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ISSUE 09 - JUNE 2015

Editor - Charlotte Barker
charlotte.barker@texerepublishing.com

Associate Editorial Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Deputy Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com

Associate Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

Associate Editor - Michael Schubert
michael.schubert@texerepublishing.com

Senior Designer - Marc Bird
marc.bird@texerepublishing.com

Junior Designer - Emily Strefford-Johnson
emily.johnson@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

Sales Manager - Helen Conyngham
helen.conyngham@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic and Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic and Audience Associate - Jody Fryett
jody.fryett@texerepublishing.com

Digital Content Manager - David Roberts
david.roberts@texerepublishing.com

Mac Operator Web/Print - Peter Bartley
peter.bartley@texerepublishing.com

Tablet Producer - Abygail Bradley
abygail.bradley@texerepublishing.com

Social Media / Analytics - Stephen Mayers
stephen.mayers@texerepublishing.com

Published by Texere Publishing Limited, Booths Hall, Booths Park, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 752883
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Distribution:
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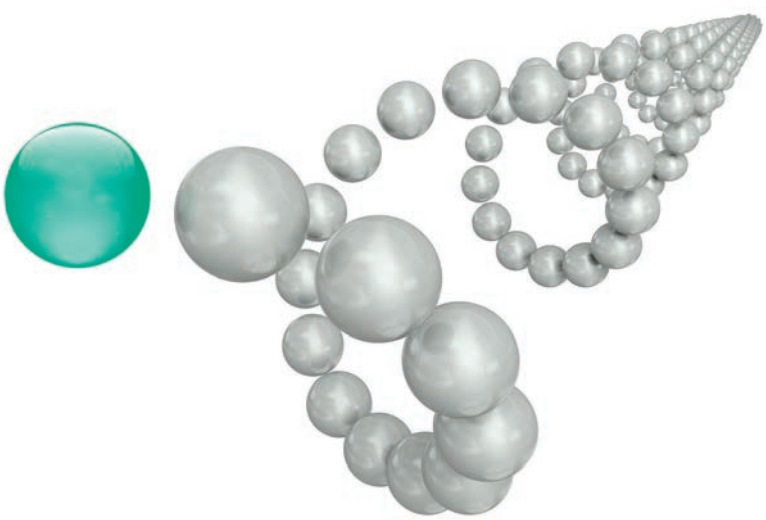

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The Price is Right?

Rising drug prices are not helping the industry's image problem

A recent survey revealed that over 70 percent of Americans believe that prescription drugs are too expensive, and of those, nearly 80 percent thought the pharma industry was mostly to blame (1). Perhaps that should come as no surprise in a month that saw an oncologist from one of America's top cancer centers – Memorial Sloan-Kettering's Leonard Saltz – use his talk at the American Society of Clinical Oncologists Annual Meeting to challenge the industry over the high price of new drugs.

It's not just in the US that controversy is brewing; rising drug prices are a hot button topic in Europe too, with the World Health Organization recently recommending that European governments collaborate to help each other control prices. They also called for more transparency from drug companies on their pricing (2).

The call is familiar, and so are the counter-arguments. The price of drugs is high but so is the cost of development. The price reflects not just the cost of developing that drug, but the ten others that never made it to the clinic. Some drugs are expensive to produce due to the raw materials or process required. But even when there is a way, there isn't always the will...

On page 24, we profile Peter Seeberger and Andreas Seidel-Morgenstern, two researchers whose work could have a huge impact on the price of crucial antimalarials. A plant is set to open shortly in Vietnam, producing artimesinin-based drugs at a fraction of the current cost, using solar power and clever chemistry. This elegant solution to a serious problem won the scientists the 2015 Humanity in Science Award (3), and yet, as Seeberger notes, it was not received enthusiastically by the pharma industry, who he suspects don't want to jeopardize their revenue from expensive drugs.

Almost all of us will be patients at some time in our lives – we want drugs to be affordable, but we also want companies to develop new and more effective medicines. Innovation doesn't come cheap.

One thing seems certain – doing nothing is not an option. As the population ages and healthcare systems come under increasing strain, we desperately need to find ways to cut spiraling costs. Is lowering drug prices the answer? And if so, how can we achieve it? Over to you...

Charlotte Barker
Editor

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3. *www.humanityinscienceaward.com*

Contributors:

James Humphrey

James Humphrey is a Market Applications Specialist working in the research laboratories of Croda in the UK. He focuses on what excipients can do to improve pharmaceutical formulations, whether it's enhancing bioavailability, stability or aesthetics. James says, "What I love about formulation is the never-ending challenge of working out how seemingly small and insignificant changes to a formulation result in massive variation in performance."

James explains why the feel of topical formulations is crucial on page 20.

Abbe Steel

Abbe Steel is Founder and CEO of HealthiVibe, a company that enables patients to contribute to clinical trial design. Previously she was the Vice President of Patient & Physician Services at UBC-Express Scripts, worked at Sanofi on global marketing programs, and was Senior Director, Patient Programs at PAREXEL. When Abbe isn't busy tweeting (@AbbeSteel) about patient centricity, you can usually find her walking a funny-looking black dog named Harper.

Abbe calls for more patient involvement in clinical trial design on page 21.

Peter Seeberger & Andreas Seidel-Morgenstern

Peter Seeberger's research covers a broad range of topics from engineering to immunology. He is a director at the Max-Planck Institute for Colloids and Surfaces in Potsdam and Professor at the Free University of Berlin. Through his work in the area of neglected diseases, Peter has also become involved in philanthropic causes – he is a co-founder of the Tesfa-Ilg 'Hope for Africa' Foundation that aims to improve healthcare in Ethiopia.

After receiving his PhD from the Academy of Sciences in Berlin and working as a postdoctoral fellow at the University of Tennessee, Andreas Seidel-Morgenstern defended a Habilitation at the Technical University, Berlin before working for Schering AG. In 2002 he joined the Max Planck Institutes, where he is head of the Physical and Chemical Foundations of Process Engineering group. Andreas is interested in heterogeneous catalysis, the development of new reactor concepts, crystallization, adsorption and preparative chromatography. The results of his work are published in almost 400 research papers.

The story behind Peter and Andreas' award-winning production method for antimalarial drugs is revealed on page 24.

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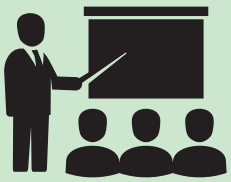

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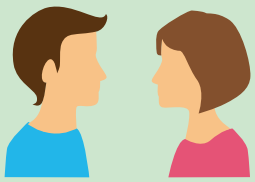

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Upfront

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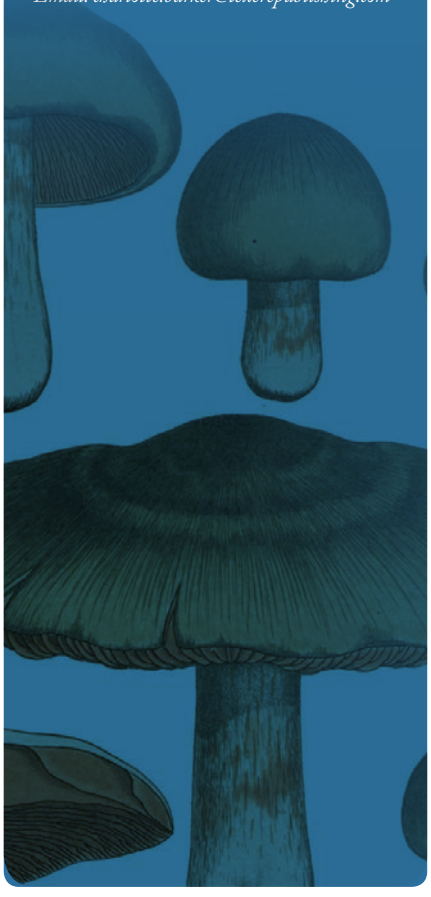


Sterility Fears at the NIH

How did the NIH get it so wrong – and how can it move on?

Aseptic processing is a complex art and it seems no one is immune to problems– or the resulting publicity backlash – including the US National Institutes of Health (NIH). At the start of June, NIH had to shut down sterile operations at its Pharmaceutical Development Section (PDS) after an FDA inspection identified several problems, including fungus contamination in vials of albumin. Drugs from the same batch have already been administered to patients in clinical research programs, who are now being closely monitored.

And the fungal faux pas was only the start of the problems. Some relate to the building, such as flaws in the air handling system, and the construction of the building itself not being best suited to facilitate cleaning, maintenance and proper operations. Operators failed to wear sufficient protective apparel when working with sterile drug products and there was a lack of training in GMP – one operator claimed to have received no GMP training whatsoever. Other problems included deficiencies in cleaning and disinfection programs, lack of validated processes to prevent microbiological contamination, and a lack of conclusions and follow ups in written records of investigations into unexplained discrepancies or batches failing to meet specification; for example, when vials were found to be contaminated with glass particles, a formulator confirmed that no root cause was identified and no preventive actions taken. The list goes on… Overall, FDA inspectors noted 17 observations during their visit in late May. The agency was reportedly first alerted to concerns at the NIH via an anonymous complaint.

Aseptic expert Jim Agalloco of Agalloco & Associates commented, "Aseptic processing, especially where it involves human operators, is perhaps the most complex, and thus the most difficult to control process in the pharmaceutical industry."

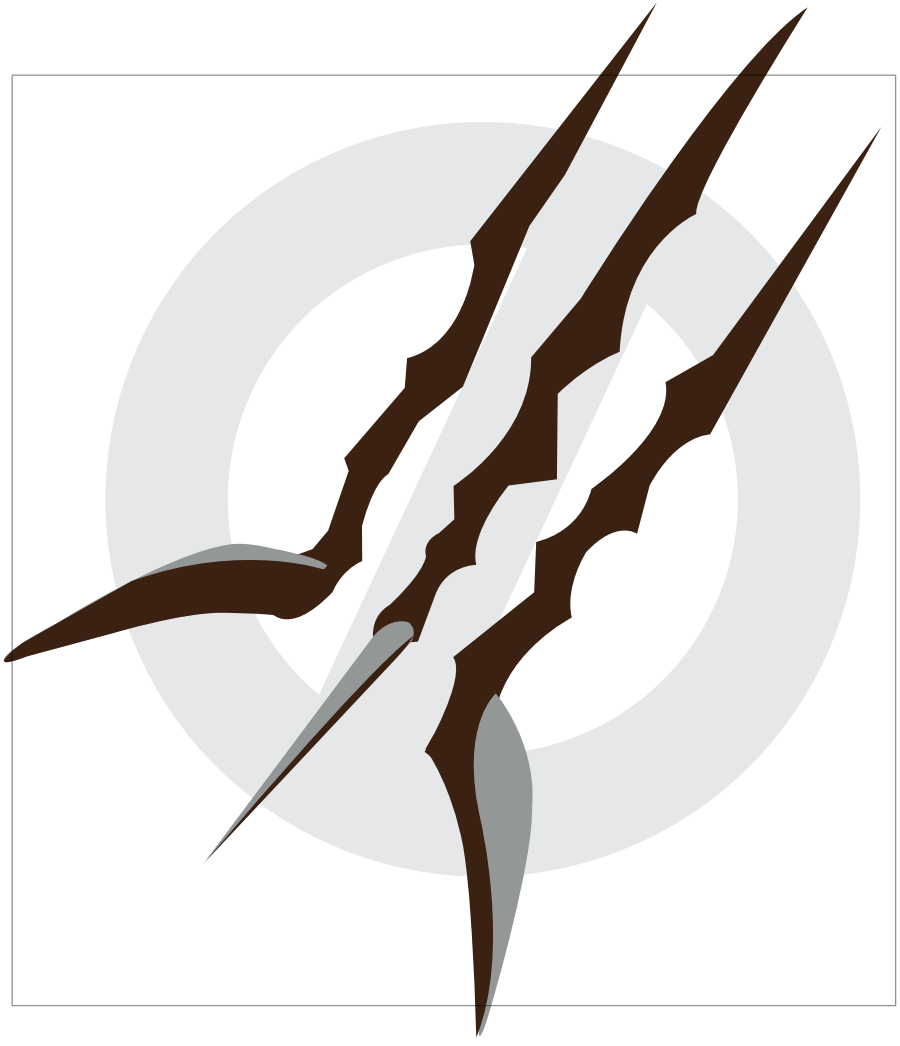
Previous problems at compounding centers have put the FDA on high alert, says Agalloco. "Compounding activities involving combination of sterile products are perceived to be simple, low-risk activities; a belief derived from the current USP <797> Pharmaceutical Compounding – Sterile Products, but that view is not shared by others working outside the compounding sector. FDA's response to the 2012 New England Compounding Center meningitis disaster in 2012 was to expect industrial scale controls to be used by compounders," he continues. "The alignment of sterile compounding practices with the controls employed by the pharmaceutical industry is unprecedented and, although well intended, may be excessive. Improvements in compounding practices appear to be needed, but how closely those upgrades must mimic industrial scale operations is open to discussion."

The NIH has acknowledged the problems, with Francis Collins, Director of the NIH, describing the situation as "distressing and unacceptable." A corrective action plan has already been submitted to the FDA, and all sterile production has ceased until the problems are resolved. To help get to the bottom of the issues, NIH will be appointing an external group of microbiology and sterile manufacturing experts to do a thorough review of the facility.

Around 46 clinical studies could potentially be affected since they were due to receive products from PDS, but NIH says it is trying to secure alternative sources. Other materials not requiring a sterile environment are still being produced by PDS. *SS*

Managing Mutations

Manufacturers must prove that new drug products are free of cancer-causing impurities



The US FDA has released a new guidance to help pharmaceutical manufacturers assess and control impurities that could cause DNA mutations in patients. Because of chemical synthesis or subsequent degradation, all drug products contain some impurities – guidance for the majority of impurities already exists but there hasn't been a great deal to go on when it comes to DNA-reactive impurities. The new guidance aims to provide a "practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities" (1). It establishes appropriate levels of impurities to minimize carcinogenic risk, and outlines recommendations for their assessment and control.

