

# the Medicine Maker™

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Jesper Kumlin  
Process Operator  
Production

# Online this Month



## *2017 Highlights*

### Global Vigilance

*February 2017*

Following the heparin tragedy, something needed to be done in terms of global safety. Rx-360 was created to help improve supply chains.

<http://bit.ly/2l8gbi2>

### The Power List 2017

*April 2017*

The best and brightest of the industry are highlighted in our celebration of the 100 most influential people in drug development.

<http://bit.ly/2qVocVY>

### Delivering on a Promise

*May 2017*

Drug delivery approaches have been growing in complexity. This article highlights the advanced techniques being developed for future therapeutics.

<http://bit.ly/2knr2Bt>

### Pharma's Green Rush

*June 2017*

Medical cannabis may be controversial, but there could be other ways that pharma can make use of the cannabis plant; certain cannabinoids may be useful sources for new drug discovery.

<http://bit.ly/2hKQtPT>

### Heal the World

*August 2017*

There's a large philanthropic side to pharma that's often overshadowed by negative press. Here, we show the effect corporate social responsibility has on the world.

<http://bit.ly/2fLqGq6>

### Twenty-First Century Cell Therapy

*September 2017*

Following the first FDA-approved T cell therapy this year, all eyes have been on the field of cell and gene therapy – an area full of promise, and possible pitfalls.

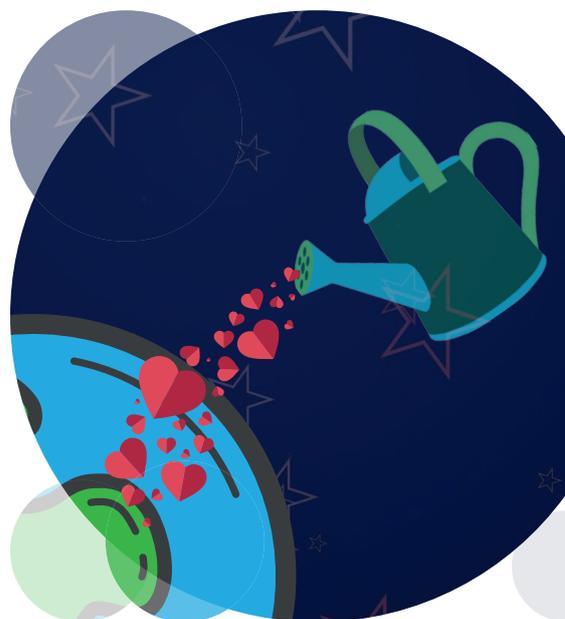
<http://bit.ly/2C64LAr>

### Exploring Pharma's Far Future

*November 2017*

Delving into the possibilities of healthcare and medicine a century from now throws up interesting questions. Will we end up in a utopian or dystopian era of health?

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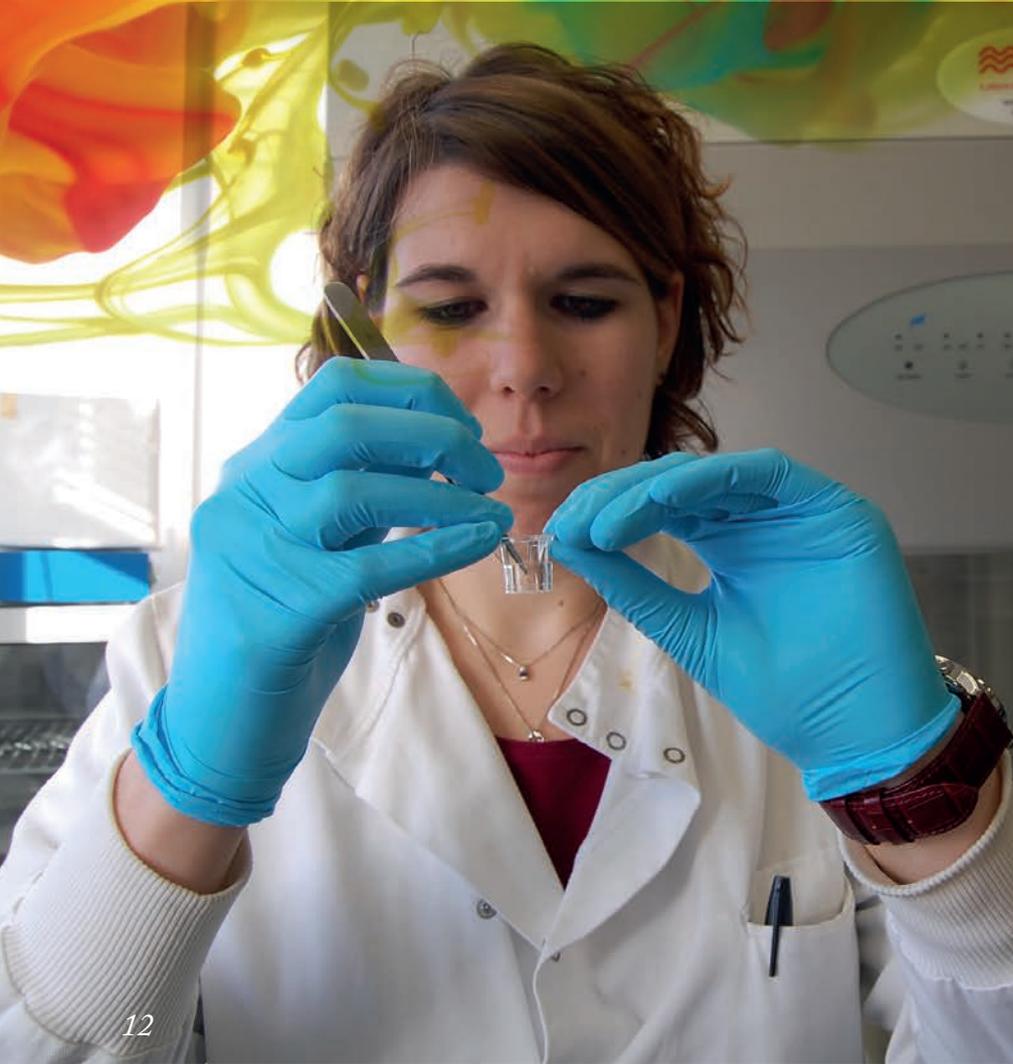


## *And Coming Up in 2018... Nominations Closing for the 2018 Power List*

The Medicine Maker 2018 Power List will be published in April – and nominations will draw to a close on February 1. The list celebrates 100 prominent and inspirational individuals involved in drug development and manufacture across four categories: Masters of the Bench, Industry Influencers, Business Captains, and Champions of Change.

Who will be included on the list? It's up to you to decide – just fill out the quick nomination form to tell us who you want to see on the list: <http://tmm.txp.to/2018/powerlist>

We accept nominations from all corners of the industry and for individuals in all roles – from top CEOs, down to unsung heroes making a mark in R&D or process development.



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Wise Words, by Stephanie Sutton

On The Cover



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of 2017 with the annual  
Innovation Awards*

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Read the story behind the winning entry of the 2016 Innovation Awards: Centinel, a CHO cell line resistant to minute virus of mice.



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## Reports

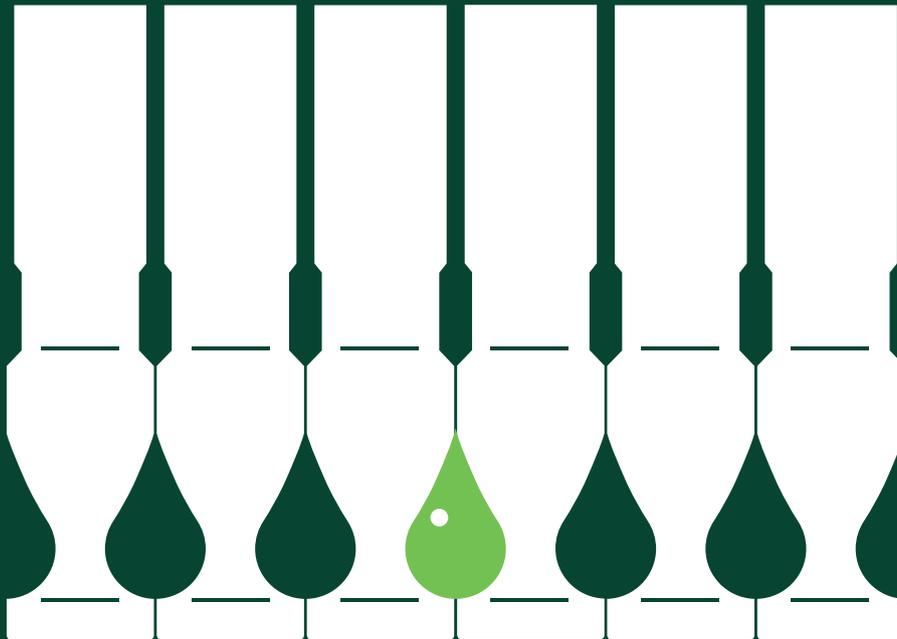
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**T**hroughout 2017, the editorial team has had the pleasure and honor of interviewing inspiring and gifted individuals in the industry. Given that the end of the year is traditionally a time to reflect on the last 12 months, I thought it would be fitting to seek words of wisdom from our 2017 “Sitting Down With...” interviews.

“This industry is changing rapidly and we need to keep pace by fostering an industry culture of lifelong skills acquisition.” Dominic Carolan, January 2017

“I’d like to see more collaboration between pharma companies – not only in terms of developing a given cell therapy, but in the development of combination treatment strategies.” Catherine Bollard, February 2017

“I get intellectual stimulation from working with very bright people, and it’s scientifically rewarding to look at the new techniques that are coming through and to try and introduce them to the labs that I work with.” Fiona Greer, March 2017

“I hope that as our understanding of disease improves we will see new therapies – not just new, advanced therapies, but also older drugs being repositioned and repurposed for different diseases.” Daniel O’Connor, April 2017

“Taking the risk of stepping outside your area of expertise exposes you to other aspects of the industry and provides a wider perspective, necessary for reaching full career development potential.” Ian Muir, May 2017

“We need to make it easier for patients to participate in clinical trials. Many patients still do not even know anything about how to get involved with a clinical trial.” Elisa Cascade, June 2017

“There tends to be something of a trickle down model in the pharma and biotech industry, where poorer communities are an afterthought of the target population. I would love to see more companies working to develop therapies with vulnerable communities in mind from the very beginning.” Steve Davis, July 2017

“The generics industry seems to go through highs and lows, and I think it’s currently going through a bit of a low, but I keep telling people that now is the time to be resilient and to have confidence in your values.” Abhijit Mukherjee, September 2017

“It’s important for everyone participating in the pharma and biotech industry to have some understanding of the critical role that outsourcing providers play today.” Cornell Stamos, October 2017

“We are living in a world where science is increasingly devalued and the role of expertise is often dismissed. But so much of what we do is underpinned by science.” Margaret Hamburg, November 2017

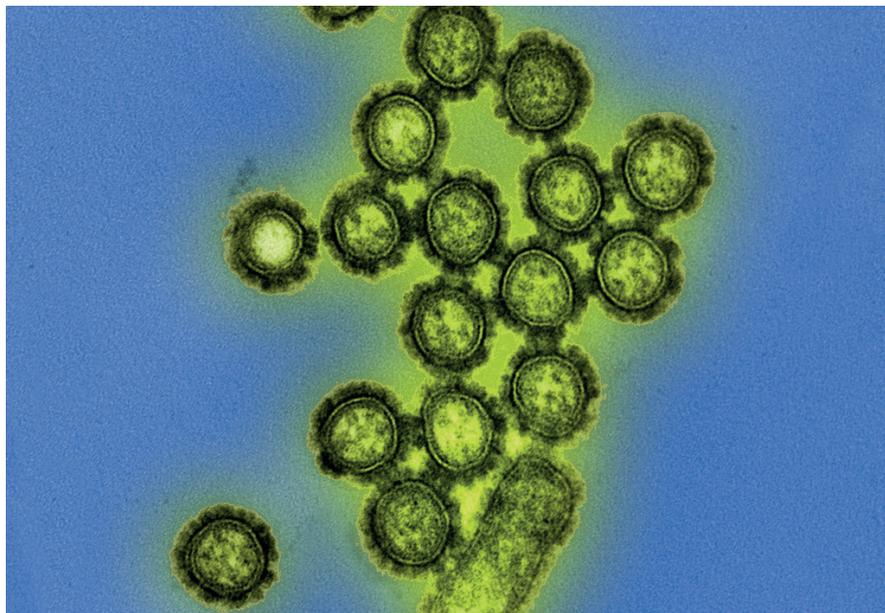
**Stephanie Sutton**  
*Editor*

*Stephanie Sutton*

# Upfront

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

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



## Flu Fighters

**Researchers look to the ancestral genes of influenza to develop a new approach to vaccination**

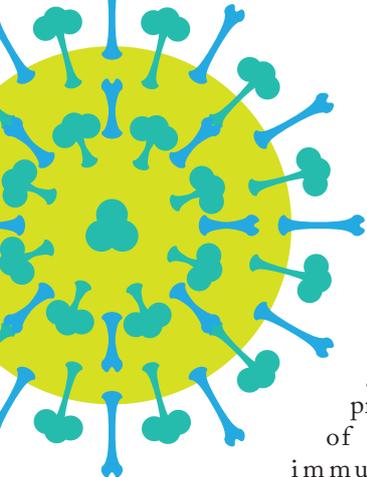
A truly universal flu vaccine continues to evade scientists, but it should be possible to develop a vaccine that offers broader strain protection – and lasts longer. Eric Weaver, assistant professor at the University of Nebraska, certainly believes we can do better when it comes to influenza vaccines; his team have developed a vaccine that carries the centralized genes for H1, H2, H3, and H5, with the aim of providing immunity against all evolved strains (1). We speak with Weaver to learn more.

What inspired a centralized gene approach?

I was introduced to this concept while working on HIV vaccines. Both influenza and HIV have very high degrees of diversity in the surface glycoproteins. The centralized genes act to reduce the genetic distance between the vaccine and the contemporary wildtype strains. Therefore, they offer maximal genetic identity to unknown or mismatched challenge viruses. We have published many research articles describing this approach and showed that it was a superior approach to using a wildtype immunogen as a vaccine.

How successful was your vaccine in the study?

