patients with acute lymphoblastic leukemia (ALL). And although outcomes in other hematological malignancies are less spectacular, they still remain extremely encouraging. We believe that the potential of CAR-Ts and eTCRs goes well beyond extending survival. In the not-too-distant future, they could perhaps provide a cure to a selection of patients with blood cancers. Solid tumors will be the next big field to tackle, although the limited clinical experience so far indicates that this will not be as straightforward as in leukemia, as the strong potency goes hand-in-hand with potentially harmful toxicities (the current mantra is "dose low, go slow").

If successful, CAR-Ts and eTCRs would become, by far, the most radical innovation to hit the field of cancer therapy in decades. They are, however, less mature than checkpoint inhibitors – the most advanced products are only in Phase II, and we're still far from having established CAR-T cures across multiple tumor types. But the field is moving extremely fast, and industry and investors alike have embraced it with great enthusiasm. This is reflected in the soaring number of CAR-T deals over the past few years, and the combined market capitalizations of the main biotechs focused on CAR-Ts, which are now reaching €12 billion (see figure 2).

Gene therapy rising from the ashes

In the 1990s, gene therapy was touted as a breakthrough that would cure many hereditary diseases. Unfortunately, safety issues linked to immune reactions and vector integration into the genome, culminating in the death of a patient in 1999, led regulatory authorities and industry alike to reconsider the risk-benefit potential of gene therapy, and plunged the field into depression.

But there have been a number of encouraging success stories recently, with gene therapy correcting monogenic diseases in a handful of patients with blindness due to Leber's congenital amaurosis (1), hemophilia B (2), X-linked severe combined immunodeficiency (X-SCID) (3), and other inherited immunodeficiencies (4). In parallel, the design of gene therapy products has improved in leaps and bounds, addressing many of

the previous concerns with novel vectors that do not integrate into the host genome.

The improvements in design and clinical outcomes culminated in the (restricted) European approval of alipogene tiparvovec (Glybera) in November 2012, making it the first gene therapy to ever be approved for marketing in any of the major pharma markets. Despite the controversial clinical efficacy of Glybera and its restricted label, the approval sends a strong signal that the EMA is prepared to consider other gene therapy products for approval, despite a decade of extreme cautiousness.

Over a hundred clinical gene therapy candidates are moving through the pipeline, mostly for rare genetic diseases such as inherited retinal dystrophies or hemophilia. Although there is still much room for optimization of the technology (for example, to improve the durability of the therapeutic effect or to address questions of vector immunity), very promising early clinical data exists in several indications, and we are no doubt poised to see more gene therapy products in the spotlight over the coming decade.

"Behind these products and companies lie exciting advances in applied science – which is becoming known as 'The New Biology'."

Curing Hepatitis C

The past five years have seen radical advances in the field of Hepatitis C (HCV); for instance, the arrival in 2011 of the new antivirals boceprevir (Victrelis; Merck) and telaprevir (Incivek; Vertex Pharmaceuticals) resulted in impressive cure rates of 70 percent in combination with interferon-based standard of care. Three years later, Gilead introduced the once-daily oral treatments sofosbuvir (Sovaldi) and the combination sofosbuvir-ledipasvir (Harvoni), which removed the need for an interferon backbone. Harvoni has pushed the efficacy bar even higher to achieve sustained virological response in over 90 percent of patients with genotype 1 HCV after only 12 weeks of treatment, with a favorable side-effect profile. In other genotypes, Sovaldi and Harvoni have also greatly increased cure rates, in combination with the standard backbone of ribavirin and/or interferon.

This latest generation of therapies has effectively turned HCV from a chronic condition into a curable disease for the large majority of patients. On Gilead's side, the HCV franchise is hugely successful, with sales forecasted to reach over €12 billion by 2020 – in part thanks to the high price tags for these therapies, which is another burning issue that we'll address later in this article…

Moving beyond HCV, HIV now appears to be the next frontier in curing infectious disease, and two recent experimental approaches may bring us closer to this goal than ever. The first one is the "shock and kill" strategy, a drug regimen that uses a "shock agent" to reactivate latent HIV-infected CD4 T-cells, which are then recognized and eliminated by a "kill agent", effectively suppressing latent HIV reservoirs. The second approach stems from the observation that people who are homozygous for a loss of function mutation in CCR5 (a cellular viral receptor) are resistant to HIV infection. Incidentally, in 2008, an HIV patient was cured after receiving a bone marrow transplant from a donor harboring such a mutation (the so-called "Berlin patient") (5). In a recent study that used a gene editing technique, the CD4+ T-cells of HIV patients were edited ex vivo to render the CCR5 gene non-functional, and then transplanted back. Promising early results have been published, with several patients achieving long-term viral control without the need for antiviral therapy (6).

The power of gene editing

The ability to make precise, targeted modifications to the genome of in-vitro and in-vivo models in a reliable and efficient manner has long been a goal in biomedical research. Gene-editing techniques, such as zinc finger nucleases (ZFNs), have been successfully used to target genes in mammalian cells since the mid-2000s. However, in 2012, a new method came to the front stage and sparked a flurry of interest from the industry: the CRISPR-Cas9 system. CRISPR enables targeted genome manipulation in a highly efficient and versatile way. Unlike prior methods that relied on proteins to guide gene editing, CRISPR employs a short sequence of RNA. For any given gene, the process of generating the guiding RNA sequence, and editing the gene, resulting in a ready-to-use assay, can be completed in just two days.

Beyond bench research, gene editing also opens up the way to novel therapeutic approaches. Leading this wave is the ongoing HIV trial we mentioned earlier – in which ZFN editing is employed to knock-out the CCR5 gene in patients' CD4+ T-cells ex vivo. Beyond ex vivo knock-outs, the long-term goal is to correct genes or insert new ones in vivo (that is to say, without prior extraction of the patient's cells), which would open the door to cures for a much broader range of diseases than current ex vivo strategies allow. Of course, we are at least a decade away from seeing such approaches being broadly and reliably applied into patients, but the advent of novel, efficient technologies such as CRISPR is certainly broadening the field of possibilities.

Tapping into precision medicine

For a long time following the genomics hype, precision medicine (also known as personalized medicine), which sits at the intersection of molecular diagnostics, therapeutics and big

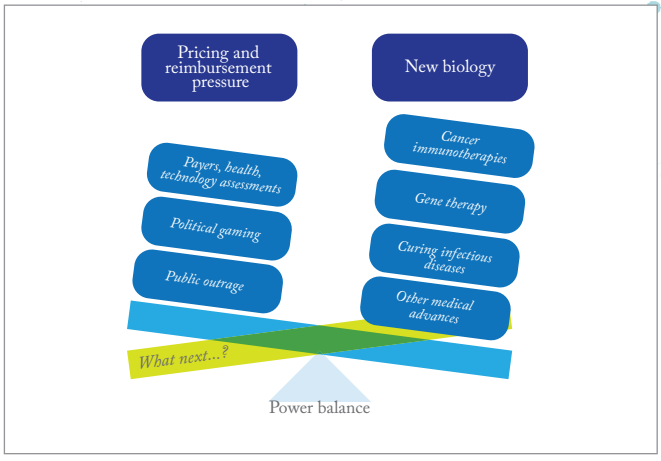

Figure 3. The power balance is tipping in favor of the biopharma industry, while payers and other actors in favor of tight pricing regulations have a limited impact.

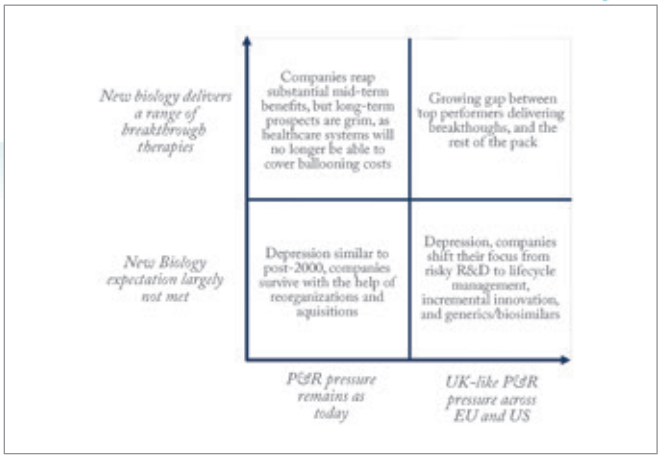

Figure 4. Possible future scenarios for the biopharma industry based on pricing & reimbursement (P&R) environment and success of New Biology.

data, was very much an unfulfilled promise. But today, that promise is coming to fruition as precision medicine is beginning to deliver real value to patients. In oncology, the genetic makeup of tumors is playing an increasingly important part in determining which treatment a patient will receive; patients with lung, breast, colorectal, skin and blood cancers routinely undergo molecular testing. Pushing it a step further, institutions like the Memorial Sloan Kettering Cancer Center (MSKCC; funded by Roche) and the US National Cancer Institute are running trials that match patients with drugs based on the mutations in their tumors, regardless of histology (so-called "basket studies").