"The focus of this guidance is on DNA-reactive substances that have a potential to directly cause DNA damage when present at low levels, leading to mutations and therefore, potentially causing cancer," the guidance states. "This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity) assay. Other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities."

So who should take notice? The guidance does not apply to existing marketed products, but it does affect new drugs during clinical development and applications for marketing, as well as post-approval submissions of marketed products and, in certain cases, new marketing applications for products containing a previously approved drug substance. It does not apply to biologic drugs or to products intended for advanced cancer indications. The guidance also states, "Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities."

It also isn't intended for leachables associated with packaging, but can be used in this application if warranted. Similarly, the FDA says the guidance is not intended for excipients in currently marketed products but it could be used if necessary for impurities in chemically synthesized excipients that are being used for the first time in a drug product.

The FDA is encouraging manufacturers to implement the guidance as soon as possible, but expects that it could take around 18 months, given the complexity of the document. *SS*

Reference

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The Innovation Game

Big pharma is turning to outside sources to fill pipelines, but how often are companies backing the wrong horse?

A growing number of pharma companies are looking outside of their own walls for innovation, turning to mergers and acquisitions (M&As) and licensing deals in the search for promising projects. Every day seems to bring a new partnership or takeover somewhere within the industry. But how many of these deals actually deliver the anticipated revenues?

Management consulting firm McKinsey decided to probe the topic. "Given the increasing rate of external innovation sourcing in the pharmaceutical industry and the focus on capital efficiency among investors, we wanted to understand how variable M&A and licensing performance has been for the top 20 pharma companies," explains Myoung Cha, a principal at McKinsey.

Cha and his colleagues conducted a study to rank M&A performance (excluding mega-mergers) in the top 20 pharma companies over the past decade. Some of the deals studied included Bristol-Myers Squibb's acquisition of Medarex (and its immune-oncology drug nivolumab), and Roche's acquisition of GlycArt (and obinutuzumab, its blood cancer drug). "We measured capital efficiency by calculating the total projected revenues in 2023 from products directly sourced from each deal, divided by the cumulative M&A capital deployed by each company between 2004 and the first half of 2014," says Cha. "For licenses, we measured performance by the hit rate of scoring a blockbuster (>$1 billion peak sales) and moderate-win (>$200 million peak sales) deals."

The super-executive summary: big pharma is not so great at sourcing the right deals.

In fact, the study rated only two companies highly – Roche and Johnson & Johnson – at both M&A and licensing over the past 10 years. "The wide variability in performance and the relatively low hit-rate for license deals overall was interesting," says Cha. "This variability in performance across deal types suggests that different capabilities and skill sets are necessary in executing M&A transactions versus licensing deals. It is striking that few companies were able to license one or more blockbuster products over the past 10 years, despite a high number of deals. Thus, the difference between an average performer and a great performer could be one or two great deals, which is not too dissimilar from the venture capital model, in which 'home runs' make up for misses."

Sourcing home-run innovation clearly isn't easy. No one can be certain which drugs in development will be the 'winners', particularly those that are in the very early stages. And the fact that the M&A and licensing arena for pharmaceuticals is competitive doesn't help; increased asset prices equals increased risk.

So there's no silver bullet for spotting a successful innovation, but Cha has noted patterns that could help increase your chances. "In our experience, the best performers develop robust forecasts for the key assets, are fiscally disciplined, and set up their innovation-sourcing teams and transaction capabilities to ensure that the right internal expertise is brought to bear and to ensure smooth hand offs through the life cycle of a deal." *SS*

Teaching Old Drugs New Tricks

Could existing drugs be repurposed as a shortcut to treating Ebola?

After testing around 2600 approved drugs and active molecular probes for activity against the Ebola virus, researchers have identified 80 FDA-approved drugs that could be promising (1). Of particular interest are bepridil, an angina treatment that is no longer sold in the US, and the antidepressant sertraline. Both drugs were able to protect against Ebola in mice – survival rates for mice infected with Ebola were 70 percent and 100 percent when treated with sertraline and bepridil, respectively. We spoke with Gene Olinger, co-author of the study and formerly a researcher at the US Army Medical Research Institute of Infectious Diseases, to find out more about the potential of drug repurposing.

How did you get involved?

I was asked to move from vaccine development to drug development for viral haemorrhagic fever viruses like Ebola. The focus was on finding medical countermeasures that could be quickly deployed during an outbreak. We wanted to use the live virus as a phenotypic screening tool to increase the chances we would find a direct antiviral. We started with a variety of small (<10,000) compound libraries and I quickly realized that with the development costs and timeframe, this was likely to be less than fruitful. We also realized that during an outbreak we would need answers quickly. The idea of repurposing drugs with known human clinical safety profiles was compelling.

Did the results surprise you?

We were hopeful about the results, but were surprised by both the number and diversity of compounds that had activity! Some, like ion transport, made sense biologically, but others were more surprising. We are still trying to dissect if these unexpected drugs are functioning through their known mechanism of action for their indication(s) or some off-target effect. The results provide a starting point to understand critical host–pathogen interactions and a lot of basic science questions.

How promising is the antiviral activity identified?

The drugs have adequate potency as antivirals. For an acute infection like Ebola, however, the ability to change the course of disease once symptoms develop is going to be difficult. Thus, we think combinations may be required. The library data may also provide insights into chemistry that may allow for novel drug development and thus increase potency.

What are the next steps?

Next steps are to assess the drugs individually in prophylactic and post-exposure conditions in guinea pig models and in the more rigorous nonhuman primate models of disease. We are also completing a combination assessment where we have identified synergistic combinations.

How is an approved drug typically repurposed?

A clinician could simply prescribe a drug "off-label". In addition, the 505(b)(2) New Drug Application process has been used for repurposing. This is a common method to reposition existing drugs. There are advantages and disadvantages (both commercial and scientific) when it comes to repurposing. For rare and neglected diseases, it is a key area of interest that is gaining traction.

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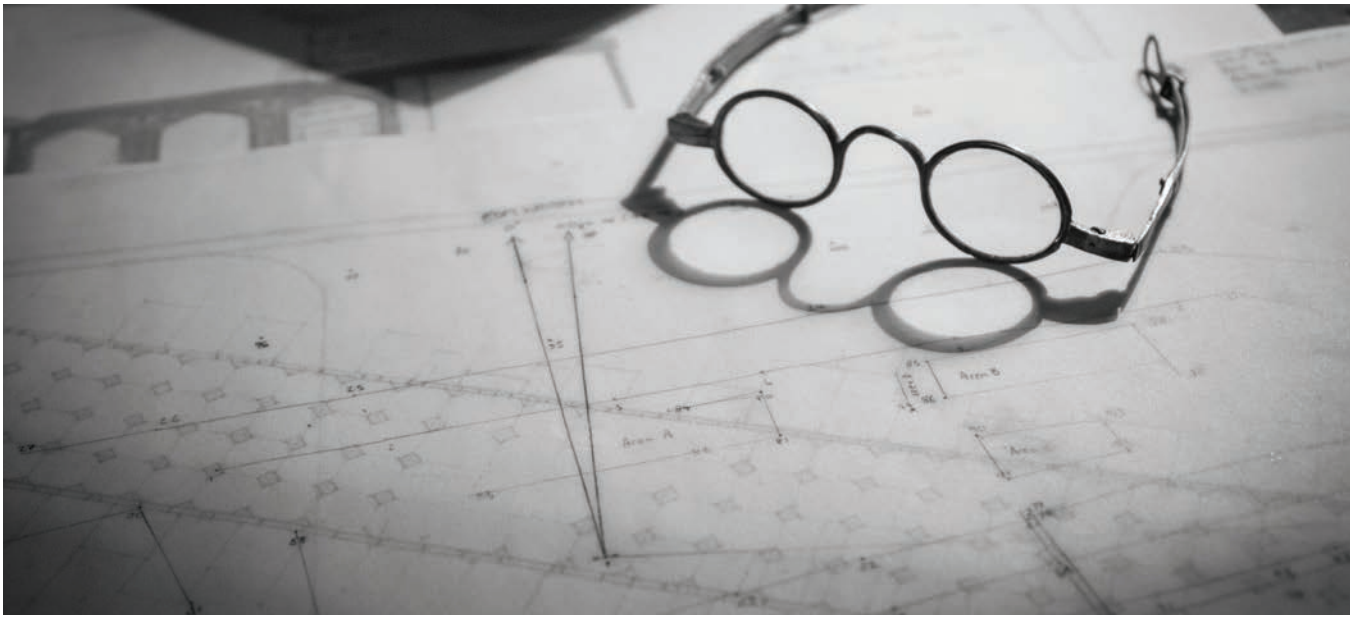

Eyes on Expansion

A round-up of the latest expansion plans and new facilities as building fever grips the industry

Summer is the season for sun, sea, sand… And a raft of new and expanded manufacturing plants. May and June have seen something of an expansion craze with companies big and small announcing new investments – and biologics seem to be a key focus.

AstraZeneca says that biotech products now make up half of its pipeline and recently announced that it was investing $285-million in a new plant for filling and packaging protein therapeutics in Södertälje, Sweden. By the end of 2018, the facility is expected to supply biologic medicines for AstraZeneca and MedImmune's clinical trial programmes, moving on to commercial products once fully operational in 2019. The company also bolstered its biologics manufacturing capabilities in the US at the end of 2014 with a $200-million project to expand its Frederick, Maryland site, which currently produces pediatric medications and investigational biologic products. But small molecules have not been entirely forgotten; in June, AstraZeneca announced that was partnering with two Algerian companies to create a new plant for small molecules in Algeria.

Meanwhile, Alexion is planning to build its first biologics manufacturing plant outside of the US, in a four-year project with an investment of over $500 million. Few details have been revealed, but the 20,000-square meter plant will be located in Dublin, Ireland, will include four 20,000-litre production bioreactors, and is being designed to allow rapid ramp-up of production as needed. The company has been building its Irish base in recent years and has already invested in an Irish vial fill–finish plant and a supply chain facility.

In Canada, Gilead Sciences will be spending $100 million on expanding its Edmonton site. The company made the announcement at the ribbon-cutting ceremony for the first of two new laboratory buildings in Edmonton. The new investment will focus on building a new process tower for API manufacturing, as well as a maintenance facility and upgrades.

Also in Canada, plant-based vaccine and therapeutics maker Medicago is constructing a new plant in a $245-million project in Quebec City's Estimauville innovation park, which will span around 44,000 sq meters and have the capacity to deliver 40-50 million doses of quadrivalent seasonal flu vaccines.

And finally, Bayer is targeting its healthcare manufacturing plant in West Java, Indonesia, for expansion with an investment of around $9.2 million; first the company is inaugurating a new warehouse, but there are also plans to increase the overall manufacturing capability. And finally, Novartis' Sandoz division recently expanded its site in Stryków, Poland by adding a new packaging center that allows packaging processes for tablets to be carried out directly on site. *SS*

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01 South Korea's generic market is projected to grow on average 5% per year between 2013 – 2018 to a staggering $23.84 Bln.

02 South Korea closely ranks after China and India as the third "best outsourcing destination" in Asia.[1]

03 Korea Drug Development Fund (KDDF) will promote the development of the Korean biotechnology sector in the Asia Pacific region aiming to produce 10 new treatments by 2019.

04 Investment in R&D and related facilities is very active and establishment of plants according to the international standards is increasing.

[1] The changing dynamics of pharma outsourcing in Asia, PwC.

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Amine Alchemy

Transforming common chemicals into complex amines is the pharmaceutical equivalent of turning lead to gold

Researchers from The Scripps Research Institute claim to have developed a new method for synthesizing amines, which they describe as being akin to "taking dirt, and then adding a bit of rust, putting it all in a blender and ending up with gold" (1).

In fact, complex amines are often more expensive than gold because they can be challenging (or even impossible) to make using traditional methods. This includes many with particularly desirable properties for drug developers, such as resistance to breakdown by enzymes in the body.

"Amines are very polar and therefore difficult to purify and manipulate without protecting groups," says Phil Baran, the Darlene Shiley Chair in Chemistry at the Scripps Research Institute, and leader of the study. "I think that one of the most exciting aspects with our method is that it might one day be used widely by industrial drug and agrochemical makers for the betterment of humanity. Many companies have already told me they are using the new method, including Bristol-Myers Squibb (BMS), who are actively using it in current medicinal chemistry programs."

BMS and Scripps have been working together for some time as part of a multilaboratory partnership. In one of their latest projects, scientists from Scripps and BMS found that mixing two abundant (and cheap) feedstock compounds – nitro(hetero)arenes and olefins – with an iron catalyst could generate a variety of complex amine-containing compounds, under very mild conditions. According to Baran, most scientists have nitroarenes and olefins on a shelf in their lab, but it is only when they are merged in a precise way that they are able to produce such a wide range of amines. He adds that the method is very simple and practical to carry out. His team has successfully used the reaction to synthesize over 100 different amines, including drug compounds, in fewer steps than would be used in traditional methods. Indeed, some of the amines produced contained sensitive functional groups that couldn't survive conventional amine synthesis reactions.

Baran says, "Our lab has always been driven by pragmatic considerations and cost. We feel that if you're going to invent a reaction it should probably be accessible to as many people as possible and not be over-engineered," says Baran. "As for how our technique will fare in the future, time will be the ultimate judge of any synthetic method so let's check back in five years. At the moment though, we are working on improvements such as rendering alkyl amines in higher yields." *SS*

Reference

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In My View

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

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

Contact the editors at edit@texerepublishing.com

One Framework to Rule them All

If regulators worldwide are to make good decisions in the face of complex risk–benefit profiles, a transparent and systematic approach is needed. I believe our 'universal framework' could be the answer.