I believe that in the context of a prime/boost viral vectored vaccine platform, our vaccine is superior to any vaccine that has been tested. The level of protection against highly divergent lethal influenza challenges is underscored in our recent study. The fact that the vaccinated mice showed no disease when challenged with 100 MLD50 of influenza virus is incredible, given this is enough virus to



kill 50 mice.

Our vaccine has great potential for proving high levels of cross-protective immunity against a very wide array of divergent influenza, and the prime/boost strategy that we used could establish a foundation for immunity that will last longer than today's vaccines.

What thoughts have you given to scale up?

We are very excited to move forward! One major caveat to this approach is that we are using a viral vector. One vector, Ad5, has been used extensively in clinical trials, but it was found that, in adults, there is a high level of pre-existing immunity that impaired the vaccine's efficacy in preventing HIV infection.

We don't know if this will happen if the vector is used for influenza. The second vector we used, Ad4, has been given to millions of military recruits and is FDA-approved for use in vaccines. It is very likely that we could translate this vector for human use.

What other influenza projects have caught your eye?

I think there is a lot of promise in the approaches by Paleses, Krammer and Garcia-Sastre with their HA "stalk" directed immunity. The stalk domain of influenza is much more conserved than the globular head, but the immune system recognizes the head domain predominantly and therefore does not induce dominant immune

responses against the stalk. These researchers are investigating novel approaches to "trick" the immune system into

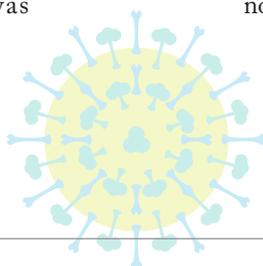
generating immunity against the more conserved stalk domain. If successful, this approach would certainly increase the breadth of immunity against divergent influenza strains. Perhaps a combination of this approach and our approach could lead to even better influenza vaccine results...

Some have said development of a universal flu vaccine is impossible...

It may be impossible to make a universal vaccine for everyone because people don't respond to vaccines in the exact same way, but that argument can be made for any vaccine that has ever been used and should not be a limitation to the pursuit of new vaccine research.

#### Reference

1. A Lingel et al., "Efficacy of an adenoviral vectored multivalent centralized influenza vaccine", *Sci Rep*, 7, 14912 (2017). PMID: 29097763.



## Spray It Again, Sam

**Vapor jet printing of small molecule drugs could have potential in candidate screening – or even delivery**

With extensive experience in vapor jet printing small molecular organic electronic materials, a team from the University of Michigan led by Max Shtein (professor of materials science and engineering) has more recently recognized that the technology could have potential in small-molecule drugs (1). By thermally evaporating an API into a stream of inert gas and spraying the vapor onto a cool substrate, the technique can create a crystalline film of API.

The research team has already tested a variety of APIs, including caffeine, paracetamol, ibuprofen, tamoxifen, BAY 11-7082 and fluorescein.

"Low solubility results in a significant number of candidate molecules being rejected before it is known if they are effective at the cellular level," says Shtein, before pointing out a striking benefit of his solvent-free solution to the problem: "The resulting morphologies from vapor jet printing tend to dissolve in water much faster (10 times or more) without changing the molecular composition."

The potential of vapor jet printing doesn't end with solubility. The technique can print drug compounds directly onto drug delivery devices, such as patches, ingestible strips, microneedles, and bandages, opening up other avenues to explore.

But would such a novel technology be readily embraced by the pharma industry? Shtein points out that the first printed drug was approved in 2015, and that there is much interest in the field. "We are in the midst of a revolution in the pharmaceutical industry, so the timing is fantastic for the deployment of organic vapor jet printing technology. The FDA is also encouraging a transition towards more personalized medicine and printing technology could be used to create custom-dosed medications."

#### Reference

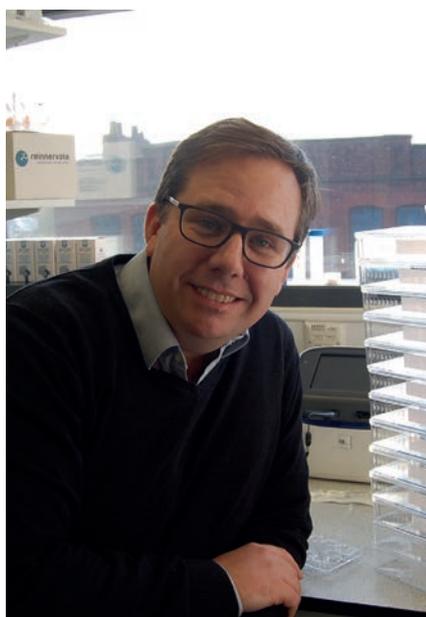
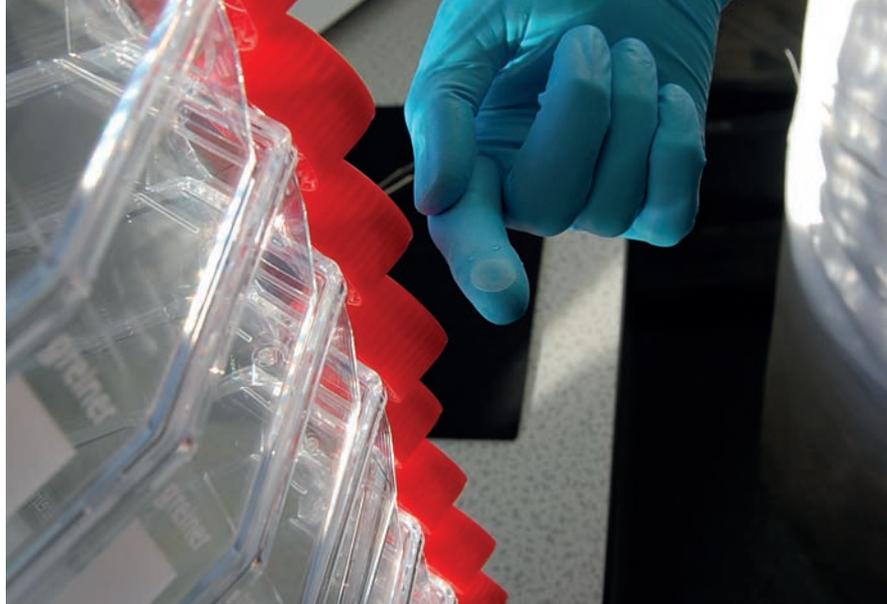
1. O Shalev et al., "Printing of small molecular medicines from the vapor phase", *Nat Commun*, 8, 711 (2017). PMID: 28955031. Available at: <http://go.nature.com/2xHAMGN>.

## Continuing the Trend

**Continuous processing is being adopted in pharma and biopharma. Could continuous cell therapies be next?**

Continuous manufacturing has been a growing trend in pharma for some time, but now researchers are urging cell therapy manufacturers to get in on the act. “Given the increase in the number and relative success of cell therapy clinical trials, treating a larger number of people is expected over the next decade,” says Che Connon, Professor of Tissue Engineering at Newcastle University, UK. “Cell manufacturing processes need to scale alongside this growth, as current systems won’t be able to meet the expected demand. For example, allogeneic heart failure therapy may require the manufacture of around  $10^9$  cells per dose. If existing batch processing can only enable lot sizes of 10–50 billion cells every two to three weeks, then the industry would require millions of batch bioreactors to be running simultaneously just to keep up with demand.”

Currently, cellular therapies are produced by growing cells on a surface until no free space remains, at which point all the cells are detached and collected. The process is repeated for the next batch. Connon and his lab have been developing a continuous approach by coating the surface with a functional coating (lipopeptides) before seeding with cells (1). After the cells grow they “self-detach” from the lipopeptide coating, allowing other immature cells to take their place, so there is no need to chemically or enzymatically detach the whole batch. “A peptide sequence can be chosen to affect the function and stability of the lipopeptide, and we have shown that once self-assembled into a supramolecular



structure, such material can form a stable coating upon a variety of surfaces,” says Connon. “Thus, it is possible to control the spatial and temporal positioning of cells across a surface if the lipopeptide contains a contiguous cell binding and endogenous protease cleavage site within the peptide sequence. In our new continuous bioprocessing approach, we tuned the system such that the rate of cell proliferation equalled endogenously-driven cell detachment by growing the cells on a rationally designed lipopeptide coating.”

Although Connon initially focused on human stromal cells, other types of adherent cells could also use the lipopeptide-based continuous approach.

Connon has demonstrated the

approach’s ability to support continuous production for one month with no reduction in cell production rate. The cell yield is around one percent per hour. “Unlike traditional batch processing, yield is not a suitable comparator; the process is continuous so the number of cells produced is theoretically unlimited,” explains Connon. “However, the rate of cell production is limited to the surface area used. The greater the surface area, the less time it will require to generate a specific number of cells. For example, using current stacked plate technologies with our coating would provide one billion cells every week. A standard sized benchtop incubator filled with these plates could produce 5–10 billion cells per week – continuously.”

### Reference

1. M Miotto et al., “Developing a continuous bioprocessing approach to stromal cell manufacture”, *ACS Appl Mater Interfaces* 9, 41131–41142 (2017). PMID: 29145726.

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## Sharing Is Caring

### EFPIA and PhRMA team up to promote responsible use of clinical data dissemination

Data sharing can be a touchy subject, and there is a perception that pharma companies don't exactly jump at the chance of disseminating clinical trial information. However, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and Pharmaceutical Research and Manufacturers of America (PhRMA) recently published survey results showing that pharma companies are, in fact, open to data sharing when given the opportunity (1).

The two organizations aimed to boost the industry's commitment to openness in 2013 when they released a set of principles outlining responsible data sharing, which covered five main areas: enhancing data sharing with researchers, enhancing public access to clinical study information, sharing results with patients who participate in clinical trials, certifying procedures for sharing clinical trial information, and reaffirming commitments to publish clinical trial results (2).

The principles were offered as guidelines to be followed on a voluntary basis, but the survey results suggest that the principles have resulted in a positive effect – 98 percent of EFPIA and PhRMA member companies share more clinical data than is required by law or regulators. The 30-question survey was used to find out how much

member companies had adhered to the principles, and to try and quantify their data sharing, between 2014 and 2016, with the overall aim of promoting the benefits and responsible use of information sharing.

#### References

1. PhRMA, "EFPIA-PhRMA principles for responsible clinical trial data sharing", (2017). Available at: <http://onpbr.ma/2AbRhWt>. Last accessed December 6, 2017.
2. EFPIA, "Principles for responsible clinical trial data sharing", (2013). Available at: <http://bit.ly/2jYAqeX>. Last accessed December 6, 2017.

## KEY FINDINGS

*Ways in which companies share clinical trial information:*

- Participation in an external data sharing platform
- Publication of trial results in peer-reviewed journals
- Presentations at scientific congresses
- Posting trial results on sponsors' own websites
- Sharing data with qualified researchers



84%

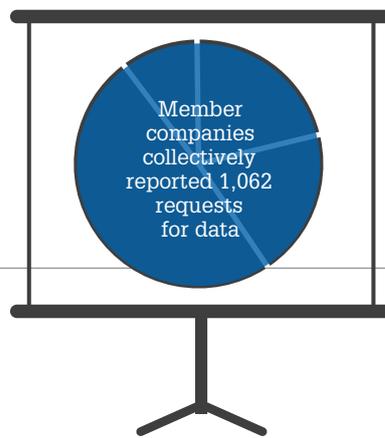
*of member companies have systems and processes in place to facilitate routine data sharing*

75%

*routinely post synopses of Clinical Study Reports soon after first registration of a new medicine*

98%

*have a strategy for publishing clinical trial results*



64%

*of requests are for patient-level data*

80%

*of the requests that had been reviewed by the close of the survey were approved*

## How to Cultivate a Quality Mindset

Using precise and reliable analytical tools to ensure the successful development and manufacture of your candidate molecule from the outset – and right through to quality control – helps avoid costly pitfalls along the way.

By Fredrik Sundberg

Characterization and quality control (QC) regulations demand that manufacturers demonstrate consistency and control over the manufacturing process. To have the best chances of success in getting your biopharmaceutical molecule from development to regulatory approval, I believe it is imperative to think about “developability” and “manufacturability” as early as possible.

Large and complex biomolecules are produced through a variety of processes, many of which can affect the protein composition. If you look at common causes of attrition, efficacy issues that arise from the process are frequently involved and often lead to insufficient bioavailability. Safety concerns, on the other hand, tend to be a result of unwanted modifications to the structure of the molecule, which can cause immunogenicity issues.

During discovery and early development, thousands of molecules are screened and evaluated in several cycles before arriving at a clinical lead candidate. The key? To only take forward molecules with the right critical quality attributes (CQAs) and then to link those CQAs to critical process parameters (CPPs) to understand the effect on the attributes during development and manufacture. From the beginning, you should be looking at potential post-translational modifications, the effect of temperature, pH and various buffers, and you should even try to predict undesirable

immune responses, viscosity issues, and so on, to avoid costly safety and efficacy problems further down the line.

A central regulatory standard is the International Council for Harmonization's (ICH) Q5E guideline, which thoroughly describes comparability (I) and forms the basis of what is required for characterization and QC. Characterization measures the influence of process changes against a reference standard, and often involves a number of analyses. QC, on the other hand, often requires fewer tests, but must confirm manufacturing consistency and product quality. In the US, a New Drug Application (NDA) must include analytical procedures that show the identity, strength, quality, purity and potency of the drug.

### Robust tools

Reliable product characterization and QC are best supported with robust and precise analytical tools, such as surface plasmon resonance (SPR). Biacore's SPR technology delivers label-free, real-time data, such as affinity kinetics, concentration, and biosimilarity assessment, that are critical for understanding biomolecular interactions. The potency and stability data generated can be used to characterize drug substance and product in pure and complex cell matrices. Essentially, SPR allows you to discriminate between candidates and study CQAs all the way from early research to QC. Modern SPR systems are multiplexing, with several flow channels, so you can measure different interactions in different channels and address multiple CQAs in a single assay. SPR-based assays also have unparalleled precision and accuracy when compared with classical immunoassays, such as ELISA. Difficulties with labeling, secondary reagents, incubation and wash steps do not apply to SPR – and the more straightforward direct binding format can detect process drift early, allowing you to identify and solve issues before your batch is released to market.

