

# the Medicine Maker<sup>®</sup>

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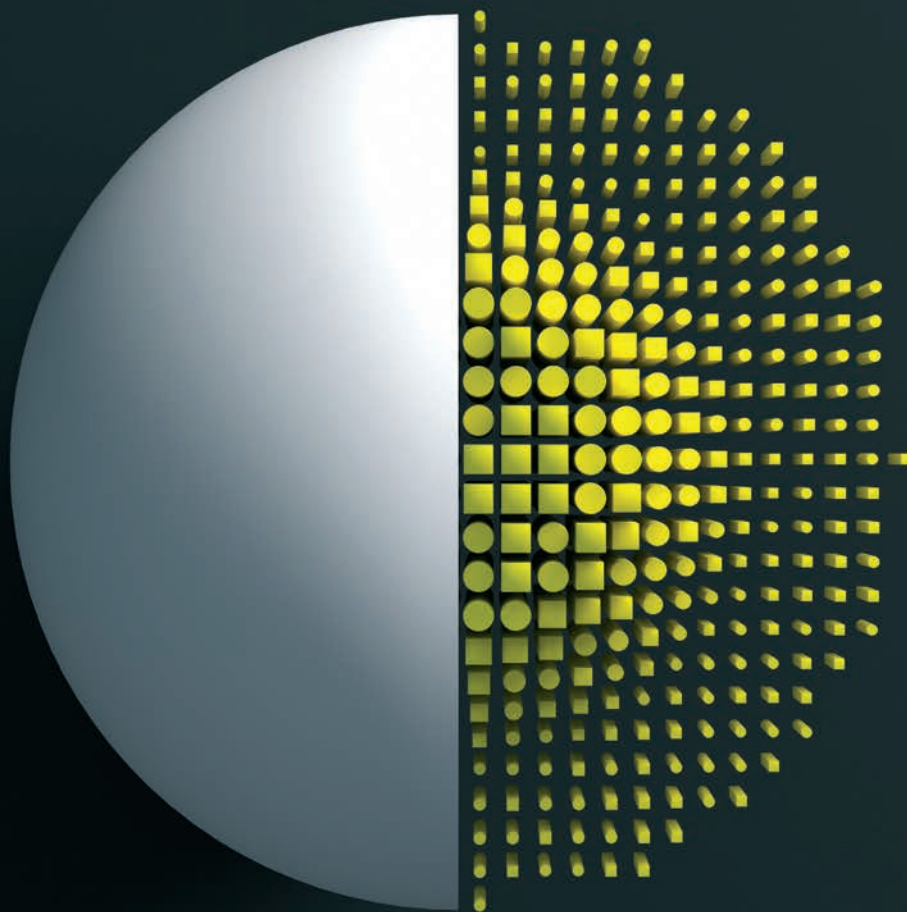
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When I started writing about the industry (quite some years ago...), small molecule drugs were still prominent in discussions, monoclonal antibodies were on an undeniable upward trajectory, and cell and gene therapies were little more than pipedreams. Continuous processing was beginning to be tentatively mentioned outside of academia. And there were conversations about whether the industry would ever accept single-use systems.

On reflection, it's quite surprising where we are today. Single-use tech is standard. Suppliers are developing continuous tech for bioprocessing. And "cell and gene" is one of the hottest topics around.

Perhaps even more surprising, we're running a cover feature on video games. Yes, video game tech is now relevant to pharma. Hard to imagine? Video games are a highly popular entertainment choice – so supporting patients using games and digital therapeutics is not as wild as it might sound. Consumer brain training games have existed for years, but Akili Interactive has gone one important step further. Their game, EndeavorRx, has received approval from the FDA to be prescribed to treat children with ADHD. Think of the game itself as a dosage form. You can read more about this – and other intriguing examples of video game tech and how it could affect medicine and pharmaceutical quality – on page 16.

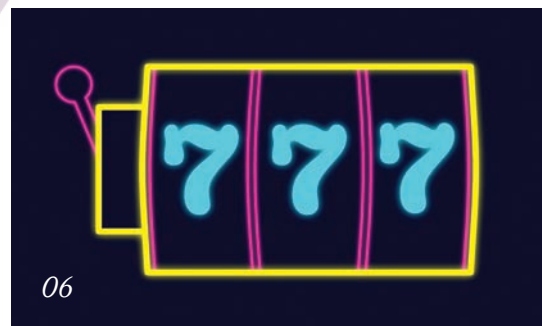
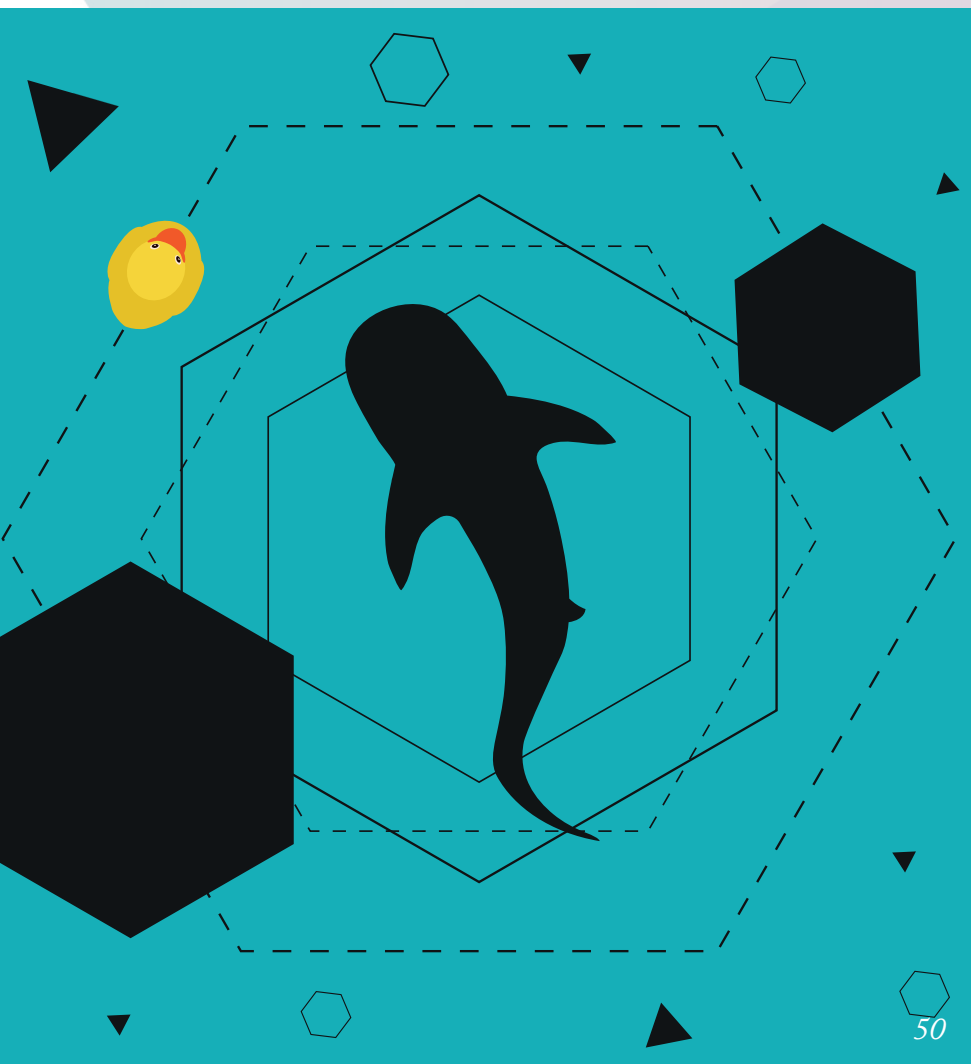
What about traditional medicine making? Traditional API-based pills and tablets are not going away. Neither are large molecules, even though some of the spotlight has been lost to cell therapy. My aim with every issue of *The Medicine Maker* is to connect you all by providing a high-level view of what is going on across the entire industry – including whatever interesting (or controversial) developments are likely to shape the future, whether in politics, video games, or something even more unexpected.

To ensure you don't miss key details in the big picture, we have introduced "Core Topics," featuring content specifically sourced for those of you in cell and gene (page 37), bioprocessing (page 41), and small molecule manufacture (page 45). We've also increased our digital coverage of the same three crucial pillars of pharma at [www.themedicinemaker.com](http://www.themedicinemaker.com).

As ever, if you have something to contribute to our Core Topics or elsewhere, please get in touch: [stephanie.sutton@texerepublishing.com](mailto:stephanie.sutton@texerepublishing.com)

**Stephanie Sutton**  
Editor

*Stephanie Sutton*



- 
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Games, Drugs, and  
Rock 'n' Roll  
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## the Medicine Maker

ISSUE 83 - JAN / FEB 2022

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Distribution: The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com). Non-qualified annual subscription cost is £110 plus postage

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## The Magnificent Seven

**A major analytics company names seven drugs with the potential to change the game in the years ahead**

The global analytics company Clarivate has named several “Drugs to Watch” in its annual report on potential blockbusters (1). Let’s take a look...

**Adagrasib (KRAS-mutant cancers)**  
Adagrasib is currently undergoing a phase II trial as a first-line combination therapy with KEYTRUDA and a phase III trial as a second-line monotherapy. Should adagrasib succeed, it will be a first and second entry for mutation-positive colorectal and non-small cell lung cancer tumors, respectively.

**Faricimab (DME and wet AMD)**  
Faricimab could outperform current standard-of-care treatments for diabetic macular edema (DME) and wet age-related macular degeneration (AMD). The treatment has performed well in trials and has potential for “real blockbuster status”.

**Lecanemab (for Alzheimer’s disease)**  
This anti-cognitive-decline treatment

is progressing down the pipeline, chasing the FDA’s 2021 approval of ADUHELM, which “opened the floodgates” for US regulatory submissions of similar mAbs. Lecanemab is currently undergoing two phase III studies – one for patients with early Alzheimer’s disease (AD) and the other for patients with preclinical AD.

**Donanemab (Alzheimer’s disease)**  
Also following in the wake of ADUHELM, donanemab could potentially offer lower risks and improve on its benefits. Donanemab’s success would help expand patients’ options and likely lower treatment costs. Phase III trials are underway.

**Tezepelumab (severe asthma)**  
Tezepelumab is already out of the gate, having been greenlit by the FDA in December 2021. It’s a first-in-class biologic treatment for patients unable to

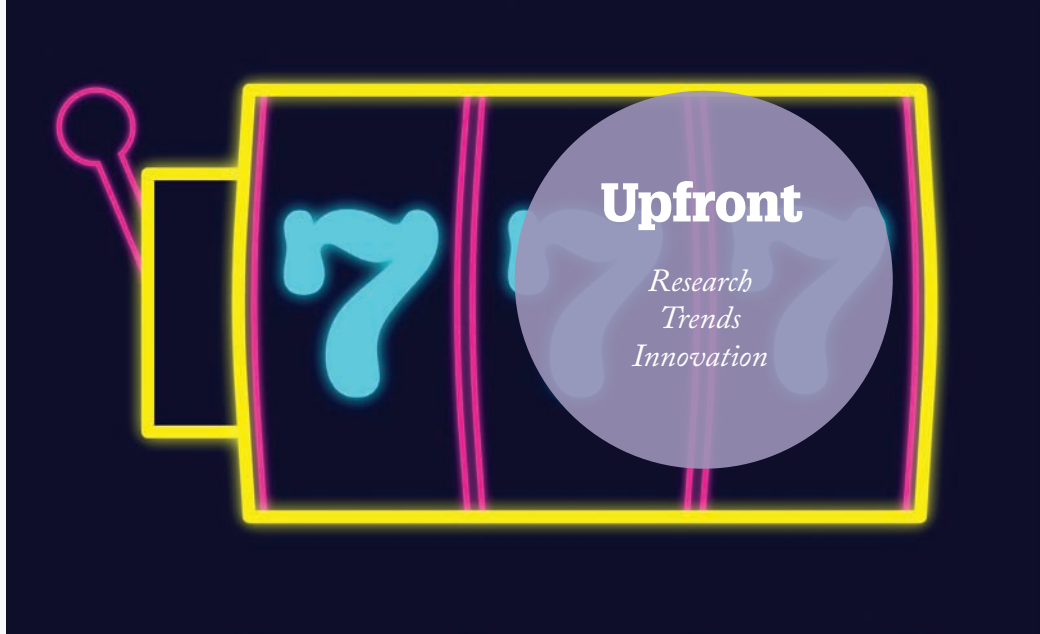
easily overcome non-TH2 or TH2-low asthma with standard-of-care inhalers.

**Tirzepatide (diabetes-related obesity)**  
As global diabetes and obesity rates continue to rise, the need for drugs like tirzepatide grows more urgent. Clinical trials indicate that this treatment could potentially induce both weight loss and glycemic control.

**Vutrisiran (amyloid transthyretin (ATTR) polyneuropathy)**  
To date, there are few treatment options for patients with wild-type ATTR polyneuropathy, a rare, progressive, and debilitating disease. According to data released thus far, vutrisiran is expected to be effective and more convenient than existing treatments.

### Reference

1. Clarivate, “Drugs to Watch 2022” (2022). Available at: <https://bit.ly/DtW-2022>.

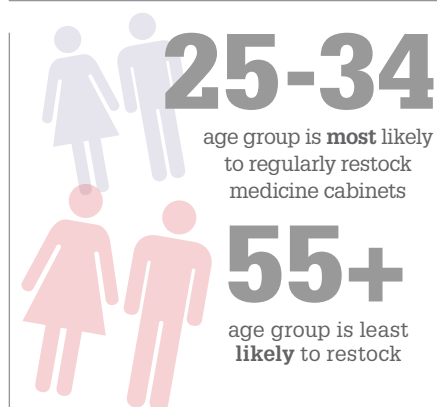


## INFOGRAPHIC

### Inside the Medicine Cabinet

**England study sheds light on patients' bad habits when it comes to OTC medicines**

Source: Chemist4U (2022). <https://bit.ly/3KnWk6N>  
Credit: Tawfigu Barbhuiya/Unsplash.com



*Most likely medicines to be stocked by patients?*

- ✕ Paracetamol
- ✕ Ibuprofen
- ✕ Cold & flu tablets
- ✕ Antiseptic cream
- ✕ Vitamins



## BUSINESS IN BRIEF

*A European data center, an American Moonshot, and a new leader for lobbying...*

- The White House has announced a suite of initiatives to accelerate work toward reducing and ending cancer. Biden aims to reduce the cancer death rate from 50 to 25 percent, and to this end has boosted funding, set up a partnership with the UK, and formed a “Cancer Cabinet”.
- For the first time, a woman has become the Board Chair of PhRMA. The new chair is Ramona Sequeira, who is also President of Takeda’s US Business Unit and Global Portfolio Commercialization departments.
- The FDA has approved remdesivir, Gilead’s supplemental treatment for high-risk non-hospitalized COVID-19 adult and adolescent patients. The approval comes following phase III data showing a risk of hospitalization 87 percent lower than treatment with placebo, and following a surge in the mAb-resistant Omicron variant.
- The FDA has postponed a meeting planned to address Pfizer and BioNTech’s submission to the FDA requesting emergency use of their COVID-19 vaccine for children aged 6 months to 4 years of age. The pause will allow the FDA to consider new recently released clinical trial data concerning the vaccine.
- The EMA has established a coordination center for data analysis named DARWIN EU. The center has been set up to grant the EMA and national authorities in EU member states access to reliable data on topics such as diseases, patient populations, and the effectiveness of medicines.



## Who’s the Coolest?

### The 2022 Freezer Challenge has begun

Nobody said being cool was easy. And when it comes to laboratory cold storage, a great deal of care and energy is needed. Good practice is essential – and that’s exactly what The Freezer Challenge assesses. From the opening of registrations on January 1 to scoresheet turn-in on July 1, competitors must maximize cold storage energy efficiency, sample integrity and access, risk prevention, and cost savings.

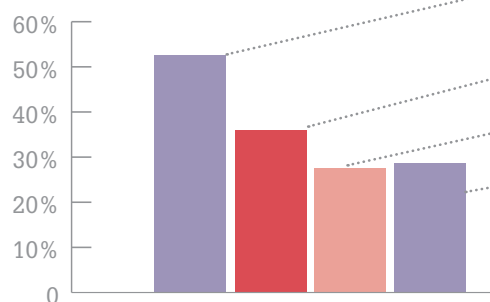
Sign up is available throughout the competition period – and it’s free to take part.

Labs receive points for taking best practice actions, such as defrosting freezers, cleaning out unneeded samples, and using high density storage. The lucky 2022 champions will receive a certificate, have their lab name and photo published in as-yet-unconfirmed online publication (in 2021, it was Nature), and will be recognized at the annual I2SL conference in mid-October.