Taken together, these initiatives are slowly leading the way to a world in which, one day, each patient could receive an individualized, dose-tailored cocktail of drugs. However, we have only just begun to tap into the potential of precision medicine to improve patient care. Actors in and outside the healthcare industry have recognized this huge potential too, as we have seen with the rise of companies like the sequencing giant Illumina, as well as with strategic alliances between Foundation Medicine and pharma companies like Roche, Novartis and Johnson & Johnson, or the multiple investments of Google in healthcare to back big data companies like Foundation Medicine, Flatiron, DNAnexus, and Predilytics. Lastly, in January 2015, Barack Obama announced the Precision Medicine Initiative, with a $215-million initial investment, and a short-term focus on cancer, and a long-term goal of developing knowledge on a broad range of conditions.

Putting a price on innovation

Although the above advances of new biology show that we are well beyond the immature science that spurred the genomics hype of 2000, danger still lurks on biopharma's horizon. The willingness and ability of healthcare systems to fund these novel therapies is a growing concern, particularly as the prices of newly approved drugs seem to reach record heights year after year; for example, the gene therapy Glybera was initially priced at €1.1 million, and Gilead's HCV Harvoni treatment reached over €66,000 per treatment course in Germany, and $85,000 in the US.

In oncology, the progressive shift of treatment standards to novel-novel combinations or cell-based therapies will push prices to unprecedented levels – the newly approved combination of ipilimumab and nivolumab in metastatic melanoma is expected to cost over $250,000 for a year of treatment in the US (without accounting for rebates and patient access schemes), for an additional 4.2 months of progression-free survival over ipilimumab alone. As a result, the public is increasingly reluctant to accept new drug prices. The outcry over the price of Gilead's HCV medicines, and the recent scandal over Turing Pharmaceuticals hiking the price of a toxoplasmosis drug by over 5000 percent, are perfect examples. And in the medical community, 118 oncologists recently expressed their concerns in Mayo Clinic's medical journal and called for new pricing regulations (7).

The fact that the pushback against pricing comes at a time when real advances in new biology are being made represents a real crossroads for the biopharma industry. And many questions must be answered as we try to decide the best path forward. What are a few additional months of survival worth to cancer patients? What is a cure worth in a disease in which only a minority of patients will develop serious, expensive complications (as is the case of HCV)? How should gene therapy be priced, if it could potentially offer a cure after only one application? And importantly, can we find a balance where drug prices allow sustainable healthcare systems, but still support R&D and innovation?

In an ideal world, new drugs would generate cost savings (for instance, by reducing the number of hospitalizations), which would lead to a sustainable, balanced system of healthcare and innovation. Although companies sometimes claim such benefits, the savings have often been unrealistic or difficult to assess in practice.

At the moment, the balance of power largely lies with the industry in that new therapeutics are brought to the market at prices that are set by drug makers (see Figure 3). This has long been the status quo, and rebates and other restrictions put in place by European and American payers have not managed to significantly counterbalance this trend. How will this evolve in the future? A likely scenario is that a pro-industry political climate and the lack of a strong, unified "payer power" will allow the status quo to remain (with prices largely unregulated) particularly in the US. In the medium term, this would be beneficial to the biopharma industry, which would stand to reap substantial benefits from the advances of new biology.

Breaking the bubble

While the above may sound advantageous for the biopharma industry, in the long-term, the prospects are grim. What will happen to patients once healthcare systems can no longer afford the ballooning costs of new treatments? In a different scenario, under a more challenging political climate for the industry, both the US and EU would implement a tighter price regulating system – perhaps one comparable to the QALY (Quality-adjusted life year) framework used by the UK's cost watchdog NICE. This system is designed to reward meaningful clinical benefits. Although the growth rate of the overall industry may be negatively impacted, there would still be ample room for success for the drug makers that can leverage new biology to bring real advances to patients.

We have put forward several arguments to show that we believe that the era of new biology is not a repeat of the 2000 genomics bubble, but there is the possibility that it will fail to deliver on its promises. Should this be the case, the growth rate of the industry will evidently suffer as companies scramble to pick up the pieces and move forward on to a new wave of innovation; but here again, the pricing environment will affect the extent to which they will be hit. If the status quo remains in place, most biopharma companies will likely manage to survive through the storm with a few new product launches and the help of reorganizations and acquisitions, akin to what happened during the depression of the 2000s.

But should the disappointment of new biology be accompanied by the implementation of tighter pricing systems in both the US and EU, many companies could find themselves in serious danger. We may end up in a situation where drug makers will shift their focus from risky, costly R&D to cheaper, more stable generics/biosimilar businesses, lifecycle management, and incremental innovation – which all comes at a great cost for innovation and, ultimately, patients' health (see Figure 4).

Forging a future path

In the light of these scenarios, where do biopharma companies – especially pharma giants – stand today with respect to these two drivers – new biology on the one hand, and pricing and reimbursement pressures on the other? On the pricing and reimbursement topic, companies have for a few years now been trying to integrate the needs of payers into clinical development, mainly by incorporating endpoints to measure the pharmaco-economic benefits of their drugs in order to make a more compelling case for reimbursement. For a handful of drugs, attempts to implement outcome-based pricing have also been made. Overall though, these efforts have encountered limited success, and the difficulty is made even greater by the heterogeneity of payers and their demands.

On the new biology side, we believe that the outlook is brighter. Big pharma companies have finally realized that size is the enemy of creativity and breakthrough innovation, and have built sophisticated externalization models to source the innovation brought about by new biology from those who do it best.

Ultimately, one thing is clear: companies will perform better and face much reduced pricing hurdles, if they are able to develop truly differentiated therapies that bring significant, meaningful improvements over existing drugs. Those that master these skills will find the right path ahead of the pack, whatever the future scenario may be.

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Product Showcase

Sponsored Section

Aptar Pharma's Ophthalmic Squeeze Dispenser – Innovation based on experience

Although the discussion about the use of preservatives is still somewhat controversial, clinical evidence suggests that patients benefit from unpreserved eye drops especially in chronic conditions. During long-term treatment of diseases like dry-eye or glaucoma, preservatives in eye drops may worsen symptoms. Science has shown that the risks for patients experiencing severe local side effects increases significantly with the use of preserved ophthalmic medications. The experience of side effects when using eye drops as well as inconvenient handling may cause poor compliance.

Recognizing the trend towards preservative-free topical drugs, Aptar Pharma in 2011 launched the Ophthalmic Squeeze Dispenser (OSD), an innovative multi-dose eyedropper for unpreserved ophthalmic preparations. In the few years since then some 70 commercial references have become available on markets worldwide utilizing this patient-friendly technology. The key advantage of this technology certainly is that it allows maintaining microbiological integrity of unpreserved formulations thanks to a proprietary dispensing system. The system relies on pure mechanical measures to ensure microbial integrity of the complete system during storage and when in use. The OSD offers also a wide range of settings to meet the requirements of various ophthalmic formulations.

The microbiological safety of the OSD is qualified with the industry's most challenging test procedures. Pharmaceutical manufacturers are consequently able to claim competitive storage and in-use periods. Patients and consumers also appreciate how convenient and intuitive it is to use the OSD. No particular instructions are required, the intuitive handling supports patient adherence.

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32-34
Dosing for Compliance
All pharma manufacturers claim to develop products according to patient needs, but is this really true? Impractical medicines lead to patient non-compliance so it's crucial to think more about the real world and what patients want.

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Are you REACH Ready?
The European Union introduced the REACH regulation on chemicals in 2006 and the final deadline is fast approaching. Lisa Allen offers her tips on how to understand the regulation and explains what pharma companies need to be doing.

Dosing For Compliance

Are current dosage forms really as easy and convenient for patients as pharma manufacturers say they are? Thinking more about real-world usage can help us design more practical drugs that patients are more willing to take.

By Sven Stegemann

Healthcare professionals typically make a diagnosis and then match the patient's condition to a prescription drug that has been subject to controlled, randomized clinical trials. But in the "chaotic world of medical practice" – to use the words of Sharfstein and Kesselheim (1) – the therapeutic outcomes observed in clinical trials are not always transferable to the real world. Indeed, some medicines – although designed to be effective – simply aren't practical for real-life patients; for example, the dosage form may not have been fully considered. What if the tablet or capsule is too large to swallow or the patient simply has too many separate medicines to deal with?

Those of us involved in developing medicines must start to focus not only on the disease and clinical parameters, but also on real-world aspects, such as how each patient experiences his or her disease, lives with the symptoms, and sometimes balances them against other ailments. Those who have cared for an elderly relative will be able to relate to how challenging it can be for them – and for us – to keep up with a complex daily medication schedule. Often, the regimen may include several different drugs, all in different dosage forms. Each pill will have its own shape, color, size and packaging designed to help us to tell them apart, but actually this diversity can add to the complexity. Further, the medicines may need to be taken before or after meals, split rather than swallowed whole, or administered in the morning or at night. And frustratingly, some medicines packaged in medicine vials or blister packs can be difficult to open. While these medicines are "effective" by clinical trial standards, they are not always sufficiently tailored to meet patient needs, which may affect other important factors, such as patient compliance.

"I have never heard a patient mention that the five-year stability of their product was something they themselves were looking for."

I doubt many readers of this magazine are doctors who prescribe medicines – rather, we are developers, academic scientists, regulators or suppliers within the pharma industry. But in many ways, we have just as great a part to play in healthcare and cannot simply accept the above issues as inherent problems. We are the ones who must actively look for solutions to help the patients who take our medicines every day.