SPR technology is mentioned in several regulatory guidelines – from the FDA (2)

for biosimilars, as well as in the various pharmacopeias often referred to as a technology to use for various ligand binding assays, such as receptor binding or as “surrogate” potency assay. There are more than 15 drugs on the market that use Biacore systems as a release test, such as GlaxoSmithKline's Tanzeum™ and Nucala®. In addition to the drugs already on the market, there are a number of batch release assays in several clinical programs also using SPR. In the coming years, I expect to see a number of new SPR-based release assays approved by health authorities globally.

I believe SPR will become a standard tool for release testing of biologics, including vaccines. Moreover, the standardization and validation guidelines for the industry are currently being further developed, which I think will further drive the implementation of SPR as a standard tool for QC. Another interesting development is the move towards process analytical technologies (PAT), which could involve integrating SPR sensors into upstream and downstream processes on-line, off-line or in-line, allowing real-time feedback during production of each batch. Ultimately, advanced PAT could significantly reduce the number of tests required at the QC lab, potentially reducing the time-to-market allowing batches to be released immediately after production.

### References

1. ICH, “Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E,” (2004). Available at: <http://bit.ly/2i0TM29>. Last accessed November 28, 2017.
2. FDA, Guidance for Industry, “Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product” (2015). Available at: <http://bit.ly/2j6OXsC>. Last accessed December 8, 2017.

Fredrik Sundberg is Global Director for Strategic Customer Relations and Market Development at GE Healthcare. GE, GE monogram and Biacore are trademarks of General Electric Company.



# In My View

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

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

*Contact the editor at:  
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@texerepublishing.com*

## De-risking Drug Development

**Metabolism-based causes of drug attrition must be tackled through intelligent and early risk mitigation strategies.**



*By Guy Weber, Scientific Manager for In Vitro and Drug-Drug Interaction Sciences, Envigo, UK.*

Risk management has become an important discipline for firms developing new prescription drugs. It is said that only one of the 10,000 molecules entering drug discovery will ultimately reach the market – and, even then, it is not certain that expensive development costs will be recouped.

There can be few industries where the risk of failure is higher than in the drug development sector. Is it possible to shorten the odds a little? I believe so, but we need to understand the causes of drug attrition and deploy appropriate resources to gauge the level of associated risk. In short, we need to get better at identifying molecules that have a better chance of surviving the development process.

One successful technique for de-risking is to use advanced in vitro technologies and analytical techniques. These methods are ideal for early phase development because they are fast and require just milligrams of investigative compound (perfect for scarce or expensive materials). De-risking can focus on various sources of

potential problems, but I believe that one of the most important is metabolic risk. Drug metabolism is often critical to a product's success, but I find it is under-appreciated by drug developers. After administration, drugs may be acted on by members of one or more families of drug metabolizing enzymes (DMEs), of which the most important is the cytochrome P450 (CYP) family. Such metabolism can have a significant effect on the pharmacokinetic profile of small molecule drugs: it may drive clearance (especially for neutral, lipophilic molecules), influence population exposure in poor- and rapid-metabolizer sub-groups, result in drug-drug interactions, and cause some forms of toxicity. Consequently, the metabolites resulting from drug-CYP interactions have a major impact on the incidence of drug-related side-effects; for example, as a consequence of post-metabolic interactions between co-administered medications. These side-effects may cause approval delays at best – and, at worst, result in commercially catastrophic post-market withdrawal.

A de-risking assessment for drug metabolism should focus on how the drug is metabolized – for example, how it interacts with CYP enzymes and drug transporters – in in vitro assays. Early detection of metabolic liability not only gives developers the option of excluding high-risk molecules, but also may provide an opportunity to change the structural chemistry of the drug candidate.

There are three main elements of metabolic de-risking. The first element is drug-induced liver injury (DILI) – the single biggest cause of liver transplant in humans, and a major cause both of post-market safety-related drug withdrawal and of development-stage drug attrition. Where preclinical assessments indicate that a drug candidate has an elevated DILI risk, further development is

highly risky. Although the causative pathways behind DILI remain unclear, there is increasing evidence that a key role is played by reactive metabolites (RM) formed as a consequence of drug metabolism. Consequently, RM detection is a key component of de-risking strategies.

The second element is drug-drug interactions (DDIs). As populations expand and individuals live longer, the frequency of individual patients being prescribed multiple, concurrent medications is increasing. This means the risk of adverse drug reactions due to DDIs is also growing, and this area of drug development is coming under increasing regulatory scrutiny. Hence, drugs with a high DDI potential may be at risk of non-approval, excessive labeling or post-market withdrawal. To test the DDI potential of a drug

candidate, regulatory authorities recommend a range of in vitro studies (basic models) designed to identify both “victim” and “perpetrator” interactions. Perpetrator studies are designed to assess how the test drug will affect other medications, while victim studies are intended to assess how the test drug will be affected by other medications. They usually determine which enzymes and transporter proteins are involved in drug clearance (substrate/phenotyping interactions). Greater risks are associated with drug candidates that exhibit a victim profile.

The third element focuses on metabolites in safety testing (MIST). Much industry attention and regulatory concern has focused on the importance of drug metabolites as sources of drug toxicity. For any new drug in development, an early understanding

of potential MIST issues is crucial to help guide the choice of animal models used in safety assessment – models must be metabolically relevant to the human condition.

Application of an intelligently designed and rigorous de-risking strategy will provide a comprehensive data set to support major investment decisions; indeed, de-risking the pipeline in this way increases the chances of developing a safe drug, and therefore increases the value of the pipeline. Increased value is clearly important to companies seeking to win external investment or aiming to sell/out-license their portfolio.

I strongly advise integrating metabolic de-risking strategies into the drug development program, especially given the increasingly risk-adverse environment in which the pharma industry operates.

## Think (Bio)Print

**Great strides are being made in bioprinting, and the end result could revolutionize pharmaceutical development and testing.**



*By Erik Gatenholm, CEO of Cellink, USA.*

In the November issue, The Medicine Maker discussed the far future of healthcare and drug development. From

my perspective, the ideal future would give everybody access to healthcare, and would enable everybody to live a long, healthy life. Three-dimensional printing and artificial intelligence were two key technologies discussed last month, but another technology that will certainly have an important role in the future of medicine is bioprinting. The possibilities of bioprinting are potentially endless. My company specializes in “bioinks” and I like to tell people that, if you collected all of the tissues being printed by our customers, you’d almost be able to build an entire human body! Other companies are printing other tissues, such as cancer tumors, which can be useful in drug development.

Like most shifts in the industry, bioprinting will come to the forefront incrementally, rather than with a single big breakthrough. With each passing year, we gain more knowledge about how cells react and work with the latest bioprinting

technology. With that data analysis, we can build better models, which help us further understand new areas, which help us build better models, and so on. Bioprinting is heading in a few different directions, with R&D groups and academic researchers wanting to experiment and play around with the possibilities. The next market step will be to break into specific industries. Toxicology and drug discovery are obvious areas where bioprinting could be a real benefit – think of how commercial drug development might change if companies could test candidate molecules in human models early on. And it could also affect personalized medicine.

Beyond that, the far future potential that we all have in our minds is organ transplants. There’s a great deal of research and technological evolution that needs to be done to reach that point, however, and we need a few champion institutions to help push it forward. With the current organ donor system, there

will never be a surplus – rather there will always be a waiting list. And we can never unleash the potential for research institutes to test theories with human organs. Bioprinting could pave the way for human organs for transplant and research – eventually. The big questions then will revolve around regulation. The industry will be massive, but will it be controlled by a pharma patent perspective or by more general regulations? How do we decide who gets priority and when, if

they're widely available? It's important for companies operating in the space to keep an open dialogue with regulatory bodies to make them aware of the various processes so these questions can be brought up and answered alongside the evolving technology.

It's a very exciting stage for bioprinting right now – and it's only going to get more exciting in the years to come. Currently, the industry and regulators are amassing a tremendous amount of fundamental

knowledge and it won't be long before smart decisions start being made. We need some good, solid, successful applications to move things forward. It has been the same with the 3D printing of metals and plastics – everybody knew that it could deliver fantastic benefits, but it has taken time for everyone to figure out how 3D-printed parts can be best used. We just need to decide how bioprinting can genuinely bring benefits to pharma development and patients.

## Brexit Hits Home

**It's all swings and roundabouts in the UK's life sciences sector with no clear view of what the future holds.**



*By Steve Maginn, Cambridge, UK.*

In November, the relocation of the European Medicines Agency (EMA) from London to Amsterdam was confirmed, with the loss of around 1000 UK-based jobs, many of which are highly skilled. The unsurprising but nevertheless bad news is a direct and inevitable consequence of Brexit, and there will certainly be further reaching effects on employment and the UK skills base – especially given that many pharmaceutical and biotech jobs in the London area exist because of the EMA's presence.

It's not all job losses. In late November, we heard of investments by Merck, Sharp & Dohme (MSD) and Qiagen into their UK operations (1,2). MSD is set to establish a UK Discovery Centre in London, with a target date of 2020 for operational readiness, while

Qiagen is looking to potentially invest in a genomics research campus in Manchester. And though this additional investment is to be warmly welcomed, does it really equalize the equation? In my view, definitely not.

The MSD investment, for example, is being portrayed by the media as bringing “950 new jobs”; however, on reading the formal press release on MSD's UK website, I discovered that there will only be 150 new posts created, all in drug discovery research. The other 800 jobs (in process research and other functions) will be relocated from existing facilities in Hoddesdon, UK, and elsewhere. The number of new jobs to be created by Qiagen in their partnership with Health Innovation Manchester is not yet clear, but is stated as having “the potential to create up to 800 jobs.” (2)

Perhaps more worryingly, academic research in the UK is also suffering from the uncertainty of Brexit – and it is the nation's vibrant, innovative and inclusive academic life sciences research scene that underpins its industrial sector. A large chunk of funding for UK-based academic research comes from the EU – can we expect the UK government to provide the same or a better level of funding? We have had no such commitment to date. Now that the British people have voted to remove freedom of movement to the UK from nationals of other EU states (and give up their own freedom of movement within the EU),

one could expect post-Brexit research in the UK to be conducted by more UK nationals. So where is the necessary investment in education to keep high quality research in the UK? Companies like MSD and Qiagen have a choice as to where they base their activities, and they could move elsewhere if they can't sustain UK facilities, so we need to make sure they have access to appropriately skilled employees.

So far, the industrial end of the research spectrum seems to be weathering the uncertainty of Brexit, but without the fundamental support of the academic sector, this resilience could prove to be unsustainable and short lived. One solution may be government financial support for industry (which will be allowable once the UK is out of the EU) and/or academia, but surely this investment of public money, made necessary by Brexit, is money that could have been spent elsewhere – the “leave” campaign's poster child, the National Health Service, perhaps?

### References

1. Merck, Sharp & Dohme, “MSD announces plan to establish UK Discovery Centre in London,” (2017). Available at: <http://bit.ly/2ABF4dy>. Last accessed December 12, 2017.
2. Manchester Evening News, “Life sciences investment will bring 800 jobs to Manchester,” (2017). Available at: <http://bit.ly/2kBRqeP>. Last accessed December 12, 2017.



HUMANITY IN  
SCIENCE AWARD

the  
**Analytical Scientist**

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**KNAUER**



Richard Jähnke

# Meet the Winner

## Richard Jähnke

Richard Jähnke from the Global Pharma Health Fund (GPHF) has received the 2017 Humanity in Science Award for “development and continuous improvement of GPHF Minilab™ ([www.gphf.org](http://www.gphf.org)), which represents a breakthrough for the rapid and inexpensive identification of substandard and falsified medicines in low- and middle income countries in Africa, Asia and Latin America”.

Richard received his award at a special jubilee reception in Berlin, Germany on October 2, 2017 hosted by KNAUER to celebrate the company's 55th birthday this year. Richard's work will feature in an upcoming issue of The Analytical Scientist.

## Could it be you in 2018?

Analytical science has been at the heart of many scientific breakthroughs that have helped to improve people's lives worldwide. And yet analytical scientists rarely receive fanfare for their humble but life-changing work. The Humanity in Science Award was launched to recognize and reward analytical scientists who are changing lives for the better.

Has your own work had a positive impact on people's health and wellbeing? Details of the 2018 Humanity in Science Award will be announced soon.



[www.humanityinscienceaward.com](http://www.humanityinscienceaward.com)

## The Problem with Poloxamers

**Poloxamer 188 has become an essential component of cell culture media, but lot-to-lot variability has been a problem for many biopharma manufacturers. By working with customers directly to understand the science of inconsistency, we're able to supply a product that can be trusted.**

*By Nina Weis*

In previous articles in this series, my colleagues have discussed the importance of well-characterized raw materials, a transparent supply chain and trustworthy suppliers (1-4). As an example of how a well-characterized product leads to benefits for biopharma manufacturers, I would now like to share the story behind Merck's Poloxamer 188, which we launched in March 2017. The product is part of our Emprove® Portfolio, which centers on supporting risk assessment and aiding the development of more robust processes – part of that involves increasing supply chain transparency and offering full GMP documentation.

I have been with Merck for almost a decade, working in various functions focused on cell culture media, including product management, strategic marketing and portfolio management. We are always closely watching the market and interacting with customers to understand their needs and devise new technologies and products that will solve biopharma challenges.

Over the years, I have been involved in many projects regarding upstream chemicals, but recently I have been very focused on Poloxamer 188, a surface-active non-ionic amphiphilic triblock copolymer composed of a central hydrophobic

chain of propylene oxide flanked by two hydrophilic chains of ethylene oxide. The lengths of the polymer blocks can be altered, allowing different forms of poloxamer to be produced with varying properties. Commonly, poloxamer is used for its surfactant properties – and often employed in drug delivery as a formulation excipient. Poloxamer 188 is a form of poloxamer initially developed for the cosmetic industry to improve or change surface properties for products, such as hand cream or shower gel. As it turns out, it can also play a starring role in cell culture media.

Out with the old

Although animal serum traditionally was an important component of cell culture media, concerns around variability and infectious agents have forced the industry to seek other alternatives and to develop chemically defined cell culture media. One of the challenges was finding a non-animal derived substitute that could withstand hydrodynamic stress in the bioreactor. The industry explored various options and discovered that poloxamer 188 works very well; it increases the robustness of mammalian cells to shear from sparging, which is the strongest contributor to hydrodynamic stress in a bioreactor. This is why poloxamer 188 became a standard ingredient in the industry's cell culture processes.