*Find out more at [www.freezerchallenge.org](http://www.freezerchallenge.org)*

Around **445 million** prescription items are thrown away each year at a cost equivalent to over **\$400 million** to the UK’s National Health Service

### Patient confessions



- ✕ 52% over the age of 55 do not throw away unused or out of date medicines
- ✕ 36% of people have taken out of date medicine
- ✕ 28% borrow medication from friends
- ✕ 29% admitted to taking medicines not prescribed for them; of these, 41% were high earners



## Gearing Up for the 2022 Power List and More

**Award Season is rolling in. Don't miss out on submitting nominations for the Power List and voting for the Company of the Year Awards**

2022 is well underway, and with the new year comes a new arrival: The Medicine Maker Company of the Year Awards. Our old faithful Power List is back too, and now it's more exclusive than ever. Entries are already open, and the clocks are ticking. Are you excited? We're excited! Read on for more information, and links to the relevant voting pages.

The Company of the Year Awards 2022 We're gearing up to celebrate the best companies in the pharmaceutical industry across six categories:

- Best Big Pharma
- Best Biopharma Equipment Company
- Best CDMO
- Best API Supplier

- Best Processing Equipment Company
- Biggest "Talking Point"

We've used various sources to select the top ten contenders in each category (but you can suggest alternatives) so now it's over to you to vote for the companies you want to see crowned the winners. Ballots close on March 17 2022, so head on over to the voting page ([tmm.txp.to/coya-intro](http://tmm.txp.to/coya-intro)).

The Medicine Maker Power List 2022 Of course, individual human beings matter too. As ever, we want to celebrate the most inspirational and influential

medicine makers out there, and we want to hear who you think they are. Head over to the nominations page ([tmm.txp.to/pl-2022](http://tmm.txp.to/pl-2022)) and drop a name into our judging pool. We're looking for ten winners in each of our three categories:

- Small Molecules
- Biopharmaceuticals
- Advanced Medicine

As with the Company of the Award, voting closes on March 17 2022. All winners will be announced in April.

*Questions? Contact [stephanie.sutton@texerepublishing.com](mailto:stephanie.sutton@texerepublishing.com)*



## Predicting Ports in a Storm

**New Swiss-American research could make gene editing a less dangerous affair**

Researchers from EHT Zürich and the Wyss Institute at the Harvard Medical School have found a way to make advanced therapies safer, more efficient,

and more predictable. Their technique works by using bioinformatic screening to predict and validate "genomic safe harbors (GSHs)". These are "landing sites" in the human genome that can house incoming therapeutic genes without triggering dangerous side effects. In their work, the scientists identified almost two thousand potential "harbors", and then narrowed this down to two sites: Rogi1 and Rogi2. They then confirmed the durability and safety of these two sites by observing

long-term transgene expression and the absence of the upregulation of cancer pathway-associated genes following transgene insertion.

### Reference

1. E Aznauryan, *Cell Reports Methods*, 2, 1 (2022). DOI: 10.1016/j.crmeth.2021.100154

*Credit: Michael Dam/Unsplash.com,  
Margarida C Silva/Unsplash.com*



## IMAGE OF THE MONTH

*Fishing for COVID-19 Therapeutics*

University of Wisconsin-Madison Graduate student Joseph Gallant feeds nurse sharks being used in US-Scotland anti-COVID-19 research. Read more on page 50.

*Credit: Bryce Richter*

<https://bit.ly/shark-VNARs>

Would you like your photo featured in Image of the Month?

Send it to [angus.stewart@texerepublishing.com](mailto:angus.stewart@texerepublishing.com)

## QUOTE of the month

*"The reality is that a novel excipient is currently only adopted and used in a drug product if everything else fails. We are really keen to change this dynamic because it doesn't help the patient, who deserves the most optimum drug therapy."*

Nigel Langley, Global Technology Director for BASF for the pharma solutions business and Chair of IPEC-Americas, speaking about the important of a regulatory approval pathway for novel ingredients. Read more on page 30.

## Farewell to the Annual Flu Vaccine?

**Can newly discovered antibodies finally bring us closer to universal flu vaccines?**

Scientists from Scripps Research, University of Chicago, and the Icahn School of Medicine at Mount Sinai has identified key flu virus antibodies that could expose vulnerabilities in the protein structure of hemagglutinin and lead to the development of a universal flu vaccine (1). While analyzing blood from people with flu immunity, the team identified 50 new antibodies capable of binding to HA's "stalk". To their surprise, many were commonly found in the human body, which could help future vaccine development.

The antibodies recognized a variety of influenza strains, including the swine-derived H1. The team believes their findings will help in the development of pertinent "pan-H1 vaccines to prevent the next influenza pandemic."

### Reference

1. J Guthmiller et al., *Nature* (2021).  
[Online ahead of print] DOI: 10.1038/s41586-021-04356-8.





## Inspections in a Very Digital World

**Millions quickly adapted to video calls, online shopping, and social distancing during the COVID-19 pandemic, but the pharma industry has had a harder time adapting to rigorous remote inspections**

*By Garry Wright, European Laboratory Compliance Specialist at Agilent Technologies*

The world of regulatory compliance continues to evolve at a rapid pace, with new guidance and expectations being introduced on a regular basis. Throw a global pandemic and accompanying restrictions into the mix, and site-based inspections by regulatory authorities have to take a hit. In fact, the US FDA only performed 6,260 in 2021 (6,099 domestic and 161 foreign inspections) (1) – a reduction of 61 percent compared with pre-pandemic inspection numbers of over 16,000 (2019).

Many regulatory authorities started using risk-based approaches to inspections during (and in some cases even before) the pandemic to maximize productivity, particularly as restrictions came in. For example, regulated companies with previous non-conformance observations are considered “high risk” and are prioritized for a site-based inspection using the local authority through Mutual Recognition Agreements (MRA) or are assessed via remote inspection (2). Companies with acceptable compliance track records are considered “low risk” and have had GMP manufacturing certificates extended until travel restrictions are

removed, and site-based inspections can resume.

Much like other industries that had to adapt to the COVID-19 pandemic – whether it was ecommerce, remote working, or telehealth – digital workflows provided the key to unlock remote inspections. Within three months of the pandemic being declared, several regulatory authorities like the US FDA, UK MHRA, EMA, and Japan’s PMDA were performing remote inspections and sharing knowledge and best practices with other authorities through the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) network who quickly followed suit.

Remote inspection strategies use modern technology to transform the traditional approach for onsite inspections. For instance, tablets and smartphones can be used to provide the inspector with a virtual tour of a manufacturing or laboratory facility using live video streaming. The inspector can see and understand the design of the facility that is being inspected, directing the tablet or smartphone operator to inspect areas of interest. The inspector can also interact with facility staff to ask relevant questions.

Document and data reviews still form a major part of a remote inspection, but companies can now share electronic formats using secure information sharing

### In My View

*Experts from across the world share a single strongly held opinion or key idea.*



platforms. Inspectors are taking an active interest in digital workflows and electronic data handling, sometimes also requesting access to supporting metadata, such as audit trails for supporting data validity, which makes it easy to determine whether any data manipulation or falsification has taken place.

Every year, regulatory authorities publish data on the types of non-conformances observed during their inspection program the previous year (3-5). The most common non-conformances observed within regulated laboratories relate to data integrity and software.

Most data integrity warning letters issued in the last 24 months relate to companies still using paper-based systems and older versions of software without the necessary technical controls

for remote inspection. Warnings have also been issued for companies using software in a basic capacity for data acquisition and manually performing data processing, reporting, review, and approvals outside of the software. The latest regulatory expectation asks companies to have access to modern software with latest data integrity controls, which ensures the complete workflow is performed within the software, providing full traceability of all activities.

Put simply, digital workflows – enabled by modern software – put companies in the safest position from a regulatory risk perspective.

And what about the future of inspections? In my view, the digital laboratory is the “new normal” mode of operation for regulated companies. We

should expect – and be prepared for – digital workflows and electronic data to be the focus of future inspections performed during 2022 and beyond. Remote inspections are the most productive way for inspectors to identify data manipulation and falsification, and to confirm the quality of drug products being manufactured.

#### References

1. FDA Data dashboard, “Inspections” (2022). Available at <https://bit.ly/3H28m3H>.
2. EMA, “Mutual Recognition Agreements” (2022). Available at <https://bit.ly/3GPUoS4>.
3. FDA, “Inspectional Observations” (2022). Available at <https://bit.ly/3AbjHKl>.
4. FDA, “Warning Letters” (2022). Available at <https://bit.ly/3GOO4u7>.
5. Eudra GMDP Non-Conformances (2022). Available at <https://bit.ly/32WJCuG>

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## The Value of Dogged Determination

**How companies can strengthen their supply chains when presented with unprecedented challenges**



*By Banks Bourne, Founder and CEO of Tanner Pharma Group and Bourne Partners*

Our industry's supply chains have been subjected to unprecedented headwinds in the last two years. Drug/vaccine developers and manufacturers must constantly be alert to potential disruptions and proactively find ways to prevent, or at least minimize, delays in the availability of raw materials and technologies needed to produce medicines for patients around the world.

But supply chains aren't just about procuring raw materials. We also need to get the final drug product to the patient. Whether due to bureaucratic red tape, logistical roadblocks, or a lack of communication among stakeholders, medications that cannot physically get to the patient are of no benefit. And though various types of regulatory-approved access programs allow patients to get medicines in geographies where they aren't commercially available, success relies on the willingness and cooperation of many stakeholders, the ability to navigate complicated supply chains, or, in

some cases, the need to create new supply pathways where none currently exist.

Undoubtedly, the pandemic reinforced the benefit of having proven, foundational operating principles that could be relied upon when facing not only access challenges but supply chain issues of all types. To minimize the effects of future disruptions, companies will have to consider how they will continue to reimagine and strengthen their supply chains.

In my view, focusing on relationship building with like-minded organizations is one of the most important factors for continued improvement. At Tanner Pharma, we had an existing relationship with a company in Bolivia that handled the "last-mile" logistics for a cancer drug being shipped from Switzerland; their role was to ensure timely and safe delivery to several institutes in different cities. Due to the worsening political and economic climate in the country, however, the company shut down operations. This company connected us to another that had good standing in Bolivia and was willing to work with us on a no-cost basis. They would receive the medication, break the shipment down, and deliver it for free because they believed in what we were doing and recognized the need faced by patients and physicians. Discussions with this new partner established confidence in their ability and commitment to the program, and formed the basis for a trusting relationship.

The situation highlighted the importance of developing robust relationships grounded in a common mission. Building good, robust relationships during the pandemic has been challenging because of reduced travel and limited opportunities for face-to-face interactions. But organizations should not be deterred by these constraints; it is important to seek creative ways to understand the mindset of potential partners and to get relationships in place before the next crisis strikes. You also need to have contingency plans. Early in the

pandemic, a US-based pharmaceutical company we worked with needed to get a drug product to Belgium for a clinical trial where it would be evaluated as a potential COVID-19 therapeutic. At the time, it was unclear what impact the pandemic would have on air transport. Given this uncertainty, and the need to ensure supply for the trial, we made the decision to pre-position stocks with partners in the UK and Germany to avoid exposing the trial to risk from a possible shutdown of US airports. Again, having pre-existing relationships with these trusted partners was critical. Though it is impossible to envision all contingencies, considering what might lie ahead enables organizations to remain flexible as events unfold.

Finally, I would like to emphasize the importance of having the determination and courage not to take "no" for an answer! Consider the case of a prominent non-governmental organization (NGO) that needed to move medical supplies and medicines from China into a remote region of Kazakhstan – more than 1200 kilometers from the capital. The initial request for supplies and a grant to the NGO had come from a multinational corporation that wanted to provide protection for its employees. Airports were closed. Rail options were deemed to be insufficiently secure. Despite these obstacles, we were able to identify an air freight partner and negotiate with the government to have the airport reopened. Our team also worked to ensure customs officials were available to receive the shipment and arranged for road transportation from known and trusted freight forwarders. The lesson here is that there must be a desire to battle any obstacle and a corporate culture that supports and encourages the relentless pursuit of solutions.

The COVID-19 pandemic will have a lasting impact on the industry. Hopefully, more than a little of its impact will be positive, leaving us better prepared for what the future might hold.



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## Regionalizing – and Democratizing – Cell and Gene Therapy

**How Merck and SaudiVax are working together to help patients in the Middle East and North Africa access the benefits of advanced medicine**

Many of the world's biggest gene therapy producers are based in the US or Europe, but what does that mean for patients across the globe? SaudiVax, based in the Kingdom of Saudi Arabia, aims to increase access to gene therapies and other key biologics for patients in the Middle East and North Africa. To achieve this goal, the company is working with Merck to design a state-of-the-art manufacturing facility. Here, we speak with Mazen Hassanain, Managing Director at SaudiVax, and Merck strategy consultants Ratish Krishnan and Nargisse El Hajjami to find out more.

**Why is it so important for SaudiVax to bring cell and gene therapy to the Middle East and North Africa?**

*Hassanain:* There are major unmet needs related to diseases that are either endemic or common in the region but not necessarily of high interest to multinational biotechnology companies. At SaudiVax, we are working hard to attract and recruit talent who can help us close that gap – supporting the region by developing cutting-edge therapeutics based on the most up-to-date scientific knowledge, regulations, and manufacturing technologies.

In the region, consanguineous marriage is common. It is socially and culturally acceptable. However, this has resulted in clusters of certain genetic diseases – not all of which are well known in the international arena. The kingdom's genomics scientists have shared their insight in some of the world's major genetic journals; as a result, we have discovered genetic mutations that are commonly inherited among certain families in the region. Gene therapy is a potential solution to some of these chronic illnesses, so there is a great deal of interest in establishing development and manufacturing capacity. Of course, building such capacity is a highly complex endeavor – and that's why we are leaning on collaborations, including our partnership with Merck.

**How did SaudiVax and Merck come to collaborate?**

*Hassanain:* I first met the Merck team around three years ago – and since then we have been learning more about one another. We have conducted workshops together in the region, and built bridges between our different teams in engineering, science, manufacturing, regulatory, and more. We've also been connecting with different stakeholders in the kingdom, including the government and regulators.

We've already collaborated on projects, including the first cell and gene therapy feasibility study, which showed how such an industry could bring value to both patients and corporations. We've now signed a detailed letter of intent whereby Merck will be supporting SaudiVax in the establishment of its facility here in Saudi Arabia, which will become a regional cell and gene therapy hub. Our journey will demand a combination of designs, facility, equipment, people, and regulatory experience – and Merck will be supporting us in all of these aspects.

**How exactly will Merck be supporting those aspects of the project?**

*Krishnan:* When we met Mazen's team through our commercial lead in KSA and learned more about SaudiVax, we realized they had an impressive objective to accomplish as part of Saudi Arabia's Vision 2030. We pride ourselves in solving our customers' toughest and most complex problems in bioprocessing. Merck has the products required for these processes, including purpose-built-products for cell and gene therapies or viral vector manufacturing, as well as fit-for-purpose products – such as technologies that have been built for traditional bioprocessing for monoclonal antibodies (mAbs) and vaccine modalities which can also benefit gene therapy manufacturing. We also provide services in characterization, cell banking, and testing, as well as the manufacturing angle with our CDMO which makes Merck a strong partner in commercializing these therapies.

We look at cell and gene therapy from a holistic point of view; success to us is not just about providing products and services. We also cherish our relationships with customers, who see us as a partner in their commercialization plans, rather than as a vendor they have a transactional relationship with.

*El Hajjami:* Ratish summarized it very well. More generally, our main focus is to empower the cell and gene therapy field and to support localization. Over the years, we've formed many collaborations with industry stakeholders, institutes, and research labs to support the continuing R&D, process development and manufacturing of these novel therapies.

Crucially, we can support customers in all aspects – from the design of the facility with all necessary equipment through to running the facility. This can include cell line development, all the different process development steps, and optimization of the overall process as well as testing services, regulatory





Merck provided end-to-end engineering services and facility design to support SaudiVax in developing their viral vector manufacturing from development through commercialization.

guidance and consultancy. Key is our ability to share our broad process expertise via technology consulting, education, and training. Cell and gene therapies are new, so it is vital to build local expertise and train the trainers, who can then continue to transfer knowledge throughout the region.

*Hassanain:* The end-to-end approach that Merck provides is, put simply, what differentiates a strategic partner from a simple vendor. When I first met Merck, I explained that we were not looking for vendors – we were looking for partners. Our project is not just about acquiring services and equipment; we need to consider every aspect, including people, skills, processes, techniques, and technology – and a facility that is adaptive continuously developing technology. I admit that it is a complicated mission and many companies in the world are competing to be at the frontier of the gene therapy industry. SaudiVax strives to be the leading company from the MENA region. Strategic partnerships are important to not only make the project

a success, but to ensure it sustainability and adaptability to serve the healthcare systems as they evolve.

How is gene therapy perceived in the Middle East?

*Hassanain:* With the recent breakthroughs, there are high levels of excitement; and the interest is huge! And the potential demand for gene therapies is really beyond imaginable at this point as a result of the development work being done with gene therapy in North America, Europe, and other countries which is inspirational. Of course, there are some concerns around access. And some members of the public have also been worried about scientific safety – but this is alleviating as time goes on and as more therapeutics are released. Ultimately, multiple pathologies could be completely eradicated with gene therapy. And that's not just exciting for patients but also for healthcare providers and payers.