Customizing capsules

The good news is that significant progress has already been made in the advancement of many dosage forms. However, for this article, I would like to focus on capsules. Capsules are easy to swallow, tasteless and odorless. They are suitable for a wide range of ingredients and are also an excellent method of protecting a drug. Over the years, capsule technology has advanced greatly and I believe that it is an area where innovations are being made that specifically addresses the physicochemical characteristics of certain compounds, resulting in more patient-centric designs. For example, the introduction of easy-to-open capsules might lead to a renaissance of multiparticulate sprinkle formulations for pediatric and geriatric applications.

Capsules can be used by all ages – including pediatric and geriatric patient populations. In their most basic form, capsules are a simple two-piece shell that enables convenient delivery of multiple drugs. Moreover, it is possible to combine different drug formulations that consist of a solid and a liquid phase – in the same capsule. The capsule can be filled as a lipophilic suspension or pellets, and then sealed by band or spray sealing technology. In instances where the two phases are incompatible, technology is now available that allows you to create a capsule within a capsule, where the solid is separated from the liquid phase. These types of innovations are highly suitable for combination or dual-release products. Other clever technologies are available too – it's just a matter of looking and thinking beyond simple shells (see 'Capsule Evolution' for a timeline of innovation).

From an aesthetic but also recognition and identification point of view, capsules provide a high level of customization too. Thousands of colors are available and it is also possible to print directly onto the capsule, such as printing the dose, drug or name of the pharmaceutical manufacturer. These features provide strong visual cues that help to prevent medication errors and confusion in patients with polypharmacy.

Once a patient population's true needs

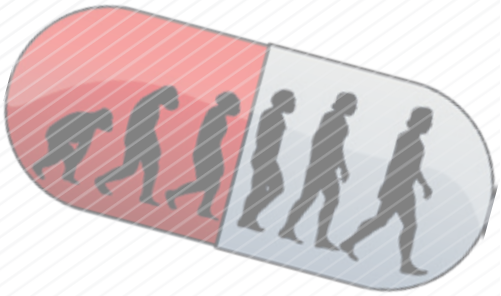
have been identified and you have an understanding of the drug product from their viewpoint, technology is key to developing the right solution. Most likely, it will be a combination of technologies that come together in one dosage form. For example, consider an elderly woman who has multi-morbidity and functional impairments. She could very well benefit from a fixed-dose combination capsule that combines the three or four individual drugs she takes in one capsule, significantly reducing her morning dose. She would further benefit if that one capsule was clearly marked by color and printed with a pictogram showing it as her "morning dose." Going a step further, it could also be beneficial if the drug was delivered as a multiparticulate formulation within an easy-to-open sprinkle capsule, which means that she could sprinkle the contents of the medication onto soft food. The capsule becomes the packaging rather than the delivery system, completely overcoming any swallowing difficulties. And the drug is well protected from environmental factors during storage and easy to transport too.

Multiparticulate formulations could also benefit other age groups, especially children. In many cases, liquid medications are the only option for children 6 months to 12 years of age. Developing a medicine for children requires a wide range of dosage strengths to cover all age-respective weight groups, clear differentiation on dosage strength to avoid medication errors, as well as administration in a beverage or soft food to mask a medicine's bitter taste. Multiparticulate technology can enable a formulation to have targeted release profiles at different dose strengths, which can be differentiated by colors and imprints. No matter if the child is 2 or 10 years old, the medicine can be mixed and consumed with a favorite food – such as ice cream.

What do patients want?

When I speak with drug formulators, I often hear claims that they always develop products according to patient needs. But unsurprisingly, I have never heard a patient mention that the five-year stability of their product was something they themselves were looking for to improve their health… or that the once-daily large tablet that must be crushed in a mortar before administration was the type of innovation they were hoping for when they asked for simpler dosing…

In 2014, we searched the literature to assess the strength of scientific studies investigating medicines for their patient-centricity and appropriateness (2). The results were disappointing – and confirmed our concern that patients continue to be left out of the dosage form design and development process. That said, there are marketing studies investigating patients' preference for dosage forms that provide evidence that patients believe the appearance of capsules, including the colors and imprints, as well as the sprinkle option,



Capsule Evolution

1860s: Launch of traditional hard capsule made of gelatin and two cylindrical parts with spherical end that is "slipped over" for closing.

1967: "Dimples" introduced in cap to mechanically fix cap on body part during transport and handling of empty bulk capsules.

1968: "Closing rings" introduced to lock cap and body tightly together after filling and closing of capsules.

1978: Introduction of body with conical open-end that improves product quality by reducing splicing on high-speed filling machines.

1986: Special capsule designed for liquid- and semi-solid formulations to provide tight closure of cap and body after closing by mechanical means.

1993: Introduction of capsule specifically designed for clinical trials (as alternative to cumbersome "double dummy" blinding technology).

1995: Capsule design optimized through debut of spherical cap end that provides higher strength and resistance in closing stations.

1997: Hydroxypropylmethyl cellulose (HPMC) capsule manufactured with gelling system for oral and inhalation products.

2007: HPMC capsule made using thermo-gelation (launched as an alternative to gelatin).

2008: Introduction of capsule-in-capsule concept to physically separate two or more products, liquids and/or solids or enhance stability to sensitive compounds.

2011: HPMC capsule further extended with launch of acid-resistant capsules for dietary products, which delay the in vitro and in vivo dissolution for up to two hours.

2012: HPMC capsule developed to meet the technological and bioperformance requirements of inhalation capsule products.

2014: Publication of two-year Quality-by-Design (QbD) project investigating the variability of empty hard capsules, showing consistency and reproducibility of capsules within specified limits.

2014: Sprinkle capsule introduced for accurate and easy dosing of multiparticulates for various patient populations.

2014: Launch of Six Sigma approach to quality control of empty capsules that supports the transition to continuous manufacturing, with real-time release for pharmaceutical capsule products.

2015 and beyond: Ongoing development programs, including capsules that provide enteric properties, allowing for advanced oral drug delivery options for proteins and peptides.

are important aspects when it comes to their preference for and acceptability of a medicine.

Some action needs to be taken on this point. I'm involved in an academic partnership with the Graz University of Technology in Austria that includes a Foundation Professorship dedicated to better understanding patient perspectives in drug therapy, with the ultimate aim of enhancing drug safety and effectiveness. Hopefully, this kind of partnership will help to produce even better dosage forms in the future. In drug development, it can be all too easy to overlook the patient's real-life situation and to focus only on clinical efficacy, but as people live longer and therapies become more complex, desired therapeutic outcomes can only be achieved when patient needs and challenges are addressed. Studies investigating poor adherence clearly show that substandard medicine design is a contributing factor (3). We must do more with our capsules and other dosage forms to ensure patient compliance; after all – irrespective of excellent R&D during development – if a patient does not take the medicine, the API has zero efficacy.

Sven Stegemann is Director of Pharmaceutical Business at Capsugel, headquartered in Morristown, NJ.

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Are You REACH Ready?

The final deadline for the European Union's REACH regulation is approaching – and the home stretch will be the most challenging, especially for pharma companies that have failed to recognize their role.

By Lisa Allen

In 2006, the European Union introduced a regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (called REACH) (1). One of the main aims is to better protect both human and environmental health from the dangers posed by chemical substances – quite a broad statement, so allow me to clarify. In 2005, a study conducted by the UK's University of Sheffield, on behalf of the European Trade Union Confederation, concluded that as many as 90,000 cases of chemical-related occupational respiratory and skin diseases could be prevented each year, leading to healthcare and productivity cost savings in the region of 3.5 billion Euros over ten years for EU member states (2). The study only considered non-malignant skin diseases (i.e., dermatitis), asthma and chronic obstructive pulmonary disease (COPD), so there could be many more injuries caused by chemicals every year. REACH aims to reduce the risks associated with chemicals by focusing on four processes: chemical registration, evaluation, authorization and restriction. Over the years, a huge number of chemicals have reached the European market (sometimes in very large amounts), but in many cases there is little information on the hazards they pose to human health and the environment. REACH is an attempt to fill in information gaps and to better understand and control the risks.

Some key aspects:

- Manufacturers and importers must gather information on the properties of chemical substances.
- The European Chemicals Agency in Helsinki will manage a database and co-ordinate evaluation of chemicals of concern.
- Some very high hazard chemicals will be substituted with suitable alternatives that have been identified.

"REACH aims to reduce the risks associated with chemicals by focusing on four processes: chemical registration, evaluation, authorization and restriction."