By Sam Salek, Professor and Chair, Pharmacoepidemiology, University of Hertfordshire, UK.

For many years, the area of benefit–risk assessment of pharmaceutical products was almost a taboo – there was no transparency, no audit trail, and no systematic approach. Compared with 15 years ago, there is now a more systematic approach being taken in many regulatory agencies. High-profile tragedies involving approved drugs, such as Vioxx, have led to revised legislation and a new emphasis on benefit–risk assessment. But there are still many regions where these complex decisions come down to a single individual. We did a survey as recently as 2013 to find out whether regulators were using any specific criteria/model when assessing benefit and risk – we found that qualitative approaches still dominate (1).

The thrust of my work over the past decade has been promoting more collaborative decision making, based on a systematic, transparent process. Nine years ago, my collaborators and I proposed a quantitative model, starting a debate about benefit–risk assessment of medicines that led to a consultation paper from the EMA in support of our model. Around the globe, regulatory authorities have been debating the issues, and we have been invited to take part in many of these internal discussions.

Opening the dialog with regulators and pharmaceutical companies has been tremendously valuable in itself. But while our original model was very thorough, its mathematical complexity meant that it was only likely to be used by the most sophisticated regulatory bodies – and then only in a handful of the most challenging decisions. We wanted to create a framework that could be used globally – a common language.

Our recently published "universal framework" was designed for this purpose (2). It is a streamlined, semi-quantitative framework that can be easily integrated into the assessment processes of pharmaceutical companies and regulators worldwide. The framework was developed in collaboration with regulatory authorities in Australia, Singapore, Canada, UK and Europe. It looked good on paper, but to be sure of its practical value, regulators tested the model as part of their routine assessment of pharmaceutical products. It proved to be a

"High-profile tragedies involving approved drugs, such as Vioxx, have led to revised legislation and a new emphasis on benefit–risk assessment."

very robust, user-friendly and relevant tool. In case studies and retrospective analyses of past approvals, the framework has often uncovered new issues, which in some cases could well have led to a different decision.

Another important issue that we hope this framework will address is the discordance between the decisions made on the same drug in different parts of the world. There are long waits for patients in some countries to get a drug that may have been approved months or years earlier in another region. In some respects, the gap is widening between the mature regulatory authorities in countries like the US, Europe, Australia, and those in emerging economies, with potentially life-saving drugs taking months or years to reach poorer nations, even aside from the affordability issues they present.

The framework lays out eight key steps to make an informed decision based on an impartial assessment of the benefits and risks, applicable for any product, in any part of the world.

1. Determine the decision context
2. Build a value tree
3. Refine the value tree
4. Look at the relative importance of benefits and risks
5. Evaluate the options available to you
6. Evaluate the level of uncertainty
7. Summarize the results, preferably involving visualization
8. Communicate the results to relevant stakeholders

The resulting documentation includes background information on the product, summaries of the non-clinical, pharmacological and clinical study results, identification of the benefits and risks, the criteria considered and a clear conclusion. It is worth highlighting the importance of visualizing the results of the assessment using graphs, such as forest plots. Graphical information is much easier for people to absorb, and a key component of the framework is its transparency.

"The time has come for pharmaceutical and regulatory professionals around the world to speak the same language."

Like any such system, the universal framework will be most valuable in situations where the risks are high and the benefit–risk trade-off is not clear cut. Consider a drug for migraine headache with a number of serious potential side effects. Migraines are not life-threatening, but can be very debilitating – for example, a surgeon who develops severe migraines may be forced to abandon their career for fear of putting patients at risk. By using a framework like ours, regulators can take into account the minutiae of the benefits and risks and make an informed decision.

The time has come for pharmaceutical and regulatory professionals around the world to speak the same language. By increasing communication and exploring joint review of pharmaceutical products, we could save time and money and, most importantly, improve access to medicines worldwide.

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How Does it Feel?

When it comes to topical formulations, I firmly believe that patients care about the way a cream or ointment feels – and that it plays a very important role in compliance.

By James Humphrey, Market Applications Specialist, Health Care, Croda Europe Ltd, Goole, UK.

When my colleagues and I are considering a new dermatological formulation, we focus on four areas: solubility, stability, sensory and delivery. We ensure that the API is at least partially soluble in the formulation and stable physically and chemically. We also consider whether the patient will actually apply the formulation and ensure that the active pharmaceutical ingredient (API) can reach the required target.

The pharmaceutical industry puts a huge amount of resource into the solubility, stability and delivery aspects of derma formulation, but the sensory aspect is something that is largely overlooked, if not ignored altogether. Is it really right to leave the aesthetics of a formulation to an afterthought?

This point was very well made by a professor of dermatology, Steven Feldman, who said "I think vehicle effects on delivery through the stratum corneum are less important than the fact that the patient actually puts the medicine on" (1). It's an irrefutable fact that no drug is bioavailable when it stays in the container.

I'm not saying that the formulation aesthetics should be considered more important than bioavailability, or indeed other aspects of designing a new formulation, but that all factors need to be taken into consideration to design a truly successful treatment. I have frequently heard the comment, "If the patient has the disease they will use the treatment", and for very severe conditions I imagine this is quite true. However, for milder conditions and many over-the-counter formulations I think this assumption is made with the mindset of a scientist. As a scientist, I know that the activity of the API often takes time; I know that I must keep applying the product for the correct number of times per day to get results. But do all users think like this? Do patients always finish their course of antibiotics, even after they feel better? Does the patient always apply the ointment three times a day? I'm less than convinced.

Compliance or concordance is essential to create a successful treatment, but there are a lot of different facets required to achieve it. Where do we start? I think that one area that the world of healthcare can learn from is cosmetics. Cosmetics are based around creating a consumer belief in the product. I'm certainly not proposing that a good cosmetic story replaces the rigorous science needed to develop a topical pharma product, but we should consider some of the psychology used.

I started my formulation career in cosmetics. In those days, I would formulate skincare products with three aspects in mind. Firstly, make sure the formulation you offer does not feel horrible; finding something that the majority of people would agree that they strongly like is difficult, and yet most people readily agree on what feels unpleasant to apply. Secondly, make the consumer believe there is an improvement in the first few minutes of application. Thirdly, make sure the formulation meets the consumer expectations in the long term.

The best example of this is an anti-aging cream. For daywear, you develop a light formulation that quickly absorbs into the skin, and for night-time use you create a more substantial-feeling product. Ingredients are added to the formulation to give what are referred to as 'instant effects'; for anti-aging creams these will give the appearance of smoother skin. This element is really important as without this immediate 'evidence' of an effect it's unlikely that the user will stick with the formulation. Maintaining use of the product actually allows the emollients and anti-aging actives to achieve their long-term effect.

I'm not suggesting that healthcare formulations require instant effects but there is something to be taken from the idea. When starting to formulate, take some time to consider the aesthetics. Can you really expect someone to apply a heavy, greasy formulation made of petrolatum or high-molecular-weight PEG twice a day? Does the formulation convince the user that it's doing some good? Can you expect a patient with sore and broken skin to apply and rub in a thick, paste-like formulation?

I believe pharmaceutical formulators need to consider a wider selection of ingredients, moving away from the trusted topical formulations used for decades, and formulate products with cosmetically acceptable aesthetics. Only then will a patient happily use the product every day as instructed, and we can move closer to achieving complete concordance.

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What Patients Want

Most pharma companies want to become more patient focused. But how? You could start by simply listening more carefully.

By Abbe Steel, Founder and CEO, Healthivibe, LLC, Arlington, VA, USA.

Are the pharmaceutical industry's clinical development programs more patient-centered than they used to be? Well, there is certainly a lot more talk about 'patient-centric' clinical trials. But if I were to pick up a protocol from today and compare it with a similar trial 10 years ago, I doubt I would notice a significant change in design or concept.

Do we think more about the patient than we used to? Yes... And yet, in over 20 years in the industry, I have seen countless missed opportunities to involve patients. For years, I worked on studies and programs that relied on patient involvement, and I saw first-hand the same problems again and again. Recruitment would fall behind, trials went over-budget, and patients had recurring complaints. Many of these issues stemmed from the original trial protocol; I wanted to find out where we were going wrong and how we could do better. The most obvious place to start was to talk with the patients. Surprisingly, this is still a novel concept.

When Nike launches a new tennis shoe, they don't just push the shoe out into the world and hope for the best. They do extensive customer research involving focus groups, testing and surveys. Do we do that for clinical trials? No. We launch trials and hope for success. I could sense a gap in the market for a company specializing in clinical trial patient 'market research.'

I was right. Our services have been in great demand right from the beginning. In a nutshell, we gather insights from patients. We use a variety of exploratory, qualitative approaches; for example, patient-advisory boards and focus groups. and we design and implement quantitative research via surveys. All patients are different, so by taking a large – and preferably diverse – group, we can validate findings from our qualitative research.

'Mock study visits' – where a doctor sees a patient at the proposed trial center for a simulated (and observed) appointment – are also popular. Many of our clients have been shocked and surprised by what they are hearing. For example, after a recent simulation, it became clear that patients were confused about how to take the drug. By re-training staff at the site, updating packaging information, and adding more patient education, we helped the company avoid potentially serious medication errors on the trial.

Planned endpoints and patient-reported outcomes can also be informed by improved dialogue with patients. You can only include indications on the label that you have assessed in a trial; it's imperative to get these right the first time. For example, determining quality of life assessments for a disease with multiple symptoms isn't always as obvious as it seems. When trying to determine which symptoms are most bothersome for the patient, their insights may surprise you.

Research with previous clinical trial participants is also very insightful. Based on our work, we have found that the relationship between the patient and staff at the site is critical for the patient's overall experience. When sponsors are selecting a site, patient population, adhering to good clinical practices, relevant equipment and experience are all important, but many companies don't always consider who will be interacting with the patients – and how. Customer service is not irrelevant in clinical trials. When you ask a patient, "how was your clinical trial experience," often they will first describe how they were treated and how flexible appointment times were. One patient described going into the same center every Friday for a year, speaking with the same receptionist – but without the slightest sign of recognition.

Every company I speak to wants to increase patient engagement. They know it's the right thing to do, and that it will be good for business in the long term. In many cases, the 'what' and 'why' are clear enough – the 'how' is the problem. My answer is simple: do something.

As an industry, our culture has always been provider or payer centered. We need a massive cultural shift; we need to put patient–centered outcomes at the heart of the business model. The most progressive companies have already started on this journey by deploying systematic frameworks and dedicated teams to oversee implementation. But you don't have to change the whole company overnight; just try a few ideas. Keep exposure and budgets low, and see what works. Introduce measurable, achievable outputs; for example, simply speaking to patients before a clinical trial or conducting a survey. Once you start communicating with patients, you will learn what they are thinking and feeling – and that could well lead to faster, more effective, and less costly trials.

How to be Fast and Flexible

The biopharmaceutical sector is rapidly evolving – can your supply chain keep up?

By Prashant Yadav, Director of Healthcare Research at the William Davidson Institute, and faculty member of the Ross School of Business at the University of Michigan, USA.

The biopharmaceutical industry is undergoing a striking transition. In developed markets, one-size-fits-all medicine is being replaced with higher-efficacy treatments for targeted populations. In emerging markets, a burgeoning middle class and larger public investments in healthcare infrastructure are resulting in rapid growth of the pharmaceutical sector. In some developed and emering markets, reimbursement lists favor domestically produced pharmaceuticals, making local manufacturing a requisite for market entry. Smaller target markets for each molecule; volatility in regulatory and political environment in emerging markets; and stronger payer influence in developed markets are resulting in more frequent changes in commercial decisions. All of these trends are stepping up pressure for speed, flexibility and reliability in the pharmaceutical supply chain.

To deal with rapidly changing market conditions and patient micro-markets, biopharmaceutical companies need highly flexible supply chains. Indeed, companies with flexible supply chains are beginning to exhibit a significant advantage over less flexible competitors, especially in high-margin product categories.

Irrespective of any macroeconomic trends, speed to market will continue to be a key competitive advantage for the biopharmaceutical industry. Many studies have shown that a faster product launch, even by just a few months, can bring additional revenue of hundreds of millions of dollars. Speed-to-market depends not only on the clinical development process, but also on the ability to quickly transition the clinical supply chain into a commercial supply chain.

In the past, supply chain flexibility and supply chain speed were often competing goals with complex tradeoffs ("cost = efficiency" was largely an afterthought). Speed-to-market implied designing a supply chain network with manufacturing centers of excellence for a particular class of compounds, where clinical supply platforms could be quickly commercialized. In the future, companies need to transcend the tradeoff between speed and flexibility and look for innovative ways to simultaneously achieve greater speed and more flexibility.

The good news is that new manufacturing technologies are now making this increasingly feasible. Modular, on-demand manufacturing technology, which has been in the making for many years, is now close to being used at a commercial scale. Pfizer, along with its partners, is implementing "portable, continuous, miniature and modular manufacturing" (PCMMM), which allows rapid deployment and faster transition from clinical to commercial manufacturing, as the same equipment can be used for both. These "pharma manufacturing pods" are designed for rapid changeovers and flexible batch sizes. The pods can be quickly deployed in warehouses and existing structures, creating immense flexibility in the supply chain network. Drug products can be manufactured on-demand in each country, alleviating the need for solving complex cost and lead time trade-offs in regional or global planning.

This idea holds the promise of considerably transforming the pharmaceutical supply chain. Over time, shared multi-company 'pod farms' may emerge to leverage the benefits of co-location of small-size manufacturing facilities.