Over time, however, with process intensification through increasing cell densities and productivities in fed-batch and perfusion processes, a new challenge has emerged: variability between poloxamer 188 lots started to be reported in the industry. Biopharmaceutical manufacturers began to approach Merck, explaining that they were seeing significant variation in their processes that caused unexpected loss of cell density and viability in their manufacturing operations. One manufacturer told us they had seen a 30 percent loss in yield, which was



finally identified as a result of bad lots of Poloxamer 188. You can imagine how variable manufacturing runs result in much higher manufacturing costs for companies to produce biotherapeutics.

It was very rewarding for us to have our customers open up to us about their problems, which highlights the good relationships we have built up with them over the years. We decided that it would be valuable to investigate the issue in detail – in collaboration with our customers – to learn what makes a good or bad lot of poloxamer, and whether it would be possible to develop a well-characterized product for biopharma applications that would result in more consistent quality and cell culture media performance.

In 2015, Merck purchased Sigma Aldrich and the two cell culture teams became one. Now, it was possible to globally work on the problem together – a huge benefit as the project ultimately benefitted from different insights, approaches, and combined knowledge in chemical and biological areas.

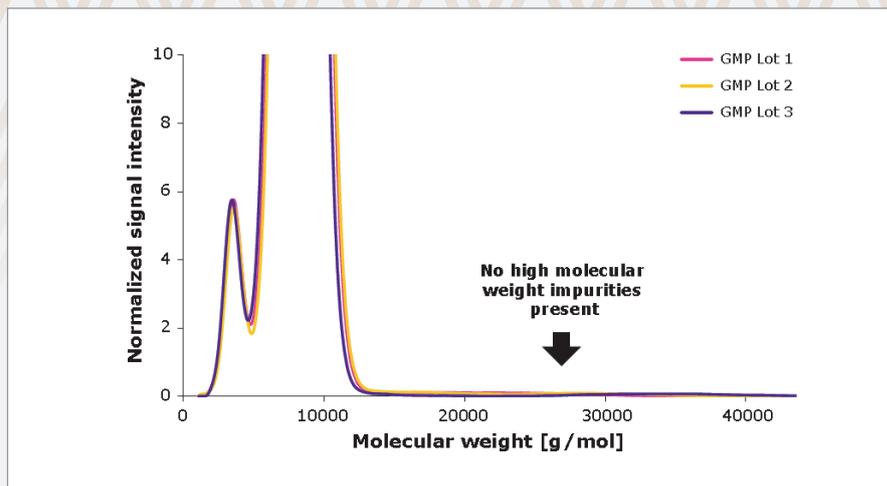
The science of variability

First of all, we had to understand why different lots of poloxamer 188 were negatively impacting biopharma processes. What was the correlation between the

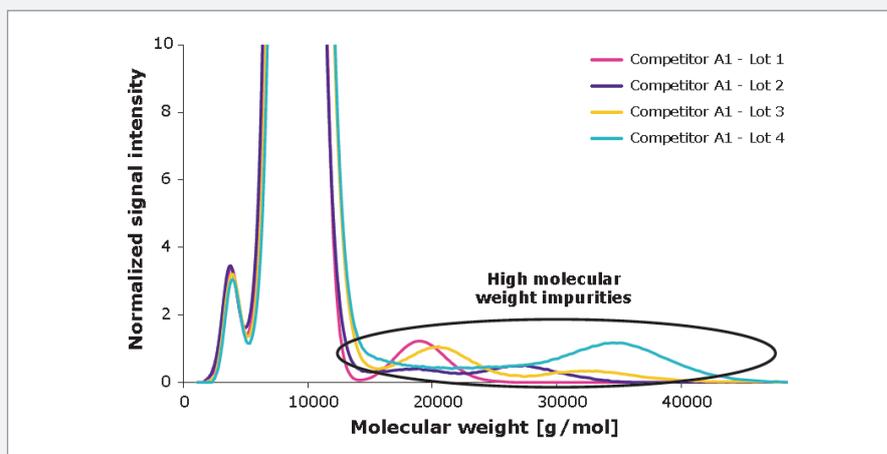
polymer, the material-chemical properties, and performance in cell culture media? It made sense to include our customers in our investigation, as we wanted to ensure that we tackled the issues that were important to them; we worked alongside them to exchange samples, characterizing good and bad lots of poloxamer. Over time, we compared our results to ensure we were reaching the same conclusions. We tested almost 200 different blind samples, which led to a reference library that can be used to reliably classify Poloxamer 188. Not only were we able to identify variation, but we began to understand what impact different poloxamer variability would have on cell culture media.

Ultimately, we were able to develop and validate two orthogonal biological and analytical methods for both evaluating the critical quality attributes of poloxamer 188 and identifying lot variability that may impact cell culture media. We now have a highly sensitive cell-based assay that classifies the shear protective effect and a cell test for standard product release. We also used size exclusion chromatography and liquid chromatography-mass spectrometry to identify high and low molecular weight impurities, and hydrophobic impurities, respectively, and have developed an analytical method for reliably separating good and bad lots of poloxamer 188. Since then, we have found a partner to manufacture the polymer in a specific way to ensure that it has consistent quality and cell culture functionality.

Our customers have been very excited to see a new source of poloxamer 188 on the market – particularly one that guarantees quality and performance. But perhaps what's most exciting is that our poloxamer was developed with direct insight from customers based on real-world problems. As well as benefitting from improved consistency, customers also have better security of supply. Previously, many of our customers relied on a single supplier, which can create



Poloxamer 188 EMPROVE Expert cell culture optimized assays to prove shear stress protection. High molecular weight species have a negative impact on performance - our Poloxamer 188 contains no high molecular weight material.



difficulties – particularly as poloxamer 188 is such a critical component for cell culture media. A new source of poloxamer gives customers greater flexibility, and I am very proud of the robust supply chain that we have developed.

We have put a lot of effort into our quality management systems to ensure that our suppliers meet certain standards – but we also perform regular audits to make sure those high standards are adhered to. The supply chain is also very transparent; our customers know where the polymer is manufactured, where it is released, where it is filled, packed and so on. Our assay also ensures that only product with material functionality is released and shipped to customers.

If you need further proof of our commitment to poloxamer 188 quality, we use the same product in our own

cell culture media! Just like you, we are only satisfied with qualified, high-quality components when it comes to all our media products.

*Nina Weis is Global Product Manager, Biopharm Materials, at Merck.*

#### References

1. B Lehr, "A Media Match Made in Heaven," *The Medicine Maker*, 35 (2017). Available at: <http://bit.ly/2jyL4bP>.
2. C Sharma, "Chasing Traces," *The Medicine Maker*, 34 (2017). Available at: <http://bit.ly/2hATxvc>.
3. C Sharma, "Know Thy Raw Materials," *The Medicine Maker*, 33 (2017). Available at: <http://bit.ly/2xnRFLi>.
4. K Kayser, "Finding That Special Source," *The Medicine Maker*, 32 (2017). Available at: <http://bit.ly/2kdAafB>.



the  
**Medicine Maker**

*Innovation  
Awards*

**2017**

# **Innovation Strikes Back**

The Medicine Maker Innovation Awards, now in their third year, celebrate the most exciting drug development and manufacturing technologies of 2017.



Every year, a diverse array of equipment and technologies are released to aid pharma and biopharma manufacture. Which technology stars shone the brightest during 2017? The Medicine Maker has been collecting nominations for months and the judging process is complete. Here, in alphabetical order, we present the top 15 innovations of 2017.

But which technology is the most innovative? The grand winner of the 2016 Innovation Awards was Centinel – a CHO

cell line resistant to minute virus of mice. You can read the story behind this innovation on page 40.

We will be sharing the story behind one of our 2017 Innovation Award winners in a 2018 issue of The Medicine Maker – and it's up to you, our readers, to vote on which 2017 innovation you want to read more about! Vote for your favorite innovation at: <http://tmm.txp.to/2017/innovationwinner>



## AFG 5000

Accurately dosing and filling both large and small amounts of powder

*Produced by Robert Bosch Packaging Technology*

Flexibility is the name of the game when it comes to the AFG 5000, with its range of versions and features. The number of filling stations can be individually selected, which leads to an output of up to 480 vials per minute in the high-performance range. Bosch has also developed a new variable transport system that continuously feeds vials into the machine, while adjusting its speed precisely to the rhythm of the individual workstations, such as filling, weighing and stopper insertion, to help avoid idle time or bottlenecks.

### Potential impact:

Every centimeter in class B cleanrooms counts in terms of operating, maintenance and cleaning costs. The AFG 5000 has been designed to reduce the amount of space that has to be cooled and cleaned with sterile, dry air. In addition, the high output and few parts help accelerate format changes, leading to the potential for more efficient processes and additional savings in space and costs.

## CADENCE INLINE DIAFILTRATION MODULE

A tangential flow filtration diafiltration device allows for  $\geq 3$ -log removal in a single-pass, continuous operation

*Produced by Pall Life Sciences*

The Cadence Inline Diafiltration (ILDF) Module is designed for continuous processing, in-process buffer exchange or contaminant removal in a number of applications. Modules are available with either Delta regenerated cellulose or Omega polyethersulfone membranes to provide high flux, high selectivity and low protein binding characteristics. Pall notes that the modules enable significantly reduced system hold-up volume, and feature an easy to use, holderless design.

### Potential impact:

According to Pall, a method for performing diafiltration in a truly continuous, single-pass mode of operation does not currently exist. Instead, diafiltration must be conducted as a batch operation, or in a semi-continuous operation that requires some level of recirculation. The Cadence ILDF device could bring the biopharma industry one step closer to implementing an end-to-end integrated, continuous bioprocessing platform.



## ESHMUNO P ANTI-A & ESHMUNO P ANTI-B RESINS

Improving patient safety by removing key contaminants from plasma-derived therapies

*Produced by Merck*

Eshmuno P anti-A and Eshmuno P anti-B are two affinity-based chromatography resins that help remove anti-A and anti-B isoagglutinin antibodies from plasma-derived immunoglobulins (Ig) – without negatively impacting process economics; the resins can be reused for at least 200 cycles, using acid or alkaline cleaning. The resins are manufactured using a combination of the company's base matrix technology and a



novel synthetic approach. The resins are released by a specific test method that evaluates performance with less variability compared with classical agglutination methods.

### Potential impact:

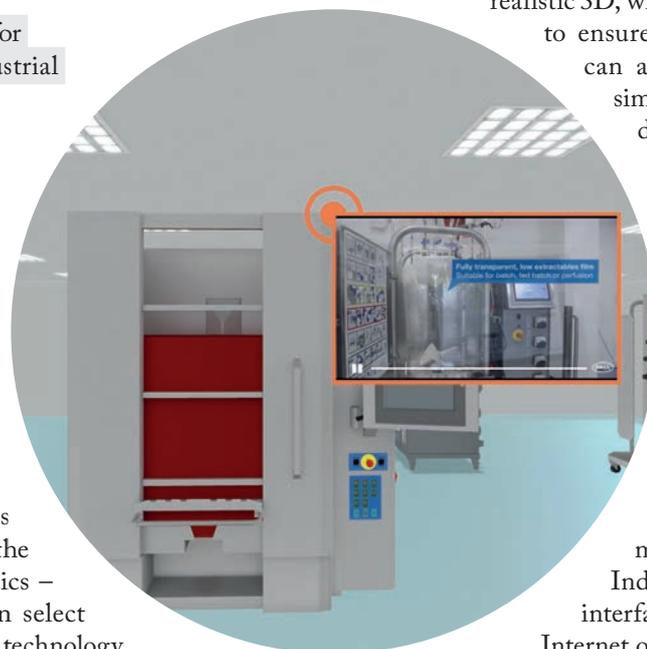
Plasma-derived Ig therapies are used to treat a variety of diseases, but trace amounts of anti-A and anti-B isoagglutinins have been associated with increased patient risk for hemolysis. Typically, human plasma is obtained by pooling the plasma of multiple donors of all blood group types, and therefore contains both anti-A and anti-B antibodies. Even using traditional filtration and purification methods, residual trace amounts of anti-A and anti-B blood group antibodies can remain. Eshmuno P resins could help mitigate this risk.