Registration ready

Over the years, many companies have been confused by REACH and what they need to do – and not everyone has been prepared for the paperwork. REACH affects any industry that uses chemicals, though some exemptions do exist – for example, substances used in human and veterinary medicines. Importantly however, this does not make the pharma industry completely immune to the regulation. What about process chemicals, including reaction-supporting agents and solvents, such as DMAC (N,N-

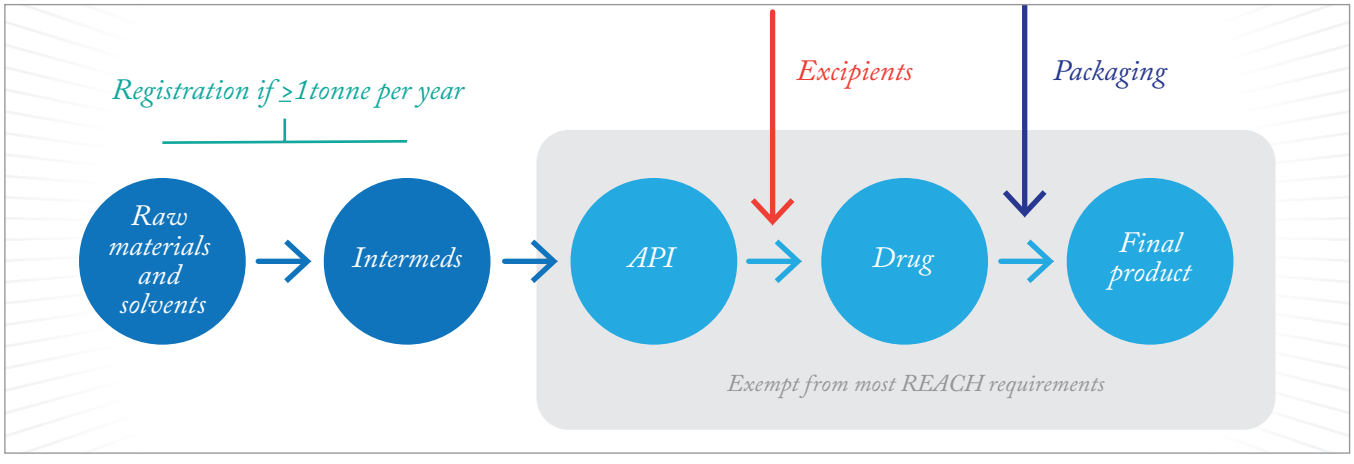

Figure 1. How REACH affects pharmaceutical production.

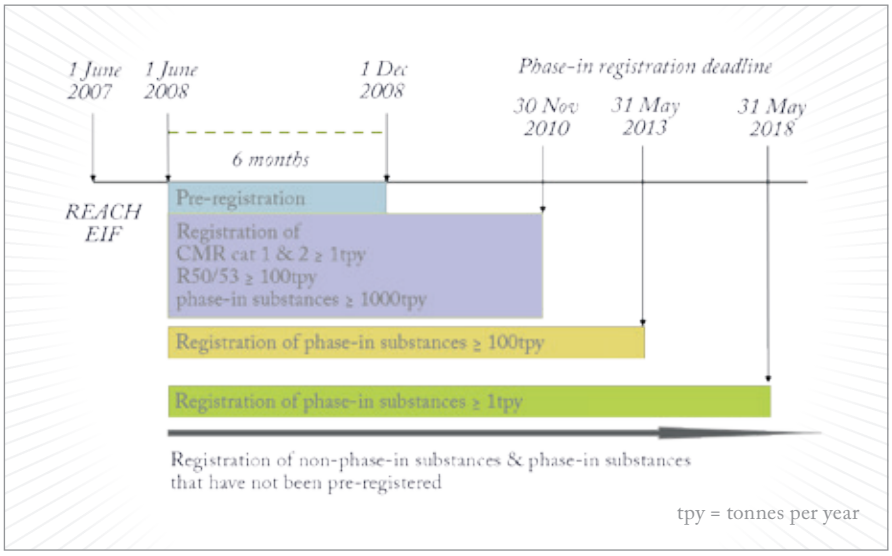

Figure 2. Registration timelines for REACH.

dimethylacetamide), and the intermediates used to make APIs? For the vast majority of chemical and downstream supply chains, someone will need to register substances with the European Chemicals Agency (ECHA). And the question is who? Is it the chemicals company? Or the pharmaceutical company? Well, it depends on the structure of your supply chain. If it's an EU-based pharmaceutical company importing chemicals from an EU-based chemical company, then it will be the chemical company who does the registration. But if an EU pharmaceutical company is importing chemicals from outside of the EU, such as the US, then the onus is on the pharma company to REACH register the chemicals.

Registration is the most cross-cutting, far-reaching aspect of REACH. It's a duty that affects any EU legal entity that manufactures or imports substances in quantities of one tonne or more per year, as well as appointed 'Only Representatives' working on behalf of non-EU producers. When the White Paper was published, it was estimated that tens of thousands of substances would need to be registered. To give industry a fighting chance of meeting this obligation, the regulators phased in the registration duty using a risk-based approach, focusing first on high-tonnage and high-hazard substances, moving progressively downwards in tonnage band to a final deadline on May 31, 2018.

As Figure 2 shows, most of the deadlines have passed. In the early years, there was much discussion about REACH, but now it has become a way of life for large chemical companies. However, the 2018 registration deadline will perhaps be the biggest challenge because it applies to low-volume manufacture and import in the 1-10 and 10-100 tonnes per year bands. In other words, it's expected to involve large numbers of small and medium sized enterprises (SMEs). Some will only have a few substances to register, but others will have wide-ranging portfolios of low-volume substances, particularly in the specialty and custom chemicals sectors.

It is still difficult to predict the numbers of registrations and unique substances that will go through the 2018 deadline. However, recent ECHA estimates suggest that up to 70,000 dossiers will be submitted, covering somewhere between 25,000 and 50,000 unique substances – that's more than three times the amount received for the 2010 deadline, and almost 20,000 more than the number of dossiers used to populate the ECHA database to date.

To register or not to register

EU chemical manufacturers and importers who fall into the above band should be thinking about registration now by addressing two key questions: "what will it cost to register this substance?" and "what is this substance worth to my business?" Where the payback period would be lengthy, either as a result of initial registration fees and data access costs or subsequent dossier maintenance costs, EU chemical manufacturers and importers might, quite understandably, choose to register only their most profitable substances. Some potential registrants in this situation may decide to cease manufacture or import entirely, or to cap their annual tonnages to avoid registration.

For the pharma companies that import chemicals from outside of the EU, the above are questions that you will need to ask. For those who import chemicals from within the EU, the situation is a little different – and could have some serious consequences. For example, post-2018, you may need to buy low-cost raw materials or process chemicals from more than one supplier. Or find a new supplier entirely. You'll need to be in close contact with your chemical supplier to ensure that the chemicals you use will be registered.

Fortunately, REACH offers some sugar-coating by way of reduced registration requirements for intermediates that are handled under Strictly Controlled Conditions (SCC). Registrants who are able to demonstrate that there is rigorous containment of an isolated intermediate throughout its lifecycle pay a reduced registration fee to ECHA. In addition, registrants of isolated intermediates under SCC do not need access to the full suite of phys-chem, toxicity and ecotoxicity information on the substance.

However, the trade-off is the potential cost of implementing SCC; companies may

need to invest in more onerous forms of engineering control, such as mechanical or air dynamic barriers. The need for rigorous containment also applies to the whole life cycle of the intermediate, which includes manufacture, purification, sampling, analysis, cleaning, maintenance… the list goes on. Thinking in particular about wastewater, registrants are expected to have an on-site wastewater treatment plant (WWTP) where chemical (oxidation) and, ideally, biological treatments are applied. The effluent from this plant must be monitored for residual concentrations of the intermediate. For some countries this could be an issue; for example, manufacturing sites with WWTP in the UK do not normally have biological treatment options. But even if a company does have state-of-the-art facilities, maintaining – and demonstrating – rigorous containment can be extremely demanding. In some cases, full registration may be seen as the easier option.

Learning to live without

The authorization aspect of REACH prohibits the EU use and supply for EU use of substances listed in Annex XIV to the regulation. Each substance listed in the annex has a transitional period for its phase-out; after which companies must have permission from the European Commission to continue to use that substance, unless an exemption applies.

Fortunately, there are more types of exemption from authorization than from registration, in particular for intermediates (which don't even have to be under SCC!) and substances used in mixtures below the relevant threshold of concern. But that's where the good news stops. Unlike registration, there is no tonnage threshold, meaning that even very small quantities of substances in Annex XIV may require authorization unless an exemption applies.

Several process chemicals – particularly aprotic solvents – are listed in Annex XIV, including 1,2-Dichloroethane (EDC), which is used extensively in drug production. The latest application date for EDC is May 22, 2016 (with an additional 18 months to its sunset date). In some sectors the remaining transitional time may be plenty to change to an alternative, but given that the pharma industry is heavily regulated in other ways, substitution cannot be taken lightly. Another potential concern is the solvent DMAC. In early 2013, ECHA recommended that DMAC be listed in Annex XIV. However, due to similarities in intrinsic properties, and interchangeability in common uses, the DMAC decision was postponed pending the outcome of an Annex XVII restriction process on n-methyl-2-pyrrolidone (NMP). It was reasoned that, under the idea of regulatory coherence, any process used to control NMP should also apply to DMAC.

Even for substances not listed in Annex XVII, there could still be trouble ahead. Under the ECHA's SVHC Roadmap to 2020 Implementation Plan (3), the authorities are encouraged to use the most appropriate regulatory mechanisms and tools to manage the risks from chemicals. ECHA and member state authorities have developed a screening method to help them identify substances with particular hazard, exposure and risk profiles – which will then be addressed using the most appropriate regulatory tools. As a result of this year's mass screening, some 200 substances, registered by around 800 companies, were selected for manual review.