While manufacturing technology is progressing to allow faster speed-to-market and greater flexibility, companies must also learn to make supply chain decisions quickly and flexibly. A fast and flexible pharma supply chain also requires strategic leaders who know when to look outside the industry for best practices. Companies in other industries have successfully embedded speed and flexibility in their supply chains to achieve competitive advantage. For example, in the fashion industry, Zara has created a supply chain that can bring new styles to market more quickly, while at the same time using a network that can adapt to the changing cost economics and long-term demand shifts.

Speed-to-market and flexibility are not just management fads; they are an opportunity for the pharma industry to fulfill its social contract of bringing innovative and higher efficacy treatments to the market quickly, while maintaining high service levels and affordable costs. In my view, the companies that imbibe speed and flexibility – in manufacturing technology, supply chain network design, and decision-making processes – will emerge as the long-term winners in our industry.

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Finding Humanity in Science

What drives someone to throw aside selfish pursuits to focus on projects with true philanthropic impact? Here, the winners of the 2015 Humanity in Science Award provide their answers.

The 2015 Humanity in Science Award (www.humanityinscienceaward.com) was presented jointly to Peter Seeberger and Andreas Seidel-Morgenstern, directors at two collaborating Max Planck institutes in Germany, by our sister publication The Analytical Scientist. Their groundbreaking work in drug synthesis also won both scientists a spot on our 2015 Power List. By coupling flow chemistry with advanced chromatography methods, Seeberger and Seidel-Morgenstern were able to manufacture artemisinin-based therapies – the most effective drugs to treat malaria – from plant waste material, air and light. The science is innovative and exciting, and the potential impact of their project – and the concepts born from it – could really shake things up in the pharmaceutical industry.

The key active pharmaceutical ingredients (APIs) of all artemisinin combination therapies are produced in one or two chemical steps from artemisinin (see Figure 1). The majority of artemisinin (~200 tons per year) is extracted from the Sweet Wormwood plant (Artemisia annua) cultivated for the purpose, and prices fluctuate with harvest yields, driving up prices. With demand outstripping supply, up to 50 percent of anti-malaria drugs sold in Africa and Asia are counterfeit – useless and sometimes toxic.

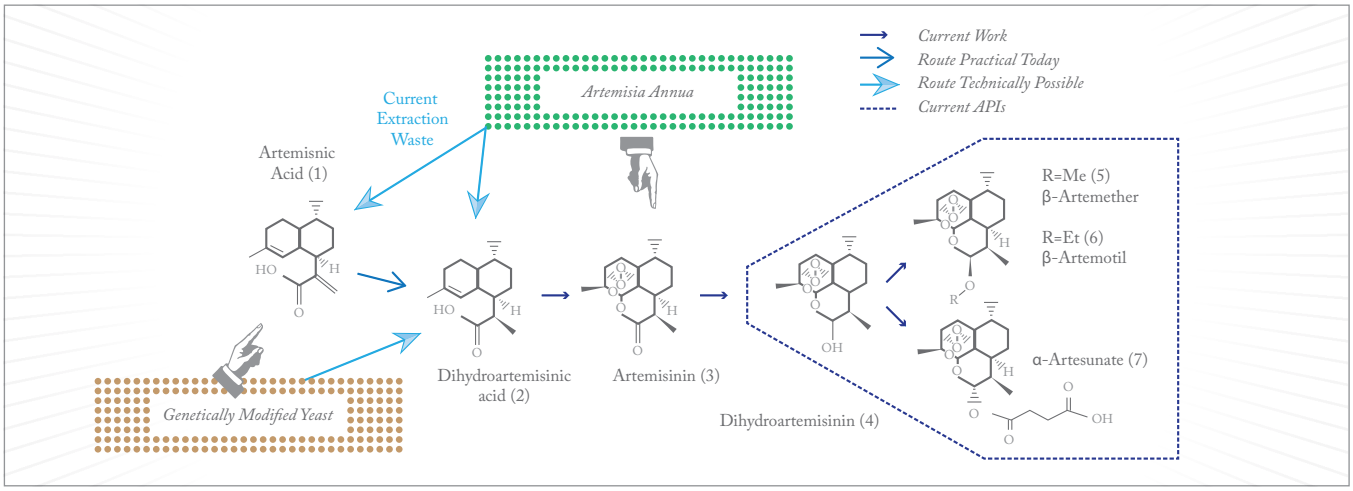

Figure 1. Production scheme of anti-malaria APIs from artemisinin obtained by extraction from Artemisia annua and genetically modified yeast combined with chemical modification. Dihydroartemisinin (4, combined with piperaquine in Eurartesim, Artekin and Duo-Cotecxin), α- artemether (5, combined with lumefantrine in Coartem), α-arteether (6, Artemotil), and α-artesunate (7, combined with amodiaquine in Coarsucam and ASAQ-Winthrop).

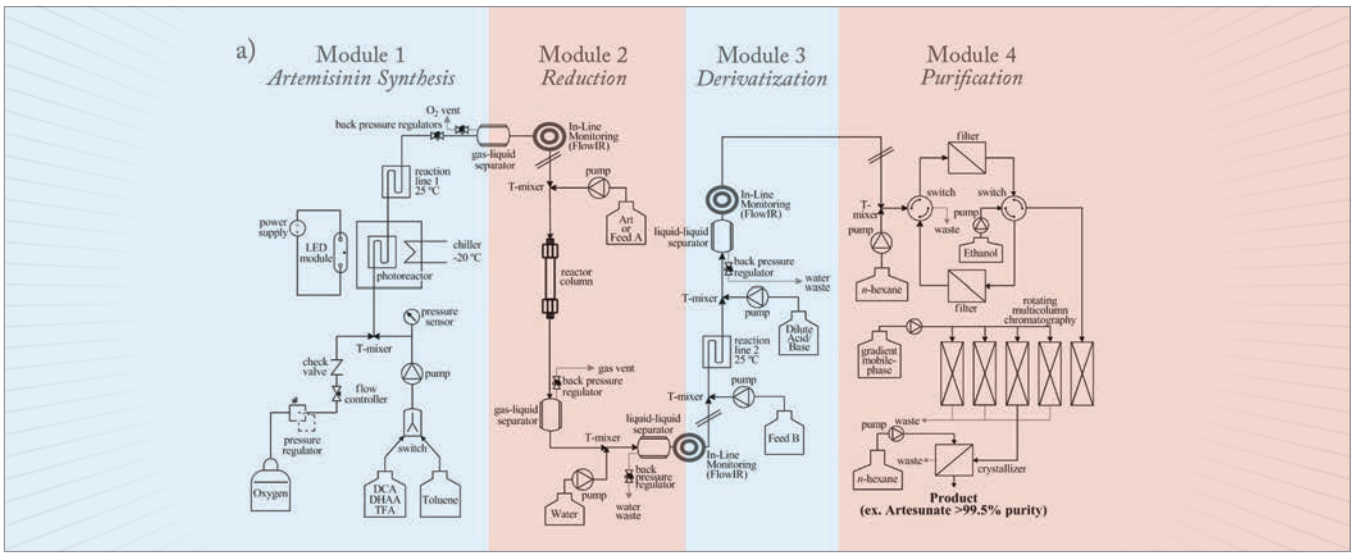

Figure 2. Four-module chemical assembly line system for the continuous synthesis and purification of artemisinin APIs. DCA: 9,10-dicyanoanthracene, DHAA: dihydroartemisinic acid, TFA: trifluoroacetic acid, Art: artemisinin.

Seeberger came up with a process for photochemical continuous synthesis of artemisinin from a waste product of the plant, DHAA. Yields were low at first – 40 percent yield at 200g per day – but careful optimization resulted in a greatly simplified process and a significantly improved yield. To demonstrate the power of the fully continuous synthesis/purification regime, Seeberger and Seidel-Morgenstern developed a continuous three-stage, multi-column chromatographic/crystallographic purification method for artemisinin-derivative α-artesunate (see Figure 2).

The combined process produces artemisinin of greater than 99.9 percent purity and is now being implemented in a pilot plant in Vietnam. Not only does the new process enable production of less expensive anti-malaria medications, it also increases participation of developing nations in the value chain of drug production.

Now, let's focus on the personal stories of the duo that led the project, to discover what seeds humanity in science.

You can read the full submission to the Humanity in Science Award online: www.humanityinscienceaward.com

Using Entrepreneurship and Chemistry for Good

Peter Seeberger, Professor and Director of the Max Planck Institute of Colloids and Interfaces, Potsdam, Germany.

How did you get into chemistry?

I grew up in Nuremberg in Bavaria and was the first member of my family to go to university. I guess I was a good high school student, because I qualified for the highest possible scholarship for Bavaria, something that is awarded to just a select few. I could have studied anything, but I chose chemistry.

I then had to do my mandatory national service in the German army, which further motivated my pursuit of chemistry – the armed forces were definitely not for me. I studied both chemistry and business to begin with, but I eventually focused on chemistry because it gave me the chance to stand out from the crowd. I studied chemistry for three years at University Erlangen-Nuremberg with a full scholarship. The program normally took five to six years to complete, but after three years I had finished and was nominated for a full graduate scholarship to go to the US for a year. I applied to both Berkeley and Colorado universities and ended up going to Colorado, which was great as I like skiing...

I finished my PhD in Colorado working with Marvin Caruthers – a member of the US National Academy who famously automated DNA synthesis and set up many companies, including Amgen. Working with him made me realize that doing very good chemistry could also help you to do very good biology. The idea of starting up companies was also interesting.

So you moved again?

Right. Bruce Merrifield won a Nobel Prize in Chemistry in 1984 for chemical peptide synthesis on a solid matrix and I thought I could do something similar for carbohydrates. To prepare myself, I applied to work with the best-known carbohydrate chemist of the time – Sam Danishefsky, professor at Memorial Sloan Kettering Cancer Center and Columbia University. He accepted me into his lab in New York, where I worked extremely hard – 18-hour days, seven days a week – for two years. I focused on developing methods for carbohydrate synthesis.

I'd already lined up a job in Germany as an assistant professor, but before I could accept it Danishefsky called me to his office at 1am on December 23 and asked me what I'd be doing after leaving his lab. He encouraged me to apply to Massachusetts Institute of Technology (MIT) – and I did. They invited me to give a talk and then I had a day-long interview. The following day I received an offer to be an assistant professor at MIT. I accepted.

Why was Danishefsky so keen to push you to MIT?

Danishefsky encouraged many of his people to apply to leading institutions. I'd published 12 papers with him and he seemed to think I would be a good match for MIT.

Moving to MIT was the best career decision I ever made, so I'm thankful to Danishefsky for pointing me in the right direction. Often, your choices in life are due to the influence of your mentors and role models. Without their influence, I would never have considered applying to top universities. When you come from Bavaria, places like Harvard and MIT are pretty far away – and not just in distance.

I did not know what to expect at MIT, but it worked out OK. I remember that in the first three days of starting my job, one of my colleagues asked me to go to the faculty lunch room and the provost said to me, "Young man, what do you think of your chances of getting tenure?" I replied that I had no idea, but I guess I was lucky because after about four years I was promoted to tenured professor at MIT at the age of 35.

Sometime later, ETH (the Swiss Federal Institute of Technology) in Zurich made me an offer I could not refuse. I'd been in the USA for 13 years and thought I would probably stay there my whole life. If I turned down ETH, I thought it would be difficult to return to Europe.

Initially, I didn't find life at ETH easy because I'd been Americanized both in the way I spoke English and in my etiquette. It was a learning process for both sides I think. I was there for six years, met my partner (who was a professor in Berlin) and had a daughter. The commute between Zurich and Berlin needed fixing.

The Max Planck society offered me a job to take over a directorship at the Institute for Medicine in Heidelberg. It was a good offer, but it would not improve my family situation (travelling between Heidelberg and Berlin is actually worse than travelling from Zurich to Berlin). However, the people at Max

Planck were persistent and suggested that I join an institute in Potsdam where they would erect a new building for us. I have to say I was anxious about the move. When I left MIT it was one of the most difficult days of my life because I was not sure whether I made the right decision. I was in a similar situation and knew there would be a lot of things I would miss about Switzerland. That said, I have been lucky in life and felt it would turn out well.

What brought you such success?

First of all, you have to pick a good area to work in. Glycosciences is a fantastic area with seven Nobel Prize winners up until the early 1970s – and glycans are everywhere. The advances in molecular biology of the mid-1970s and the new-found ability to manipulate DNA for proteins meant carbohydrates took a back seat and the technologies for enabling glycomics and glycobiology were lacking. I had expertise in DNA and peptide and carbohydrate chemistry that no one else had at the time. Many said that my idea for automated synthesis of carbohydrates wouldn't work, but it was a smart choice given my background.

I also work really hard – I'm very driven. I don't think I'm more intelligent than the next guy, but perhaps I am able to see interesting areas that enable long-term programs rather than just solving little puzzles.

And that approach fits in with your work at Max Planck where you are building platforms?

Yes – and that's how I got interested in flow chemistry, which is part of the work we received the Humanity in Science Award for. It's something I've been involved in since my days at MIT, where I remember hearing a talk by a physicist who had begun working on flow chemistry while he was in Germany. He talked about how you do chemistry in pipes instead of buckets, and that really appealed to me.

I started building systems and platforms. And we slowly began to get involved in medicine – after all, though my students are very well trained in carbohydrate chemistry, they need experience with drug molecules to improve their employment prospects! In fact, most of the people we train go into industry; more than 200 of them have left to get really good jobs. But I've also seen 47 professors come out of my lab.

It's fantastic to have the opportunity to convince talented young chemists to work with me. I give directions to make sure we get to a certain point, but the important work is done and implemented by the young scientists we train. If our students weren't as diligent, things could have gone in a very different direction.