*El Hajjami:* The demand and interest in cell and gene therapies in the Middle East region is really high because of the genetic diseases experienced by the population.

It's fantastic to see companies like SaudiVax thinking outside of the box and working to localize such novel therapies and develop the necessary knowledge and expertise. We are very happy to support them in their endeavour.

*Krishnan:* I don't think the excitement is limited to the Middle East region – globally, gene therapies are heralded as potentially curative and a true sense of hope to patients suffering from rare and ultra-rare diseases! Gene therapies represent an area of high investment year over year, and viral vector bioprocessing continues to advance. I also think the COVID-19 pandemic has helped all of us better understand the importance of localization in manufacturing. The Middle East, like most regions, has perhaps been dependent on supply from other countries in the past, but the scenario is changing gradually. Merck has a great deal of experience in bioprocessing and we hope that this helps companies like SaudiVax leapfrog some of the learning curves to quickly commercialize high-quality therapies to patients in need.





# THE NEXT LEVEL

The landscape for making medicine is changing. New tableting technologies, better bioreactors, AI-enabled drug discovery, 3D printing... and the boundaries continue to be pushed. We're now seeing FDA-approved therapeutics that transcend traditional pills and injections. Get ready for medicine making level 2 as video games come to healthcare – backed with clinical trial data that demonstrate their efficacy.

*By Stephanie Sutton*



## STEPPING UP THE GAME

### How Akili won FDA approval for EndeavorRx – the first “game-based digital therapeutic” for children with ADHD

In June 2020, the FDA granted marketing authorization to EndeavorRx for children aged 8 to 12 years old with ADHD. New therapeutics are approved by the FDA all the time, but this one broke the mould. Rather than popping pills, patients race around alien worlds saving lifeforms from extinction...

But how can a video game ever work as well as a drug treatment that chemically or biologically elicits a therapeutic effect? First, the video game is just the way the medicine is delivered, like a capsule or syringe delivering a pharmaceutical API. Underneath the game are patented stimuli and algorithms designed to target the areas of the brain that play a role in attention function.

The game isn't intended to be a stand-alone therapeutic – and the company has stressed that it's not a substitute for a child's medication. But Akili Interactive, the company behind the innovation, has delivered compelling evidence that shows how EndeavorRx improves attention function in children with ADHD, as measured by the Test of Variables of Attention (an FDA-cleared objective test of attention), as well as other assessments such as reports from parents and physicians. Studies were conducted in more than 600 children – and, perhaps unsurprisingly, there were no serious side effects (although adverse events included frustration, headache, dizziness, emotional reaction, and aggression) (1).

Video games don't have the best reputation in certain circles. For as long as video games have been around, there have been concerns about how they impact children. But with video games continuing to increase in popularity, some researchers have started to focus on the positive side. Studies have emerged showing how video games can improve mental health; for example, a paper published in 2021 by researchers at the UK's University of Oxford claimed that video gameplay was positively correlated with mental health (2).

Also in 2021, scientists from UC San Francisco's Neuroscape translational neuroscience center reported that they had developed a virtual reality video game that could potentially help improve memory in healthy, older adults (3).

But the approval of EndeavorRx really takes the game to the next level. Here, I ask Anil Jina, Chief Medical Officer at Akili Interactive, how the approach works and why gaming should not be dismissed as a gimmick when it comes to neurological disorders.

What's the story behind Akili Interactive?

It started when our co-founders, Adam Gazzaley (Chief Scientific Officer), Matt Omernick (Chief Creative Officer), and Eddie Martucci (CEO) found themselves thinking about the same problem – but from different angles. On the science side, Adam was (and still is) a neurologist with UC San Francisco. He heads up the university's translational neuroscience center, Neuroscape, and has written books around the cognition crisis. Our cognition is being bombarded and declining due to various intrinsic and extrinsic reasons. Adam wanted to find ways not only to assess this but also to improve cognition. Cognitive training does exist, but the tasks are usually delivered in a human way, on a one-to-one basis, and you cannot deliver multiple tasks simultaneously. Adam wanted to find ways to deliver different cognitive tasks together, but the only way to do this is to make it digital.

Adam then met Matt Omernick, who comes from the gaming world and has experience in big gaming houses on the US west coast, including EA and Lucasfilm Games.. Matt explained that there was a trend in the tech sector exploring gaming for good, as well as interest in using video games to help improve generic cognition and attention. Eddie Martucci is a biologist by training and comes from the venture capitalist side in Boston; after seeing the research, he became very interested in the concept. And that's how the three of them linked up – and how Akili Interactive began.

To an extent, cognitive function is practiced almost daily. For example, I'm having to concentrate on this video call with you right now. I have to ignore my wife, who is on a Zoom call in the other room, and I have to ignore all of the things on my desk. There may be other things in the home that I have to ignore too. A more intense example? Consider playing a sport like soccer. You need to think about the ball, think about the other players, think about movement and space, think about how you handle the ball, how you position your hands and feet – all while abiding by the rules of the game.

In 2013, Adam co-authored a paper in *Nature*, which made the cover and distilled a lot of research about cognition, multitasking, and the potential of using a custom-made video game to enable cognitive training and improve multitasking performance (4). Ultimately, the paper showed that it was possible to formally embed cognitive tasks from the ground up in a video game. A custom designed game was used to assess the cognitive performance of players – and it showed a linear, age-related



decline from 20 to 79 years of age. We all know that cognition declines with age – which is disappointing for everyone – but the game specifically showed that it was a steady decline.

The paper also showed that when the 60 plus age group was “treated” using a specially designed game for a month (about a half an hour a day; five days a week), their cognition improved and, crucially, was sustained for six months. This provides evidence of a neuroplastic effect – something happens in the brain cells and pathways that enables the cognitive training to embed itself, rather than just disappear. All of this is very different from drug development, where you have a molecule and receptor that bind together, exerting an effect that lasts until the drug is metabolized or actively released.

The researchers also looked at EEG data and saw that the brain activity promoted by gaming was in the prefrontal cortex – the location of the attention networks. After a month of playing, older adults showed a different picture of neurological activity compared with before playing. Notably, the activity was similar to that in the baseline 20–40 year old group. Players who received all the tasks

at once – forcing them to multitask rather than playing different subsets of the game – saw the largest improvement.


All of this research fed into Akili’s strategy. Gaming and medical specialists were hired to work together on the task of developing a game as a medical device. Here, I’d like to note that the development of the game followed the same rigorous development as a drug in terms of clinical trials with clinical endpoints.

In June of 2020, we obtained regulatory clearance from the FDA for EndeavorRx to be prescribed for children aged 8 to 12 years old with primarily inattentive or combined-type ADHD who have demonstrated an attention issue (5). This isn’t meant to replace ADHD drugs that are working for some kids, but it’s a great new option that parents can turn to as part of their child’s treatment.

Did you face any scepticism at the outset?

There was a lot of scepticism about using gaming in such a manner, but we were not deterred. Ultimately, no one fully understands how the brain works – we’re only just scratching the surface of a





lot of the functionality. Given our collective lack of knowledge in this area, it could be considered naïve to assume that a different approach is not viable. And to be blunt, if existing drug therapies are so good, why do we still have cognitive decline and so many neurological issues?

In my experience, there is scepticism or uncertainty around cognition in general. I am a trained physician, so I know that those studying medicine learn very little about the functional aspects of cognition – this is the realm of psychologists, cognitive scientists, and behavioral therapists. But when I worked as an anaesthetist, I often saw people coming out of anaesthesia with cognitive dysfunction – and it would commonly affect older people for longer. When I worked in the neuroscience space on schizophrenia, bipolar disorder, and depression, there was certainly an awareness of cognitive dysfunction – but because no treatment existed it was not a focus.

But the world is changing – and we're now seeing more acceptance of the cognitive deficits presented in many disorders. "Brain fog" is a term frequently used by patients to describe symptoms of various disorders – including those who have recovered from COVID-19. Here, perhaps some type of inflammatory or microvascular mechanism is causing cognitive function to be depleted. For most physicians, this brain fog or decline in cognitive performance becomes almost irrelevant compared with the immense physical impact of the original symptoms/disease. However, if many people in the general population are saying, "I'm not sick anymore, but I can't work or look after my children or go grocery shopping," the impact would be huge. We should not ignore those cases where an improvement in cognition lags behind physical improvement.

There is only so much that doctors can do, but I hope new approaches – for example, home-based cognitive training (potentially using gaming) that adapts to a patient's changing needs – will ultimately be able to help.

*"The development of the game followed the same rigorous development as a drug in terms of clinical trials with clinical endpoints."*

What makes gaming such an intriguing approach for cognitive training?

In short, it's truly new. I was super excited to join the company just over three years ago because it wasn't simply digitalizing an existing medical therapy (there are a lot of digital therapeutics out there that are digitizing traditional cognitive behavior therapy, standardizing and simplifying to improve access. Akili Interactive has created a new therapy that can only be delivered by this game. And nothing else like it exists on the planet!

The game incorporates multiple tasks that deliberately hit different aspects of attention including processing speed, sustained

attention, divided attention, conflict resolution, focus, and interference processing. Cognitive scientists or therapists can measure these with different tests and offer certain therapies but they can't give you something that targets all of these at once. A game can. And it does this in a fun and engaging way that is also adaptive.

Why choose ADHD as your first target?

We looked at several diseases and disorders – and there are a number of areas where we believe our approach could have benefits; however, we had to keep in mind the scepticism we would undoubtedly encounter. We felt it was important to focus on an area where people might intuit that a game-based approach

could work. We didn't want huge leaps of faith – we needed people to think, "Okay – yeah – that actually makes sense."

After much discussion, we settled on children with ADHD for two key reasons. First, children typically love games! And second, our game had been designed to focus on the attention networks of cognition, rather than something like memory. Attention is clearly a critical part of ADHD – and, importantly, established scales and clinical outcomes for ADHD already exist. In other words, if the game could boost the attention network in patients, we should be able to measure the improvement on



the scale. In other disorders, such as schizophrenia, there are fewer scales that measure cognition, so it's more difficult to prove the benefits of therapy.

We met with the FDA to explain our approach and we also shared results from a pilot study. We discussed what could be improved and we agreed on endpoints that made sense from both an ADHD perspective and a regulatory perspective. We did the study and the results were positive. With data from five clinical studies in more than 600 kids with ADHD, the FDA approved the game in June 2020 as a class II medical device. It was such an amazing accomplishment. Sadly, we didn't get to have a celebration party because of pandemic lockdowns!

#### What is the gameplay like?

The meta story for the game is that the player is a space cadet who travels from world to world to participate in missions. Each world has a different landscape and there are certain tasks to accomplish. Often, the planet is collapsing and the player needs to save different alien creatures from extinction. The player must

follow a meandering path – which could be a stream, lava, a road, or even just space, depending on the world – through the level and capture creatures to put in their space farm.

Ultimately, all of this world building is just a mask to disguise a set of challenging cognitive tasks...

The player's avatar rides a hover platform through the level. The road meanders randomly and the player steers by tilting their phone or iPad left and right to avoid hitting the edges. Depending on the level, there may be gates to pass through (like in ski racing) or barriers to avoid. This cognitive navigation task requires sustained, selective attention.

Gameplay also incorporates conflict resolution inhibition. As well as steering and avoiding or hitting certain obstacles, the player is tasked with capturing aliens. At the start of the level, players are shown the different alien creatures that inhabit the world – usually three, but it can increase on the harder levels. They are told to capture just one of them – perhaps the blue one, the spiky one, or whatever. As the player is steering through the level, alien creatures jump at the player from the side of the screen. The player must tap when they





Anil Jina, Akili Interactive

see the correct alien and suppress their urge to tap when they see the others. The game also draws on working memory requirements as the player needs to remember the type of alien they need to capture.

Because a multitude of cognitive tasks targeting the attention network come at the player simultaneously, the player cannot just focus on one aspect – steering or capturing aliens – they must divide their attention between both.

The team has also incorporated other aspects you would expect from a video game. For example, completing levels and tasks earns in-game currency that can be spent on different costumes. Players can also customize their spaceship and unlock additional missions.

Perhaps most importantly, the game constantly adapts and is personalized for each patient in terms of the speed, frequency of the gates and obstacles, and the targets coming at the player. This cognitive load is balanced in a staircase fashion on a second by second basis. If the level of cognitive stress on the attention is too much and the player makes too many mistakes, such as hitting the edges or catching the wrong alien, the speed is reduced. If they are steering really well, avoiding obstacles or hitting the gates correctly, and making the correct no/go decisions on the aliens, the game speeds up.

This is a big difference between EndeavorRx and most standard video games. In a regular game, all players start at level one and require the same level of aptitude to reach level two, level three, and so on. Because EndeavorRx adapts to the player's cognitive function, "level one" will vary from player to player. Some children

with autism and ADHD may be at the lower end of the functional spectrum, but others can be highly functioning. Because the game adapts to ability, all kids can progress to levels that are relevant to them. Once the baseline is set, the game follows an algorithm that tries to challenge and push the player's cognitive function enough to stress – but not overstress. In other words, every child has a meaningful experience, regardless of their cognitive ability.

This "baselining" happens at the beginning of the game, but it also continues throughout the child's gameplay based on data that is collected second by second. The game tries to keep the player at the right level and will adapt if they start to find it too easy or too difficult.

Kids will be kids, and so a few have tried to "game" the game – purposely performing badly at the beginning so that they can start on an easy level and do better. But, like all good game designers, we already anticipated that behaviour, and EndeavorRx quickly adapts to their true ability!

Could the game be used in other neurological diseases – such as Alzheimer's disease?

In every patient population we have studied, we have seen cognitive improvements. The big challenge lies in answering two questions: Would the improvement be clinically meaningful? And would it last? I cannot answer these big questions right now because the studies haven't yet been conducted. My gut feeling is that it's worth trying.

Doctors keep asking us about Alzheimer's, and I think it would be great for us to expand into other areas. The indications we've studied the most are ADHD, multiple sclerosis, autism and depression – and we're starting to publish more scientific and medical data so that others can read and interrogate our findings (6). But I'd like to reiterate that the studies we do are rigorously designed to answer clinical questions – and they are just as robust as the type of studies I would have done in my previous roles at Pfizer, Sanofi, and Shire.

What are your thoughts on the "over-the-counter" equivalent in the world of digital therapeutics?

In gaming, this is known as the wellness space. And there are many companies who have developed consumer "brain-training" games, but they can't make claims from a disease perspective or they'll run afoul of advertising standards and regulatory bodies. For example, such companies cannot say, "This game can improve your cognition, which is important for diseases, such as Alzheimer's." When targeting the general wellness market, you can only talk about common or general health.

Interestingly, there are companies in the wellness space who, perhaps after seeing what we have done, are trying to develop a more regulated version of their product. Equally, there may be the potential to do the reverse too. Personally, I'm glad we've done the hard part first!

The great thing about games is the high safety and minimum

side effects. Yes, there are still side effects, but things like frustration and headache – not in the same league as some drugs. From that perspective, games are well suited to be used as wellness products.

How have traditional pharma companies reacted to your work?

Some have recognized the potential of the space. Shire, for example, which does a lot of work in ADHD, was an early investor. We've also had interactions with pharma companies working in other disease areas.

But some pharma companies are very conservative and see products like ours as fitting in very differently to standard therapeutics. At a consumer electronics show a few years ago, our CEO stated that we are happy to talk with pharma companies but made it clear that we are not the toy in the Happy Meal. A great analogy! His point being that pharma companies make a lot of money on drugs and are always looking for other offerings that could help better position those drugs. We want our product to have the focus and respect that it deserves. We don't want to be a side giveaway to promote greater use of a company's drug.

Healthcare is now evolving beyond traditional providers, pharma

companies, and device manufacturers. The likes of Amazon and Google have an interest in health too. I know one thing: this market is going to change. In the future, I hope – or even expect – to see a greater understanding of the scientific rigor behind products like ours.

Essential last question: Do your employees play the game for fun?

When the game was in development, employees across the company were involved in “testing” But now that we have FDA approval, the game is classified as a medical device and is only available by prescription. If we were focused on diabetes, employees could not try out the insulin! In short, we have put restrictions in place.

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## A PAIN-FREE REALITY

Enter the world of immersive therapeutics – where VR is being explored as an alternative to traditional medicines for pain

Can virtual reality be used to control pain? Yes – and it's already FDA approved. EaseVRx, a prescription-only virtual reality (VR) system used to help with pain reduction in patients with chronic lower back pain, was approved by the FDA in November 2021.

There are many therapeutic options for controlling pain from various medications to implants and surgery, but these approaches aren't successful for all patients and some options can lead to other problems – the US opioid crisis being an extreme example.

AppliedVR focuses on “immersive therapeutics” – particularly using VR. The company's concept relies on flooding a patient's neural system with alternative signals to help them focus on something other than pain, while also helping them to develop skills to cope with it. Since its inception, the company has been building evidence – by working with pain experts, psychologists, and neuroscientists – to show that their VR modality works. The AppliedVR platform includes a curriculum of content, delivered via VR of course, that teaches patients how to manage pain. Is immersive technology truly a new category of medicine? We connected with AppliedVR co-founder and president Josh Sackman to find out.