Where screening indicates a potential concern, and where there is sufficient information to substantiate that concern, voluntary Risk Management Option Analysis (RMOA) is carried out by ECHA or member states to determine whether they should propose more controls. In some cases, no further action may be required and, even if it is, other regulatory mechanisms exist that can also control risks from chemicals of concern on an EU-wide basis, for example harmonized classification and labeling, and exposure limits for the workplace.

A long-standing yet active debate is whether substances with community-wide occupational exposure limits (IOELVs) should benefit from an exemption from authorization for the uses covered by those limits. Decisions on the inclusion in Annex XIV of other previously recommended aprotic solvents, such as N,N-dimethylformamide (which has an IOELV), are currently on hold – with Italy recently notifying its intention to propose a restriction on the manufacture and industrial use of this substance. If the case can be argued successfully that to subject such substances and uses to authorization is disproportionate to the risk, and that the workplace risks are already sufficiently and properly controlled, we may see a paradigm shift. Inclusion of chemicals of concern in the authorization process could become the exception, not the norm…

But whatever may happen, REACH is not just a matter for chemical companies. Perhaps one of the main difficulties for pharma companies (among other industries) has been how to interpret the legislation. Another difficulty is how exactly you get ready for REACH – who in your supply chain is responsible for registration? The final deadline is close at hand and nobody wants to fall on the final step. Make sure you are prepared and understand the potential consequences.

Lisa Allen is a manager at REACHReady (UK).

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The Rise of Asia's Biotech Tigers

The western world could be considered king of the biotech jungle, but eager biopharma tigers from the east are hungry for a piece of the action – and they are gaining ground. Can single-use technologies help them to catch up even faster? Jinghui Xu believes so.

The potential for biopharmaceutical growth in Asia is no secret – and it is estimated that around 50 percent of the world's new bioprocessing facilities are being built by companies in Asia, including both local companies and international giants. Jinghui Xu's goal as GE Healthcare's product leader for single-use in Asia is to use his background in polymer science, plastics and bioprocessing to help companies truly understand the best single-use components for their products and processes.

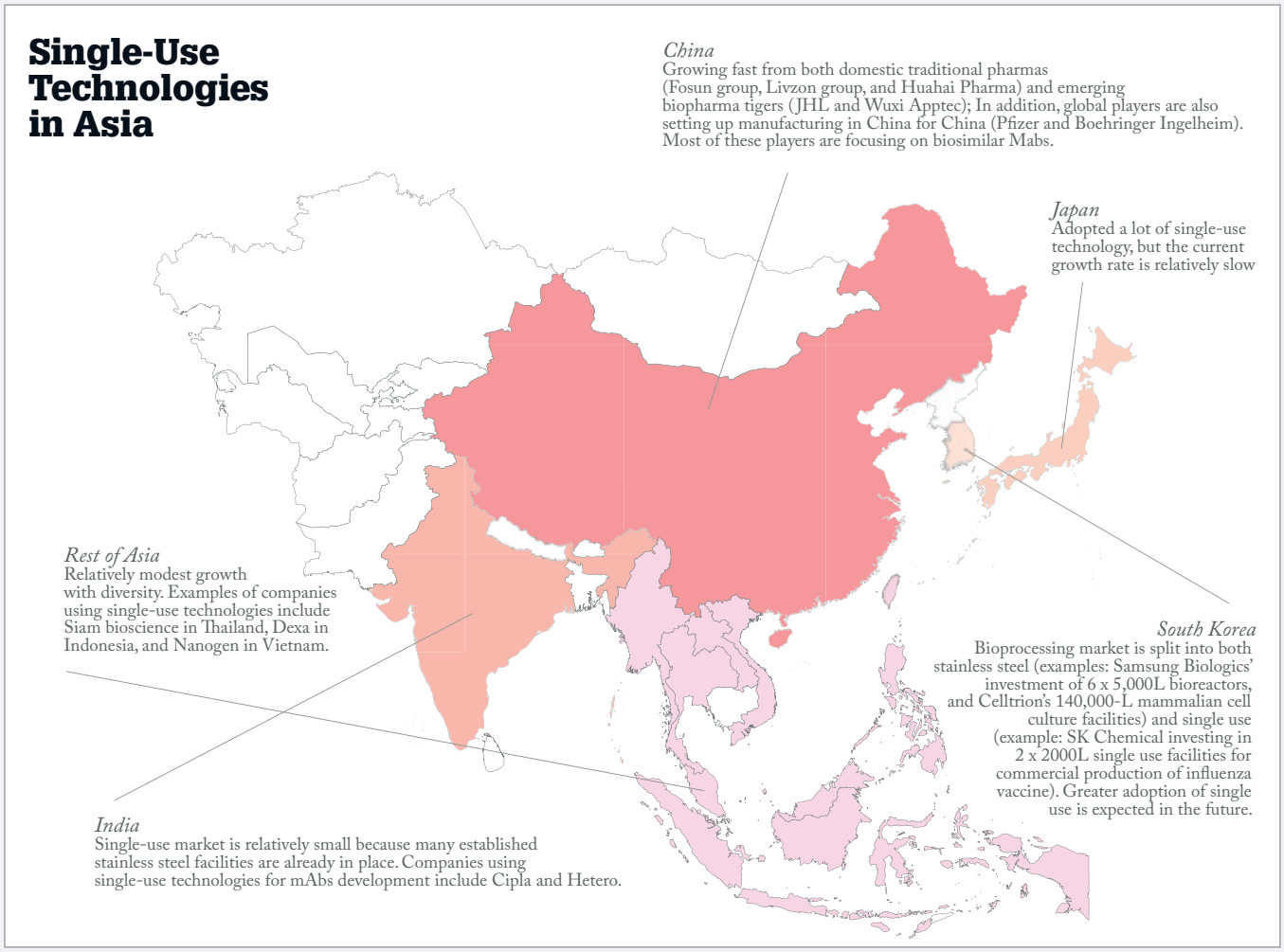
What are the latest trends in bioprocessing in Asia?

The biopharma industry in Asia started much later than in the West, but it's catching up rapidly. A number of Asian 'biotech tigers' are emerging and growing rapidly; to name just a few, Shanghai CP Guojian and Wuxi Apptec in China, Dr. Reddy's and Cipla in India, Chugai and Takeda in Japan, and Samsung Biologics, and Celltrion in South Korea. And there are many more that are also growing rapidly. That said, western biopharma companies are not sitting by idly; 60 percent of the world's population live in Asia, representing an enormous market opportunity, and many global companies are establishing a manufacturing footprint in Asia to supply the local markets.

The main focus in Asia at the moment is on biosimilars – particularly biosimilar monoclonal antibodies (mAbs). China is a big force in this area, with over 100 mAbs being developed by various Chinese companies. Vaccines are another large area for Asia, as governments develop initiatives to immunize their populations. Not surprisingly, these companies are keen to use single-use technologies as their benefits enable them to bring biotherapeutics and vaccines to patients more efficiently. Right now, the main focus is on upstream operations, such as suspension and adherent cell culture processes, aseptic connections, and mixings, as well as in later process steps including single-use chromatography, final formulation and storage.

And what differences are you seeing between individual countries?

Although there are common trends, each country in Asia has its own specific dynamics. I tend to divide Asia into five main geographies: China, India, Japan, South Korea, and then the rest of Asia. Currently, China is probably growing the fastest thanks to a combination of governmental support and an outpouring of private investments. It is also leading the way in terms of the implementation of single-use technologies. Chinese companies seem to be well aware of the advantages of these technologies; I mentioned before that biosimilar mAbs are a focus in the country, but one problem is that many companies are focusing on the same molecules, which creates competition. This competition drives urgency in getting their products



to market quickly and single-use technologies are a good way to achieve this since they are easy to deploy, flexible and eliminate the need for cleaning and cleaning validation, among other advantages.

India is currently recognized as the world's largest biosimilar producer and it also has a very well-established vaccine manufacturing industry. It has been building its biopharma industry for quite some time now and, as with the West, there are a lot of fixed stainless steel facilities. The focus now is further growth and industry upgrade. The appetite for single-use is perhaps not as strong in India as in certain other areas of Asia, but some companies are still seeking a competitive edge by choosing to upgrade aspects of their processing operations with single-use systems.

Japan is a developed country with a well-established and highly respected healthcare industry – and biotechnology is one area that the government is actively promoting. One of the drivers is that the country is considered to have the world's oldest population, with 33 percent of citizens being older than 60 years, according to data from 2014. This is a demographic challenge for the country and a catalyst for continued investments to ensure good medical supply in the future. Japan has adopted a lot of single-use technology – and is the second largest single-use market in Asia. However, the current growth rate is relatively slow compared with the country's overall biopharma market.

South Korea is reacting to biopharma the same way it reacted to the rise of the electronics industry – by making enormous investments in infrastructure and providing incentives to business willing to grow locally. I would say that the bioprocessing market is split between both stainless steel and single-use in South Korea, with investments being made in both areas. However, the emerging companies seem to prefer single-use – and a growing number

of established companies are looking to implement single-use in certain operations to improve efficiencies.

As for other markets throughout the rest of Asia, there are vast differences between the developed and developing countries. In Singapore, Amgen announced a $200-million biomanufacturing facility, which uses single-use in 90 percent of the plant's operations. Indonesia, Vietnam, Malaysia and many other countries throughout Asia are also investing in local biotechnology development programs that bring biotherapeutics and vaccines closer to their populations.