What drove you to explore antimalarial drug manufacture?

Early on in your career, you want to make sure you publish the best possible papers. Then one day you ask yourself: "Do I want to publish another paper or do I want to make a real impact?" I knew that if I wanted to have impact on a global scale, I needed to work on something that could improve other people's lives, particularly those who have little chance themselves. So, that's why I started to think about things like malaria and HIV (we're also working on cheap antibiotics and anticancer medications). The artemisinin project was the first step in that direction. I'd usually work on vaccines – a cheap means to prevent disease – but with artemisinin, it became clear that the medication is there, but a huge part of the global population (the ones who most need it) can't afford to buy it. You can talk to people who travel to Africa and they will tell you that they had to lock up their antimalarial drugs to prevent the cleaning staff from stealing them. The inequality at the heart of the problem is just wrong.

I thought, "we can do something about this problem". But it wasn't enough to simply publish a new method – we had to take it further than that. It is very difficult to translate published research into something that can be implemented and taken to market; it's very frustrating to see good existing solutions that are simply not being implemented in developing countries. And it's sad that so many people are leaving Africa because of the bad conditions – the real solution is to help these people have better lives without them having to leave. I can only make a small contribution, but one of our goals is to convince governments to do something regarding technology, but even there I see some reluctance.

But much of the world is governed by economics – and that has to change, right?

When the artemisinin story first broke, it was all over the news. People said, "This is great, congratulations!" But without a lot of effort, it won't see the light of day because the big companies will try to bury it. Pharma companies are traded on the stock market so they have to make profits. One of the big questions of our times is how are we going to evolve drugs in the future? For example, I know that if any of us were investing in a pension


"It wasn't enough to simply publish a new method – we had to take it further than that."

fund, we'd expect the fund managers to make the best decision about putting our money into a drug company or into a car company. Is the drug company expected to give a big discount or free drugs to Africa? What about the car company? Does it have no obligation to give a discount? Right now, the system is not really geared towards improving health for a large part of the global population.

Unfortunately, I don't have a total solution to that problem – just a small piece of the puzzle. But wouldn't it be great if some really smart people stopped to think about changing the world of pharmaceuticals – not just how they are manufactured, but also how they evolve and how they are paid for. I do believe in a free market, but the population of poor people around the world is growing and being left behind – that can't be right. I don't think it's good to live in a world where very few people are very rich and a greater number of people have nothing. If I look back on my own life in Germany in the 1970s and 1980s, there were very few poor people and very few rich people. We see in many countries that the middle classes are being dissolved – the polarization of society. I don't think it would be fun to be part of these societies – even if you are rich.

Preparing to Change the World

Andreas Seidel-Morgenstern, Director of the Department of Physical and Chemical Foundation of Process Engineering, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany.

Take us back to the early days...

I grew up and worked in what was East Germany – right up until I got my PhD, which I did in 1987 in the former Academy of Sciences' Institute of Physical Chemistry in East Berlin. It was an interesting time, but also very political. In fact, my scientific career was more or less over after I completed my PhD because I refused to become a member of the East German communist party. Later in life, I read my Stasi [The Ministry for State Security] file, which noted that I wasn't loyal and should not benefit from promotion. At the time, I did not really appreciate how strict the system was.

Then in 1989, the wall came down. It was a new world for me. I had my PhD and I wondered what I should do next. Because the "iron curtain" no longer trapped me, I contacted the Technical University in West Berlin where a colleague (who later became my boss) helped me become a more active member of the German chemical engineering community. Later, I thought I should move to an English-speaking country to see more of the world.

So you moved to the USA?

Right. My wife is a chemical engineer as well – we met in the old East Germany and we already had a family, but we were not married. One day she came home and said the company she was working for was collapsing, but there was an opportunity in Tennessee, USA. That evening I was thinking about a few papers I'd read from a guy in Tennessee – I could not recall his name so I searched my files and found him: Georges Guiochon, University of Tennessee, Knoxville.

The next day I wrote him a letter to ask if he had any positions open. About three weeks later the answer came back: "yes." I included a research project idea in the letter – a smart move – Georges liked it. He offered me a post-doc position and my wife and I married to make it easier to move to the USA with the children as a family.

Why do you think Georges was so keen to work with you?

Georges' mathematical oriented views on chemistry and in particular chromatography meant he always had very good foreign experts. I guess he liked to work with anyone – foreigners included – that fit in with his strategy. I brought a new idea that was related to my PhD (how to calculate competitive adsorption isotherms) and I think he saw this field as a chance to enrich his own scope.

I could have stayed longer in the USA, but I applied for and received a grant from the German Science Foundation to support three-years at the Technical University of Berlin to do my habilitation. At the same time, Georges suggested that I should stay in the USA – this was a tough decision. However, we returned to Germany. We had young children and were still very poor; it was financially risky to remain in the USA – and my widowed mother was alone back home in Germany.

So, in 1992, we returned to Germany and I did a relatively rapid


“Devising strong, widely applicable technologies is what interests us the most.”

habilitation. I had many results so it was easy. Unfortunately, I did it too quickly because the grant rule agreement essentially said, "when you finish, we stop paying you". To make ends meet, I got a job with Schering in Berlin, but I wasn't there for very long; my boss encouraged me to apply for academic positions, noting an opportunity in Magdeburg, which I took.

And that was the connection to the Max Planck Society?

Yes. Three years later, there was an unexpected situation in Magdeburg. Germany was united and the Max Planck Society (supported by taxes) started to invest in the former East Germany to ensure an even distribution of funding throughout the German states. Up until then, Magdeburg and the federal state Saxony-Anhalt had not received much support. The society decided to form a new institute on Dynamics of Complex Technical Systems, which now houses more than 200 people.

I became director of the institute in 2002, and we now have many projects in various engineering areas – chromatography is just one of them. By training, I am a reaction engineer and so we also do a lot of analyzing and quantifying reaction processes, which broadens our separation science based scope.

The Max Planck Society meets once or twice a year at annual meetings, and that's how I met Peter Seeberger. I quickly realized we were well matched; his group was strong in chemistry whereas we had expertise in designing continuous separation processes. We connected and now have quite a few stories to tell.

How do you work with Peter?

Peter's group focuses on certain target molecules and constantly comes up with new and fascinating chemistries. Very often, his reaction pathways are challenging (and very clever), but connecting them directly to our separation processes can be difficult. We started studying a simple model reaction. Then we worked intensively on artemisinin and artesunate. Currently, we are looking together for new target molecules to further contribute to this area.

My overarching goal is to develop universal methods that can be applied generically. Devising strong, widely applicable technologies is what interests us the most. Nevertheless, we are not naïve; we know that every separation problem brings its surprises. We need sufficient flexibility to fine-tune what we do.

The malaria story is wonderful. Our job was to establish a separation concept to isolate a valuable component from a complex mixture. And we have many other examples of similar problems in biotechnology. Typically, a single product will exist alongside many conflicting by-products. How can we structure the separation problem in a more generic way? If you think of chromatography, you could have a sample containing 100 components, but component 17 is your target. How do you get it? We consider this a pseudo ternary separation problem. One to 16 forms a big fraction before the target – the first fraction. The second fraction is your target – component 17 in a very narrow window, followed by another big third fraction (18–100). If you find a process that looks at the problem in the same way – for example, ternary simulated moving bed (SMB) chromatography – you can tune various pump flow rates representing the crucial process parameters to enable you to isolate any target from any mixture. Of course, in practice you have to connect several process steps together and you need to recycle streams if you want to be efficient and not lose valuable materials. That's characteristic of our way of looking at problems.

What would you like to leave behind for future generations?

We now have expertise in separating enantiomers and I would like to expand that knowledge into new chiral compounds. Agrochemistry, for example, is an interesting area. We apply large amounts of agrochemicals onto fields, but they are often chiral meaning that we could often be wasting 50 percent of these products simply because we don't understand their exact mechanisms and we do not have access to the active form. If we separate these mixtures into pure enantiomers, we will find that one will be more effective than the mixture. These are very cheap molecules compared with pharmaceuticals, so the agrochemical industry is not keen on using costly SMB technology, complicated columns, or high-pressure pumps. They need cheap separation technology and that leads us away from chromatography and into crystallization. Now, we are working very intensively on a fantastic process called preferential crystallization that might be suitable for resolving the enantiomers of chiral agrichemicals, which should offer a much cheaper solution.

In general, I dream of creating and developing more efficient and cheaper separation alternatives that take greater advantage of molecular interactions between solid and liquid phases.

What do you find most scientifically rewarding?

From a scientific perspective, I like to to quantify processes.

Organic synthesis chemists like Peter validate the success of their synthesis reactions using proven analytical methods. That's not enough for me. Quantification means finding ways to predict the outcomes of processes and to design them with respect to a specific objective; for example, to decide how big a reactor or a chromatographic column should be to do a certain job in an optimal manner. To reach such goals we need to know many details – the rates of the reactions taking place in the reactor, for example. To understand these rates, we need to understand molecular aspects that create them, which requires a broader perspective that bridges multiple scales.

Thermodynamics teach us that our fantastically organized planet is not a stable system – it can't last forever. The multiscale approach looks at this problem in a quantitative and systematic way, covering multiple time and length scales. It proceeds from molecular models, macroscopic kinetic and thermodynamic models, models for specific apparatuses, calculations on the plant level to simulations evaluating process impacts at the earth level and beyond. The challenge is to develop tools that transfer the knowledge to the next level without losing too much precision and resolution. This multiscale view, which attracts increasing attention within the various communities, needs more research on all levels. People who have expertise in connecting various scales will be important and highly sought after in the future.

In addition, I think that researchers should be happy to work intensively with young people, who always ask new questions. Currently, I teach a lot and I like it very much. I fully support the classical view of Wilhelm von Humboldt that universities always need to balance and unite teaching and research. Indeed, besides doing good research, we should all endeavour to be good teachers.

Architects of Quality

Quality by Design: we've all heard the phrase – and know we should be fully on board with the philosophy. But how?

Long used in automotive and electronics manufacturing, quality by design (QbD) is strongly endorsed by the FDA and other regulators. After all, why increase risk and spend time and money 'firefighting' preventable problems?

Kay Schmidt is vice president of R&D at Catalent Pharma Solutions and an engineer by training. Like most engineers, Kay loves elegant solutions, so the concept of QbD – solving problems before they become problems – immediately captured her attention. Now a QbD practitioner, Kay is the perfect person to answer all those questions you never dared ask...

In a nutshell, what is QbD?

QbD might sound complicated, but it really boils down to a simple concept: get it right first time. At the highest level, QbD is trying to mitigate risk and drive towards safe and effective drug manufacturing as early in the process as possible. Traditionally, we have waited until the end of the process and used empirical testing to set specifications. QbD turns that upside down, setting the specifications first, and refining throughout the development process. The fact is, you're going to have to spend the money and take the time anyway – QbD means you can do it in a controlled manner, rather than in crisis mode. By testing to failure and to specification, you may actually reduce costs through the commercial lifecycle of the drug product. You should have fewer rejected batches, higher yield and greater reproducibility. Other industries have seen great success with these approaches, but pharma has lagged behind.

How widely is it applied?

Over a decade ago, Janet Woodcock outlined the FDA's vision for QbD in the pharma industry, defining QbD as "product and process performance characteristics scientifically designed to meet objectives, not merely empirically derived from performance of test batches." Since then, with encouragement from the FDA, the industry has seen steady adoption of QbD principles. At the moment, we are seeing a pick and mix approach, with individuals and companies using elements of QbD that they feel most comfortable with or that seem most applicable. A holistic approach is still some way off.

What is standing in the way?

One of the roadblocks is a culture that is wary of change. QbD involves putting more work in at the start of the process, to save time and money further down the line, and that initial outlay can cause concern.

"I find it very energizing to find and fix problems while you have the time and resources to do so."

Considering the extra costs and delays of a problem that is not discovered until a late stage in development; managing in crisis mode is no fun at all.

Sometimes people get too hung up on the rules and tools of QbD, and lose sight of the big picture. If you're doing a risk assessment, for example, it's easy to get into a lengthy debate on whether a specific risk is 'critical' or 'major'. It is much more important that you know there is a risk and that you need to do

something about it. In such situations, an experienced facilitator can help keep the discussion moving.

How do you bring QbD into your projects?

As early as possible (at the development plan stage) we start talking about QbD concepts so that we can incorporate them into our engineering batches and lab-scale designs. Some customers are already on board with QbD, and will have a Quality Target Product Profile (QTPP) and various other documentation ready to go in our kick-off meetings. Others are not so prepared, but we're always happy to talk them through the different tools.

Some customers do have concerns, but I always say, "Just give it a try." Even if you only include a few aspects of QbD at first, you're changing the way you approach development and reducing risks through the lifecycle. Usually once people have tried some of the tools, the benefits speak for themselves.

What are the main tools you use?

I like to use the failure modes and effects analysis (FMEA) – looking at risks and assigning them a priority number, and setting goals at each subsequent milestone to reduce the risk number. Even a simple QTTP – a quality document that sets out what the product is intended to do – is surprisingly impactful. Writing down your goals assures shared awareness. The QTTP defines the characteristic you are trying to achieve, the target, and the justification for the target. After that, the rest of the development process is just a case of filling up that justification with experimental data.

Why are you so passionate about QbD?

I find it very energizing to find and fix problems while you have the time and resources to do so – rather than in an emergency. Inefficiency is simply not rewarding.