What research has been conducted to prove the benefits of the VR approach?

There's actually more than 20 years' worth of academic research on using VR for behavior change, but when we launched in 2015, VR was known largely as a gaming and entertainment platform. We've now received two NIDA-funded studies looking at the opioid-sparing impact of therapeutic VR in chronic low back pain and post-operative pain, and ultimately received FDA approval of EaseVRx based on our 2020 pivotal randomized controlled trial (1). All in all, we've had to do a lot of foundational research to establish the credibility leading up to this point.

We published our first feasibility study in 2016 (2), in collaboration with Cedars Sinai. This initial feasibility work tested patient and clinician reactions to the use of a VR device. The responses were promising, so Cedars and many other academic centers started exploring the use of VR in a number of clinical settings, including Children's Hospital Los Angeles for

phlebotomy and IV insertion; Cedars Sinai for inpatient pain management and childbirth; and George Washington University for emergency medicine – as just some examples.

We envisioned a future where every home and office have a VR headset for chronic disease and wellness management. We started working on feasibility studies to demonstrate outpatient use in patients with pain, initially for a single session, then for several weeks of use, and ultimately in our pivotal trial to validate the safety and effectiveness of our chronic pain product in an 8-week trial, with three-month and six-month follow-ups (publication pending).

I hope that our commitment to research as well as the regulatory pathway have really established the credibility needed to establish a new modality of pain care with immersive therapeutics.

What does EaseVRx treatment look like?

EaseVRx delivers pain management training based on cognitive behavioral skills and other behavioral methods. It delivers VR content while incorporating biopsychosocial pain education, diaphragmatic breathing training, mindfulness exercises, relaxation-response exercises, and executive functioning games. The software includes an eight-week, VR-based program that helps people reduce symptom severity and the impact of their pain. The immersive environment and content of the program provides immediate relief while allowing users to actively engage in skill-building exercises to cultivate enhanced control over pain. Users are motivated to shape their central nervous system by repeatedly interacting with the virtual environment via their breath and attention.

By following the treatment program for two months, patients should see clinically meaningful and lasting reductions in pain intensity and pain interference.

What sets your approach apart from traditional cognitive behavior therapy?

EaseVRx shares many of the effective therapeutic principles of cognitive behavior therapy applications in chronic pain. For example, both treatments focus on developing skills to cope with unhelpful thought patterns and feelings of helplessness, which are common with chronic pain, and help



empower people to have better control over their pain.

However, our approach is to build skills within an immersive, highly engaging virtual environment. Our data from multiple studies show that our immersive treatments for chronic pain yield effect sizes that exceed those reported for other studies involving multi-session behavioral medicine treatments for chronic pain. The extant VR literature suggests that enhanced learning and positive neuroplastic changes are key mechanisms of actions for VR treatments; and our future research will directly study the treatment mechanisms of EaseVRx.

In addition, on-demand access to treatment is a clear advantage over other therapies, such as cognitive behavioral therapy, which rely on a scheduled appointment and a live instructor.

Can you talk about the data you needed to gain FDA approval?

The FDA evaluated the safety and effectiveness in a randomized, double-blinded clinical study of 188 participants with chronic lower back pain, who were assigned to one of two eight-week VR programs: the EaseVRx immersive 3D program or a control 2D program that did not use skills-based CBT methods of treatment. After enrolment, participants were followed for a period of 8.5 months in total – from baseline to end of treatment. We also followed up on months one, two, three and six post-treatment.

At the end of treatment, participants in the EaseVRx group, on average, reported clinically meaningful improvements, including a 42 percent reduction in pain intensity, a 49 percent reduction in activity interference, a 52 percent reduction in sleep interference, a 56 percent reduction in mood interference, and a 57 percent reduction in stress interference.

At the six-month follow-up, all participants in the EaseVRx group continued to report a 30 percent or greater improvement in pain intensity and pain interference. In contrast, the control group reported a reduction in each pain measure below 30 percent.

What's the most rewarding feedback you've received from patients?

We are truly grateful for the numerous patients who have shared their stories and the impact that our immersive therapeutics have had on their lives. Here are just two that I welcome readers to look into.

1. A video featuring Bob Jester, who ended up paralyzed below the waist and in excruciating pain after an accident (3).
2. Madora Pennington frequently shares her thoughts on the treatments she has tried for her Ehlers-Danlos Syndrome and life after disability (4). In this video, she explains how VR disengaged her brain from the pain perception cycle at a much deeper level.

You've gained FDA approval – an exciting milestone. What's next for AppliedVR?

First, we'll be making EaseVRx available in the US on a limited basis through select providers toward the middle of 2022.

Overall, we are focused on making prescription immersive therapeutics accessible to all. And that means building out the infrastructure required to distribute this next-generation

modality at scale. Ultimately, our vision is to have a VR headset in every home in the US and beyond! And to essentially create a VR pharmacy that dispenses both our own and third-party VR prescriptions.

As the next big step toward our vision, we are starting to work with both commercial and public payers to establish the reimbursement pathways. As part of that, we are launching the largest health economics and outcomes research study of its kind in immersive therapeutics. We are also working to expand our label beyond chronic lower back pain.

*“Our approach is to build skills within an immersive, highly engaging virtual environment.”*

What interest have traditional pharma companies shown in the field?

Pharmaceutical and medical device companies have taken a large interest in the digital therapeutics space. Managing complex chronic diseases often requires a multi-modal approach to treatment; medications alone are rarely enough. Digital therapeutics are unique in that they are effective while low risk and do not interfere with pharmacological interventions. A few examples in this space are the partnership between Otsuka and Click Therapeutics for major depressive disorder, Sumitomo Dainippon and BehaVR for anxiety disorder, and Sanofi and Happify for multiple sclerosis. We expect to see many more partnerships between immersive therapeutics and pharma/device companies in the future.

*The full reference list can be viewed in the online version of this article at [www.themedicinemaker.com](http://www.themedicinemaker.com)*

## UNDERSTANDING BAD BEHAVIOR

### Can games be used to predict human behavior – such as unethical decision making in a production environment?

In the previous two articles, we examined how gaming technology can be used as treatments for certain patients, but could gaming have an impact on the pharma industry in other ways? As part of her PhD, Heather Campbell used video games to study human behavior when making decisions about the quality production of drugs. After all, a company can have the perfect machinery and perfect chemistry – but, in manual processes, human behavior can change everything. Campbell's supervisor, Robert Lodder, a Professor in the Pharmaceutical Sciences Department of the University of Kentucky College of Pharmacy, explains, "Games can help predict what people will do. If you want to know how people are going to break your system, try playing some serious games."

So can games really tell us how people might break a drug quality system?

### FROM ANALYTICAL CHEMISTRY TO COMPUTER

With Robert Lodder

I received my PhD in analytical chemistry from Indiana University Bloomington, but I really enjoyed combining computers and chemistry. Over time, I became good at using computers, and I even won first prize in an international IBM supercomputing competition in the life science division. I've spun out a few drug and medical device companies from academia, and I've also worked on projects with the likes of DARPA and the Department of Homeland Security. For example, Homeland Security had an analytical method they wanted to test to look for chemical weapons being placed in the US food supply. We came up with a gaming approach that used simulated attacks to test their method (in some cases proving the analytical method wouldn't work).

Such gaming approaches can be used in many different industries – and I've been working with Heather to show how gaming can be used in drug quality.

The University of Kentucky Hospital is the only hospital in the US that has a regular, full-time program analyzing incoming injectable drugs before they are used. The program was launched in late 2019 and testing began during the pandemic. The program has found a number of potential problems that have already been reported to the FDA through



MedWatch and Citizen's Petitions as well as published. Pharma companies must adhere to GMP and GLP – and there are regulatory inspections to enforce this. In her research, however, Heather read that Valisure (a company in Connecticut that tests oral dosage forms) found around 10 percent of drugs have something wrong with them.

Drug companies often buy their ingredients from China or India. Companies will look at the label, the chain of custody, and then test the ingredient, too, before using it. On the other hand, when a pharmacy receives a drug, they look at the label and the chain of custody only – and then use the drug. If we want to eliminate the last 5 to 10 percent of problems, pharmacies need to test drugs on-site before they are used. And if the drug isn't right, they need to send it back to the manufacturer and tell them to try again! We should not assume that everything is equivalent. Generics, for example, are all assumed to be the same as the brand product. During the pandemic, the FDA halted foreign and even many domestic inspections. Even in normal times, there are still things an FDA inspection won't always catch (like the employee running down the hallway with bags of shredded documents as described in Catherine Eban's book, *Bottle of Lies*). Many inspections are announced beforehand so companies will be able to prepare. In other words, there is always a danger of low quality drugs entering pharmacy supply chains. Counterfeit products are also an issue.

Even at our hospital, we don't have the manpower, space, or equipment to test everything when it arrives so we prioritize drugs for testing. Some of the considerations include the manufacturer's Form 483s from the FDA, whether the company is the sole source of a drug, how much a drug costs and how profitable it is to counterfeit, among other things. Typically, however, that information can be months or even years old. Current prediction models tend not to fare well when faced with unexpected events – like the COVID-19 pandemic. They are also not always good at predicting human behavior.

Heather's work looked at how a serious gaming approach could simulate how humans react in a pharmaceutical environment. If we can understand how humans behave – and the quality shortcuts they may take in the pursuit of profit – it may help us to understand where the biggest risks lie and help to improve current risk prediction models.

## A GAME TO TEST ETHICS

With Heather Campbell



My undergraduate degree is in mechanical engineering and then I opted for a PhD in pharmaceutical sciences. At first, I was in a formulation lab focusing on spray drying and traditional pharma stuff, but then I started working with Robert Lodder. He suggested that I do something with games for my project. "Games?" I thought to myself. "What on earth can we do with games?"

I initially thought about a way to simulate the spray dryer, but the industry already has that kind of simulation technology for manufacturing. Games are really about humans and can allow you to model human decisions, so I thought about it some more – and how human behavior and decisions can affect drug quality.

I programmed a Python shell and combined it with an off-the-shelf video game: Big Pharma. Big Pharma is a game released by Twice Circled where players build and run a pharmaceutical factory. They have to build processing lines, choose different ingredients and make different APIs in the right concentrations. There are also different aspects to the game, such as marketing your drugs. You can even make the API concentration lower than it should be (and sell it to your customers!). And yes, you can commit various types of management fraud too, including concealing clinical trial results. It was something I could get started with quickly rather than inventing a new game from scratch.

The custom Python shell kicks in every now and then during gameplay by stopping the game and adding different activities – many of which are SOP related. For example, a pop up message might say, it's time to inspect the equipment, or perform cleaning. It may also flag other problems, such as rust particles in products or record keeping issues. Players can choose to ignore the message, take action, or, in some cases, fire the person who raised the problem. Taking action to remedy a problem or conduct maintenance or inspection costs money – just as it would in real life. There were also options for workers to leave early or to sign off on cleaning without actually doing it.

And herein lies the problem – unethical practices can be rewarded with monetary gain (until you get caught!). Doing things properly and adhering to quality standards doesn't always come with visible rewards.

We had pharmacy students play the game – and most of them were very good and ethical even though the player



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with the highest profit won the largest cash prize! Obviously they are trained to do things properly (and I think they were aware they were doing this in front of a professor!). But there were “cheaters” who made some very unethical decisions. And these players did a lot better in terms of profit than our ethical folks. In many cases, they were selling sub-potent API (active pharmaceutical ingredient) and engaging in substantial price hiking.

We had students play through three different game variations. In the first game, the aim was to make the most profit. In the second game, players had to gain the most quality points. The third game asked players to maximize profit and quality. Those who engaged in more unethical practices had the largest profit, but rewarding quality with quality points did help improve the behavior.

I have also been working on a second, more detailed game, which more closely resembles a real 3-D pharmaceutical production environment. You have to scan your badge to enter the lab and will have to put on cleanroom gowns in classified areas. You can look at the equipment, inspect it, adjust valves, among other conventional procedures. There will be scenarios where the equipment is filthy – and you will need to ask if you have enough hands to clean it. It’s about replicating scenarios that may come up in real life. This game will provide a deep dive into the shortcuts people might take. Do you rush your cleaning and go home early? Or do you stay late and clean the tank properly?

#### What’s the score?

People can (and will) take far more risks in a game because there are no real world consequences. When real patients and lives are involved, we all want to believe that manufacturers will take the highest care. But there is no getting away from the fact that the results from Campbell and Lodder’s game are familiar. Sub-potent APIs are a relatively common occurrence in the industry – whether through genuine manufacturing errors, operator error, or a more devious management strategy to save money. In 2020, for example, a drug quality study at the University of Kentucky found impurities and low levels of API in the injectable diuretic, acetazolamide (3). According to

Campbell’s research, two of the companies selling the subpotent versions of the medicine were also selling substantially higher compared with another version of the drug, which remained on the market without quality issues. Interestingly, the same scenario was seen in the gaming situation, with many players choosing to sell their sub-optimal APIs at significantly hiked prices. Campbell also notes other studies that have observed higher prices for low quality drugs (4).

The conclusion may be a sobering thought for pharma manufacturers: the drive for profit can lead to problems, especially when companies prioritize profit over patient safety. Currently, all generics are assumed to be equivalent

and companies compete only on the basis of price. Campbell and Lodder suggest that a system that rewards quality could have real-world benefits. Testing such a system in reality would be expensive and time consuming, but here we have a virtual gaming approach that shows how it could work. Pharma companies are still run by humans – and the simple truth is that humans need to be motivated.

And even if we can’t adequately reward quality or identify all potential culprits, the results from gaming scenarios could at least lead to better risk models – either for pharmaceutical companies themselves or regulators or labs performing limited independent analysis, like the Drug Quality Study (DQS) at the University of Kentucky Hospital.

What lies ahead? Campbell is moving on to start a career in drug quality. Meanwhile, Lodder is thinking about running a larger experiment using gaming to explore drug quality using a gaming tournament approach. He also says that people shouldn’t be quick to dismiss the work as a gimmick. He says, “After all, flight simulators have been used for years to successfully train pilots. What about simulators to teach people to make better drugs?”

*You can read Campbell and Lodder’s paper in full at <https://bit.ly/3LdD3VY> or Campbell’s full dissertation at <https://bit.ly/3ryvXnf>.*

*The full reference list can be viewed in the online version of this article at [www.themedicinemaker.com](http://www.themedicinemaker.com)*

*“This game will provide a deep dive into the shortcuts people might take. Do you rush your cleaning and go home early? Or do you stay late and clean the tank properly?”*

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# MOVING AWAY FROM “QUALITY BY FEAR”

Fear of the unknown has made pharma companies reluctant to use novel excipients. And excipient manufacturers – due to uncertainty in realizing business benefits in developing new excipients for pharma are reluctant to make significant investments. The result? Limited innovation in novel excipients to support the new drug modalities coming through industry pipelines – and less than optimized drug formulations reaching patients.





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*In September 2021, the CDER launched a Novel Excipient Review Pilot Program to allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in drug formulations. We had the privilege of speaking with five gurus from IPEC-Americas about the pilot, who explained why this is so important for formulators. IPEC has spent years advocating for ways to break down the hurdles associated with novel excipients – including fear of the unknown. The full panel discussion is available at: [tmm.txp.to/ipecvideo](https://tmm.txp.to/ipecvideo). But here is an abridged version to whet your appetite.*

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*Featuring Nigel Langley, Kathy Ulman, Priscilla Zawislak, Meera Raghuram, and Dave Schoneker*

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### Why does the pharma industry need novel excipients?

NL: There are currently many unmet needs and challenges with formulating drugs. For example, many small molecule drugs are poorly soluble, poorly bioavailable and, in some cases, poorly permeable. In addition, to improve the stability of biologic drugs, excipients are used to stop proteins and peptides from agglomerating – and there's still a great deal of room for improvement. There are also other applications that could benefit from novel excipients, such as taste masking very bitter drug actives for pediatric and geriatric medicines. These patient groups often find it difficult to swallow conventional tablets, but if you're going to make an alternative form then masking the bitter taste with the appropriate excipient is very important.

Novel excipients could also help improve manufacturing processes; consider continuous manufacturing, which is an important development occurring in the industry. New materials can help make continuous processing more efficient. And then there is 3D printing, which could potentially be used to make tablets and different dosage forms for personalized medicine; again, we need the right excipients to make the optimum printed drug.

In addition, it's important to consider that many of the excipients that formulators currently use were developed more than 50 years ago – and often weren't developed specifically for the pharmaceutical industry, so formulators don't necessarily have excipients designed specifically for the challenges they face. At the same time, drug modalities have been accelerating, with advances in different therapies. At IPEC-Americas, we feel that excipient use lags behind need.

DS: It has also been extremely difficult to bring forward a novel excipient with any degree of certainty – and that has resulted in many companies no longer developing novel excipients. Ironically, there has never been a greater need for truly novel excipients. It's a real problem.

KU: Nigel summed up the importance of novel excipients well. Novel excipients could bring so many benefits to formulators – and to patients. They don't just influence drug delivery, but can also improve stability and manufacturability.