It seems single-use technologies are particularly enticing for Asian manufacturers...

Yes, Asian customers are very positive about single-use. A representative comment came from Scott Liu, CEO of Henlius Biotech, part of the Fosun Group in China, who told me, "Single-use is really changing the world of bioprocessing, and it is one great technology capable of delivering quality, speed, flexibility, and economy for us and the industry."

In Asia, a huge number of bioprocessing facilities are being built up; many of which are intending to use single-use technologies. I think this appetite for single-use is one important enabler in Asia's rapid biopharma growth. Many Asian biopharma companies are relatively new and are building their first bioprocessing plant, which means that they can select the most advanced bioprocessing technologies from the start when planning and building their facilities.

Some of the hottest discussions around single-use in Asia focus on economic comparisons between stainless steel and single-use. Cost is something that drugmakers must take into account, both in terms of establishing the facility and coping with the running costs throughout the projected life of a facility. Many studies cover this topic from various angles, looking at everything from different types of molecules to manufacturing processes, throughput, and scale – and in general they have shown that single-use has cost advantages over stainless steel. I believe that single-use is a great enabling tool to help the Asian biotech industry catch up with the developed bioprocessing plants in the western world.

What are the common demands of Asian companies?

There are three generalizations. Firstly, the supply chain in Asia wants both improved supply of single-use consumables and lower costs. Currently, most single-use consumables are made in the west. Manufacturing single-use consumables more locally for the Asian market would help resolve some of the problems – which will become more pressing as the region's demand for single-use consumables rises as commercial production increases.

Secondly, given that many Asian biopharmas are relatively new, they need more intimate support (technical, application, training, and so on) from suppliers. For example, they may need more advice than a western company in selecting the right single-use systems for their processes. Close collaboration is also important in terms of having a secure supply of consumables. For example, single-use becomes an indispensable component in continuous manufacturing processes, so both the manufacturer and the supplier need to set out a consumables forecast and mechanism to support constant manufacture.

The third point is the need for the evolution of single-use from a local regulatory perspective. The good news is that Asian regulators have started to place more emphasis on single-use and are developing regulations and guidelines. I'm seeing Asian regulators, end users and suppliers working closely together to understand single-use, in terms of how the components are designed and manufactured, and how they are used and applied in order to deliver appropriate guidelines. Currently, I am representing GE in working with the Chinese FDA on an 'International Single-Use Application Technology and Regulation Codification,' which will be published in early 2016.

Given the rapid pace of growth, do you foresee Asian biotechs potentially overtaking those in the west?

If we look at other industries, such as the automotive and electronics industries, you'll note that a lot of the big industrial leaders are now based in Asian countries (in particular, Japan and South Korea). Could the same thing happen with the biopharma industry? I think that Asia's biotech tigers have the ambition and capability to reach the same scale as western companies. But if we just look at the market in terms of single-use technology adoption, the Asian market is growing much faster than that of the western world. Western companies have existing stainless steel facilities that need to be used, and although there are opportunities for process improvements by introducing single-use in various parts of those facilities, it's much easier if you are building a new site from scratch – which is what many Asian companies are doing. They are also in the fortunate position where they can learn from the history and experience of bioprocessing in the west, selecting the most advanced bioprocessing technologies to form a really modern, cutting-edge facility. The very fast biotech growth that is currently being seen in many regions in Asia will probably slow as the markets mature, but I believe that the rapid adoption of technologies like single-use systems will allow Asian companies to reach a more level global playing field far more quickly than we as an industry have witnessed previously.

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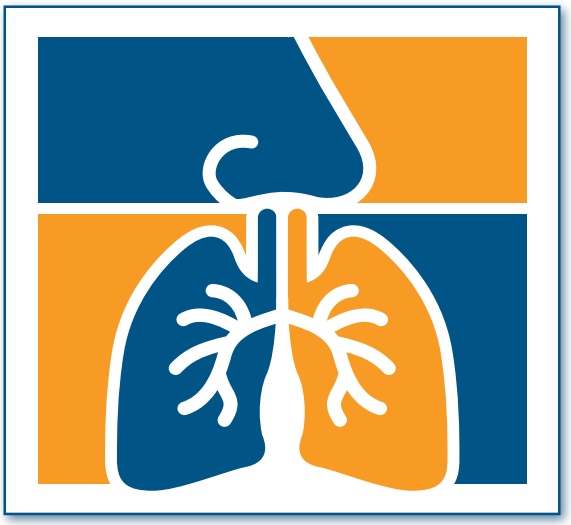

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A Call for Cell Support
Incredible advances are being seen in cell therapy engineering, but ongoing research is only part of the puzzle. Vendors and contract manufacturing organizations need to get involved too by ensuring that the equipment and expertise is in place to help turn research into life-changing medicines.

A Call for Cell Support

Engineered cell therapies hold exciting potential for the pharmaceutical industry – but only if contract manufacturing organizations and vendors play their part in the revolution.

By Miguel Forte

I've always been someone who enjoys bringing new treatment options to patients, particularly those with unmet medical needs. For much of my career, I've focused on developing monoclonal antibodies for auto-immune diseases, but today I work with cell therapies – an incredibly exciting area. The technology is certainly new, but it has great potential. In fact, you could say that we are on the cusp of an industry revolution – the cell therapy revolution.

The potential of cell therapies – the use of living cells to treat disease by replacing damaged or missing cells – comes at a cost; it adds layers of complexity to the drug development process not seen with traditional small- or even large-molecule drugs. I describe cell therapies as a three-dimensional approach because of their multiple mechanisms of action. Small-molecule drugs are generally simple with a one-dimensional way of working, since they tend to act on specific molecular targets. When we move onto biologic medicines, we are working with more complicated molecules that make it more difficult to define the product since they can work in many ways and have unexpected effects. With a cell therapy, the complexity increases even more but it also produces opportunities – the therapeutic agent in question is a living organism, able to sense and assess its surroundings, and react and deliver effects through multiple mechanisms of action.

Our current focus is on T cell engineering. But all of the ongoing research into cell therapies can only benefit patients if we can solve the manufacturing challenges too. Here, as well as highlighting some of our research, I'd like to focus on the manufacturing hurdles. In particular, we need to find new business and manufacturing models that suit these therapies – and we need contract manufacturing organizations (CMOs) and equipment suppliers to help us along the way.

"All of the ongoing research into cell therapies can only benefit patients if we can solve the manufacturing challenges too."

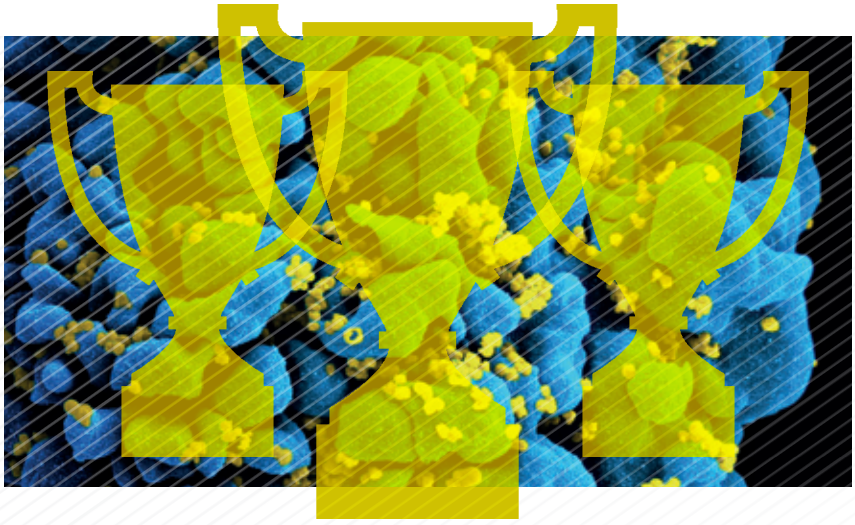
Engineering living agents

Much of the hype around cell therapies centers on the potential of cell engineering. Cells are live agents and they are very powerful – able to carry out functions that we can't accomplish with small- or large-molecule drugs. If we can harness cells as cell therapies and program and direct them using cellular engineering, then we have the power to

moderate and direct therapeutic effects – with virtually unlimited opportunities. We've seen this with the CAR-T approach in oncology, which involves engineering patients' own immune cells to attack their tumors. Only a few trials have been done so far, but the results have been promising.

Engineering cell therapies could also be used to tackle other therapeutic areas – I've mainly focused on autoimmune and chronic inflammatory diseases. My company holds several patents on regulatory T cells (Tregs) – naturally occurring blood cells that help induce tolerance against foreign antigens taken up by inhalation or ingestion, for example. Their role in the body is to control inflammation using various mechanisms of action through proliferation including pro-inflammatory cell inactivation and cytokine production. Our research has shown that they may hold therapeutic potential in a number of autoimmune and chronic inflammatory diseases in different experimental animal models. Our founder was involved in the discovery of these cells in 1997, and much of our work has centered on translating their therapeutic properties into actual medicines.