## HAKOBIO

A 3D and digital reality space for simulating and optimizing industrial processes and plants

*Produced by OUAT!*

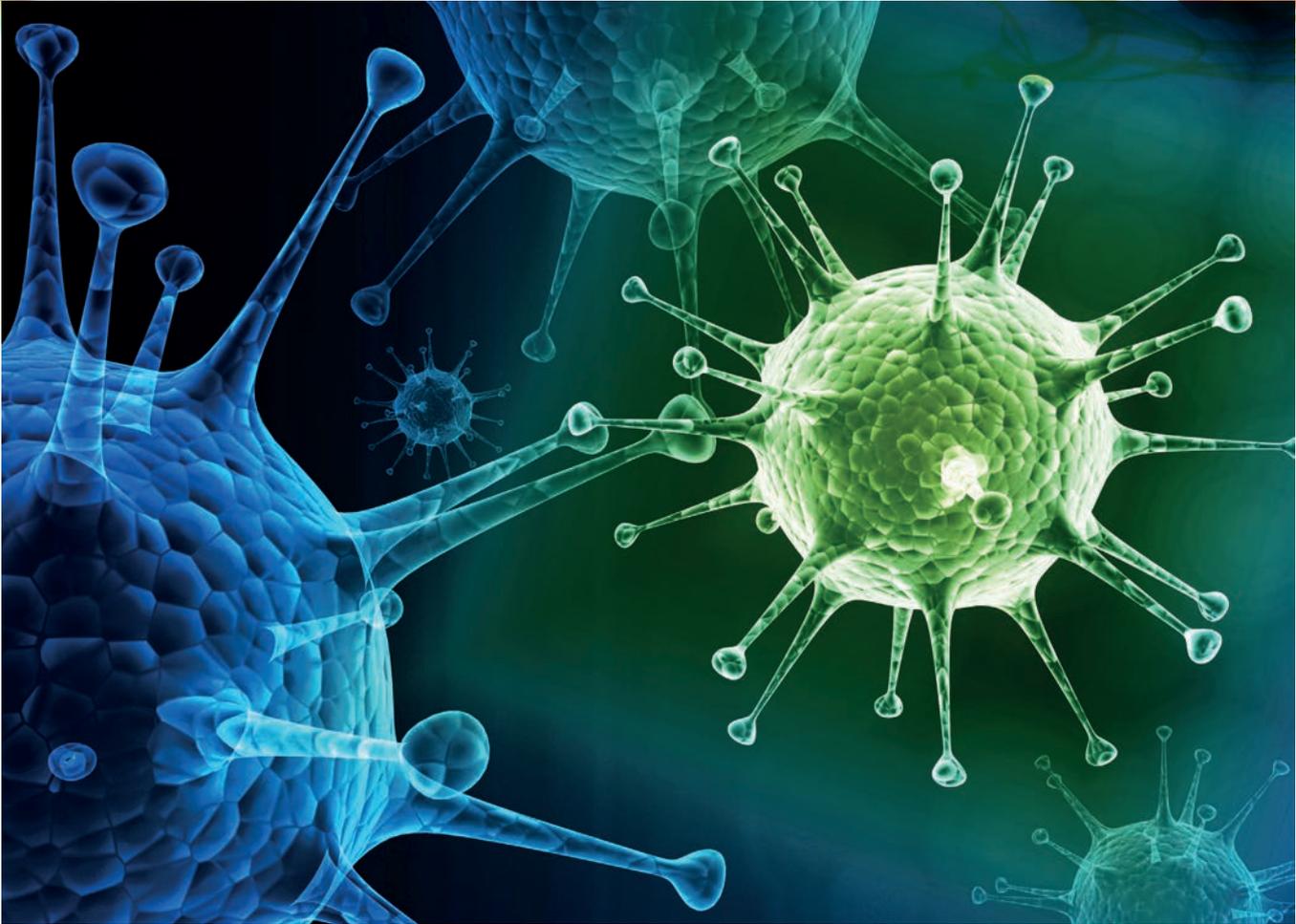
HakoBio was previously used exclusively by Pall Life Sciences, but the technology was commercially launched in 2017, with users now including the UK's Cell and Gene Therapy Catapult, Sanofi, and Beckman Coulter. HakoBio is a simple web application that allows users to create processes or design labs, and then view the creation – and assess ergonomics – using virtual reality. Users can select from a vast array of biopharma technology



(including specifications and functionalities) modelled in realistic 3D, which can be dragged and dropped to ensure it fits your lab. The interface can also be used for cost and flow simulations, as well as training and data management.

### Potential impact:

The platform can be used to easily simulate different processes and factories to get an idea of what may fit in a facility, without needing to consult experts. Creations can also be shared with colleagues. OUAT! believes that HakoBio will facilitate the digital transformation of manufacturing and the switch to Industry 4.0, by providing a visual interface to allow configuration of an Internet of Things platform.



## H3N2 CHALLENGE VIRUS

An influenza virus that can be used as a challenge agent to emulate wild-type infection

*Produced by SGS*

This influenza challenge agent has lineage from the seasonally epidemic, non-haemagglutinating H3N2 viruses that arose in the 2010–2011 influenza season, and that have come to predominate since 2014–2015. Thus, the H3N2 Challenge Virus represents one of the most common current circulating strains of influenza of a pandemic origin and can be used for testing the H3N2 portion of prospective prophylactic and therapeutic vaccines. It shows clear and progressive symptomology characteristics of a mild influenza-like illness. Previous influenza challenge agents

can demonstrate egg-adaptation and amelioration of disease (both infectivity rates and viral shedding).

### Potential impact:

When seeking FDA approval for a vaccine, manufacturers require proof of real-world efficacy, which can be achieved in studies in the community; however, the trials are expensive and the low rates of infection can lead to the need for an enormous patient pool. A challenge agent with a high infection rate – used in conjunction with controlled, human infection studies – could help reduce reliance of efficacy programs on the seasonal incidence of influenza. The efficacy of the vaccines can be determined directly by measuring both virological and host (clinical) endpoints. Maintaining the safety of subjects, whilst maximising data relevance (quality), allows informed go/no go decisions to be made earlier in the pipeline development cycle.



## iQ

Standardizing different drug containers to run on the same filling line

*Produced by Schott AG*

The iQ platform standardizes ready-to-use (RTU) syringes, vials and cartridges within a single tub format to run on the same filling line. By standardizing the format, pharma manufacturers can fill various drug/container configurations on the same filling line with only a few minutes of changeover in between. Schott has collaborated with a number of companies during the development of iQ to make the platform compatible with over 30 machines from leading and upcoming vendors.

### Potential impact:

Drugs today need to be manufactured in increasingly small batches in shorter periods of time, while adhering to higher quality standards. Currently available RTU solutions require drug manufacturers to fit the filling machines to the specific tub format; by standardizing this part of the process, iQ helps to reduce complexity. With the packaging also being fixed in nests, the risk of glass-to-glass contact is minimized. Schott also believes that the platform could ignite more discussion around issues such as glass breakage and particle reduction.

## KLV 1360

An automated system for leak detection

*Produced by Robert Bosch Packaging Technology*

The KLV 1360 for vacuum leak detection can measure leaks resulting from hole sizes of less than five micrometers and can achieve an output of up to 600 vials per minute by using inspection chambers that test groups of vials. The system features an integrated robot system and uses automatic individual re-inspection, which only rejects leaky vials within a conspicuous group. Reference samples help continuous internal process control to ensure maximum testing reliability.

### Potential impact:

Leaks in vials can pose a serious risk for patients as the active ingredient may be altered. In particular, non-destructive container closure integrity (CCI) testing technologies are becoming increasingly important in the pharma industry, with the US Pharmacopoeia calling for more quantitative, validated CCI test methods. The KLV 1360 is a sensitive and non-destructive technology that can aid patient safety, while protecting manufacturers against product loss and product recalls.





## MABSELECT PRISMA

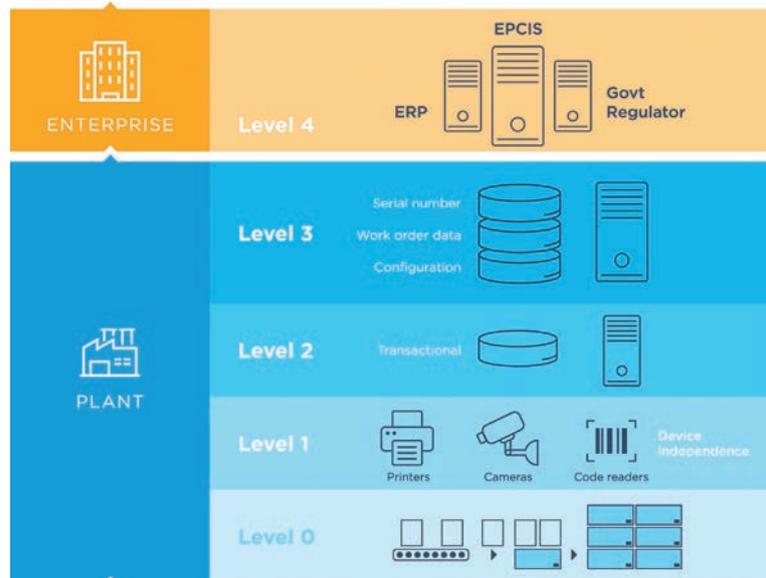
An efficient Protein A resin specifically designed to boost mAb purification capacity

*Produced by GE Healthcare Life Sciences*

According to GE Healthcare, MabSelect Prisma can help mAb producers to improve their purification capacity by up to 40 percent thanks to enhanced binding properties. Protein A chromatography resins play a fundamental role in mAb purification efficiency thanks to their high selectivity, but the drawback is a lack of chemical resistance and the relatively low productivity of many protein A resins. MabSelect Prisma has been developed using high-throughput screening methodologies to identify and resolve weaknesses in the protein A molecule that make it susceptible to sodium hydroxide degradation – allowing MabSelect Prisma to be cleaned with a higher concentration of sodium hydroxide to better control cross-contamination and bioburden risks.

### Potential impact:

Historically, the binding capacity of Protein A resins has lagged behind other chromatography resins. GE Healthcare claims that co-optimization of the chromatography bead and the final ligand construct has given MabSelect Prisma a binding capacity on a par with other techniques. Increasing mAb purification capacity can have a significant impact on equipment decisions. If overall productivity of existing equipment is improved, capital investments in new columns and facilities can be delayed until financial risks are reduced. The increased capacity also allows the use of prepacked columns.



## PRODIGI

Managing serialization requirements with a cloud-based solution

*Produced by Adents*

Prodigi is a cloud serialization solution based on the Microsoft Trusted Cloud Azure platform (selected by the European Medicines Verification Organization to build the European Hub). The platform helps pharma companies generate, exchange, manage and analyze serialization data, and also includes a connection interface that facilitates the on-boarding of trading partners by reducing IT resources, connectors and costs.

### Potential impact:

Adents has passed the certification process for the European Medicines Verification System (EMVS) – a pan-European system designed so that medicines can be verified at the point of dispensing), meaning that Prodigi can connect securely with the European Hub for the EMVS, and that Adents can now legally vouch for its customers concerning serialization compliance.

The platform meets regulatory requirements regarding unit traceability, but is designed to go beyond compliance to deliver business benefits resulting from the generated data. Serialization data can be structured for business intelligence analysis and serialization data can also be enhanced with external information, such as cold chain monitoring data.



## MICROCAL PEAQ-DSC

An automated analytical system for characterizing protein stability

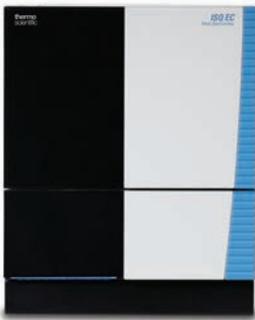
*Produced by Malvern PANAlytical*

Based on differential scanning calorimetry (DSC), the MicroCal PEAQ-DSC analytical system delivers data to guide biopharma development, from protein engineering, through pre-formulation and process development, to formulation and manufacture of the final product. The system provides high throughput, sensitive protein stability analysis with low sample

consumption. It is also a fully automated system – all cell filling and cleaning functions can be performed while unattended.

### Potential impact:

DSC is a powerful analytical tool for characterizing the thermal stability of proteins and other biomolecules. The technique measures the enthalpy ( $\Delta H$ ) and temperature ( $T_m$ ) of thermally-induced structural transitions of molecules in solution. This information provides valuable insights into factors that stabilize or destabilize proteins, nucleic acids, micellar complexes and other macromolecular systems. The data can be used, for example, to predict the shelf-life of biomolecular products to enable batch-to-batch and biosimilar versus innovator molecule comparisons.



## Q EXACTIVE HF-X HYBRID QUADRUPOLE ORBITRAP MASS SPECTROMETER

Powerful mass spectrometry system to garner greater understanding of biomolecules

*Produced by Thermo Fisher Scientific*

Thermo Fisher Scientific's Q Exactive HF-X Hybrid Quadrupole Orbitrap Mass Spectrometer provides sensitive and reproducible analyses of highly complex samples to help improve the understanding of biomolecules as drug targets, disease markers, and therapeutic agents. The system uses a high-capacity transfer tube for maximum ion loading, an electrodynamic ion funnel that accommodates and transmits ions over a broader mass range, and a high-field Orbitrap mass analyzer. Benefits include rapid and accurate mass analysis, two-to-three-fold sensitivity improvements, and up to an eight-fold improvement in signal-to-noise ratio compared with previous models.

### Potential impact:

Harnessing the power of the Orbitrap technology, the new system is designed to help scientists comprehensively profile and quantify the proteome, discover and verify novel biomarkers, and fully characterize complex biotherapeutics. According to Thermo Fisher Scientific, the system was used by Jesper Olsen, associate professor and deputy director of the Novo Nordisk Foundation and Center for Protein Research at the University of Copenhagen, Denmark, to identify 1,100 unique peptides per minute – a new world record.

## VALOR GLASS

Durable glass packaging designed to eliminate delamination

*Produced by Corning*

Valor Glass is engineered with higher internal energy than conventional glass packaging and has been developed to address several longstanding challenges with conventional borosilicate packaging. The composition and uniform interior surface of the new containers eliminates delamination, resists damage and breakage, and reduces particulate generation. In addition, the glass is chemically durable with uniform surface chemistry and low extractables, and has been designed to run more smoothly on filling lines at high speeds.

### Potential impact:

Valor Glass could offer benefits to both manufacturers and patients. Glass delamination can cause adverse patient events and lead to expensive recalls for manufacturers. Damage introduced on filling lines or during shipping can create sub-visible flaws and cracks in conventional packaging, which could lead to contamination. Valor has been designed to resist cracks and damage during processing and transit, as well as during in-home and clinical settings.



## VARIOSYS MOVE

An automatic transport system for exchanging production modules and processes

*Produced by Bausch+Ströbel*

The company's VarioSys production system comprises custom-fit modules – that can be interchanged at any time – interlinked with a Skan isolator system. VarioSys Move is one of the newest additions to the range. The system that automatically brings machine modules from the parking position to the isolator and back again. It can follow a programmed sequence or be controlled by an operator using a remote control to bring the module to the isolator, and from there they are transported automatically.

### Potential impact:

The aim behind VarioSys is to provide flexibility via a plug and play format, and VarioSys Move enhances the system with further automation. The right module is guaranteed to be delivered to the right place in the VarioSys line.



## VHP DC-A DECONTAMINATION CHAMBER ATMOSPHERIC

Atmospheric VHP biodecontamination chambers for safe particulate-controlled material transfer

*Produced by STERIS Life Sciences*

The concept of minimizing bioburden on the surfaces involved in transfer of material to clean room classified areas is not new but, according to STERIS, such equipment is typically designed as material airlocks equipped with gaseous decontamination equipment. The VHP DC-A Decontamination Chamber Atmospheric series is designed to sterilize the surfaces of various loads in a similar way to steam sterilizers, but by using low temperature vaporized hydrogen peroxide. The system also uses a specific fan design for high airflows to ensure a total cycle time of just 45 minutes, as well as an integrated VHP generation process using continuous humidity control that minimizes peroxide consumption down to 20 ml/cycle.