MR: When you look at therapies today, there are new dosage forms and breakthrough therapies that simply didn't exist 20 years ago, such as targeted immunotherapy agents and certain combination products. They require unique formulation solutions – and that means more novel excipients.

PZ: Meera is right. The traditional formulations and solutions we have do not always work for the types of drugs that need to be developed today.

DS: A good example is the mRNA COVID-19 vaccines. It was a novel, lipid nanoparticle type of excipient that had not been previously used that really facilitated some of the development work on the vaccines. It is a clear example of where a novel excipient helped the industry meet an unmet patient need in a critical situation.

### Why has the development of novel excipients not been a priority?

MR: I wouldn't say that it hasn't been a priority; the perceived hurdles and unknowns about what is needed to achieve success are really to blame. We have to recognize that excipients are generally a small part of a chemical industry manufacturer's portfolio and significant investments just for pharma are often limited due to a lack of clear pathway on how they could achieve market success. There is no clear answer on what it takes to market a novel excipient because historically there hasn't been an independent review pathway – the approval of novel excipients has always been dependent on the drug approval process. In other words, even if you have a very promising excipient candidate that provides unique performance, you may not be able to bring it to market.

Additionally, one major aspect of novel excipient development relates to toxicity and safety studies. Although there is pharmaceutical safety evaluation guidance from FDA, which was issued in May 2005, it doesn't provide a clear pathway for an excipient and there are many factors that are ambiguous. The guidance alludes to exceptions to testing, so there are exceptions where you can use various scientific reasoning to evaluate what safety testing is needed. But an excipient manufacturer will only



## Five Excipient Experts

Clockwise from far left

### KATHY ULLMAN

*"I'm the President and owner of KLU Consulting. I retired from the role of Global Regulatory Manager for Dow Corning's healthcare business in 2016 after 40 years in their silicones business. I am a consultant with IPEC-Americas. I'm also the Vice Chair of the Regulatory Affairs Committee."*

### PRISCILLA ZAWISLAK

*"I'm the Global Regulatory Affairs Advocacy Manager at International Flavours and Fragrances (IFF). I have over 40 years' experience in the industry with food additives, excipients, and APIs. I'm the Immediate Past Chair of IPEC-Americas."*

### MEERA RAGHURAM

*"I'm the Director for Regulatory and Sustainability at Lubrizol, where I manage the regulatory strategy and policy for our health, home, and beauty business. I lead IPEC-Americas' Regulatory Affairs Committee and I'm also on the IPEC-Americas board."*

### DAVE SCHONEKER

*"I'm the President and owner of Black Diamond Regulatory Consulting. I've been involved in the excipient industry for over 43 years. I am the former Director of Global Regulatory Affairs at Colorcon and I am one of the original founders of IPEC-Americas."*

### NIGEL LANGLEY

*"I'm the Global Technology Director for BASF for our pharma solutions business. Since January 2022, I have been the Chair of IPEC-Americas and will hold the position for two years."*





get clarity and definite input if the excipient is picked up by a drug applicant and goes through the drug approval process.

**DS:** It comes down to risk and uncertainty. There is often a misunderstanding where people claim that regulators are making it difficult and preventing innovation, but it's not really an issue with the regulators. Regulators are perfectly willing to look at any safety data submitted as part of a drug application. If you have the appropriate information, there shouldn't be a problem. But pharmaceutical companies are risk averse and concerned about uncertainty the first time a novel excipient is used. Is there enough information to support the safety? What will FDA or other regulatory agencies say about that data? Will it create a potential delay in getting my drug approved?

Something we have been talking about within IPEC-Americas for many years is how to lower the risk level so that pharmaceutical companies no longer have the fear of the unknown. We want to give them more confidence to use novel excipients.

I know of circumstances where pharma companies have actually made decisions to avoid the use of a novel excipient, even though they've looked at the research and said, "Wow, this would solve all of our problems!" Formulating with an existing excipient to produce a drug that is not as good as it could have been is not quality by design – it's quality by fear.

**KU:** Drug companies develop new drugs, so their application will focus on the new API or the new therapy. To put a new excipient on top of that adds uncertainty and makes it more complex. So you can understand why they have that view.

**PZ:** There are technical issues with developing novel excipients for new drug applications, but you also can't take the business factors out of this. As Meera said, excipients largely come from chemical companies and their R&D timelines are much shorter than pharma companies, who look 10 or 15 years out. There has to be not only a technical advantage, but also a business advantage to justify the amount of time and money it takes to develop a novel excipient. And, as Dave was saying, pharma companies also see risk when using novel excipients. There are challenges for both parties.

**DS:** Imagine if you are an innovator in an excipient company. You come up with a great idea for a new pharma excipient and you take the idea to your boss. Your boss asks, "OK, well how long will it take before we break even on the cost of tox studies and so on?" Your reply is, "Maybe after 20 or 25 years we might sell the first kilo." You're probably not going to have a job in research for very long.

**NL:** Something that I personally have heard when visiting customers is, "We're very interested in your novel excipient, but come back when somebody else has got it approved." In this industry, companies want to be first to be second! The reality is that a novel excipient is currently only adopted and used in a drug product if everything else fails. We are really keen to change this

dynamic because it doesn't help the patient, who deserves the most optimum drug therapy.

**DS:** Pharmaceuticals is the only area that I know of where an ingredient currently has no pathway to be assessed outside of the finished drug application. Although we understand the need to look at the context of use in the drug application, the safety data on the excipient is the safety data. Just like when you're looking at a food additive, you're looking at data that determines whether or not there is an acceptable daily intake, which can be looked at independently of the food. And this is why the FDA's new pilot program is so important to move forward with.

### Over the years, how has IPEC been working with the industry and the FDA on this topic?

**KU:** IPEC-Americas celebrated its 30 year anniversary recently and we've been developing a regulatory strategy for new excipients since its inception! In fact, the 2005 guidance mentioned earlier, which describes some of the studies that need to be done on novel excipients, was largely based on some of IPEC-Americas' recommendations. Then around 2008/2009, IPEC-Americas established a novel excipient evaluation procedure – an independent external review of excipients that we hoped would allow regulators to view excipient safety information from an independent panel of toxicologists, facilitating the approval of novel excipients.

Unfortunately, it didn't take off the way we hoped. Around 2015, we realized that we needed additional support from the industry, so we reached out to the IQ Consortium and asked them to partner with us to help promote an independent review of excipient safety. Members of IPEC-Americas and the IQ Consortium were then granted a meeting with the FDA. As a result, the FDA suggested some potential pathways in our pursuit of an independent review process.

And then we were all delighted in 2019 when the FDA opened a docket where people from the industry could provide comments on whether or not a novel excipient program would be beneficial. We believe those comments influenced the FDA in coming out in September 2021 with their Novel Excipient Review Pilot Program. We were ecstatic when that happened!

**NL:** The meeting in 2017 with the FDA was pivotal because we felt that we really connected with the agency on this topic. The FDA then stimulated interest through the USP to issue a global survey, aimed at formulators – and with specific questions that some of us on the panel actually provided input into. It's important not to overlook the USP's role.

**DS:** When IPEC-Americas tried to develop its own independent panel, it involved world-class toxicologists, but users may have had concerns that the FDA was not part of the assessment. This is, I think, why the program did not take off. But in the last five or six years, discussions with the FDA have intensified; it understands



## THE PILOT: IN A NUTSHELL

Novel excipients had to meet two criteria to be considered for the program. They must not have been used previously in any FDA-approved drug product and must not have an established use in food.

Proposals for the pilot were only accepted until December 7, 2021. Excipient manufacturers were required to submit brief summaries describing the novel excipient, its proposed use, and the public health or drug development need addressed by the excipient, as well as a summary of supportive data generated so far.

The FDA will select four proposals with which to move forward – two for the first year and two for the second year. Decision criteria will include the potential public health benefit of the novel excipient (the FDA mentions excipients that may facilitate opioid abuse-deterrent formulations or excipients that promote the development of new therapies for serious or life-threatening diseases), the likelihood of the manufacturer submitting a complete package in the timeframes, and the overall potential of the novel excipient to “meaningfully” improve pharmacokinetic characteristics

Developers whose excipients are selected for the program will be required to submit a full package, including toxicology and quality data.

that novel excipients are needed for innovation in drug development. It's been a matter of getting the stars, the moon and the sun to align – so that everybody understands the need for novel excipients.

**KU:** Going back to what Nigel said about the USP; when we tried to get our program up and running before, we spoke with USP and they agreed that the pending monograph system, similar to that for APIs, could be adapted for excipients, so that when a novel excipient or a drug containing a novel excipient was approved, the monograph would be ready. However, the discussions didn't go any further. Now that we have the FDA pilot, we hope the USP will consider moving forward once again with a pending monograph system for excipients.

**PZ:** Kathy brings up an excellent point about the USP's pending monograph process. Unfortunately, this is restricted to APIs. With our novel excipient program, we worked with USP to see if we could get a pending monograph process incorporated for excipients, but that would also require FDA approval as the USP can't make that decision alone. But there may be a possibility to extend the pending monograph process to novel excipients, so that the FDA and USP process are concurrent.

**DS:** We had some really good discussions with USP, but there was some concern about how novel excipients could fit in with their current policies. This new pilot program could open the door to initiating those discussions again with both the USP and the FDA. Having a quality standard already developed and ready to go when you have completed the safety assessment would give everybody everything they need to minimize risk and move forward. It would be nice to know that a standard has been established when the material starts being used in a drug product for the first time.

The USP can't publish a monograph on something until it actually has a precedence of use, but this concept of a pending monograph – if we can get over some of the internal policy hurdles that exists – really would have some benefits and facilitate the use of novel excipients.

**NL:** Ultimately, this is an industry challenge. It's challenging to tackle independently, but through collaboration we are now starting to see progress. Going forward, we're also going to need to think about this globally – it is a global issue! The US FDA is just one regulator and we're going to need more stakeholders to be successful on a global level.

### The window for proposals for the pilot closed recently. What kind of innovations are you hoping to see?

**PZ:** The pilot program will only involve two excipients each year for two years. It is an excellent start, but there are many novel excipients for which companies have been trying to gain traction for years. If this pilot is successful – and we have every expectation that it will be – I hope that future expansion will incentivize companies to develop more novel excipients and encourage pharma companies to consider using them.

Building on what Nigel said earlier, I also hope the program will stimulate excipient innovation in the global pharmaceutical industry. This is a US program, but it could have global implications because so many countries look to the FDA. We recently met with Pharmacopeial Discussion Group (which involves USP, EP, and JP) and we've asked them to look at novel excipients because, as the FDA looks at developing a regulatory process in this area, the compendial process becomes a part of that too.

**DS:** If the pilot is successful and becomes a full program, I honestly think it will be the greatest innovation in excipients and drug development that I've seen in my career.

But it is critical for the scope of the program to be expanded to allow for all types of novel excipients to take advantage; it cannot just be focused on new chemical entities or chemically modified materials that have never been used before. I think the biggest benefit of this program long term is if it expands to

co-processed excipients, new routes of administration, higher levels of use, and use of food additives and cosmetic ingredients for the first time in a pharmaceutical application.

A topic that needs to be discussed with the FDA down the road is a refined definition for novel excipients. Many things fall into the classification of novel excipient, but in some cases it could be argued that they are not so novel; they may be unique in that they haven't been used in a specific way before but some materials have been around for years and there may be ways to perform bridging studies as there should be very little concern from a safety perspective.

*PZ:* We've mainly talked about the benefits for excipient manufacturers and the pharma companies, but ultimately the potential public health benefit of novel excipients is really key. The absence of a regulatory pathway is leading to less than optimized drugs.

*DS:* I think one of the things that shocked the FDA was when folks from IQ consortium – and from big pharma and innovator companies – presented specific case studies of where drug products that would have significant patient benefit were killed because of the fear of using a novel excipient. These stories came from multiple companies and I think it was an important point to bring home to the FDA.

*PZ:* Our company has submitted a candidate for the pilot, but we've been working with customers for a number of years on things that aren't just new chemical entities, but more modified excipients for different levels of use. Formulators often run into the phrase “formulate by IID” – the FDA's Inactive Ingredients Database. If it doesn't fit the IID parameters, then there's been a lot of reluctance to move forward – even with a modified excipient because it is still considered novel. As the program advances, I hope we can get away from formulating by IID and be able to use novel excipients and existing excipients in novel ways. The generic industry is really clamoring for this type of approval process.

*NL:* What I would like to come out of all of this is a future where pharma companies and excipient companies work much closer together – with more transparency about what pharma companies need and how we can collaborate to find a solution. Meaningful conversations early on in development will help a lot.

*MR:* I'm very excited about the program, and so is industry in general. But something to keep in mind is that, when the pilot program announcement came, there wasn't much time for everybody to make their submissions – and not everyone would have had their dossiers fully ready or the amount of pharm tox data required for the submission. I think there was some hesitancy too about how the data will be evaluated and what information will be posted publicly. I think it would be really useful for the program to be expanded and extended to make further decisions.

## Once the program concludes, what are the biggest priorities?

*PZ:* In summary, I think the pilot is a great idea, but I'd like to see it expanded to all types of novel excipients to get away from current paradigms. I also hope other countries will look at the process and adopt certain aspects.

*KU:* It will be important for pharma companies to partner with their excipient manufacturers to develop the packages that are going to be necessary for the evaluation. The safety studies alone are very expensive and if the excipient company is taking on that full responsibility there could be problems. Management at chemical companies can change quickly and they may not want to spend money on something that won't be commercial for a while. Partnering with pharma companies and working together – perhaps with the pharma company doing some studies with the excipient and their active drugs – will really help.

*DS:* To sum up my thoughts, I think there are two critical areas for the future success of the program: i) expansion of the program to all types of novel excipients and ii) globalization to get similar approaches used by other regulators. Pharmaceutical companies like to have one formulation for the world – they don't want to have one formulation that works great with novel excipients in the US, but then have to do something else in other countries.

I think it is critical that FDA and the industry turns this into a permanent program which can be used for all types of novel excipients – otherwise there will be major problems in drug development down the road. Once we do that, perhaps we could even pursue an ICH guide to help with global acceptance. It may take a while to get to this stage, but we've already been advocating for an independent pathway for novel excipients for over 30 years and we're not going away now!

*PZ:* Now we're at this stage, I like to think it won't take quite so long to get to something like ICH level!

*NL:* I agree with everything that has been said. As a final thought, I also think that more of the science will come through. Excipients are more functional than inactive and perhaps in the future we could see better acknowledgement that excipients have true functionality. The science will show that there is an equal place for excipient makers in the industry, which will drive the design of future materials that are fit for specific pharmaceutical applications. I think we have a very bright future, both from the regulatory landscape, the adoption of novel excipients, and also in terms of scientific progress.

*MR:* The panelists have covered almost everything. Last but not least, I hope that FDA will issue some policy and guidance, especially an update to the 2005 pharm tox guidance, which would give the industry a chance to anticipate and to be responsive.

In the field of medical devices, innovation is being spurred by allowing developers to consult with the FDA on their projects with no strings attached. Such consultation with the excipient industry could be very helpful to promote the development of novel excipients.



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## Core Topic Cell & Gene

**Godspeed, Doug!** Research published by Carl June and his colleagues describes how they found that CD4+ CAR T-cells persisted for over a decade after infusion, with immune memory. Though the authors are careful not to use the word “cure” in their title, “Decade-long leukaemia remissions with persistence of CD4+ CAR T cells” is perhaps as close as one may come in an academic journal. Researcher David Porter has said he’s feeling more comfortable with the “C word” in the case of patients like Doug Olson, who after ten years in remission has celebrated his 75th birthday and taken up half-marathon running (JJ Melenhorst, “Decade-long leukaemia remissions with persistence of CD4+ CAR T cells”, Nature, 2022).

**SEAKing a treatment.** Scientists at the Sloan Kettering Institute in New York City have developed retooled CAR T cells able to serve as “micropharmacies” for cancer drugs. Specifically, these synthetic enzyme-armed killer (SEAKER) cells are engineered to produce an enzyme that activates a systemically administered small molecule prodrug at the site of the tumor. The scientists tested their SEAKER cells on cancer cells in vitro and in mouse models – and, in both cases, they performed better than regular CAR T cells. The researchers say their approach has the potential to treat not only cancer, but also a variety of other diseases (TJ Gardner, “Engineering CAR-T cells to activate small-molecule drugs in situ”, Nat Chem Biol, 18, 216–225, 2022).

**3 + 11 = 95%.** The Zhang Lab in the University of Michigan Medical School has struck CRISPR gold. In a paper published in the journal Molecular Cell, researcher Yan Zhang and his team demonstrated how Cas11, a newly discovered “hidden internal translation product,” was able to improve the efficiency of CRISPR-Cas3 gene editing from 10 percent in stem cells to 50 percent in stem cells – and up to 95 percent in other human cell lines. The Zhang Lab team say that these findings have significantly boosted their ability to engineer long-range genome edits (R Tan, “Cas11 enables genome engineering in human cells with compact CRISPR-Cas3 systems”, Mol Cell, 2022).