One approach is priming Treg cells to specifically recognize an antigen present at the site of inflammation. The chosen antigen then triggers Treg activation locally in the inflamed tissue, resulting in local immunosuppression. We're working on a manufacturing process that involves using a single blood sample from a patient, educating the cells ex-vivo to specifically recognize a chosen antigen, and then mass producing and freezing the cells, which will be administered to the patient via injection. When the patient's own Treg cells are re-injected, they target the site of inflammation. Following success with antigen targeting, we are now developing engineered Tregs with the ability to



Cell Successes

Oncology

Chimeric antigen-receptor (CAR) T-cell therapy involves harvesting T lymphocytes from patients, modifying them in vitro to recognize malignant cancer cells and then infusing them back into patients. It has generated a lot of excitementation in oncology and in December 2014, scientists reported that a Phase I trial examining the potential of a CAR T-cell therapy to treat refractive acute lymphoblastic leukemia saw remission in 24 out of 27 patients (1).

More CAR T-cell therapies are now being trialed by a number of companies and research institutes, with some studies also focusing on solid tumors.

Ophthalmology

In early 2015, the European Medicines Agency recommended Holoclar (manufactured by Holostem Terapie Avanzate) – a stem cell therapy used to replace cells on the cornea that have been damaged by burns – for approval in the EU (2). The treatment involves taking limbal stem cells from the eye's limbus, growing them in the lab, and transplanting the cells back into the eye to repair the cornea after injury. This is the first stem cell therapy to receive regulatory approval in the Western world.

Stem cells have also been investigated as a treatment for macular degeneration with a number of trials taking place. For example, in September 2015, a trial for wet macular degeneration was initiated in the UK at Moorfield's Eye Hospital (3).

Heart regeneration

In October 2015, Cell Therapy Ltd began the application process for a conditional marketing authorization in Europe for Heartcel – an allogeneic stem cell therapy to regenerate areas of the human heart damaged by heart attack or heart failure (4). Filing is planned for mid-2016 and the company has already had a pre-submission meeting with the European Medicines Agency.

Diabetes

In 2015, ViaCyte's stem cell-derived, encapsulated cell replacement therapy for type 1 diabetes began a Phase I clinical trial (5). VC-01 cells are implanted under the skin of the patient; the cells then differentiate to produce mature pancreatic cells that synthesize and secrete insulin.

"Very few CMOs can handle cell therapies, but capacity and knowledge is growing."

deliver their immunomodulatory action independently of traditional antigen presentation using chimeric antigen receptors. This approach is very inspiring because, with genetic engineering, we have the opportunity to meet an even wider spectrum of chronic inflammatory and autoimmune conditions compared to antigen targeting alone.

Manufacturing models

As noted, although early studies have demonstrated the potential of engineered cell therapy, there is a large hurdle to overcome in bringing such therapies to patients. We must consider the challenges of producing and selling cell therapies on an industrial scale.

Cell therapy manufacture is currently specialized and expensive – and tends to involve slow, manual processes. We need to move to a business model that will allow us to more easily bring large batches of cell therapy to patients at an acceptable cost. Even in the early stages of cell therapy research and development, companies need to start thinking about their target patient population, expected capacity needs, and how they will reach the market. In some cases, it will be better to use CMOs than to build a new facility – which is the route we're taking at TxCell; we've partnered with a CMO in Belgium. Outsourcing is commonplace with traditional small molecules and biologics, but when it comes to cell therapies it is a little more difficult to simply hand these products over. Very few CMOs can handle cell therapies, but capacity and knowledge is growing. In the future, I expect to see – and we certainly need – significantly more CMOs that are able to cope with cell therapies.

As well as a lack of CMOs, there is also a lack of suitable equipment. Contamination is a particular problem for cell therapy manufacturers due to the challenges of working with live products – and the fact that the final therapy cannot be terminally sterilized at the end. Correctly sizing manufacturing setups and automating line manufacturing will prevent congestion problems, which will also help prevent contamination down the line. But developing closed systems, whereby all samples are isolated, is key to preventing contamination. Unfortunately, few automated technological solutions exist that can aid in cell therapy manufacture at all – let alone closed solutions. But if we have a vision of where we want to go as an industry, then the technical solutions will emerge. We've seen this happen before in biologics – the boom in bioreactors and other equipment for biomanufacturing didn't happen overnight, but it did happen. Five years ago, there were few companies contributing to the cell therapy area in terms of coming up with technical solutions for manufacturing. Now, I see more companies working on this. At the moment, we often seem to be seeking solutions that don't exist… But given the real and growing need, there is a clear business opportunity – and that means innovation will come.

The challenges of cell therapies are certainly significant – but we scientists love challenges that make things interesting, don't we? I really believe that cell engineering will transform cell therapies and the field of medicine. In the future, we may be able to engineer biological robots – cells that can precisely target certain sites within the body to deliver specific effects. These therapies do not fit into traditional business or manufacturing models so companies will need to have the courage to take risks and to try out new things. I think that the pharma industry as a whole tends to be very risk-averse, but as we see more cell therapy successes, I believe more activity and established business models will begin to emerge.

We're already seeing a rise in cell therapy applications in oncology and it will spread to other fields too. But rather than waiting and following the crowd, companies that want to get involved in cell manufacturing must start preparing for the future and trying out new strategies. At TxCell, we've carefully defined our product profiles, as well as how manufacture will evolve and how the product will be used. Other companies should be doing the same.

Miguel Forte is SVP, Chief Operating Officer, at TxCell.

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Screening, Identifying, and Quantifying Potential Genotoxic Compounds with High Resolution LC/MS

Analysis of chlorhexidine drug substance using an Agilent 6545 Accurate Mass Q-TOF System and MassHunter Mass Profiler Software.

Syed Salman Lateef, Agilent Technologies, Inc., Bangalore, India

This study demonstrates a routine screening of drugs to identify and quantify potential genotoxic compounds. In this Application Note, we used an Agilent 6545 Q-TOF LC/MS system to acquire accurate mass data of samples containing chlorhexidine as the drug substance. Agilent MassHunter Mass Profiler software was used to mine the data and compare different samples to generate a differential list of compounds. An accurate mass database search against the differential list identified 4-chloroaniline, a potential genotoxic compound. All Ions MS/MS acquisition mode was used to confirm 4-chloroaniline by MS/MS library matching, and quantify it using external standards. This workflow is suitable for batch-to-batch sample analysis for detecting and quantifying known potential genotoxic compounds.
The full Application Note can be found online: tas.txp.to/0116/GenotoxicApp

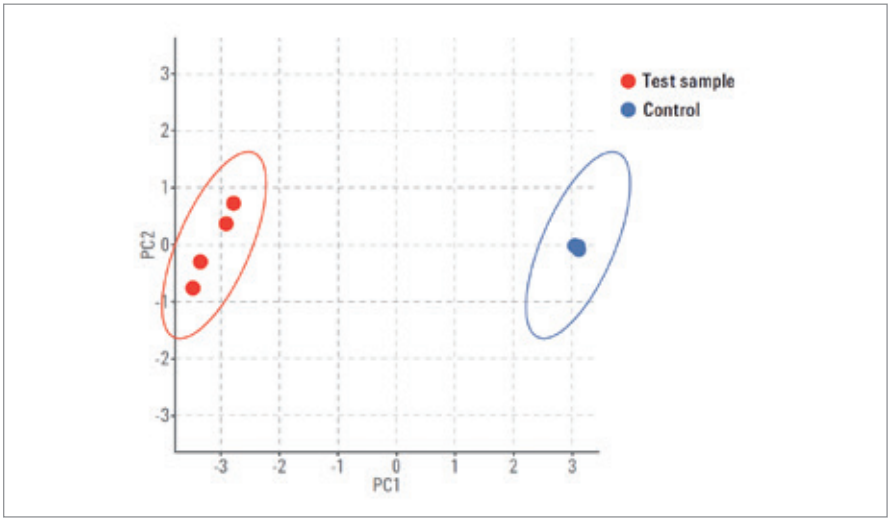

Figure 1. PCA plot showing different sample grouping. Red dots represent test samples and blue bots represent control samples.

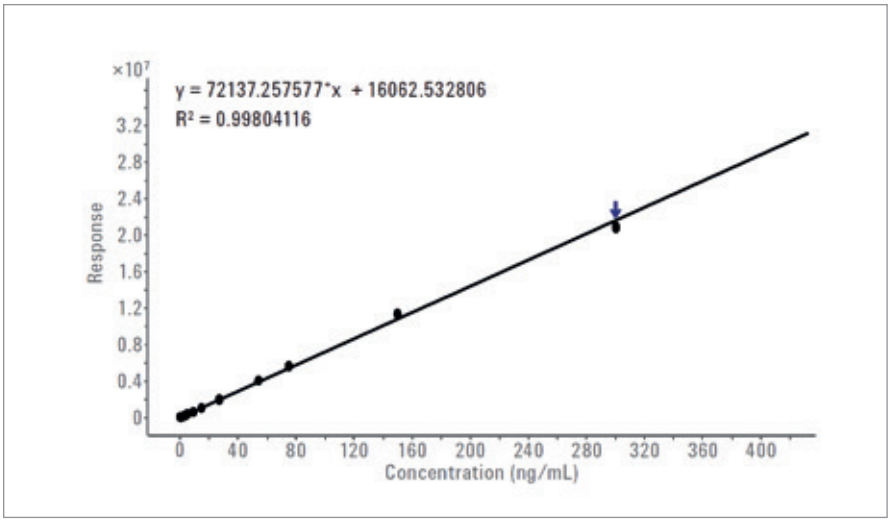

Figure 2. Calibration curve of 4-chloroaniline calculated using All Ions MS/MS.