### Potential impact:

The best outcome for aseptic processing is to minimize the particulate amount – and thus risk of contamination – entering clean rooms. Automated systems can help achieve this and STERIS also claims that its VHP decontamination process accomplishes a 6-log bioburden reduction. From an operations perspective, a stand-alone design, with no HVAC connections required, facilitates install and validation

## X500B QTOF

Boosting routine biotherapeutic characterization with a benchtop QTOF system

*Produced by SCIEX*

Built specifically for biologics characterization, the X500B High-Resolution Quadrupole Time-of-Flight (QTOF) system aims to boost analytical capacity, simplify workflows and accelerate throughput. SCIEX has designed the system to simplify standard characterization workflows with intuitive software that allows even novice mass spectrometry users to run intact mass and peptide mapping analyses quickly and easily.

### Potential impact:

Biotherapeutic protein development depends on efficient product characterization at different parts of the process; liquid chromatography-mass spectrometry (LC-MS) techniques are essential in this endeavor. Many LC-MS analyses are now mature enough to be adopted in routine and high-throughput labs. SCIEX believes that the X500B is a streamlined solution that makes the power of mass spectrometry for standard intact mass and peptide mapping workflows accessible to every scientist, regardless of expertise level.





# THE INNOVATORS 2017

Whether better ensuring patient safety, improving process efficiency, or just making life in the lab or facility easier – meet the companies advancing pharmaceutical development and manufacture.



## iQ™. THE GLOBAL RTU STANDARD.

*A holistic concept standardizing ready-to-use containers within a single tub format to run on the same filling line.*

With its new iQ™ platform, SCHOTT standardizes ready-to-use (RTU) syringes, vials and cartridges within one tub format to run on the same filling line.

Thus, less changing of machine parts is necessary when switching from one container to another. This allows pharma manufacturers to fill various drug/container configurations on the same filling line with only a few minutes of changeover in between. Considering that drugs today need to be manufactured in ever-smaller batches in shorter periods while adhering to higher quality standards, the iQ™ standardized tub format increases flexibility and greatly reduces complexity for pharma manufacturers.

A case study has shown that iQ™ decreases the need for format parts among others, which enables companies to reduce investments by up to 40 percent, clean room space by up to 60

percent and running costs by up to 40 percent. The platform from SCHOTT is compatible with over 30 machine platforms of all leading and also upcoming machine vendors. Close cooperation with the world's largest elastomer component suppliers enabled the offering of pre-validated and flexible container/elastomer systems. This further reduces testing efforts, improves quality and accelerates time to market.

Moreover, the nested configurations of iQ™ containers eliminate glass-to-glass contact during filling, transport and storage. Thus, the risk of scratches and contamination is decreased significantly, which ensures and improves patient safety. Therefore, the platform also provides a solution to various industry discussions, such as glass breakage and particle reduction.

*Learn more at [www.schott.com/iQ](http://www.schott.com/iQ)*

# A TIME FOR VALOR

*Corning's innovative glass solution for injectable drug packaging draws on generations of problem-solving with science*

A revolution is forming in the way cutting-edge medicines are manufactured and delivered to patients. At the heart of it all – a new-age version of one of the world's oldest materials.

Corning Incorporated – the New York State-based technology company – this year introduced Corning Valor™ Glass, damage-resistant and chemically durable pharmaceutical packaging for today's medicines.

The innovation will create opportunities for pharmaceutical companies to manufacture their products more efficiently and to more safely deliver their products to patients.

Corning began developing what would become Valor Glass after a 2011 advisory issued by the U.S. Food and Drug Administration. The FDA noted at the time that several drug products had been recalled due to a formation of glass lamellae in certain injectable drugs. The formation of these glass flakes is called delamination.

The delamination process can lead to fine glass particle contamination in the drug. A longtime customer and leading pharmaceutical company looked to Corning for a damage- and delamination-resistant glass.

Corning was up to the challenge, bringing more than a century and a half of glass science and manufacturing leadership to the table.

## Long history of innovation

Since its earliest days in the mid-1800s, Corning attracted researchers with a passion for glass science, optical physics, and manufacturing engineering.

They discovered that the ancient material – mostly familiar to the world in ordinary soda-lime compositions – could be endlessly changed, enhanced, and transformed to create new properties.

From its lab in upstate New York, Corning began partnering with the great innovators of the day.

In the 1880s, Thomas Edison turned to Corning to develop a clear, heat-tolerant encasement for his electric filament. Later, Corning created a process for mass-producing those bulbs quickly and cheaply, bringing electric lights to the masses.

Durable cookware and labware, along with mass-produced

television tubes, were among Corning's innovations in the early 20th century.

And in the post-World War II era – as the company consistently invested more than 10% of its revenues into research and development – Corning continued its discoveries that changed everyday life and transformed industries.

- Telephone systems in the late 1960s were built on copper wire that couldn't reliably handle growing traffic. Corning invented low-loss optical fiber, unleashing a communications revolution.
- When the US government introduced the Clean Air Act in 1970, Corning developed an innovative honeycomb structure for trapping emissions. It has helped automakers meet stringent new regulations for decades.
- Corning's precision glass for advanced displays has helped bring flat-screen TVs and monitors to homes and offices everywhere.
- And the consumer electronics innovation that has defined the past decade – smart mobile devices with brilliant touchscreens – has been made practical by Corning® Gorilla® Glass. The tough, beautiful cover glass is on more than 5 billion devices worldwide.

## A remarkable innovation

Corning glass scientists have a deep understanding of how different formulation and fabrication techniques combine to determine the atomic state and structure of a glass, which in turn control the glass' mechanical, thermal, and optical properties.

The company is well known for its quality-by-design approach – combining material and process knowledge to create groundbreaking technologies. Corning Valor™ Glass is a perfect case study for the company's approach to innovation. The inventors designed a glass for pharmaceutical packaging and leveraged the company's existing manufacturing and engineering platforms to develop and manufacture it.

Valor Glass has its own unique composition optimized to address



longstanding quality issues with conventional pharmaceutical packaging. Through a root-cause analysis, Corning scientists were able to eliminate the root cause of delamination (1). In addition, the glass was designed to prevent the formation of stable through cracks and dramatically reduce the probability of glass particulate formation (2,3). Valor Glass containers provide a safety benefit for patients using sterile injectable drugs by lowering the potential risk of contamination or loss of sterility due to cracks and particles.

In addition to helping protect patients, Valor Glass improves operational efficiency for manufacturers. Valor Glass was designed to be compatible with existing filling lines as a drop-in solution for manufacturers, requiring no capital investments to modify equipment or lines in order to adopt.

Glass on filling lines is a rate limiting factor in terms of speed and throughput. Valor Glass improves the operational efficiency of filling lines, as it enables smoother overall operations. For manufacturers this means fewer line interventions and glass-related rejects, which improves the effective throughput of the line.

Ron Verkleeren, vice president and general manager of Corning Pharmaceutical Technologies, says Corning sees

Valor Glass as a large opportunity for the company.

“We are thrilled to be working with development partners and customers on the adoption of Valor Glass to store and protect medicines. The manufacture of sterile injectable drugs is not an easy thing to do, it has its challenges, but the glass package intended to protect medicines should not contribute to those challenges.”

“We want the glass to enable pharmaceutical companies to efficiently manufacture and deliver quality drug products to patients.”

#### References

1. Schaut, Robert A. et al. “Historical Review of Glasses Used for Parenteral Packaging.” *PDA Journal of Pharmaceutical Science and Technology*. July/August 2017.
2. Schaut, Robert A. et al. “Enhancing patient safety through the use of a pharmaceutical glass designed to prevent cracked containers.” *PDA Journal of Pharmaceutical Science and Technology*. 19 September 2017.
3. Timmons, Christopher et al. “Particulate Generation Mechanisms during Bulk Filling and Mitigation via New Glass Vial.” *PDA Journal of Pharmaceutical Science and Technology*. 15 May 2017.

# REIMAGINE CAPACITY FOR SUCCESS – MABSELECT™ PRISMA PROTEIN A CHROMATOGRAPHY RESIN

*The area of therapeutic monoclonal antibodies (mAbs) is growing rapidly, and much effort is put on intensifying processes to increase productivity and cost efficiency. Ever increasing titers in upstream production demand increased efficiency in downstream purification. GE Healthcare works intensively to help improve throughput in the large-scale manufacturing of mAbs.*

As most of today's upstream processes are of high feed concentrations, mass throughput rather than volumetric throughput is the main target for downstream process improvements. Protein A capture is the initial downstream purification step of most mAb processes. As such, the protein A capture step is subjected to large quantities of crude sample feed. To prevent protein A capture from becoming rate-limiting for the manufacturing process, high efficiency of this step is crucial. To improve performance of protein A capture, GE Healthcare has worked on optimizing both the ligand and the base matrix to develop a next-generation protein A resin that exhibits increased productivity over current protein A resins.

Co-optimization of the ligand and the base matrix is necessary, as large pores reduce steric hindrances but at the expense of available surface area, and long ligands increase the number of binding sites but can increase steric hindrances. To improve cleaning efficiency, weak points in the protein A ligand were identified and subjected to mutations to enhance alkaline stability. More than 400 different constructs were evaluated using high-throughput screening methodologies. A library of ligands was generated using a design of experiments approach, and Biacore™ surface plasmon resonance technology enabled quick evaluation of the different modifications introduced to the protein A ligand upon decision of final resin design.

## Addressing higher demands for maximized productivity

The final product, MabSelect Prisma, is built on the heritage of former MabSelect products. However, with the enhanced properties of both the agarose base matrix and the protein A

ligand, MabSelect Prisma offers significantly increased capacity compared with its predecessor resins. The improved capacity allows for handling of the increasing upstream titers to resolve bottlenecks in downstream mAb processing. The high capacity of MabSelect Prisma enables an increased mass throughput per purification cycle, improving productivity of current chromatography columns and systems without costly capital expenditures. MabSelect Prisma allows for up to 30 percent more product to be purified using current equipment. Alternatively, the increased binding capacity can be used to decrease the resin volume required to achieve a given mass throughput.

## Optimizing cleaning and sanitization for improved process efficiency

Efficient cleaning prevents impurities from building up on the chromatography column and reducing the capacity of the resin. Efficient cleaning and sanitization protocols also help prevent growth of microorganisms and inactivate potential endotoxins. A high alkaline stability of the resin enables the use of high concentrations of low-cost sodium hydroxide as a cleaning agent, supporting both cleaning efficiency and good process economy. MabSelect Prisma exhibits more than 90 percent retained dynamic binding capacity after cleaning with 1.0 M NaOH or more than 95 percent retained dynamic binding capacity after cleaning with 0.5 M NaOH between runs for 150 cycles. The significantly enhanced alkaline stability of MabSelect Prisma ensures a better process economy, while meeting the requirements of a stringent bioburden control.

Learn more at [www.gelifesciences.com/mabselectprisma](http://www.gelifesciences.com/mabselectprisma)



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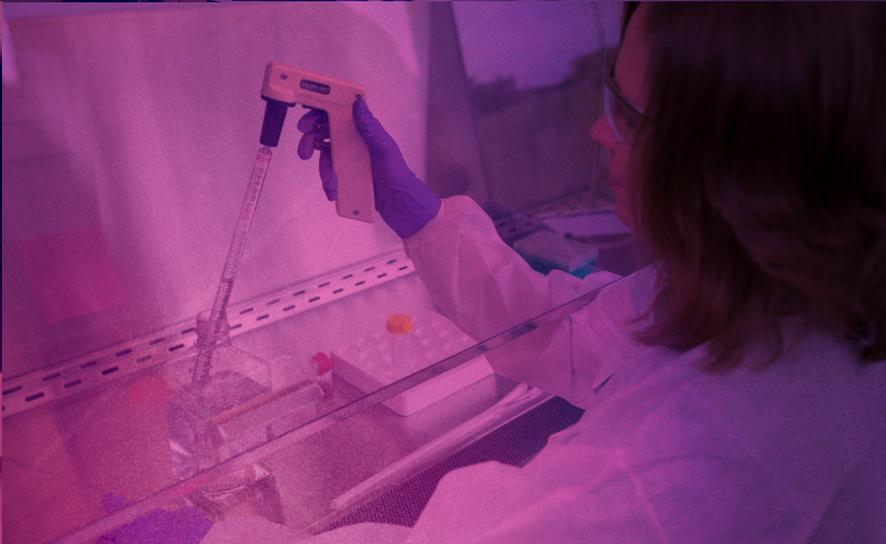
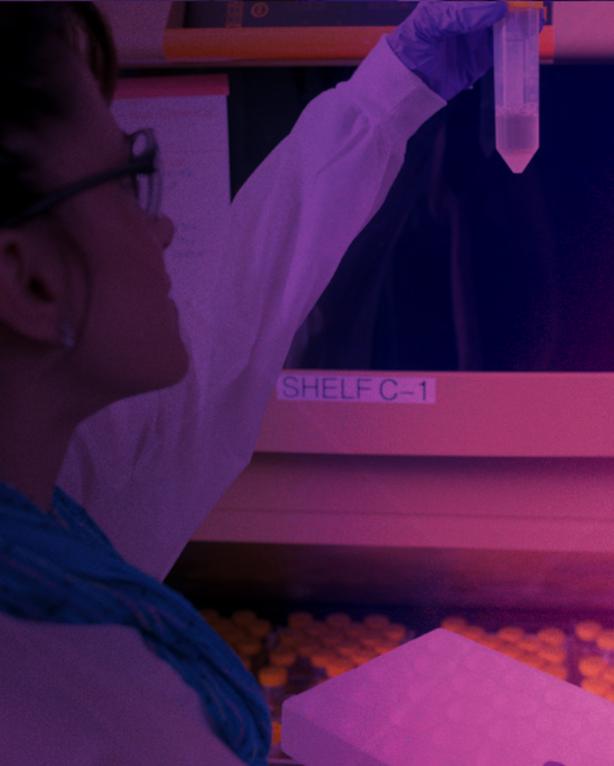
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## NextGen

*R&D pipeline  
New technology  
Future trends*



*40-42*

*Fantastic Vaccines and Where to Find Them: Lessons Learned with Nima Farzan*

*With many companies focusing on the bigger vaccine areas, specialty vaccines are often overlooked. Nima Farzan aims to change this.*

*44-46*

*The Best Defense Is Good Science Centinel – a CHO line resistant to Minute Virus of Mice – was the overall winner of The Medicine Maker 2016 Innovation Awards. Here, Kevin Kayser reveals the story behind its development.*

## Fantastic Vaccines and Where to Find Them: Lessons Learned with Nima Farzan

**The field of specialty vaccines can feel underloved, but with growing interest from public health groups, previously under-served diseases may soon have hope.**

Vaccines are one of the greatest public health achievements

I've been working in life sciences since my undergraduate days, starting with a human biology degree at Stanford University, California. Following business school, I worked for Novartis for a number of years covering different roles that took me from Switzerland to the US, and from marketing to R&D. Then an opportunity opened up to enter the vaccines space. Novartis acquired Chiron for their vaccine work and wanted to open up a vaccine division; I was offered a position and ended up loving it. The passion of the team working in that space and the impact your work can have on patients is unparalleled. When working with vaccines, you are combating powerful diseases and working to strengthen public health, which are powerful drivers for motivation. At Novartis, I had previously worked in hypertension. High-blood pressure kills many people, but each new drug is only usually marginally better than the previous one. Having the opportunity to develop an entirely new vaccine, which could substantially change disease and health rather than incrementally managing it, is exhilarating. It really gets into your

blood (no pun intended!) and I have never looked back.