**Peking primates, Beijing blood glucose.** A team working on stem cell transplants for diabetes in Peking University’s Stem Cell Research Center has published results from a study in which they gave diabetic non-human primates a one-dose infusion of human pluripotent stem-cell-derived islets (hPSC-islets), which effectively restored endogenous insulin secretion and improved glycemic control. In all primates that received the treatment, fasting and pre-prandial blood glucose levels saw a significant decrease, and overall body weight increased. Until now, hPSC-islet transplantation had not been tested in large and physiologically-similar-to-human animal models (Y Du, “Human pluripotent stem-cell-derived islets ameliorate diabetes in non-human primates”, Nat Med, 2022).

## IN OTHER NEWS

*Novartis says it will acquire Gyroscope Therapeutics in a deal that includes a US\$800 million upfront payment, and potential for \$700 million in milestone payments*

*Cambridge researchers show it is possible to modify the mitochondrial genome of live mice using a “mitochondrial base editor”*

*EMA’s Committee for Medicinal Products for Human Use recommends Bristol Myers Squibb’s CAR T-cell therapy Breyanzi for approval*

*Researchers at Canada’s Northwestern University develop a microfluidic tool that can recover potent TILs from solid tumors*

*Former San Diego Blood Bank CEO David Wellis launches CDMO named Excellos, and secures \$15 million in funding*

## Champions of Cell & Gene Therapy

**In this new article series, we ask industry leaders to answer one key question**

This issue's question is: Where do the biggest skills shortages exist in this field – and how should we address the problem?

**Matthew Durdy of the Cell and Gene Therapy Catapult says:**

In our 2021 Cell and Gene Therapy Skills Demand Survey, we found that between 2021 and 2026 the UK's cell and gene therapy industry will need employees to be split across three main roles as following, with bioprocessing staff most in demand:

- 74 percent in bioprocessing
- 11 percent in research and development
- 7 percent in support services

Moreover, 62 percent of employers are intending to recruit to expand their workforces within the next two years, with most companies looking for skilled and experienced people. In my view, the greatest shortage will be in the demand for sector-specific skilled people.

In the UK and across the world, the current demand for talent is a good problem to have; it is a testament to flourishing investment and innovation. But we need new initiatives to help develop a new wave of talent in advanced therapy, such as apprenticeships that expose apprentices to the most cutting-edge developments in the field, to cultivate the skills that the market lacks.



It would also be beneficial to look at how we can bring transferable skills from other sectors into our own.

At the Cell and Gene Therapy Catapult, we are doing our part with an Advanced Therapies Apprenticeship Community program.

**Anshul Mangal of Project Farma says:**

The cell and gene therapy industry has experienced exponential growth in the last three years and, as funding for the field continues to break records, there are no signs of a slowdown. With 2,261 ongoing clinical trials in regenerative medicine, the FDA expects to approve between 10 and 20 new cell and gene therapies a year by 2025. However, this means that the need for solutions to the industry's biggest bottlenecks are growing daily.

The advanced therapeutic revolution has resulted in a significant talent shortage across the industry, particularly in manufacturing. Even with recent advances in automated technology for



cell and gene therapies, the sector is still heavily reliant on manual processes, so these technological leaps cannot yet backfill the workforce gap.





Though the talent shortage is a complex problem, the industry is making great strides to come together to find solutions. Leveraging private–public partnerships and continuing to disseminate experiences and information across the industry will help elevate the current generation of skilled workers. In an effort to focus on the next generation of talent, funding is being poured into universities to support advanced degrees for the industry’s incoming technical workforce. For example, last April the US National Science Foundation awarded a \$573,347 grant to a Pennsylvania community college to support efforts in elevating the advanced technical workforce for the cell and gene therapy industry.

**Bruce Levine of the International Society for Cell & Gene Therapy says:**

I believe that we need a virtual Rosetta Stone for the cell and gene therapy field. To explain what I mean, here’s a quick history refresher.

The Rosetta Stone was a tablet



Scholarship opportunities and training will also be important to address the unfulfilled need for cell therapy training.

**Carl Taylor, Chief Digital Officer of TrakCel says:**

I’d like to offer a different perspective on the skills problem. Economic expansion and a swell of therapies approaching commercialization have increased the pressure on many aspects of advanced therapies. In response, companies are turning to IT and technical solutions to help them automate, streamline, and increase the productivity of their processes. Unsurprisingly, the field now faces a growing shortage of programmers, test engineers, analysts, and product development positions.

There is high competition for tech talent across all industries, amplified by a pandemic-induced rush for software to manage a world in lockdown. The situation is tight, but also hopefully inspiring more young people to consider careers in the field.

Inspiring those young engineers early to turn to life sciences and advanced therapies will be key.

Organizations will need to be aware that the competition for talent is tight. Organizations should also bear in mind that they will constantly be assessed by talented and in-demand employees. It will be critical to attract and retain these people by maintaining and cultivating in company culture, development and training, and – of course – remuneration.

*What other cell and gene therapy questions would you like to see experts answer? Contact [angus.stewart@texerepublishing.com](mailto:angus.stewart@texerepublishing.com)*



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## Core Topic Bioprocessing

**The Aduhelm controversy.** Contention continues over Biogen's Alzheimer's drug, Aduhelm. The Centers for Medicare & Medicaid Services in the US have proposed the provision of insurance coverage for mAbs that target amyloid plaques – but only for patients enrolled in qualifying clinical trials. CMS acknowledges the potential for “promise” with the new treatment, but also the potential for harm due to the risk of severe side effects, such as brain bleeds. The final decision will be made in April 2022 and CMS has invited the public to submit comments. As to be expected, Biogen isn't happy with the decision and says it will be making a formal response.

**Going green.** How bad are single use technologies used in bioprocessing for the environment? A recently published, open access paper (K Budzinski et al., “Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture,” *New Biotechnology*, 68, 2022) performs a life cycle assessment for a mAb made via a single use manufacturing process and, among other findings, concludes that the “contribution to the environmental footprint from end-of-life due to the use of plastic SUT was extremely small.” According to the authors, the best strategies for reducing lifecycle environmental impact are operational changes that increase process efficiency and decrease time in plant.

**Revised use for COVID-19 mAbs.** FDA has revised the emergency use authorizations for two mAb cocktails against COVID-19 – Eli Lilly's bamlanivimab and etesevimab, and Regeneron's casirivimab and imdevimab – to limit their use in patients. Why? Because they aren't effective against the Omicron variant, which makes up the majority (99 percent) of COVID-19 cases in the US at present. The National Institutes of Health had previously discouraged use of the treatments, but they were still reportedly being used across the US.

**Rise of the machines.** Interested in how machine learning and AI are affecting biopharma development? These two papers may be just up your street. An author from Lonza details how in silico tools can be improved using machine learning to better predict post-translational modifications in monoclonal antibodies (S Vatsa, “In silico prediction of post-translational modifications in therapeutic antibodies,” *mAbs*, 14, 2022), and researchers from MIT and AstraZeneca explain how machine learning models can predict antibody aggregation and viscosity, and describe their work in identifying the best machine learning models (P-K Lai et al., “Machine learning prediction of antibody aggregation and viscosity for high concentration formulation development of protein therapeutics,” *mAbs*, 12, 2022).

## IN OTHER NEWS

*Want regular news about the biopharma industry straight to your inbox? Sign up for our newsletter on biopharmaceuticals at [tmm.txp.to/biop-cutor](mailto:tmm.txp.to/biop-cutor)*

*Atara Biotherapeutics and Fujifilm form manufacturing partnership; Fujifilm will acquire Atara facility for \$100 million and companies will form long-term supply agreement*

*Merck KGaA/MilliporeSigma strengthens CDMO mRNA offering with acquisition of Exelead for around \$780 million*

*West and Corning agree collaboration to create new packaging solution using West's NovaPure components and Daikyo Flurotec coating with Corning's Valor glass and Velocity vials*

*Lonza launches bYlok technology platform that helps prevent heavy and light chain mispairing when designing bispecific antibodies*



# Inside the PenCycle Recycling Scheme

**Novo Nordisk explains how we get from injector pens to chairs and light bulbs**

**What's the story behind PenCycle?**

PenCycle was inspired by Novo Nordisk's 'Circular for Zero' ambition to have zero environmental impact.

Every year in the UK alone, we learned that around 23 million of our FlexPen and FlexTouch devices are incinerated or sent to landfill. Unfortunately, it is not possible to make plastic prefilled injection pen devices from recycled plastic as, being a medical device, they need to comply with strict quality requirements and current recycled plastic contains impurities that may deteriorate product quality. So, we set ourselves a challenge of finding a viable and sustainable solution. Our answer? PenCycle.

PenCycle is the first ever UK recycling initiative for plastic prefilled injection pen devices. As part of the scheme, users of Novo Nordisk's FlexPen and FlexTouch will be able to recycle their devices, which will then be returned to Denmark as part of a circular supply route on ships already returning to port, to be turned into chairs and lightbulbs. To make this initiative possible, we have partnered with a recycling partner, KMT, who have the facilities to recycle these devices.

The first PenCycle pilot actually took place in Denmark in 2020, but it was launched to UK pharmacies on November 1, 2021, in three pilot locations—Leicestershire and Rutland, Greater Manchester, and Glasgow and Clyde. Once participating pharmacies are set up, people living with obesity, diabetes, and growth disorders will be able to recycle

their empty prefilled FlexPen and FlexTouch devices via community pharmacies, pre-paid Royal Mail post boxes, or through a home collection pilot service for people using Novo Nordisk growth hormone pens.

**What are the general challenges of recycling injection pens?**

Recycling plastic prefilled injection pens is extremely complex because they are made from several components that need to be separated and sorted with high-tech equipment. And that's why it has taken until now to launch a viable recycling scheme.

Currently, we estimate that between 98–99 percent of all materials will be recycled in KMT's specialized treatment plant. A fraction of the material will not be able to be recycled from day one, but, by optimizing recycling processes, we will work towards recycling every component of the pens in the future. We are committed to disposing of any materials that cannot be recycled in the most sustainable way. To give you a benchmark, without the PenCycle initiative, between 7–23 g per pen ends up in landfill (depending on whether patients dispose of the pen in their sharps bin or general waste). With PenCycle, this figure will be 1.37 g per pen.

**What challenges did you face in developing the scheme?**

Aside from the challenges of designing a viable recycling process, our main challenge was to develop an initiative that would actually be used by patients and pharmacists. We spent a long time collecting insights from pharmacists and people living with diabetes to identify their priorities. We found that convenience, trustworthiness, and flexibility were the key priorities for the patients, while safety and simplicity were key for pharmacists.

**What are your hopes for the future of the program?**

We hope to set an industry standard for the recycling of plastic medical devices in the

UK. The pilot initiative alone aims to recycle over 150,000 plastic prefilled injection pen devices, ensuring over two tonnes of plastic materials are diverted from UK landfill.

Although PenCycle is currently only available for Novo Nordisk's FlexPen and FlexTouch devices, our ultimate goal is to find an industry-wide solution that will allow us to recycle other medical devices made by other companies and roll the scheme out on a wider basis.

At the recent COP26 summit, Novo Nordisk announced its commitment to net zero emissions across our entire value chain by 2045 at the latest. We have also proudly joined the UK NHS's Net Zero International Leadership Group in support of their aspiration to rapidly reduce emissions from the healthcare sector.

In recognition of our action to champion sustainability, we have been awarded the Terra Carta Seal by HRH The Prince of Wales. Terra Carta has been awarded to just 45 companies who all have a shared ambition to drive innovation in pursuit of a more sustainable future.

**Why is sustainability so important to you?**

I truly believe that the health of our environment is inextricably linked to the health of people around the world, and the recent COP26 summit has laid bare that we need to act now and act boldly to secure the future health of our planet and communities. This will only be possible if major companies, like Novo Nordisk, make the commitment and investment to re-imagine their entire value chain, with the ultimate aspiration of having zero environmental impact. We are leading the way in this change, but we cannot do it alone. The only way we can achieve a greener future is by working together towards common goals that put the planet and people at the centre. We still have progress to make and it is by no means an easy task, but I hope that other companies will soon join us in adopting this circular mindset.



## Don't Get a Raw Deal

**While you're busy scaling up your bioprocesses, don't forget about the secure supply of all critical raw materials – both in terms of quality and quantity**

*By Hunter Malanson, Senior Field Application Specialist at Thermo Fisher Scientific*

Scaling up the biomanufacturing processes established during early phase development is an exciting, challenging – and critical – step in the journey of a biologic. After all, the scaled-up process will be used throughout the product lifecycle – and it must be developed to be both cost-effective and sustainable in the long term. That means decisions must be made to not only maximize productivity, but also to enable a secure supply of raw materials to reduce the risk of disruption and late-stage process changes.

Given that impurities in raw materials can be amplified during the scale-up process, the quality of the raw materials used during manufacturing should be a primary focus when scaling up. In particular, any impurities found in raw materials used in the cell culture medium can have a profound impact on performance parameters, including overall titers, cell growth, and consistency, which will likely result in variable product performance and batch-to-batch fluctuations. Even minor trace element contamination can dramatically impact the manufacturing process. For example, unexpected trace metals can alter

protein glycosylation patterns, leading to aggregation, insolubility, and a subsequent reduction in overall protein yields.

In addition to improving process consistency, high-quality raw materials feed into the critical quality attributes of the biologic as production is scaled up. Any deviations in these attributes can change the molecule's biological activity, which can prevent a biologic from getting to (or staying on) the market.

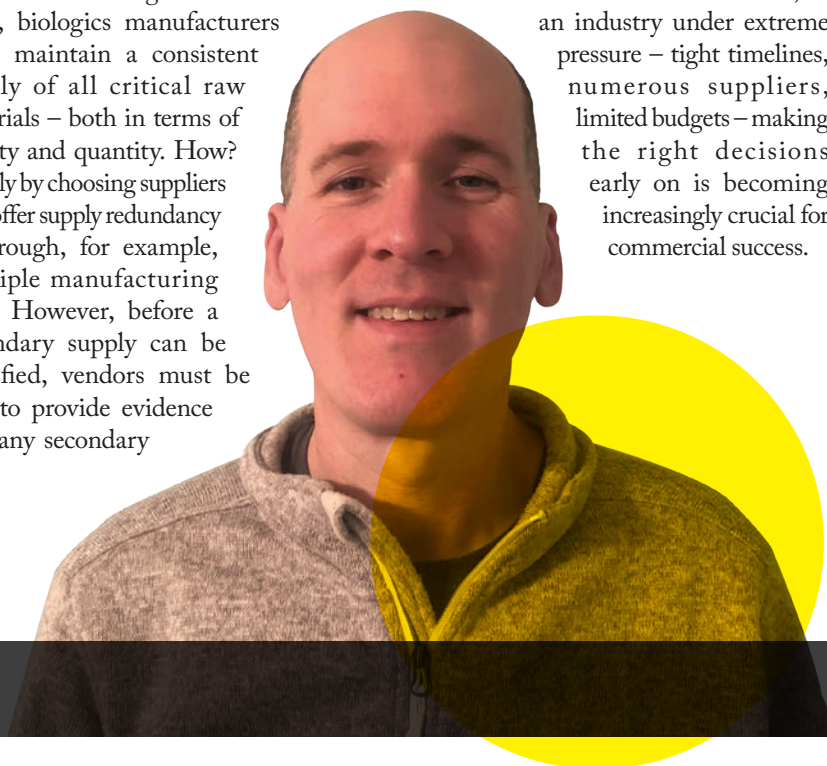
Given the clear importance of maintaining high raw material quality standards, it is no surprise that, over recent years, the analysis of raw materials has been a growing focus within the bioprocessing industry. Subsequently, there has been an increased demand for companies that use sophisticated analytical techniques and electronic data sharing to monitor impurities and contamination in their raw materials, keeping manufacturers informed of any variations.

Another potential issue associated with raw materials is supply disruption. To avoid delays when working at a commercial scale, biologics manufacturers must maintain a consistent supply of all critical raw materials – both in terms of quality and quantity. How? Simply by choosing suppliers that offer supply redundancy – through, for example, multiple manufacturing sites. However, before a secondary supply can be qualified, vendors must be able to provide evidence that any secondary

sites can meet the same specifications as the qualified primary site. To minimize the risk of variation when qualifying a secondary site, vendors should have a comprehensive and multi-faceted equivalency program, featuring equipment validation, staff training, and even their own raw materials supply (if they are supplying a complex raw material, such as pre-formulated cell culture media).

If you, as a manufacturer, are pursuing an animal origin-free process, you'll also need to conduct a careful assessment of the comparability of the facilities' contamination mitigation strategies to reduce the potential risk of transmission of viruses and other potential contaminants from animal-origin materials. Make sure your suppliers can detail equivalent risk reduction procedures, including the strategic clean room layouts and de-gowning procedures implemented at each site.

There is no doubt that scale up can be a complex period in any biologic's lifecycle, with numerous factors that need careful consideration. Furthermore, in an industry under extreme pressure – tight timelines, numerous suppliers, limited budgets – making the right decisions early on is becoming increasingly crucial for commercial success.