Introduction

Drug substances may produce potential genotoxic compounds when they are stored for extending periods of time, or when they are stored inappropriately. Detection, identification, and quantification of genotoxic compounds is a time-consuming process. Regulatory authorities (1) require reporting of the formation of genotoxic compounds. Recent advances in software tools enables the fast and cost-effective detection of potential genotoxic compounds in complex samples. Agilent MassHunter Mass Profiler (MP) software allows the comparison of two sets of samples, and the determination of any significant differences between them. Principal component analysis (PCA) tools within MP assists the classification of compounds based on identified differentiation markers. A differentiation marker is a compound that exceeds a defined concentration, when compared to a control sample. A custom-built accurate mass database was used to identify the differences between samples. In this study, MP analysis of degraded and nondegraded chlorhexidine samples gave a list of statistically different compounds between samples. Using an Agilent ID

Browser feature within the MP software, these compounds were searched with a custom database containing potential genotoxic compounds. Compounds were further confirmed using accurate mass library matching, then quantified. Figure 1 shows the workflow used in this study.

Experimental

See full Application Note for details: tas.txp.to/0116/GenotoxicApp

Results and Discussion

Screening by differential analysis

The data files from the LC/MS analysis of degraded and control samples were processed using recursive molecular feature extraction in Mass Profiler software. Height filters of 4,000 counts for extracted compound features, quality score 100 and >4-fold change were used for statistical analysis. A greater than 4-fold change was applied to detect those features that differed significantly from control samples. See full Application Note for more details: tas.txp.to/0116/GenotoxicApp

PCA plot

The PCA plot reveals that the degraded chlorhexidine samples are different and distinct from the control sample (see Figure 1). This indicates that the degraded chlorhexidine sample contains features that are different from the control group. The control groups do not show significant separation, indicating no variation (blue dots) between samples.

Compound identification

A customized accurate mass database and library was created using standard compounds. The database also included literature reported mass, formula, and structures of chlorhexidine impurities. Post-statistical analysis, the differential list of compounds was searched against the accurate mass database using the ID Browser feature within Mass Profiler. The results indicated the presence of a potential genotoxic, 4-chlorhexidine in the degraded samples.

Feature summary of compounds

See full Application Note for details: tas.txp.to/0116/GenotoxicApp

Confirmation and quantification of potential genotoxic compounds

A shorter data-independent acquisition method was used for the targeted confirmation and quantification of 4-chloroaniline. In data-independent acquisition (All Ions MS/MS) of drug samples, both MS and MS/MS information are generated. The fragment ions in the MS/MS spectra of the personnel data compound library (PCDL) were used to extract ion chromatograms from the high energy channel. The extracted ion chromatogram (EIC) of the precursors from the low energy channel were aligned with fragment/production EICs to obtain the coelution score. The 4-chloraniline was confirmed based on accurate mass fragment matching and coelution of the precursor and product ions. 4-Chloroaniline was found with three qualified spectra in the library MS/MS spectrum where the fragments are selected from high energy MS analysis. The selected spectra were used with the qualifier and quantifier ions for the quantification method.

The qualifier and quantifier fragment ions, together with compound names, retention time, precursor ion, fragment ion, collision energies, and relative abundances were exported to MassHunter Quantitative Analysis software to set up a quantitative method. The most intense ion was used as a quantifier trace, while the less intense and unique fragment ions were used as qualifiers. A calibration curve with > 3 orders of magnitude was plotted from 0.1 to 300 ng/mL (see Figure 2). The 6545 was calibrated and tuned in high sensitivity mode. In addition, tuning for low mass (50–250 m/z) using Swarm autotune was enabled since some of the product ions for 4-chloroaniline were of low mass. The results of sample analysis showed an average value of 29 ng/mL in the degraded sample. Potential genotoxic compounds typically have a limit for reporting of 0.05 %.

When 1 mg chlorhexidine is dissolved in 10 mL solution, a 0.05 % limit would require quantitation down to 50 ng/mL. Therefore, any assay must be capable of a lower LOQ. The method developed in this study can detect impurities present at a concentration <1 ng/mL.

Conclusions

This Application Note demonstrates that potentially genotoxic compounds can be screened, identified, and quantified using high resolution LC/MS. A streamlined workflow was achieved by combining All Ions MS/MS data with Agilent MassHunter Mass Profiler software (Rev. 7.0). Automated differential marker analysis revealed significant differences between sample and control sets. The workflow also included the automated detection and identification of potential genotoxic impurities as target compounds using a PCDL. The All Ions MS/MS methodology was used to generate both quantifier and qualifier ions. This enabled the quantification of the target compound. The test sample processed with this technique was determined to be at a concentration of ~29 ng/mL or 0.02 % of 4-chloraniline (assay linear range from 0.1–300 ng/mL). This workflow can be used as part of routine drug sample analysis for the identification and reporting of potentially genotoxic compounds.

Reference

1. *EMA Guidance on the limits of genotoxic impurities, EMEA/CHMP/QWP/251344/2006 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf*

Thinking Inside – and Outside – the Box

Sitting Down With... Diane Paskiet, Director of Scientific Affairs at West Pharmaceutical Services, USA.

How did you decide the focus of your career?

You're probably wondering how you can get excited over packaging! But medicines save lives and packaging is an important element in the protection and safety of medicines – it's very rewarding. Packaging materials and configurations must be proven suitable for each pharmaceutical product and process throughout the whole lifecycle of the product. It is stimulating to look at all the different dependencies and measurements that influence the performance, safety and compatibility of each packaging component, as well as what happens under various processing conditions and with different types of pharmaceutical products. That's what really excites me – and, even after 25 years, the learning never ends.

How did you get started in industry?

I started out as an associate analytical chemist. I worked in a small contract lab that specialized in applied research and I worked with some brilliant scientists who really took the time to teach. We worked across many industries and the role gave me a great opportunity to understand material chemistry and applications. I was there for about 20 years. West purchased our laboratory and we combined forces – West's expertise in drug delivery and packaging, and our lab's knowledge of analytical chemistry. It's a great combination in light of the emphasis on quality by design to meet the needs of patients. You begin by identifying the patient's target needs, and then build a final product to meet the defined requirements. Having appropriate packaging – and evidence to support its compatibility and safety – is a key part in that process.

Outside of your day job, you're very much involved with industry groups and associations…

Yes – it's like my second job, although I don't get paid for it! It's a great avenue to help connect with like-minded colleagues and to share knowledge – and in the end we all grow. I've been involved with the Parenteral Drug Association (PDA) for around 20 years. Most of the activity there has focused on leachables and extractables, and my background in materials analysis is really good for this type of discussion. I also chair conferences and co-develop training courses for the PDA on leachables and extractables, and I'm involved in ongoing efforts to modernize and update chapters in the United States Pharmacopeia (USP). I am now in my sixth year of serving on committees and expert panels. In 1999, I was nominated to be a member of the Product Quality Research Institute (PQRI), which is a forum that promotes critical thinking to advance drug product development and I have been participating in Working Groups ever since. It's a huge benefit and a great experience because you can see the full circle of how analytical chemistry and the results are being used to solve real-life industry problems.

What is your current focus with these industry groups?

Right now, I'm chairing PQRI's working group for parenteral and ophthalmic leachables and extractables. We're working very closely with the US FDA to understand the agency's perspective and what it thinks should be included in best practice guides in this area. One of the great things about PQRI is that the forum allows exchange of relevant (non-competitive) information without judgment or consequence, so ideas can be discussed very freely. It's very much about working together to overcome problems. One revelation for me from talking and meeting with people from the FDA was that they looked to us for help on understanding appropriate information on leachables that will ultimately help patients. Helping people to understand good science is the mission of our PQRI working group; we provide recommendations for best practices on leachables and extractables – and then travel nationally and internationally to explain and train others on the concepts.

What are the hot topics in packaging?

Some of the most-talked about issues are container-closure integrity, particles and compatibility, among other safety issues. The ever-growing field of biologics is another area of focus since the many types of materials used to manufacture, store and deliver biologics can impact the products' quality and safety. The risks to patients really depend on the combination of each unique packaging system with the biologic – and identifying and mitigating these risks from the outset, which is much easier than trying to fix them once they've occurred. It's a huge area that we're still learning about. A lot of work is being done on correlating biologics to different types of container closure system interactions. The key lies in acquiring appropriate data and interpreting that data.

How do you think the industry should tackle the challenges?

I believe that we must build trusted partnerships that can advance the science and innovation of product development. Unfortunately, intellectual property remains a challenge; it's not always possible to share certain information while protecting business intelligence or when looking for a competitive advantage. I enjoy working with outside organizations because it's a non-competitive environment where I can work to understand and advance science based on common interests. There can be tension between suppliers and pharmaceutical companies but alignment of expectations and cooperative scientific exchange will enable quality medicines to be delivered to patients. I'd like us all to work closer and I'm sure that we will be able to find ways of doing this in the future – we certainly need to.

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