Manufacturing challenges are significant. As fulfilling as working with vaccines is, there are definitely many unique challenges. The first, and most obvious, challenge is the significant safety hurdles you have to jump over. Vaccines are given to healthy people and there can be no severe side effects. Imagine developing a new pediatric vaccine that you aim to give to 4 million healthy American babies every year – no one will agree to the vaccination if there are any health risks.

A second challenge is scale of production. Whereas a chemotherapy drug may reach production levels of 10,000-30,000 doses per year, vaccines need to be produced to the tune of over one million doses per year – seasonal flu vaccines can even reach the scale of 70 million doses. Being able to get your costs to a reasonable level per dose is essential – and there are many potential vaccines that have never seen the light of day because it would be impossible to manufacture them cost effectively at the necessary scale.

Vaccines are not always appreciated by the public

Governments, payers and individuals do not seem to have the same willingness to pay for new vaccines as they would new drugs. I think it's partially psychology; we humans invariably wait for a problem to emerge before dealing with it, rather than taking steps to avoid it. There is also the concept that vaccines are a right and a public good, and therefore the price needs to be as low as absolutely possible (which I certainly do not disagree with). Very low vaccine prices, however, lead to less innovation. For example, even large-scale products, like seasonal flu vaccines, still use egg techniques that have been around for over 70 years. Of course, this doesn't mean there is no innovation – there are exciting technologies in use such as virus-like particles (VLPs), which enable vaccines

to be developed without any living virus. Companies are also focusing on vector vaccines, although none of these are yet on the market. In comparison to pharma fields, however, vaccines still have a lot of room for growth.

The anti-vaccine movement can also have an impact on public perception of vaccines. Anti-vaxers generally target high-profile vaccines rather than smaller, specialty ones, but they have a noticeable effect – the immunization rate in Marin County, California, is lower than some countries in the developing world. As an industry, we haven't done much to combat the impact of anti-vaxers, but there have been huge debates between public health leaders, academics, and pharma companies about how to tackle the issue. Do we engage, or do we ignore them and remain silent? It's a tough debate, but undoubtedly public health is being damaged.

Market gaps allows smaller vaccine players to succeed

Big pharma is consolidating its vaccine efforts. Novartis, for example, sold its vaccines business to GlaxoSmithKline in 2015. Today, there are only a handful of big pharma companies working with vaccines and most tend to focus on the bigger opportunities; the routinely used vaccines sold at large scale. Smaller, specialty vaccines, such as vaccines for travelers, the military, and the developing world, are being neglected, which could ultimately impact the developed world (consider Ebola).

After leaving Novartis in 2011, I joined PaxVax, which focuses on providing vaccines in underserved markets. At first, PaxVax was based on a more traditional biotech structure, focusing on the technology around vectors to develop new vaccines – many of which can be found in the clinic today. But, along the way, we had a bit of a pivot while working on new technologies. It was frustrating to see so many diseases being overlooked and we

started to pay greater attention to specialty vaccines. Our journey began when we licensed CVD 103 HgR from UMB and then developed Vaxchora, a vaccine for cholera, approved by the FDA in 2016. We also spotted an opportunity with Johnson & Johnson's typhoid vaccine, Vivotif. The vaccine was similar to Vaxchora – both are live attenuated oral vaccines. We were able to acquire Vivotif and J&J's manufacturing facility in Switzerland, which was a great opportunity for us; it gave us access not only to high capacity but also to a team well used to FDA and European inspections – extremely valuable for a small company just entering the market. Today, Vaxchora and Vivotif are commercially available in the US, and Vivotif is also commercially available in Europe. We've ramped up our R&D pipeline to include vaccines for chikungunya, Zika, hepatitis A and HIV. We also co-promote some smaller products for other partners in Europe.

It's actually quite unusual for a small company to manufacture and commercialize their own products; many instead look for partners. But there is a danger: your commercial partner may not be as interested in your product as they are in their own portfolio. And it's very easy for niche products to get lost in a large portfolio. With J&J and Vivotif, for instance, we hypothesized that the product was largely being ignored in the larger suite of drug and vaccine opportunities because it was a specialty product. There are very few vaccine-focused companies out there, which is why I think there is a real market opportunity for a company like PaxVax!

Small companies can be very successful in the vaccine space. Development costs can be lower for specialty indications, and as production is scaled down with specialty vaccines, manufacture is much easier. Building out a full manufacturing facility can be extremely challenging for a small company, but there are options out there; for example, we have used pod technologies – mobile suites – that enable us to get a



## Facts and Figures

\* Figures obtained from the World Health Organization and CEPI

An estimated  
**2–3 million**  
deaths are prevented every  
year thanks to vaccines

Over 10 years,  
the global costs of  
epidemics could total  
**\$600 billion**

Around  
**116.5 million**  
children receive basic  
vaccines every year, but  
**19.5 million**  
miss out

A virulent respiratory virus  
spreading as fast as flu could  
spread to all major global  
capitals within

**60 DAYS**

Estimates suggest that such  
a virus is capable of killing 33  
million people within

**250 DAYS**

GMP commercial production suite up and running really fast. They are only small scale, but very easy to roll out.

Balancing global need, innovation, and cost is a challenge

A constant challenge is how we can support innovation in overlooked disease areas when prices are so low? For example, there is a global shortage of yellow fever vaccine in both the developing world, and for travelers from the developed world. We could develop a new yellow fever vaccine – current yellow fever vaccines are made with egg-based techniques, and we certainly have a few innovative ideas – but current vaccines cost around \$2 per dose. Agencies don't want to pay more, so how can we justify the costs of developing a new vaccine? Revenue opportunities aren't huge for vaccines so it's important to have multiple products. As we focus on overlooked diseases – which almost invariably affect the developing world – we are working to further reduce costs and

overcome the cold-chain hurdle, among other things to better serve those regions.

Collaboration opens new doors

The US Department of Defense (DOD) is very interested in vaccines for neglected diseases because soldiers can also be affected – and medical supplies are limited on the battlefield. We currently have a number of partnerships with the DOD. One of our focuses is on chikungunya, a mosquito-borne viral infection. It's a disease that has been infecting people in Sub-Saharan Africa and Asia for decades, more recently spreading to Brazil and the Caribbean. Similar to Zika, chikungunya is episodic – an outbreak may tear through a community, but be followed by a period of relative stagnation. Unfortunately, unlike Zika, an effort to find a vaccine for Chikungunya hasn't really been a priority for the pharma industry. In collaboration with the DOD, and with technology licensed from the US National Institutes of Health (NIH), we have a chikungunya vaccine in phase II.

We may also be able to do something with Zika. Our potential chikungunya vaccine uses VLP technology (many vaccines in our pipeline focus on VLPs), and we are seeing some interesting pre-clinical results by partnering VLPs with Zika antigens. We are working with the Centers for Disease Control and Prevention (CDC) on further development.

Smaller companies will always be limited by resources, rather than the number of opportunities. Working with groups like the DOD, NIH, and CDC are part of the benefits of working with vaccines – the public health infrastructure really helps provide valuable scientific input, as well as helping to integrate costs. I believe that collaboration is crucial to overcome the challenges of working in the vaccine space. At the World Economic Forum in January 2016, a new public health alliance launched, called the Coalition for Epidemic Preparedness Innovations (CEPI). CEPI was founded by the World Economic Forum, Wellcome Trust, the Bill & Melinda Gates Foundation, and the governments of India, and Norway, to prepare for the next potential waves of infectious diseases that could affect public health and to develop new vaccines (1). CEPI helps bring priority vaccine candidates through to the end of phase II clinical trials and supports vaccine platforms that can be rapidly deployed against known and unknown pathogens.

A few of the diseases identified as focus points are Lassa fever, Nipah, and MERS. Over 70 organizations are part of the initiative and I am a member of the board. With all of this collaborative power, we have to be able to make a difference. I truly believe that one day we will be able to prevent epidemics before they occur.

*Nima Farzan is CEO of PaxVax, California, USA.*

### Reference

1. CEPI, "Mission", (2017). Available at: <http://bit.ly/2yx6Ntu>. Last accessed November 27, 2017.



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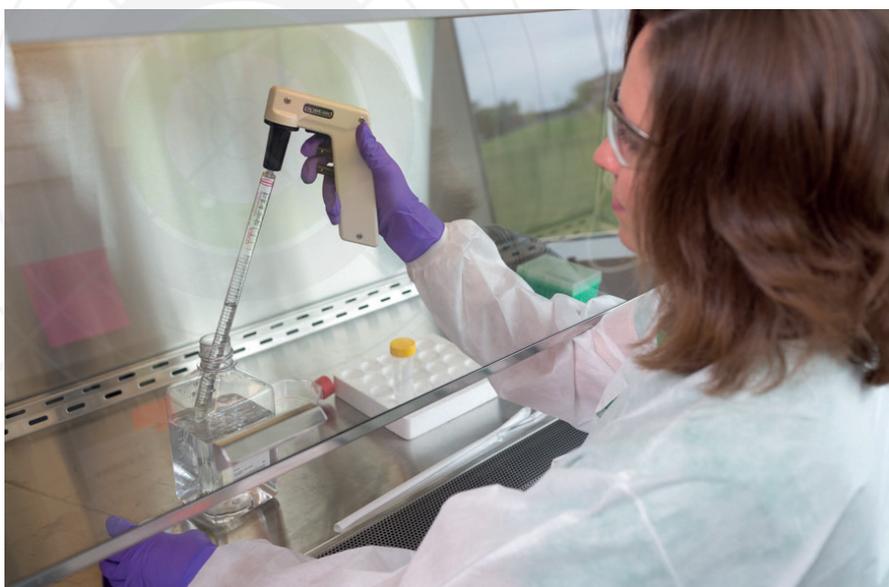
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## The Best Defense Is Good Science

Starting from fundamental virology, Kevin Kayser and the upstream R&D team at Merck discovered the mechanism by which Minute Virus of Mice (MVM) infects CHO cells, and the respective genes involved in viral uptake. Their work culminated in Centinel: the first MVM-resistant CHO cell line.



Before joining Sigma-Aldrich in 2002, Kevin Kayser, now Senior R&D Director at Merck (known as MilliporeSigma in the US and Canada), worked as a professor and researcher, using gene editing to stabilize proteins in industrial microbial systems. He applied those skills to the fundamentals of viral infection at Sigma-Aldrich, which was acquired by Merck KGaA in 2015. Their aim was to genetically engineer a line of CHO cells that would be immune to

Minute Virus of Mice (MVM) – and they didn't know whether his goal was remotely feasible. The work culminated in Centinel, described as “intelligent virus defense”.

Centinel is a gene-editing technology that can make CHO cell lines completely resistant to MVM. Centinel claimed the top spot in The Medicine Maker 2016 Innovation Awards. Here, Kayser talks us through the development process, and why insurance against MVM contamination is so important.

Why is MVM such a big problem for the industry?

Going back to the early 1990s, Genentech had a contamination event with MVM which cost them in the region of \$10 million. However, the real



*“The contamination disrupted patient drug supply, facilities had to be shut down, and the stock price plummeted.”*

impact of a viral contamination event in biomanufacturing was witnessed during the Vesivirus 2117 contamination at the Genzyme facilities in 2009. The contamination disrupted patient drug supply, facilities had to be shut down, and the stock price plummeted. The impact on the business as a whole was tremendous. These types of contamination events are quite rare, but can be catastrophic when they occur.

Today, cell culture media comprise

dozens of different components, each coming from different suppliers, often from all over the world. MVM is a parvovirus. Parvoviruses are quite common (and most frequently studied) in domestic animals; usually found in animal feces and urine. Typically, the virus enters our industry through raw materials, such as wheat hydrolysates; wheat fields can contain potentially infected field mice, and infected mice can also get into warehouses. In other words, when you're procuring from a wide variety of sources, contamination is a possibility. For this reason, critical review of vendor supply management is crucial.

As far as I know, MVM is the only virus that has been associated with chemically defined cell culture media – most contamination events come from serum and more complex raw materials. MVM is extremely durable and virulent, which means just a few viral particles in the environment can have fairly significant implications. Genentech revealed that one virus particle per liter of cell culture was enough to infect the entire process.

How did the Centinel project get started?

The project was the brainchild of David Onions (now Director of Orsus Medical) and me. We thought that it would be great to genetically engineer cell lines that were resistant to common viral contamination events. At the time, however, we knew nothing about how the viruses actually infected these particular cell lines. Our team spent a lot of time delving into the fundamental science of MVM infection, which was rewarding because in industry you don't often get the chance to put on your academic hat to do basic research. When we started, we had no idea if we would ultimately end up with a commercial product. It was possible that the processes involved

## Genetic Code Breaking

By Kevin Kayser

I've been involved in gene editing for most of my career. When I started, we were using microbial systems, and eukaryotic gene editing was the holy grail of the early 2000s. In 2007, I edited a book that chronicled where gene editing was at the time – and the major techniques used today, such as CRISPR-Cas9 or zinc finger nucleases (ZFNs), weren't even mentioned! CRISPR-Cas9 has placed gene editing in the spotlight, but for our purposes zinc fingers are preferred. You need a lot of skill to design zinc fingers, and they can provide greater specificity and precision, with little or no off-target effects – we are always concerned about introducing additional modifications that might affect the CHO cell line. If we're doing research into how a mechanism works, we'll use CRISPR-Cas9, but in the final product development we use ZFNs.