(De)signed, Sealed, Delivered…

By Bill Hartzel, Director of Strategic Execution at Catalent Pharma Solutions

This month, the NIH Clinical Center suspended operations after an FDA inspection revealed fungal contamination of injected drugs, with some of the affected lots already administered. The case has caused shockwaves, with commentators drawing comparisons to the 2012 New England Compounding Center meningitis outbreak. Microbial contamination is not the only risk facing sterile drug manufacturers – foreign particulates, including glass shards from the vials themselves, also present a serious risk to patient safety. Cases are thankfully rare, but rejected batches and recalls are expensive, time consuming and affect consumer confidence.

To help prevent these problems, we developed ADVASEPT® technology – an advanced aseptic process utilizing blow–fill–seal, based on the principles of QbD and applied to the fill/finish industry.

The essence of QbD is knowing the product and the process and then 'designing in' quality and efficiency, rather than 'inspecting out' problems. With ADVASEPT technology, automation removes variation and minimizes human intervention in the process. The plastic vial is produced, filled and sealed within the sterile 'class A' environment of the machine. The virgin plastic resin is extruded into a two-stage mould that first forms the body of the container before product is then automatically filled and a rubber stopper is applied. Finally, the second stage of the mould is closed and the product sealed. This process is complete in a matter of seconds. Compared with a traditional glass vial facility, the sterile area can be up to 100 times smaller, and therefore much easier to control. In addition to the design of equipment, we have built a specialized microbial challenge facility and run extensive tests to better understand the critical control parameters. For example, we filled the room with 10^6 Bacillus subtilis before running a series of media fills in different conditions, to better understand the crucial factors in sterility

However, it is not just about the process. We have also made considerable efforts to provide data on the new container closure to allow a smooth transition from glass to plastic.

For example, plastic is not impervious to moisture vapour and oxygen permeation in the same way as glass. So we have done two-year real-life stability testing with water and saline to better understand the permeation rates. Every company will have to carry out their own tests, of course, but we have data available on extractables, permeation, particulates and so on, which is a good basis for future testing. Additionally, we are conducting a case study with a monoclonal antibody (mAb) manufactured from our Madison facility to compare the stability of the mAb in glass vial versus ADVASEPT vials. This was to confirm that the heat used to melt the plastic won't affect the mAb during the filling process and understand the change in container closure over time. We carried out 16 different analytical tests, from peptide mapping to activity, and found comparable results after nine months, with longer-term testing ongoing.

For over 30 years, we have been making sterile pharmaceutical products and to make sure we "get it right the first time" we have spent millions of dollars identifying critical parameters, minimizing variables and testing the system. Now, the power of QbD is coming to fruition as we look to improve the reliability of supply of injectable products through the advanced aseptic processing of ADVASEPT technology.

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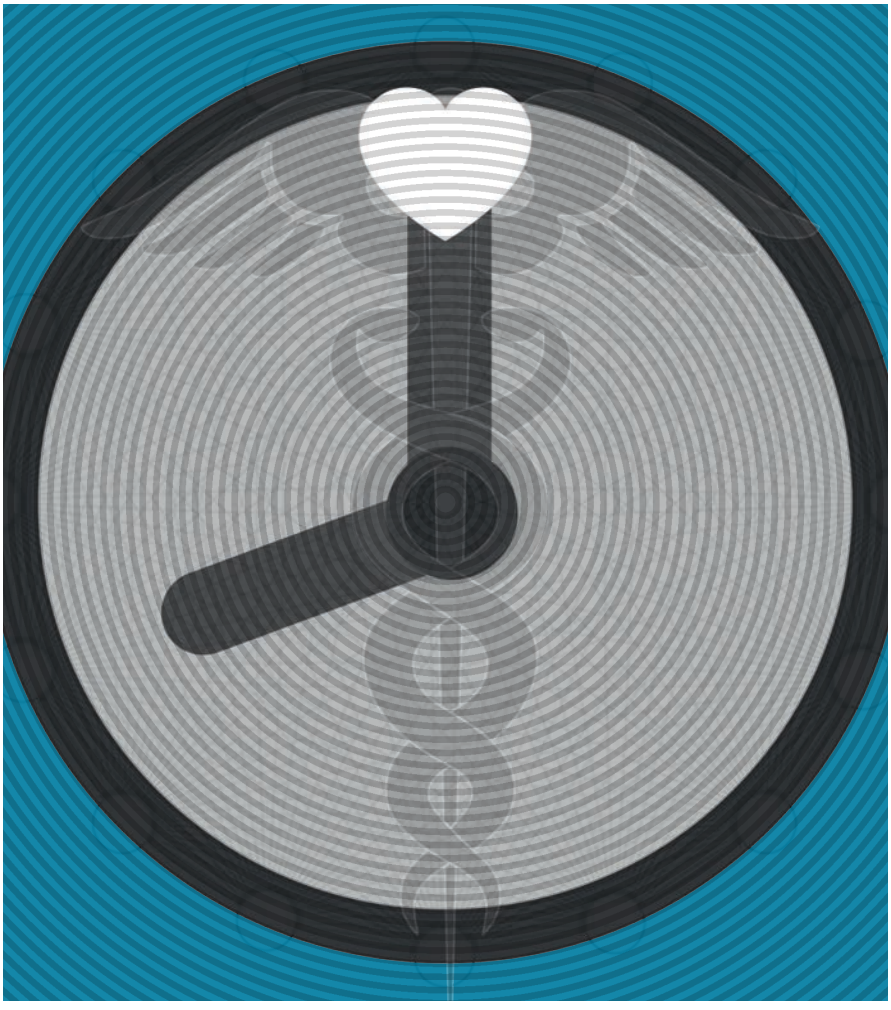
Countdown to Cures

Is pharma keeping up with the latest innovations? US legislators say no, and are looking to a new act to accelerate approvals.

By Stephanie Sutton



Since The Medicine Maker first launched in September 2014, we've covered many 'next generation' developments – from personalized medicine to nanotechnology to new manufacturing techniques – that have the potential to advance the pharma industry and healthcare. But harnessing the latest scientific breakthroughs for the benefit of humankind takes time... Too much time, apparently. Indeed, there are those who argue that regulatory hoops are unnecessarily delaying innovative new therapies; they say, "medicine has changed, and regulation must change with it."

Admitting that the current law has not kept pace with innovation, US legislators are developing a new bill: the 21st Century Cures Act. Its main purpose? To modernize approval processes for new medicines, particularly for conditions where other treatment options are lacking. The latest draft of the Act (which has been in development since April 2014 and revised twice in 2015 already) is over 300 pages long and includes dozens of sections, covering discovery, development (the most extensive area in the draft) and the delivery of new medicines to patients (1, 2). If the Act becomes law, it could have a significant impact on drug development; for example, requiring the FDA to provide guidance on topics such as precision drugs, biomarker development, and incorporating adaptive designs and Bayesian statistical modelling into clinical protocols. For some examples of sections included in the latest draft that companies should begin to look at if they want to stay ahead of the game, see "The (Highly Abridged) 21st Century Cures Act" on page 40.

"When the Affordable Care Act was implemented several years ago (which also led to the Sunshine Act coming into play) some companies were behind the times and unprepared for aspects such as electronic health care records," says Garrett Davis, a research associate at Best Practices LLC, and author of a white paper released in March (3). "It's important to get ahead of the curve, to understand the rules and legislation that will be coming down with the 21st Century Cures Act, and to plan for what is there now with the understanding that there will probably be more changes."

So, you need to be prepared for change, but there's also the question of what impact the draft – and further amends – will have on the FDA. In particular, can the FDA keep up? Dale Cooke from PhillyCooke Consulting comments, "I'm excited at the increased funding for the National Institutes of Health (NIH). NIH has been underfunded for a long time, but I'm also concerned that the 21st Century Cures Act includes

massive changes for the FDA, and the funding being discussed doesn't seem commensurate with the changes. The FDA keeps getting expanded responsibilities and not quite enough funding to meet those responsibilities. FDA employees only have so many hours in the day and if you require that they spend time drafting certain specific guidances, then by definition they won't be working on other topics, unless you give them enough resources to cover the expanded workload."

According to Rachel Sachs, an academic fellow at the Petrie-Flom Center at Harvard Law School who has been following the Act with interest, 21st Century Cures has the potential to completely overhaul the existing system for bringing new treatments to the public. "The titles of the three main parts of the Act say it all. Often, a statute will address a single one of these goals. For instance, the 'Doc Fix' legislation passed in April 2015 addressed the Medicare delivery system, and every five years a new version of the Prescription Drug User Fee Act presents an opportunity to alter the FDA's review process. An opportunity to address all three important areas – discovery, development and delivery – at once is potentially very exciting."

The politics of change

It was over a year ago that the US Energy & Commerce Committee, headed by Fred Upton, first announced its intent to work on a new Act concerning medicine development, and a number of roundtables were held in 2014 followed by a series of white papers. But it was all hearsay until a draft for discussion finally appeared in January 2015. "It was a huge 393-page document, covering all of the different issues that they wanted to include in 21st Century Cures," explains Davis. "Many of the elements in the draft came from little bills and acts concerning drug discovery and development that never made it to final approval. The discussion draft also contained open fillers – parts they wanted to add in but had no idea what to write at the time. These topics have been discussed with trade associations, bio/pharma companies and patient advocacy groups."

The first draft was met with both praise and criticism – but also politics. Davis says, "Chairman Upton (Republican-Michigan) partnered with Representative Diana Degette (Democrat-Colorado) to make this a bi-partisan act. However, the initial draft document was not publically endorsed by Degette. Since the draft was subject to change it has gone though two different updates. Now, it has been unanimously approved by the Energy and Commerce Committee, which is a rarity."

But the changes to the drafts have been significant. "The first version was nearly 400 pages long, even with several sections listed as 'to be supplied'. The second version was much shorter, at just 200 pages, but the third is back up to 300," says Sachs. "There are many major additions and deletions. For example, the second version of the Act added provisions creating a separate NIH Innovation Fund, which would increase the agency's budget by $2 billion a year for five years. Total NIH funding has been stagnant or decreasing for many years now, with sequestration and budget cuts, and these funding increases are hugely important." The first version of the Act also contained a provision that would have given drugs intended for "unmet medical needs" fifteen years of FDA exclusivity. "This was one of the most controversial parts of the Act, and it's not present in the second or third version of the document," Sachs continues. "The argument in favour of the provision is that it would promote more investment into drugs for 'unmet medical needs'. In my view, the proposal would likely have encouraged some research that wouldn't otherwise have occurred, but the much greater effect would be to replace the five, seven, or twelve years of exclusivity given to most drugs at present with a fifteen-year period, increasing costs for both consumers and the government. Even now, most drugs are approved to treat 'unmet medical needs'. The provision wasn't narrowly tailored enough to avoid the effects on consumers that we often worry about in this context."

"Despite the significant revisions that have already taken place, aspects of the latest draft remain hotly contested."

Cooke also noted that sections concerning social media have been omitted from the later drafts: "The first draft included a provision that would have required FDA to revise existing regulations and guidance to accommodate so-called 'one-click'. Because FDA has never endorsed any one-click provision, there are several different versions of the idea floating around," he says. The basic concept of one-click is that it allows prescription product marketers to provide 'some' information about risks a single click away from the initial message on benefits. "FDA has repeatedly taken actions that demonstrate it does not endorse such a view, but the first draft

The (Highly Abridged) 21st Century Cures Act

Discovery
- NIH funding
- NIH planning and administration
- Supporting young emerging scientists
- Facilitating collaborative research

Development
- Patient-focused drug development
- Qualification and use of drug development tools
- FDA advancement of precision medicine
- Modern trial design and evidence development
- Incentives of certain products for limited populations
- Enhancing combination products review
- Domestic manufacturing and export efficiencies
- Sensible oversight for technology which advances regulatory efficiency

Delivery
- Interoperability
- Telehealth
- Disposable medical technologies
- Medicare pharmaceutical and technology ombudsman

of the Act would have mandated FDA to change its position. However, the 'one-click' provision was removed at FDA's request and has become a piece of stand-alone legislation sponsored by Congressman Billy Long," says Cooke.

And despite the significant revisions already made, aspects of the latest draft remain hotly contested. An article written by two doctors raised concerns that the Act would lower the standards for approving new uses of existing medicines. The latest draft, if implemented, would encourage FDA to approve drugs on biomarker information rather than clinical trials (4).

"However, all of the discussions we're having about the Act are fairly speculative, and it might be that the FDA is able to circumvent the intent of Congress in various ways," says Sachs. "For instance, the Act instructs the FDA to issue guidance regarding the development of biomarkers. The intent is clearly to encourage the FDA to rely more on biomarkers and less on true endpoints in evaluating drugs for approval; the question is whether the FDA would take advantage of that discretion. It might feel pressured to do so, but it's not clear that it necessarily has to relax its standards in a harmful way."

Be prepared to keep up

The Act has passed a unanimous vote from the US House Committee on Energy and Commerce and will now pass to the full House of Representatives. That said, full implementation is still some way off; even after the Act has been passed, the rollout will be staggered. "The Senate will still have to pass its own bill on the subject. Although the Senate Health, Education, Labor, and Pensions Committee has released a report suggesting that it is largely in support of the House's efforts, there is no draft bill in the Senate just yet, and most observers think it is likely to be months before they move on the subject," says Sachs.

Davis agrees that it will take time. "I can almost guarantee that a lot of this stuff will not make it to the final version. The initial expectation was that the 21st Century Cures Act would be in the President's office for final sign off by the end of this year, which would be fantastic, but I'm not sure it will happen. That said, the people involved want to move this forward as fast as possible. In 2016, the House, the Senate, and political and advocacy groups will all be focusing on the next Presidential Election, which would put 21st Century Cures on the back burner."

There is clearly a great deal of uncertainty on the timing and content of the Act – and that could leave you feeling reluctant to consider its implications. But Davis says, "Even if just 10 percent of the current draft is implemented, it will drastically change how things work in the industry. And that's why in these early stages, companies should be following it closely. As it gets closer and closer to becoming a reality, I can see a lot of people scrambling to figure out exactly what's going on."