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## Core Topic Small Molecule Manufacture

**Drugging the undruggable.** Arrakis and Amgen have signed a multi-year deal worth \$75 million to support five new drug development projects. The partners will use their expertise to create a roster of RNA degraders – small molecule drugs capable of drugging previously undruggable targets. Amgen will drive the preclinical and clinical development of successful drug candidates.

**An intelligent approach.** AI-driven pharmatech company Exscientia has partnered with Sanofi to develop drugs to target several disease areas including cancer and immune-mediated diseases. Using the company's AI and human tissue sample, Exscientia will identify and test small molecules to shorten the R&D lifecycle. They will also receive \$100 million in funding, which will drive the development of up to 15 medicines. "Our expanded collaboration with Sanofi will utilize the breadth of our platform to test AI-designed drug candidates against patient tissue models, potentially providing far better accuracy than conventional approaches such as mouse models. When you consider the change this represents – testing candidates against actual human tissue years before a clinical trial – it's transformative," said Andrew Hopkins, CEO and founder of Exscientia in a statement.

**Treatment demystified.** Looking to solve a decades-long puzzle, researchers at the University of Texas have shed light on the mechanism of action of praziquantel – the only antiparasitic approved to treat schistosomiasis. The team found that the drug triggers parasitic death by binding to cells' transient receptor potential channels resulting in calcium ions flooding into the intracellular environment. "We have one drug to treat this huge population of parasites, and it works, but it is not perfect. Now, for the first time, we have a better idea about how praziquantel targets the parasite," said Winka Le Clec'h in a statement, a staff scientist at Texas Biomed and first author of the paper behind the discovery.

**Clearer reporting.** Transparency in clinical trial reporting has been a longstanding challenge for some segments of the industry, but a study published in PLOS Medicine reveals that antidepressant developers' attitudes towards clinical trial reporting are changing with close to 50 percent of trials conducted between 2008 and 2013 reporting negative results. The data suggests that developers are more forthcoming about sharing the outcomes of unsuccessful trials. But Andrea Cipriani, coauthor of the research, believes that there is still room for improvement. "We do not have full transparency yet. Researchers, patients, and clinicians should not naively accept published research findings at face value," she said in a statement.

## IN OTHER NEWS

*The FDA approves the first generic iteration of Restasis – a drug used to treat dry eyes. The brand-name drug has lacked generic competition for years*

*Aurobindo Pharma receives FDA warning letter regarding the lack of cGMP practice implemented in its API production*

*FDA to investigate the mortality risk associated with lymphoma drug, Ukoniq*

*Cabenuva, the only FDA-approved HIV treatment, is granted expanded approval allowing for two-monthly dosing*

*Partners at the University of Illinois Urbana-Champaign and collaborators at Revolution Medicines develop an automated machine for accelerated small molecule manufacturing*



## Join the Resistance

**Jane Hemingway, Founder of iiCON, explains how the industry can work collaboratively to tackle antibiotic resistance**

*By Maryam Mahdi*

Decisive action against antimicrobial resistance (AMR) is needed now. The problem isn't a looming threat but a challenge that impacts and has impacted lives globally for decades.

As the clock ticks down and the issues associated with AMR further manifest, what role will pharma play in the fight against the spread of infectious diseases? As I looked for opinions on the issue, I came across iiCON (Infection Innovation Consortium). iiCON brings together industry, academia, and the NHS in a £174 million collaborative infectious disease R&D programme to accelerate the discovery, development and deployment of new antimicrobial treatments and products. Led by Liverpool School of Tropical Medicine (LSTM), its partners are Unilever, Evotec, Liverpool University Hospitals Foundation Trust, The University of Liverpool, and Infex Therapeutics.

I asked Professor Janet Hemingway, founding Director of iiCON, to outline the scale of the problem and why collaboration is a key factor in reducing the effects of AMR.

**What challenges does pharma face as antibiotic resistance grows?**

The most pressing challenge the industry faces is that the innovation pipeline for new antibiotic compounds has slowed. This unfortunate hurdle is rooted in the fact that we have turned

everything from pills to vaccines to diagnostics into commodities. Though the commodification of these interventions has meant that large numbers of people have been able to access them at low prices, profit margins have taken a downturn for the companies developing them.

Pharma companies are, at the end of the day, businesses. So, increasingly we've seen large-scale companies move out of this area and into more lucrative markets, such as oncology. The mass exodus means the development of new, pertinent treatments has all but ground to a halt, and resistance to available drugs and antibiotics is building.

**Why did you launch iiCON?**

In 2005, I launched a product development partnership to develop new antibiotics. It struck me that there was

a need for a similar collaborative group consisting of experts from academia, industry, and healthcare partners to address the broader challenges of developing new drugs, vaccines, and diagnostics. I wanted to explore how we could accelerate the R&D process in a cost-effective way.

We launched iiCON in 2020. Our newly formed team has received funding both from pharma companies and organizations like The Bill & Melinda Gates Foundation – players who really understand the process of drug development from an industrial perspective. We've not been around long, but we've already helped bring eight products to market. And we have a very healthy pipeline of further products – from very early-stage development all the way through to new products that are almost ready for commercialization.



Momentum is building and that's very exciting.

**What lessons have been learned since launch?**

The COVID-19 pandemic has really been a turning point for us all. With development times drastically truncated, we've seen products reach patients in record times. A major contributor to the accelerated R&D lifecycle was effective communication. iiCON has been around for just over a year and we've helped get 2.5 billion units of new treatments out to patients. It shows how great the demand is for pertinent therapeutic interventions and how consistent communication with our partners helped get things moving.

We hope that the positive legacy of COVID-19 will help in pushing through new treatments to address

other infectious diseases we're interested in, especially as we're currently in talks with the governments of the UK, US, and Canada. These authorities have played a massive role in getting vaccinations to patients throughout the pandemic. If they can maintain the same attitude towards other diseases, we should be able to make significant progress in their management.

**What more can pharma do to resolve problems related to infectious disease and AMR?**

The onus isn't only on pharma when it comes to addressing AMR. We all need to work in partnership to develop the medicines, technologies, and techniques that will benefit patients worldwide. Collaboration will also help upskill the pharmaceutical workforce.

However, I would advise the pharma

companies who haven't been involved in infectious disease drug manufacture or who left the field to test the waters. For those who have stayed involved, it's important that they increase their activities so that the broad spectrum of infectious illnesses that exists today can be addressed. Crucially, this scale-up must happen cooperatively. A problem shared is a problem halved. The more information sharing and support we can provide for each other, the better we can address patient needs.

*To read the full interview visit [themedicinemaker.com](http://themedicinemaker.com)*

*Reference*

1. OECD, "Antimicrobial Resistance: Policy Insights," (2016). Available at: <https://bit.ly/305h93S>.



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## Prizewinning Pillmaster

**What does it take to win awards? For one young scientist, it was quantity, quality, and excellent excipients.**

DFE Pharma's Alberto Berardi is one of 10 winners of The Journal of Pharmaceutical Sciences' 2021 Outstanding Early Career Scientists award. Berardi was recognized for "the most original and significant scientific findings", based on his work on superdisintegrants – excipients that make tablets "burst" (1). Here, Berardi shares his journey in academia and pharma across Europe and the Middle East – and wonders where it will take him next.

**Describe the path that led to your prize...**

After completing my PhD in 2013, I started as an Assistant Professor in Pharmaceutical technology at the Applied Science Private University in Amman, Jordan, and was promoted to Associate Professor in 2018.

During my scientific journey I have been involved in a variety of different research projects, with the common denominator being oral solid dosage forms and oral drug delivery. To name a few projects, I've studied the stability of biopharmaceutical products in gastric and intestinal fluids, the formulation of oral solid dosage vaccines, and the development of controlled-release oral solid dosage forms using natural polymers.

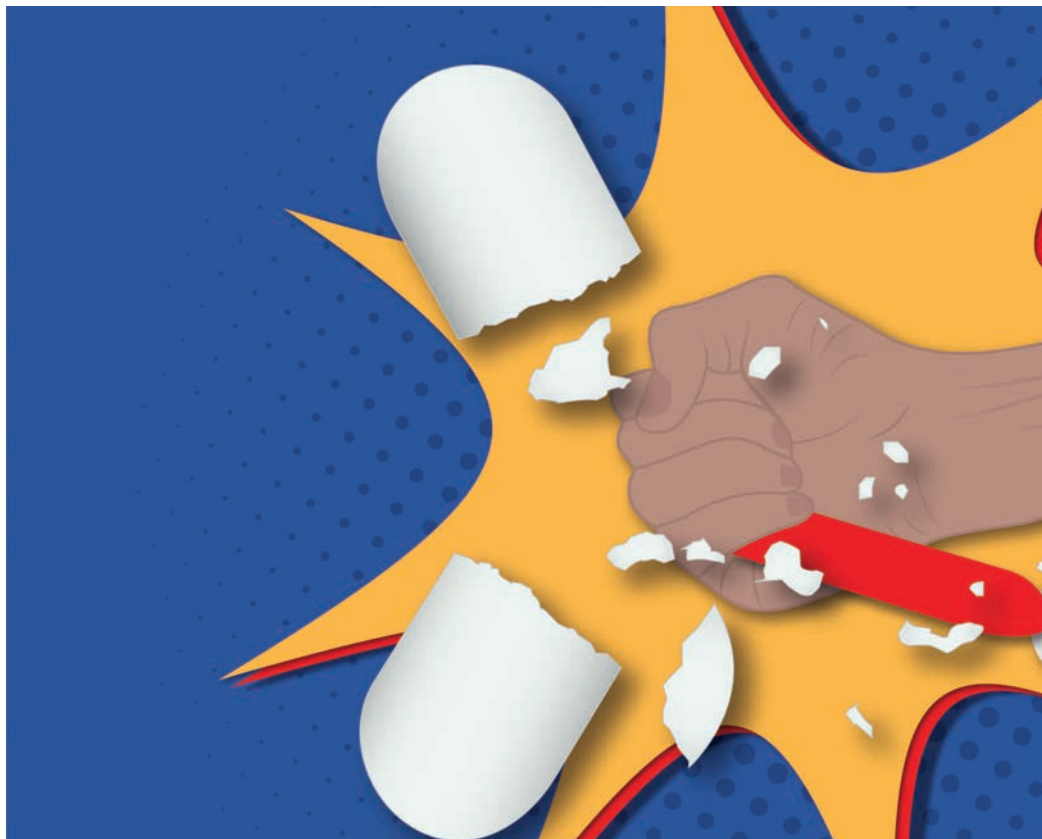
Over the last three years my research has mainly focused on the development of a mechanistic understanding of the disintegration phenomenon, and on investigating the ranges of applications of conventional and non-conventional superdisintegrant excipients. Driven by

my passion for oral solid dosage forms and the excipients within them, I joined DFE Pharma as a Product Application Specialist in 2021.

Since 2017, I have published a total of 28 scientific articles in international scientific journals within the fields of pharmaceutical technology and drug delivery.

**Tell us about the work that won you this award...**

The work published in The Journal of Pharmaceutical Sciences focused on the aforementioned topic of superdisintegrants – functional excipients used in oral solid dosage forms that cause a tablet to disintegrate in the gastric fluids of the stomach and thus enable prompt release of the drug. Superdisintegrants are often not interchangeable within a formulation







study, on the other hand, compared superdisintegrants' performance using more realistic conditions; for example, in the interest of increasing the practical relevance, we included aspects like hydrophobicity and storage effects in the design of the study.

#### How can your findings be applied?

The study shows how the three most commonly used superdisintegrants function and induce disintegration in hydrophobic tablets stored in harsh conditions. The article also provides a mechanistic explanation of why certain results were obtained.

Some findings of this study contradict traditional disintegration selection criteria – criteria that were derived from (overly) simplified systems. For instance, according to the conventional wisdom of formulation, croscarmellose sodium should be preferred as a disintegrant in soluble matrices, but not in insoluble matrices.

But, on the contrary, in our work we showed that croscarmellose is also the disintegrant of choice in insoluble hydrophobic tablets, particularly when storage is a factor. Our work also highlighted the reduced disintegration performance of crospovidone – compared with croscarmellose and sodium starch glycolate – in hydrophobic tablets and after storage.

Our work represents one step forward – or one more piece in the intricate puzzle of the disintegration phenomenon. But one limitation of all studies on disintegration is that findings are often specific to the formulation and experimental conditions tested and cannot be generalized. Therefore, although our study provides indications on disintegrant selection in hydrophobic matrix tablets, extending our findings to

*“We included aspects like hydrophobicity and storage effects in the design of the study.”*

different formulations should be done with care.

Overall, the study can serve as a guide for the selection of superdisintegrants in hydrophobic formulations. The work could also set an example for how the design of studies on superdisintegrants should be guided by the challenges of “real-life” pharmaceutical formulations.

#### What are you currently working on at DFE Pharma?

DFE Pharma is a really exciting place for me to work because it is at the forefront of research on pharmaceutical excipients. To give some examples, we are using our knowledge of current excipients to develop novel excipients optimized for particular applications, such as continuous manufacturing.

In another project, we are exploring excipients' characteristics at a level that will enable us to predict whether or not their variability affects their functionality. In this way, we aim to provide a scientific approach to de-risk the use of our excipients in customer formulations.

#### Reference

1. KL Audus, “2021 Outstanding Early Career Scientists”, *JPharmSci* (2021). DOI: 10.1016

and appropriate selection is key for effective disintegration performance. Specifically, the study shows that in a hydrophobic matrix tablet formulation, croscarmellose and sodium starch glycolate can provide rapid disintegration under harsh storage conditions, while crospovidone cannot.

#### Why do you think your article stood out from the crowd?

Well, it was selected by the journal as the featured piece of that monthly issue, so that really helped it garner the attention of the scientific community. The article is also different from previous works thanks to the experimental design of my study.

Other previous studies have evaluated superdisintegrant performance in placebo, hydrophilic, and simplified formulations without considering the effect of storage on disintegration. Our

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# Nurse Sharks and VNARs

A collaboration between Scottish and American researchers has snatched potential treatments for COVID-19 from the jaws of... Jaws

*By Angus Stewart*

The first sharks existed 150 million years before the first dinosaurs, and it's exactly that brain-breakingly ancient pedigree that makes these oft-maligned species so compelling when it comes to developing new therapeutics.

We spoke to Caroline Barelle, CEO and founder of the Aberdeen biotech Elasmogen, and her overseas collaborator, Aaron LeBeau, Associate Professor of Pathology and Radiology at the University of Wisconsin Carbone Cancer Center, about their work on sharks – and how it could lead to new therapeutics for COVID-19 – and many other diseases.

What makes sharks so special?

**Barelle:** Sharks are uncanny creatures. Despite being almost half a billion years old and living on a branch of the evolutionary tree far from homo sapiens, their immune systems are strikingly similar to those of mammals. This seeming contradiction is exactly what

early pharmaceutical research into these ancient creatures wanted to understand. One point of difference that research honed in on is the existence within sharks of IgNAR variable domains (VNARs) – antibody-like molecules that are a mere one tenth the size of human antibodies, yet far more stable and effective at fighting disease. VNARs also do not have an antibody lineage; they began as something else in the animal, and by some convergent quirk in evolution became part of the shark's defensive arsenal. Today, scientists like Aaron and I are working to bring VNARs into humankind's own pharmaceutical arsenal.

We isolate VNARs from the blood samples of immunized sharks or from a library of billions of synthetic (lab-made) shark VNARs, screen them against the target, select the most effective one, and ultimately humanize it into a product suitable for clinical use.

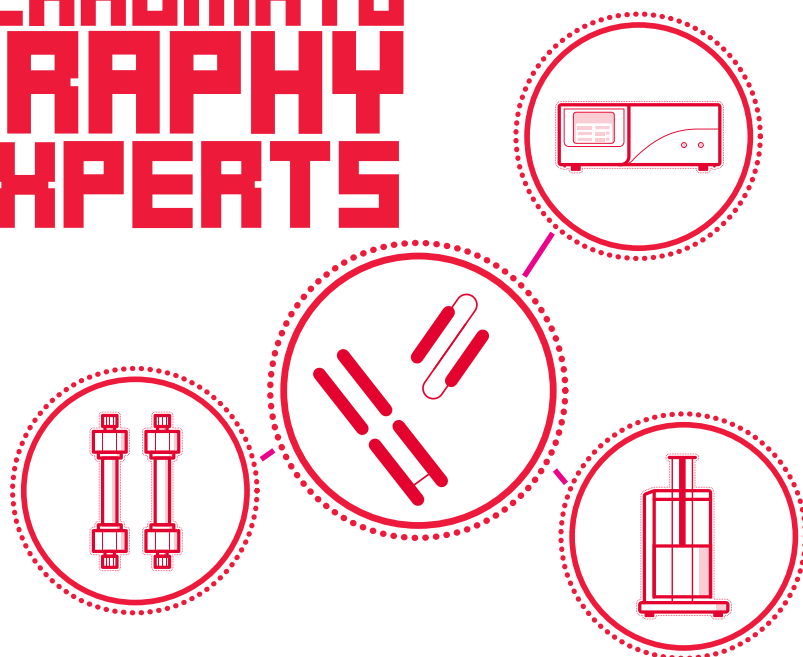
Now over to humans. Tell us about your backgrounds...