There are, of course, some legitimate concerns with gene editing. I recently read about a self-titled “biohacker” who was injecting himself with CRISPR-Cas9 in an attempt to build better muscles! Clearly, there are issues around who should have access to the technology and what they should be allowed to do with it, but gene editing most definitely has a tremendous amount of potential. I believe that it should be possible to create a “super” CHO cell line with a variety of traits that would allow it to produce safer and more efficacious drugs. Today, we are already seeing new cell lines being developed with reduced host cell proteins, better glycosylation patterns, faster growing rates, and so on.

As well as performing gene knock-outs, it's also possible to do knock-ins to turn up the expression of genes or endogenous proteins, or to create new therapeutic variants. There is also the potential to introduce more human characteristics to the cell line to reduce the chances of immunogenicity. These are the likely routes forward.



(ZFN) gene editing technology. It just so happened that some of the mutants resulted in modifications in the binding receptor for MVM, which led to the discovery that the virus attached to the membrane associated protein via a specific sugar. When we screened our already existing library, we found some mutants that were resistant, or partially resistant, to MVM infections. When we witnessed our “infected” cell lines growing, and saw that the virus couldn’t dock, we knew that we had cracked it.

*“When we witnessed our ‘infected’ cell lines growing, and saw that the virus couldn’t dock, we knew that we had cracked it.”*

in MVM viral binding and uptake would be core to the biology of the cell line, making it impossible to knock-out the relevant genes. We didn’t know whether we would be able to find the receptor and characterize the binding event. It was pure exploratory research and very exciting.

When did you know the project was feasible?

It was actually serendipitous. As part of a separate project, the team created a series of gene knock outs within the CHO cell line to understand glycosylation patterns. Glycosylation can impact the efficacy of the therapeutic protein in human patients. So, in our efforts to modify the sugar structures on the therapeutics, the team engineered a series of glycosylation mutants using our zinc finger nuclease

event jumping in right away to partner with us, which affirmed that this is a genuinely desired product.

Most of our partners tend to be larger organizations – and I think that’s likely down to the fact that they manufacture larger volumes of drugs; the larger the bioreactor, the greater the risk. Smaller organizations tend not to have experienced a contamination event, and I get the impression that some believe, “It will never happen to me.” And of course there are cost pressures for smaller companies.

How will you be expanding the product in the future?

MVM was a logical first choice. Other viruses can be associated with serum and more complex raw materials, but MVM is the only one to be associated with chemically defined processes. However, we are continuing to expand the program in several areas. I don’t think there will be further “product launches” akin to a catalog item. Rather, we’re focusing on custom-made solutions for our clients; if a client has a particular virus they’re concerned with, we will work with them to build a program. If major contamination events with new or unknown viruses occur then we will of course explore those.

What other projects are you working on?

It was only a few years ago that the CHO genome was sequenced and we are actually sequencing our own cell lines right now. We are experimenting with removing parts of the genome that aren’t needed for the cell to produce therapeutics, which could potentially divert more energy to therapeutic protein expression. We can also remove the retroviral scars that have been accumulating in the genomes of all organisms. Once we have done that, we may be able to expand into adjacent industries, like vaccine production.

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## The Transformation to Excellence

How a customer focused mission to boost single-use assembly product quality and supply security led to the Mobius® MyWay Program and a manufacturing site transformation.



Back in 2016, Merck began a multi-phase program to prepare themselves – and their customers – for a high quality, scalable and secure single-use future.

Phase I of the “Mobius® Transformation” was underpinned by the launch of the Mobius® MyWay Program – a segmentation of Merck’s single-use portfolio into three product offerings: Mobius® Stock, Mobius® Select, and Mobius® Choice. The aim? To reduce custom assembly lead times and enhance supply security (1). Behind the scenes, however, other high-impact transformations also had to occur to execute the mission, including reorganization of all departments to support a 24/7 schedule, Lean Six Sigma training for employees, and expansion of the company’s Danvers, Massachusetts site – ultimately, leading to its new status as a single-use Center of Excellence.

Phase I was completed in early 2017, but Phase 2 – ensuring continuous improvement and further enhancing supply security – is an on-going journey.

We spoke with Pascal Perrotey, Head of Operations at the Danvers site, and William (Bill) Faria, Production Manager, to discuss the single-use market, as well as the Mobius® transformation – and what both mean for single-use customers.

The exciting challenge of a double-digit growth market

Single-use technology represents an exciting and rapidly growing market, as Perrotey

notes, “Ten years ago, single-use accounted for 15 percent of the market, but today it’s 30–35 percent – and in ten years’ time? It’s likely to be more like 75 percent.” Although growth is positive and invariably welcomed by most, it also brings challenges when it comes to scaling up production to meet increasing demand. Merck recognized the potential capacity challenge early on – and proactively formulated a transformation plan. “We recognized that it’s not just about solving a short-term problem in capacity, but also about preparing for continued growth into the future,” says Perrotey.

However, capacity isn’t the only challenge. “End users also want their products faster,” says Faria. “Quality expectations are also changing. How do you get more out the door, faster and with higher quality than before? How do you meet customer needs and requirements when the bar is continuously being raised?”

The answer lies in a different approach – and a new way of looking at the challenge – in other words, a transformation.

The past, present and future of Danvers  
The heart of the Danvers site is split into two main parts: single-use bag manufacture and final assembly, where the appropriate components are connected. “It sounds straightforward, but the reality is there are many different designs, varying in complexity, which forces us to be very flexible in production,” says Faria. “It also

means that there are plenty of opportunities to streamline processes and focus on ‘right-first-time’ production to achieve the highest quality. Reliable delivery and best-in-class quality were two of the key drivers of transformation at the Danvers site – and ultimately enabled us to become a Center of Excellence.”

“Phase I of the transformation identified nine work-streams to address critical growth enablers, which fed into five overall objectives,” says Faria (see Sidebar: How does transformation occur? Phase I in action). “I think it’s fair to say that it was an ambitious program! But it actually boiled down to three main themes: people, processes and infrastructure.” Faria notes that getting the “people” aspect right was absolutely critical – and it involved a complete re-organization of workflows and personnel, from the shop floor to design, engineering, and quality assurance.

There was also a cultural shift. “We wanted the whole team to play offense rather than defense! We wanted a more proactive attitude to finding solutions. We wanted people to think about what we could do, rather than should do, and to take big swings and make huge changes for the better,” says Faria. “People were really motivated not only by knowing that they were improving processes and products for the benefit of our customers, but also that they were creating a better place to work!”

The process – and the people it seems



## How does transformation occur? Phase 1 in action

For Merck, “transformation” isn’t just a word – it represents a well-defined and multifaceted approach that, in its initial phase, addressed nine work-streams across five areas.

Nine work-streams:

- Design and staffing
- Performance culture
- Output optimization
- Prototype lead-time reduction
- Segmentation and portfolio
- Supply chain alignment
- Danvers expansion
- Capacity expansion
- Proactive quality

Five overall objectives achieved:

### 1. Capacity Expansion

Implemented a 24/7-shift model to increase production capacity and output, expanded clean rooms, additional automated lines and ancillary facility requirements to support extra output.

### 2. Prototyping Capabilities

Reduce prototype lead times and enhanced supply security by 50 to 75 percent with dedicated prototyping resources, including facilities and team.

### 3. Portfolio Optimization

Segmented single-use portfolio into three distinct product offerings – Mobius® Stock, Mobius® Select, and Mobius® Choice – to drive improved custom assembly lead times. Notably, custom assembly lead-time for Mobius® Select is now only 6 weeks.

### 4. Supply Chain Improvements

Streamlined warehousing with a new 35,000 square-foot raw material warehouse, reducing the risk of component shortages and improving supply security.

### 5. Quality Enhancements

Instilled a proactive quality culture, with “right-first-time” performance, to boost product quality.

members from other sites, who haven’t visited us for a while say it’s a completely different site... almost unrecognizable. In fact, one customer asked if we had applied for any external awards to celebrate the work that has been done, which was an unexpected compliment!” says Faria. “Other customers have noted how the culture that we are instilling matches up to the culture they are trying to build in their own organizations. We’ve also had more interest in collaborations to foster best practice, which is great – after all, that’s what being a Center of Excellence is all about!”

Customers also recognize the direct benefits of the changes. Perrotey adds, “A few weeks ago, one of our top customers visited and told me that, from his perspective, our transformation represents a real competitive advantage – one that would further reinforce our strong relationship. We were delighted and honored by such a comment because it means we’re already being successful.”

Overall, the transformation is a reflection of the increasingly essential partnership between single-use supplier and customer. “We always emphasize that we do not simply produce plastic bags and components,” Perrotey says. “In fact, we are part of a wider promise to improve health and life. And I know that every single employee feels proud to contribute to new solutions and our ongoing efforts to help our customers develop and manufacture better medicines.”

#### Reference

1. S Bell, “Single-Use That’s Ready When You Are,” *The Medicine Maker*, 35, 48-49 (2017). Available at: <http://bit.ly/2AXRCvw>.

– are the product, which is what makes the new Center of Excellence the perfect partner for the Mobius® MyWay Program philosophy. “Now, we can offer greater quality with more automation, improved process control (and so less variability), and a highly engaged workforce with a defect-free product mindset,” says Perrotey. “We have improved supply security with fast and reliable on time delivery, higher capacity and a highly flexible production model.”

Given customers are integral to the ongoing mission, they also have an essential role to play. “It’s great when customers come to visit, because we’re able to have interesting discussions about real-world needs, which leads to the opportunity to collaborate and further improve,” says Faria.

Adds Perrotey: “As the market continues to evolve, it’s important for us to continue to learn from our customers; likewise, they can also learn from us – it’s this kind of collaborative relationship that really enables successful transformation, not just for us, but the whole industry.”

The result

The big question: have people noticed the transformation? “Customers, and

A portrait of Richard Markus, Vice President of Global Development at Amgen, USA. He is a middle-aged man with dark hair, wearing black-rimmed glasses and a blue button-down shirt. He is smiling slightly. The background is a dark, textured surface with bokeh light effects in white, yellow, and red.

# Breaking Barriers to Biosimilars

Sitting Down With... Richard Markus, Vice President  
of Global Development, Amgen, USA.

How did you get your start in pharma?

I've always been interested in science, especially biology, but my first job after college actually involved statistical programming in the pharma industry. As I learned more about the industry, my interest in it – and particularly in clinical research – grew. So my next step was to go back to school and earn my MD and PhD, with the expectation of going back to the field of drug development as a physician. I started working at Amgen around 11 years ago as a physician scientist. I worked with a fantastic team to develop a bone-targeting agent (XGEVA; denosumab) for cancer patients, which was in phase II trials at the time. It was a very large effort involving multiple studies in patients with different cancers, so it was an exciting way to start my career.

But then you moved into biosimilars...

Right. My roles progressed until I had the opportunity to help start Amgen's biosimilars business – an entirely new division for the company. Back then, there wasn't much clarity on how to develop biosimilars; the regulatory environment was still evolving (and it still is today). Indeed, biosimilars represented a whole new class of product; they are not innovator drug products and certainly not chemical generics. It was a once in a lifetime opportunity to be involved in the creation of a whole new type of product.

How has biosimilar development changed?

Earlier biosimilars were based on smaller and generally simpler products, but in the last couple of years biosimilars have been involved in much more complex antibody treatments. They are not just more complex because of their size, but because they consist of multiple parts with different functionality or activity. For example, one part may bind the primary target on the tumor, while another binds T cells or the immune system – the combination is what provides activity, and each different part of the biosimilar must have no clinically

meaningful differences in function or activity compared with the originator. Technology advances in the last two decades have not only enabled us to manufacture such complex biologics, but also to evaluate them with high confidence. And that's allowed us to expand our biosimilar pipeline from three products to ten.

What have been the biggest highlights of the division so far?

I am really proud of our work with trastuzumab – a biosimilar that we are developing with Allergan. The collaboration with Allergan began very early in our program and focuses on oncology products. We are both mature companies in terms of our goals; we know who we are and what we want to contribute, which makes for a successful partnership. It's important for us both to have a high-quality product, and to have the clinical data to confirm and support the level of similarity, because it gives patients and physicians the confidence to make an informed decision about the drugs they want to use. Trastuzumab is currently in review in Europe and the US for market authorization and we are looking forward to the anticipated approval.

And what about personal highlights?

The biggest highlight for me has been working with fellow scientists at Amgen. Many companies outsource much of their biosimilars work, as they don't have the capacity to do it themselves. We have built our biosimilars business with the same laboratories, manufacturing facilities, and the same group of scientists who I've been working with for years, which has been a great pleasure.

I think I am very fortunate in my role. I still get the fun of working with scientists and data – and making decisions about the program and the molecules themselves. I also interact directly with regulators, who have been really well engaged with the field from the very beginning. Working with regulators is very rewarding; I like to think

we have made a meaningful contribution to shaping the field and helping patients.

If you could change one thing about the biosimilars field, what would it be?

There was actually a recent change in the biosimilars field which we are pleased with, and which we will continue to support. In the US, the Centers for Medicaid and Medicare Services (CMS) reversed a policy for biosimilars that used blended billing and reimbursement codes that ultimately followed a generics reimbursement paradigm. As a manufacturer of innovative biologics and biosimilars, we are pleased that CMS put patient needs first and will now ensure that each biosimilar product will have its own billing code and individualized reimbursement rate. This will facilitate efforts to support product traceability and ultimately foster a more competitive biologics market.

In the generics world, there have been many shortages of critical chemotherapies, partly because of how policies have played out in terms of incentivizing (or disincentivizing) certain methods. I think it is important that we actually learn from those issues and make different choices for biosimilars. We need to be able to ensure consistent quality with continuous competition – both in the short term and long term.

The challenge is creating sustainability for healthcare assistance – particularly in oncology – because patients are often treated with two or three product combinations at a time, which is expensive (and a cost that is endured through second and third line treatments as well). It's great that we can help save lives, but to maximize the number of lives we can save, the cost of drugs needs to be addressed, and healthy competition is the solution.

All of this said, the biosimilar payment environment in the US is still evolving, but Amgen supports a “level playing field” for how reference products and biosimilars are paid for.

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