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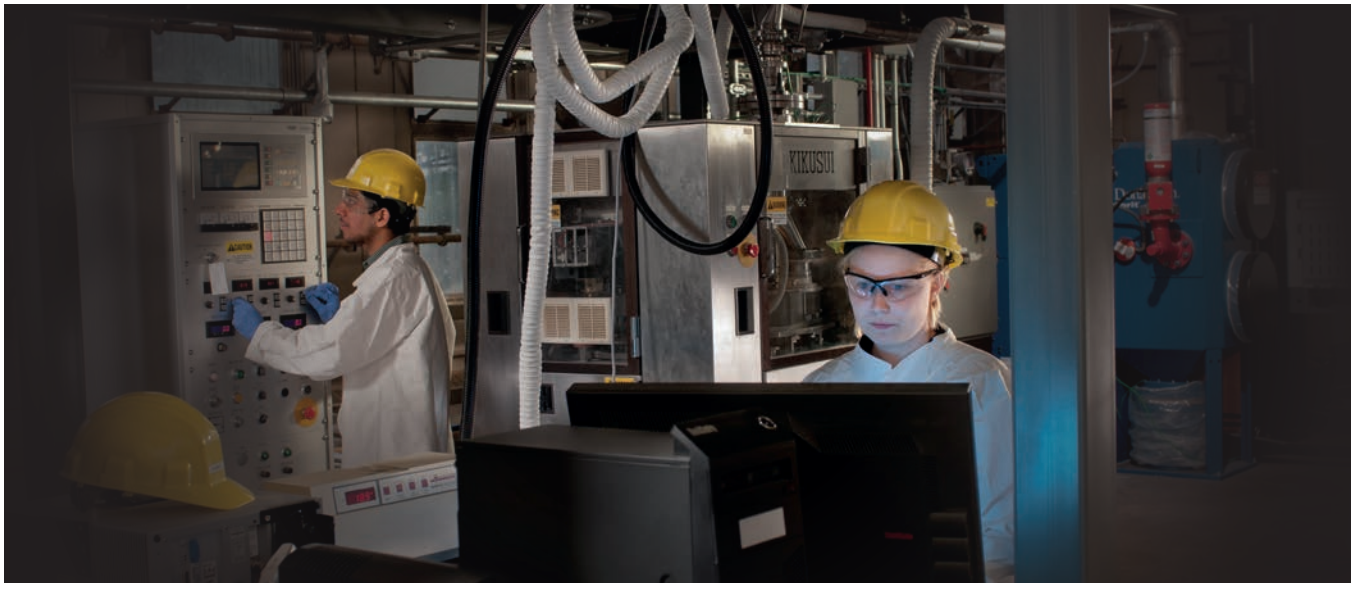

Continuous Progress

Resistance is futile – big pharma has spoken and continuous manufacturing will be in commercial use in the near future. But let's not stop there – now it's time to explore the full potential of the technology.

By Doug Hausner

Implementation of continuous manufacturing (CM) is long overdue in pharma. High margins and intense regulatory scrutiny has left us lagging behind other industries. But as the market gets tougher and regulators make it clear they want to see more sophisticated manufacturing, the roadblocks are crumbling. Change is coming, like it or not.

The advantages are well documented, both in terms of improved quality and lower costs. Because you're working with a much smaller amount of material at any one point, scrutiny and control of the process is enhanced. On the cost side, the biggest savings come from improved efficiency, reduced batch rejection, faster production and fewer staff.

There are also huge savings to be made in development. For example, here at the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), we worked with one company to develop a continuous process for an existing product. To carry out design of experiments (DOE) for the process using a batch model required around 4000 kg of active pharmaceutical ingredient (API); a continuous process cut that down to 150 kg. Given that the API in question carries a price tag of up to $10,000 per kg, it was a huge saving. Savings of this level more than cover the capital expense of a new facility and manufacturing line.

Another area where CM comes into its own is in combination products. We recently worked on a project involving a combination product with six different dosage ratios, with impressive results. In a CM line you can switch between dosage ratios in real time – there's no need to shut down and re-calibrate – it's as simple as entering a command into your control system.

What's the hold up?

I still run into some industry veterans who believe that CM will never enter the mainstream. Beyond a general resistance to change, there are some valid reasons for caution. CM may not be right for everyone, at least not right now. There is an obvious benefit–cost analysis to be made with regard to capital equipment, and the savings won't stack up for every product at every company. So where is CM most cost-effective? Two types of production are generally considered obvious targets for a continuous approach: large-volume manufacturing, where small per-pill savings add up quickly; and new products, where development costs can be substantially reduced. Facilities producing medium- or low-volume products already on the market are unlikely to be early adopters.

For smaller companies, the cost of equipment is a major factor. But I believe the biggest roadblock to implementation is regulatory uncertainty. The whole ethos of CM is very different as compared to

"Now is the time to get off the fence and get planning. You don't want to be left behind."

a standard batch approach, and there is continued apprehension from some companies that the regulators aren't going to welcome these new methods. In particular there is uncertainty about how regulatory bodies beyond the FDA, EMA, and Japan's PMDA will respond. At this point in time, there is no regulatory guidance specifically for CM. Instead, people are looking at the existing guidance and trying to understand how that applies to CM, which sometimes causes confusion. One thing people always ask is, "If I'm doing a continuous process, how do I define a batch?" If you look closely at the guidance, the definition of a batch doesn't exclude CM – a batch is simply the amount of product you would recall – but any uncertainty is unsettling for companies who stand to lose huge sums if approval is delayed.

For their part, the FDA see CM as a way of improving quality and getting more breakthrough therapies to patients. They know that there is a desire from the industry to move forward, but that aspects of the regulatory process are causing hesitation, so they have asked C-SOPS and our collaborators to help them put together some initial guidance specifically for CM. The role of the Center will be to facilitate the process and provide technical input. By speaking with company and academic experts early on, they hope to avoid releasing potentially unclear guidance, as with PAT and QbD, with uncertain implementation direction resulting in slow adoption.

Both parties want to move faster, but the knowledge base on both sides is the sticking point. The academic research we and others have done in the past few years has filled in many of the gaps in our knowledge – now we just need to keep the conversation going between industry and regulators.

Don't stop me now

Ultimately, companies with the motivation and resources to pursue CM are not put off by the (real or perceived) regulatory or financial hurdles. Big pharma are the first-wave adopters and all the major companies have emerging or ongoing programs at this time. There has been slow and steady progress in CM over the past decade, but in the last year and a half the pace has picked up dramatically, as several companies have made big strides towards commercialization – companies like Vertex Pharmaceuticals, who are now working with the FDA to get approval for their 4,000-square-foot continuous manufacturing facility in Boston.

Once these trailblazers have safely negotiated the regulatory pathway, a larger second wave of adopters will follow in their footsteps. That tipping point is getting ever-closer, as evidenced by a change in the number and type of people contacting us to discuss working with the Center. In the past three or four months, we have started to get calls not only from research and development departments in big pharma, but also from regulatory departments and even generics companies – no-one wants to be left behind.

Continuous control

The ability to model processes and predict outcomes is one of the most powerful aspects of CM. This is easy to see in the petrochemical industry. An oil refinery needs to be able to work with different feedstock and still produce the same quality of gasoline, diesel, and so on. Operators use advanced modeling to adapt the process to the feedstock and desired end-product and continuously monitor quality. The problem with applying those models to a pharmaceutical plant making solid oral dosage forms is that historically the flow chemistry of liquids has been much better understood than that of powders. To be able to model powders effectively, a lot of additional research was needed, both from academic centers like ours and from software companies. There is still work to do, but we now have tools that are very similar to those in the petrochemical industry, which will save time and money by validating the process in advance, and make the FDA's work easier by flagging potential risks.

In batch manufacturing, the ingredients may spend upwards of two weeks in the production cycle, with checks between each step, whereas in CM there may be as little as 5–10 minutes between the product entering the system and the tablet being formed. The window for identifying any problems is much shorter. To maintain process efficiency and product quality, you need continuous monitoring and feedback, like the smart sensors found in modern cars that keep you in the proper lane. The big question now is how much of this control is needed to keep the process safe. It all comes down to risk: the more risks associated with the product, the more monitoring is required. For an over-the-counter medicine you wouldn't need the same degree of sophistication in control systems as you would in a highly potent drug. But exactly where those boundaries lie is an area of discussion with regulators.

C-SOPS has several research programs focused on advanced modeling. One of our newer exciting projects is building a material properties database for CM. Companies focused on breakthrough therapies are very interested in the ability to design formulation space. By having access to information about the material properties of a large number of excipients

and APIs and their behavior in a CM process, the database will allow us to model how a new API is likely to behave in a given formulation. When working with a very expensive API, we can characterize its material properties from a small sample, and identify a cheaper 'stand in' material for use in early-stage process development.

Academic acceleration

We believe academic institutes like ours have a key role to play in harnessing the potential of CM. C-SOPS is the world's largest academic-led research organization dedicated to pharmaceutical manufacturing. By combining their resources, the 40-plus industrial consortium members can advance the field at a much faster pace than they could individually – in addition to aligning their efforts so that regulators have a single, unified approach to work with.

We recently received a new round of funding from one of our long-term collaborators, Janssen, to continue what has already been a very fruitful partnership. Around seven years into the life of the Center, we launched a project with funding from Janssen and the National Science Foundation, to design Janssen's first continuous direct compression process. We designed and built a full-scale CM plant at Rutgers University, which was used as a model for Janssen's plant in Puerto Rico. The Puerto Rico facility was built just a year later and is now being submitted to the FDA for approval. Together with pilot plants at Purdue University and the University of Puerto Rico, building a production-scale plant from scratch has been invaluable in terms of technical lessons learnt; the model plants are now being used by other companies to refine their own plans.

Aside from the teething problems you might expect when using new equipment, the build of the model plant went very smoothly. We were able to confirm the efficiency of CM and show that the continuous direct compression process is much more versatile than the equivalent batch process. CM keeps segregation to an absolute minimum and we were able to run the process with extremely highly segregating materials, while keeping relative standard deviation values well within acceptable levels. From our experience with the model plant, we concluded that somewhere in the region of 80 percent of pharmaceutical products could be made by direct compression – another financial driving force for CM. We're now starting trials in wet granulation, a more complex proposition.

Looking towards the future, the increasing trend for more targeted therapies may bring new challenges for CM. A continuous process is less appealing for smaller-volume manufacturers, due to the time and cost of cleaning out the equipment between products and the challenge of maintaining accuracy when working with small quantities; when you have 1000 kg per hour running through the system, a gram or two either way is irrelevant, but as quantities come down the margin of error tightens. We'll need to focus more effort onto this aspect to keep CM relevant for very small-scale production (as often needed in the early development phases) and in the growing area of personalized medicine.

There is nothing from a regulatory or technical standpoint, at least in the US or Europe, to stand in the way of CM. Two years ago, companies might have been able to treat CM as an off-shoot – something to keep an eye on. But with new research making the process ever-more efficient – and major pharma companies announcing plans to move 80 percent of their production to CM over the next five years – now is the time to get off the fence and get planning. You don't want to be left behind.

Doug Hausner is Associate Director for Industrial Relations and Business Development at the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), Rutgers University, NY, USA.

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Shark Attack

Could the unique properties of the shark immune system help us create biologics with more bite?

By Charlotte Barker

When scientist Caroline Barelle tells people that her research involves sharks they tend to jump to conclusions. "People often imagine I work next to a tank full of great whites – and that anyone who disagrees with our science becomes lunch!" she jokes. In fact, the sharks Barelle and her team work with are not man-eaters but spiny dogfish (Squalus acanthias – shown above), a common species off the coast of Scotland, where their lab is based. Though the diminutive dogfish may not be auditioning for a part in Jaws any time soon, the technology that Barelle and her colleagues are developing has dramatic potential.

Sharks have been attracting attention as a potential source of therapeutic proteins since the 1990s, when scientists found that, despite evolving some 450 million years ago, they have an adaptive immune system that is surprisingly similar to a mammalian one. The researchers identified an antibody-like molecule – immunoglobulin new antigen receptor (IgNAR) – that forms part of this adaptive response (1,2). While standard mammalian antibodies are made up of heavy and light chains, IgNARs have only heavy chains.

Barelle first came across shark proteins in 2006 when she joined the antibody drug discovery biotech Haptogen. The company spotted the potential of these small antibody-like molecules for targeted therapies. The first thing to catch their eye was that the molecules are very small, less than a tenth of the size of human antibodies, and yet bind with great affinity to their target. They also have much greater stability than mammalian antibodies, thought to be a result of an interesting quirk of shark biology – their blood has a very high

"People often imagine I work next to a tank full of great whites – and that anyone who disagrees with our science becomes lunch!"

concentration of urea. The resulting high osmolarity prevents saltwater from dehydrating the animal, but also creates a harsh environment for proteins. The secret of how shark antibodies retain their stability in these conditions is being unraveled by researchers in Germany, who hope they can apply the knowledge to improve monoclonal antibody therapies (3).

Spin-out soloMERs

Convinced of their therapeutic value, Barelle has been working on shark proteins ever since, first at Haptogen, then at Wyeth and Pfizer, before joining the University of Aberdeen to head up their shark protein research program. But it wasn't until now that she had the opportunity to bring together the whole IP portfolio into one company, focused solely on the technology.

The resulting company – Elasmogen Ltd, soon to be spun-out of the University of Aberdeen – will use humanized versions of the IgNAR variable domain (VNAR). The VNAR domain is produced either by

"The diminutive dogfish may not be auditioning for a part in Jaws any time soon, but the technology has dramatic potential."