**LeBeau:** The fact I'm a scientist is also something of a quirk in evolution. I was raised by hippie parents, and, as a teenager, I was most interested in art, photography, and so on. At college, I began as a classical art and archeology major, but chose a chemistry course as one of my minors. I loved it, and was hooked by science. I ended up graduating with a major in molecular biology. From there, I went to grad school at the Johns Hopkins University School of Medicine, where I worked on my PhD studying proteases and their role in prostate cancer. Following that, I worked at the University of California, San Francisco as a post-doctoral fellow studying antibody engineering. Seven years ago, I started my independent research career at the University of Minnesota, and last year my laboratory moved to the University of Wisconsin.

**CB:** I'm the CEO and founder of Elasmogen, a company that takes its



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## TOSOH BIOSCIENCE

name from “elasmobranchii” – a subclass of cartilaginous fish. Sharks are part of that family and furthermore they are the stars of my company.

In 2015, when I last spoke to The Medicine Maker (1), I was preparing to spin Elasmogen off from the University of Aberdeen after nine years of working on sharks and their immune systems – first with Haptogen, then with Pfizer, and then with the university itself. Much has changed since then – both in my company and in the world at large. The spinoff came in 2016 and was a huge landmark for Elasmogen. Our early-stage science had cohered into an investable platform, and so we began to seek collaborations that could multiply the breadth and scope of the innovations we can bring to modern medicine.

How did the two of you link up?

*CB:* Back in 2015, Elasmogen was working with a spiny dogfish local to Scotland. They're tough animals and were a great match for the kind of research that we were doing at the time. But looking ahead, we decided that we should take the existing literature into account and switch to a better-understood species: nurse sharks. We knew that getting these warm water sharks all the way from balmy Florida to the somewhat less balmy northeast coast of Scotland would be challenging – for us and the animal – so we needed to find a collaborator with access to nurse sharks, who could set up the right environment for them to ensure their continuing good health. And that's where Aaron enters our story.

The seeds of our collaboration were planted in a very “pre-COVID” corridor moment at the 2019 PEGS Europe conference in Lisbon. There I met a wonderful young scientist named Joseph Gallant, who was a member of Aaron's team in Minnesota. Joe knew about VNARs, and he knew I liked them too. It all took off from there.

At my very last conference before lockdown – the 2020 World ADC

event in London – Aaron and I had the opportunity to meet in person. There's no question about it: I think we're very similar individuals. We have the same sense of humor, the same passion for science, and – crucially – we have complementary scientific expertise.

*AL:* Joe deserves the real credit here. I sent him – a second year grad student – to an international conference in Europe, and he really went for it. Rather than devoting hours to running around Lisbon having fun (as I might have, at his age!) he attended every single session and that's how we met Caroline. It's safe to say Joe's plane tickets paid for themselves.

Prior to meeting the “wonderful shark

lady” of Aberdeen, my team and I had been most interested in using llama antibodies for our research in prostate cancer. At a certain point down the line, we had actually become interested in sharks and their VNARs, but then ran into hurdles and dead ends when trying to acquire them. As you can imagine, those encounters with Caroline in Lisbon and London marked the start of a turning point for us.

And what are the challenges of looking after sharks in the lab?

*AL:* Nurse sharks are really quite friendly animals – a little like a family dog. Whenever I walk into the room, they swim over to me. We pet them, play fetch with them, and feed





Graduate student Kendahl Ott (left) and research technician Abigail Jackson assist in the feeding

them by hand. They're also very curious animals. They like to investigate new things. To meet that urge, we popped a little rubber Thermo-branded ducky into the tank. The sharks immediately swam up and began to nudge it, play with it, and pass it around. Now the ducky lives in the tank with them – though we do need to take it out every now and again to keep the novelty from wearing off. My tip: keep your sharks sharp!

Sounds like everything was going swimmingly(!) – but then COVID-19 hit. What happened next?

**CB:** We actually had to exit our labs. From a business perspective, it was a dire moment for Elasmogen. We faced serious questions concerning R&D and maintaining the flow of the company's lifeblood – investment.

Funding from the Scottish government's Chief Scientist Office came at a critical point for us. They were keen to leverage any available platforms that might prove useful for combating SARS-CoV-2. Therefore, it made complete sense for us to pull Aaron into the conversation. While Elasmogen handled the frontend – isolating the receptor-binding domains of the virus – we drew on the wealth of coronavirus expertise, materials, and equipment that Aaron and his colleagues possess.

**AL:** When the pandemic hit, every university in the US was shut down and we had to cease all research except for coronavirus research. My laboratory metamorphosed from a prostate cancer research laboratory to a coronavirus laboratory in a matter of 12 hours.

We started this new work developing

llama-antibody-based therapeutics for the coronavirus spike protein, but when Caroline suggested using VNARs against COVID-19, we were game. We sent our spike proteins across the Atlantic to Elasmogen, and they sent back their findings. Then, very talented biologists in my laboratory took those findings and used them to form critical assays to try and neutralize a pseudovirus.

Through a collaborator, we were then able to test these VNARs against a live virus. The results floored all of us. These tiny little shark proteins worked as well as – or better than – the antibody cocktails currently on the market. The VNARs were so effective because they were so small and could recognize the spike protein in areas that were inaccessible to conventional antibodies.



Nurse sharks in Aaron LeBeau's lab feed on pieces of squid.

How were you able to pivot to neutralizing SARS-CoV-2 so quickly? And what role do you expect VNARs to play in the future?

**CB:** At Elasmogen, we have two solid platforms available for immediate deployment. The one we used for the COVID-19 project is our synthetic platform, which is a little like having thousands of sharks in a test tube that we can use to interrogate any target, including the spike protein that Aaron's team sent over to us.

All the preparation and upgrades we've implemented since 2015 have enabled us to switch from one target to another with relative ease. So when the pandemic hit, everything was in place to handle a rapid shift from our usual oncology and autoimmune targets to a deadly viral protein. We were ready to rock and roll.

**AL:** When thinking about the future, we shouldn't forget that worldwide vaccination rates remain very low. Roughly 40 percent of the world population have not received a

single dose, and in low-income countries that figure leaps to around 90 percent. In addition, there are many people who simply refuse the vaccine outright. With these factors in mind, we are purposely selecting for further virus variants. We are now at "Omicron" and I expect that we will be marching through the remainder of the Greek alphabet in short order.

As mutations in the virus accrue, it's highly possible that the current vaccines will become ineffective. When that happens, we will be facing a huge gap in therapy because the neutralizing antibody cocktails from Regeneron and Eli Lilly don't even work on the Omicron variant. The anti-COVID-19 armory will need to be retooled. We just found out that our VNARs are as effective against Omicron as they are against the non-mutated virus. This suggests that VNARs could be effective against variants yet to arise. We are investigating this right now as we speak.

Where else will shark VNARs likely make a difference?

**CB:** Elasmogen's furthest developed programs are in oncology. We have a wonderful ongoing collaboration with Almac Discovery, in which we are combining chemistry with our biology domains to create VNAR drug conjugates. We've seen again and again that VNAR's unusual interactions with their targets can translate into increased efficacy and potency.

The target we are focused on right now is triple negative breast cancer, and that work has already produced some beautiful disease model data. At present, we are working through the relevant toxicology safety studies. The next step will be our entry into manufacturing. It's all very exciting – this therapy has the potential to be our first shark VNAR in patients.

#### Reference

1. C Barker, "Shark Attack", *The Medicine Maker* (2015). Available at: <https://bit.ly/VNAR-2015>



# Through the Fire

2021 was another year of COVID-19-related challenges. As we enter 2022, will the pandemic flames finally fade?

By Maryam Mahdi

Congratulations! We've made it through another challenging year! Though the global community continued to feel the pressure of managing the repercussions of COVID-19, several therapeutic breakthroughs have saved many lives and prevented more severe damage to health and societal infrastructure.

Here, we look back on key moments that defined the COVID-19 response in 2021 and on page 56 we ask industry experts how they expect 2022 to shape up.



## Key COVID-19 Interventions in 2021

**March 5**  
EMA's human medicines committee decides that bamlanivimab and etesevimab can be used to treat COVID-19 patients

**Feb 4**  
FDA changes emergency use authorization parameters for convalescent plasma – narrowing its use to immunocompromised and hospitalized patients in the early stages of disease

**March 5**  
FDA issues a warning against the use of ivermectin

**March 11**  
EMA grants conditional marketing authorization to Janssen COVID-19

**May 28**  
EMA's human medicines committee recommends an extension of indication for Corminaty (BNT162b2), allowing children aged 12–15 to take the vaccine

**May 26**  
FDA approves Xevudy (sotrovimab)

**June 24**  
FDA grants emergency use authorization for the use of Actemra (tocilizumab) in hospitalized patients

**July 6**  
WHO recommends the use of IL-6 receptor blockers including Actemra (tocilizumab) and Kevzara (sarilumab)





**How will the events of the past two years influence future aspirations? We asked three companies for their views.**

**Digitizing Supply**

*Karan Singh, Managing Director at ACG, and John Carey, ACG Engineering*

Exposing considerable weaknesses in supply chains across the globe, the pandemic has compelled the pharma and healthcare sectors to move from a “just-in-time” approach to a “just-in-case” approach. In 2022 and beyond, we will see a rise in new delivery models built on a resilient value chain by leveraging the benefits of digitalization. But how can this be achieved? Smart, connected, and intelligent systems based on Industry 4.0 technologies will play a key role in these efforts.

Manufacturers will likely look to automation, data analytics, machine learning, and the Internet of Things (IoT) to address existing challenges. Smart factories that can use real-time data analytics and machine learning to reduce costs, improve quality, and reduce capacity constraints will be essential. Developments in predictive analytics will also make it possible for manufacturers to draw on vast pools of data, including information on resource consumption, machine performance, and storage conditions on factory floors to troubleshoot problems, optimize processes, and boost productivity.

Another prominent trend for 2022 is the move towards creating larger batch sizes. Larger batches mean companies can be more efficient by reducing costs associated with quality control and validation.

As we look to the future, the value of digital technologies is increasingly hard to ignore – especially for companies that are keen to stay ahead of (or even keep up with) the rest of the market.

**Outsourcing on the Rise**

*Jim Hall, President at Lifecore Biomedical*

Over the last two years, 75 percent of new drug development in small-to-midsize pharma has been outsourced. There is also a particular demand for vial and syringe manufacturing capacity to meet the appetite for injectable products, which make up around 55 percent of the drug development pipeline and 44 percent of all NDA approvals.

The CDMO industry is arguably designed to be nimble with a model that allows for adaptation. We can invest holistically and plan capacity against the growth of companies' diverse development pipelines. But that means CDMOs must take a proactive approach to trend assessment – and then be willing to commit to investing in the necessary capabilities to meet the market's emerging needs. Investments must do more than cover process capabilities; it's also crucial to support the growth of expertise to build on existing systems to enable more long-term strategic partnerships with customers rather than focusing on transactional service provision.

These are complex times. Being able to adapt ahead of the curve will be the difference between the winners and losers. Creating flexible work schedules, identifying second and third sources of supply for critical components, and investing in multiple facilities will all be key if CDMOs want to please their customers and help the industry navigate today's tricky landscape.

**New Opportunities on the Horizon?**

*Paul Smaltz, Head of Pharma, Roquette Pharma Solutions*

The COVID-19 crisis has challenged global pharma supply chains, with many companies forced to take remedial

action to meet fluctuating consumer demand. At the very beginning of the crisis, for example, consumers began stockpiling supplies, which led to a huge rise in demand for OTC products, before quickly declining again. And then, when healthcare experts started experimenting with possible cures, we saw increased demand for specific drugs, until they were deemed ineffective. Meanwhile, we witnessed an increase in demand for new vaccines as manufacturers raced to find an effective solution against COVID-19.

Companies must be aware of how they can overcome supply-related challenges moving forward. We managed to overcome such issues mainly through alternative logistical measures and building stockpiles. For instance, in cases where we experienced problems with sea freight, we switched to air freight. This had wider cost implications of course, but it was necessary. Now, many global organizations are re-assessing drug manufacturing supply chains to reduce the risk of supply interruptions in the future.

What lies ahead now as some normality returns? The pandemic has reinforced healthcare as a major governmental priority across the world and we are seeing pick-up of new drug projects. In particular, pharmaceutical companies are capitalizing on the demand for specialized dosage forms, including pediatric/geriatric-friendly formats that melt in your mouth, and controlled-release formulations to help patients adhere to their medication regimen.

The expiration of blockbuster drug patents in 2022 could also be interesting for the development of the excipients market too – ushering in a new wave of product innovation amongst generic drug manufacturers looking to produce their own versions of once groundbreaking medicines and treatments.

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A portrait of Thomas Otto, a middle-aged man with short, light brown hair and a friendly smile. He is wearing a dark grey suit jacket over a white button-down shirt. The background is a bright, out-of-focus window with blue and white tones.

# The Greener, Cleaner Path

Sitting Down With... Thomas Otto,  
Managing Director of Vetter  
Pharma-Fertigung, Ravensburg,  
Germany



Have you always wanted to work in pharma?

As a child, I wanted to drive trucks! Later, I thought I might like to be a teacher or to work in a technical role of some kind. I was working as a bus driver to pay my way through college with those goals in mind when a passenger asked what I was doing. I explained my story and she told me that her company was looking for people like me.

She was the head of HR at Vetter and that was the starting point. I didn't plan to work in the pharmaceutical industry, but I'm very glad I'm here.

What was your first role at Vetter?

I started as a project engineer in packaging development. Back then – in 1990 – Vetter was pretty small, with about 300 employees. In fact, there was nobody in the packaging development group, so I helped launch it. Five years later, I took over the responsibility of the whole development group and in 2002 I became a managing director.

Whenever I talk shop with my old college classmates, they tell me changing jobs and companies is necessary for a good career. But this has never been necessary for me thanks to Vetter's strong growth. I've had the chance to witness so much and take over so many responsibilities. I'm fortunate that the company has been expanding quickly enough to accommodate all my growth as a professional. It's been exciting to be a part of that growth story!

What are the day-to-day responsibilities of your role?

We do not have a CEO position in Vetter. I run the operational business together with my colleague, Peter Soelkner. Each of us is responsible for a certain part of the company; I'm responsible for development, pharmaceutical production, quality, technical services, and internal project management –

including all of the investment projects, as well as finance and controlling.

I like to say I'm the “inside minister” and my colleague Peter – who took over functions such as key account management, HR, IT, and the supply chain – is responsible for “the outside.”

Vetter has embarked on a number of sustainability initiatives. Why is this so important to you?

Today, sustainability should be paramount. And that means adopting a culture of responsibility and acting in a sustainable manner. It's important to us, it's important to our employees, and it's important for the world community and its future. Obviously, some investment is necessary to achieve sustainability. But, in the long term, the company will not only grow in a stable manner – it will profit as well. When I talk about “savings,” I'm not just thinking of reductions in carbon and kilowatts. Environmentalism is an investment with returns!

What sustainability milestones has the company hit over the years?

Vetter has invested in various energy efficient and environmentally friendly technologies. Greenhouse gas is one of the main drivers of global warming, and so we put a lot of work into that area. At all our sites, we have worked to reduce emissions. Since 2014, these technologies have resulted in an overall saving of more than 15,000 tons of carbon dioxide, which I think is remarkable.

One huge milestone became reality in 2020, when our German sites turned climate neutral. We are very proud of the fact we no longer have a carbon footprint. In 2021, our international production sites and offices also achieved CO<sub>2</sub> neutrality – made possible by the interaction of many components all working within the scope of a long-term CO<sub>2</sub> strategy within the company.

Another significant sustainability project was the construction of our center for visual inspection and logistics. I believe it is a unique facility! It has environmentally friendly block-heating, harnesses geothermal energy, makes comprehensive use of excess energy, and runs photovoltaic systems. All of this runs together to make it really efficient.

How have customers reacted to Vetter's focus on sustainability?

We find that sustainability is increasingly a focus and concern for our customers. Green factories are important to them – and we see many more inspections with this in mind. We are really pleased and proud that we began the necessary work years ago – otherwise we would be behind rather than ahead of the curve!

What drives you personally in your role and in your career?

At the start of my career, I just wanted a satisfying job! But as I moved deeper into the pharmaceutical business, I realized that I was working in an industry that saves lives. That reality left a really deep impression on me and that's why I've stayed in the industry.

At Vetter, if you want to take on more responsibility, you can – and the company helps you. In a sense, you can create your own job, which is really satisfying. Working with people to help them to achieve good results is truly rewarding for me.

When Senator h.c. Udo J. Vetter, Chairman of the Advisory Board and member of the owning family, first spoke to me, wanting to hire me as a project engineer, I said, “No. I will never work in the pharmaceutical industry. There's too much regulation! It's just not for me!” Six weeks later, my outlook had changed completely. Now look at me – I've been with his company for more than 32 years!



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