From the Deep…

Shark VNAR domains were discovered by chance and scientists believe that many more potential therapies are hiding in the animal kingdom. Given that 95 percent of the earth's oceans have yet to be explored, who knows what life-saving compounds could be lurking in their depths. Here's just a few secrets the sea has given up so far…

Ocean oncology

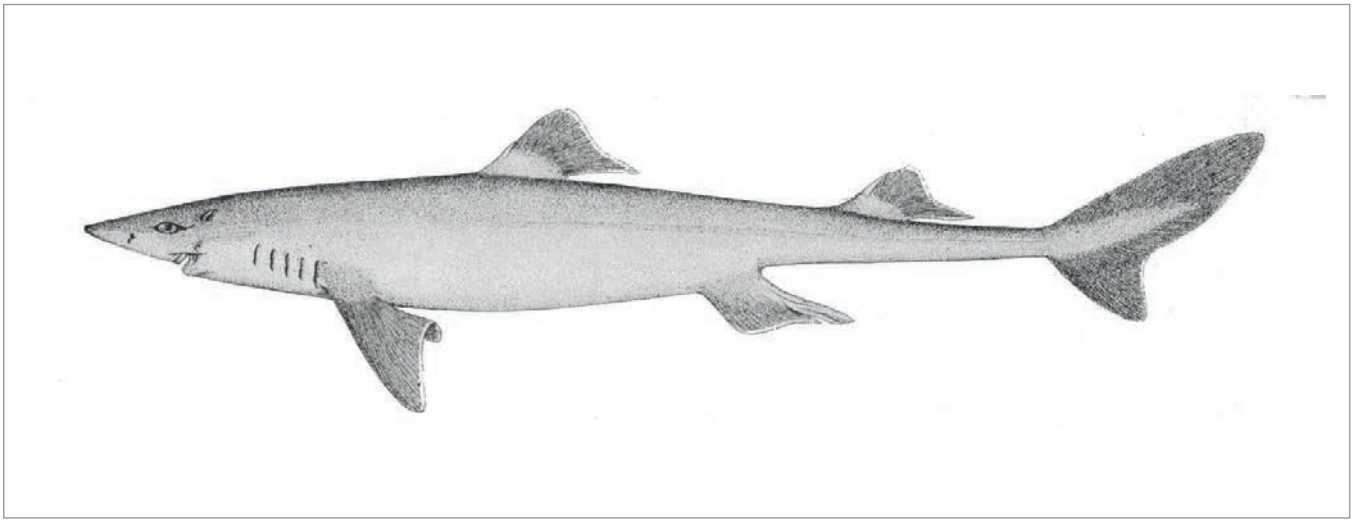
Lissoclinum patella, commonly known as the sea squirt, could provide a new class of drugs in the fight against cancer. It's not the most glamorous of marine creatures, but the symbiotic microbes hosted by the sea squirt have been found to contain compounds, known as patellamides, active against a number of cancers. Another species of sea squirt was the original source for the chemotherapy drug trabectedin, now being used to treat soft tissue sarcomas.

Ouch!

A cone snail can cause a painful sting to unlucky humans who cross its path. But it seems that the venom also contains a number of analgesic molecules, which could have unique benefits for patients suffering chronic pain. Biochemist David Craik told a meeting of the American Chemical Society that a compound based on the venom was up to 100 times more potent than morphine in a rodent model, with no evidence of addiction.

Caring coral

Coral reefs have been a rich source of medicines for decades, with azidothymidine for HIV and anticancer agent cytarabine just two of the drugs that have their origins in these fragile ecosystems. A type of soft coral, gorgonion, produces several compounds with promising anti-inflammatory properties, with applications both in medicine and cosmetic skin creams.



"I find it fascinating as a scientist that such diverse animals have evolved such similar molecules as part of their adaptive immune response, It's a great example of convergent evolution."

immunizing the sharks and taking a blood sample or, to spare the sharks (and perhaps researchers' fingers), assembled from a synthetic library of billions of shark VNARs created in the laboratory.

The team then isolates VNAR domains against the target, selects the most effective, and humanizes it to produce a product suitable to be further developed for clinical use – a soloMER™.

"Antibodies are incredibly successful therapies that generate a lot of revenue", says Barelle. "However, mammalian antibodies have a number of limitations. They are very large, complex molecules that cost a lot to make, so antibody therapies are typically expensive. The size also limits what tissues the therapy can penetrate and the type of targets they can go after."

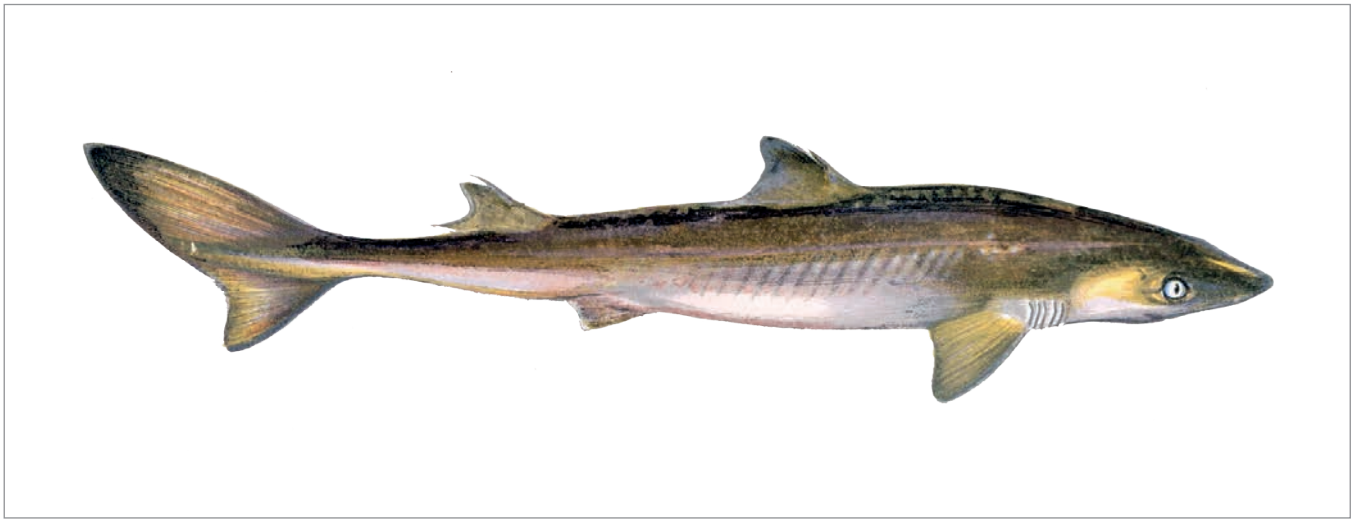
VNARs are single-chain domains, which makes them easier and cheaper to manufacture. Indeed, their small size and an unusual shape means they can reach targets that

Perfect fit

It was these special qualities of soloMERs that led Almac Discovery to approach Barelle's team. "We knew about the work at Aberdeen and the Elasmogen team," says Iain James, Vice President of Preclinical and Clinical Development at Almac. "We have a site-directed coupling technology for proteins that we are interested in using for antibody–drug conjugate (ADC)-like approaches, and this seemed like a great match," he adds. Almac Discovery is focused on anticancer therapies, and the group was hunting for technologies that would allow better penetration of protein conjugates into solid tumors.

The collaboration was equally attractive to Elasmogen, who are looking for partners with complimentary technology to bring soloMERs into the clinic. Almac's proprietary coupling technology joins small-molecule drugs (in this case cytotoxic anticancer therapies) exclusively to the C terminal end of the protein, rather than the random coupling more commonly seen in antibody–drug conjugates. "We will know exactly where the cytotoxic is coupled, and how many cytotoxics are coupled to each protein. That way we can be in a lot more control of the manufacturing process and we have a much better defined product and possibly a better side-effect profile," says James.

The initial stages – production of the protein and screening for the most promising VNAR domains – will be carried out in Elasmogen's lab in Aberdeen. They will send the



candidate VNAR domains to Almac Discovery, based in Northern Ireland, who will further develop the proteins and be responsible for pre-clinical and clinical development.

But the potential for soloMERs goes beyond cancer therapies, according to Barelle. Their extreme stability means that they could survive the harsh environment of the gastrointestinal tract (even after boiling, the team found the soloMERs would still bind to their target). An oral formulation for biologics is somewhat of a holy grail right now, and the team are keen to investigate this further. Another avenue to be explored is delivery to the eye. "Current ocular antibody therapies may involve regular injections into the eye – we hope that the small size of soloMERs could make them suitable for topical or site-specific application," says Barelle.

To find out what soloMERs are capable of, the team at Aberdeen are on the lookout for further collaborations with pharmas or biotechs developing compatible technologies.

Camels and convergence

Sharks are not the only animals whose immune molecules are inspiring interest. Camelids (a group that includes camels, llamas and alpacas) also produce single-domain heavy-chain antibodies, in addition to the usual mammalian immunoglobulins. "I find it fascinating as a scientist that such diverse animals have evolved such similar molecules as part of their adaptive immune response," says Barelle. "It's a great example of convergent evolution."

What do sharks and camels have in common that means they independently evolved stable, single-domain antibodies? We can't know for sure, but Barelle speculates that an extreme environment may be a factor – after all, many camelids face an inhospitable desert environment, while sharks must overcome the dehydrating effect of salt water.

Camelid antibodies are being commercialized for the clinic by Belgian company Ablynx in collaboration with a host of big pharma companies, with several programs already at clinical stage, a success that Barelle's team finds encouraging. Although there are some similarities with the single-domain antibodies of camelids, VNARs are quite distinct – they have more binding loops, are smaller and, importantly, are phylogenetically distinct from antibodies, which the Aberdeen team hope will make them even more clinically effective and commercially attractive.

"It's been a very exciting time for me over the last few years," says Barelle. "I have moved from being a director of science to building a business and setting up new partnerships, like the one with Almac. To be even a small part of developing a drug that gets all the way into the clinic is immensely rewarding and I look forward to starting Elasmogen as a fully independent company in the coming months."

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Rebel With a Cause

Sitting Down With... Kiran Mazumdar-Shaw, Chairperson and Managing Director of Biocon, India.

From Master Brewer to The Medicine Maker Power List Top Three. How?

In India in the 1970s, it was really tough to get acceptance as a female brewmaster, and I quickly realized that although I was very keen to pursue this profession, it was going to be tough to earn credibility within the brewing fraternity. People believed that a woman would find it difficult to deal with male employees and trade unions – a lame excuse, especially as even then I was being consulted for advice on operational issues by leading breweries! Disappointed with the system, I took up a job offer with a leading brewery in Scotland and was preparing to fly out of India when I had a chance meeting with an Irish entrepreneur who offered me an opportunity to set up a biotechnology company in India. I thought, why not start my own business and show them what a woman can do? It was rebellion and the desire to prove myself that made me take up the challenge. In those days, biotechnology was an unknown area in India and enzyme technology, which I started with, was unheard of.

Who inspires you?

I'm inspired by people who are change-makers – people who go off the beaten track. While building my own company, I was inspired by Anita Roddick (founder of The Body Shop) because she is someone who has changed the rules of her business. I was also inspired by one of the leading bankers in India, who acted as my mentor. He was one of the first Indian bankers to go into venture funding with Biocon. When I first discussed my business idea with him, he got very excited. In those days the normal way of funding a business was to take a debt-based loan, but he told me that instead of giving me a loan he would like to fund me in exchange for a small stake in the company – that was music to my ears! Through my entrepreneurial and business journey I have always challenged the status quo and tried to create a new business model. In fact, I've always tried to do things in a different way. I think the difference lies in my DNA.

What do you consider your greatest achievement?

For 20 years, I developed innovative enzyme technologies for a large number of industries. Then, in the 1990s, I decided to transform my business model and leverage our strengths in technology for cutting edge innovation towards one goal – to produce biopharmaceuticals. That was a great inflection point in my entrepreneurial journey. I'm glad I made that decision because I'm really passionate about delivering affordable biotech-based drugs around the world. One of the biggest challenges in the developing world is affordable access to these very expensive complex biological drugs. As an Indian, my whole ethos is to address that problem. I often say a blockbuster drug should not be measured by the billion dollars it earns, but by the impact it makes on a billion patients.

What's next for Biocon?

The drugs we have in the pipeline are very exciting. For example, we have an oral insulin under development, which could be a huge game changer in diabetes management. Early insulin therapy can be hugely beneficial to diabetic patients but compliance is poor for injected insulin so it is usually only prescribed in severe cases. A tablet form will be easier to administer, so has a lot of potential for diabetes management.

We also have a range of monoclonal antibodies. I'm very excited by the whole area of immunology. The immune system has a major role to play in a large number of diseases, especially those treated with biopharmaceuticals – whether it is diabetes, cancer or autoimmune diseases. The importance of antibodies is gaining a lot of traction and there are so many inspiring discoveries being made. This makes it very exciting for me as a scientist and as an entrepreneur.

"A blockbuster drug should not be measured by the billion dollars it earns, but by the impact it makes on a billion patients."

Where do you see the company in five years' time?

Depending on the success of our programs we could be a very, very different company in five years. We are building the company on a high-impact portfolio of products, which will allow us to support other novel programs in future. If we can take oral insulin to the market then it will absolutely change the way the company is looked at, so I would love to have that as a blockbuster drug from our stable. Additionally, we have developed another novel biologic ALZUMAb (Itolizumab), which is the world's first anti-CD6 monoclonal antibody launched in the market for psoriasis, and has blockbuster potential to treat several other autoimmune conditions.

Finally, what are the top three attributes of a successful entrepreneur?

You need to really believe in what you are doing, have a deep sense of purpose and enjoy taking on challenges!

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