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Big Risk and Big Reward

The pharma industry's response to COVID-19 is widely accepted as exceptional, but there are clear winners and losers among the pandemic players

At the recent IPEC-Americas Excipient World event, Pfizer Associate Research Fellow Roger Pak gave a presentation that highlighted the amazing work that went into finding a vaccine. Pfizer and BioNTech agreed to expand their existing flu collaboration to COVID-19 by signing a letter of intent on March 17, 2020. By May 2020, the vaccine was in the clinic, with a data readout in July. Rolling regulatory submissions began in October. The pace of progress was incredible.

And Pfizer has been rewarded financially. The company reported full-year revenues of almost US$81.3 billion for 2021 – up from around $41.7 billion in 2020 (1). The company's COVID-19 vaccine, Comirnaty, made almost $37 billion alone in 2021.

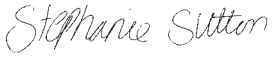
But not all COVID-19 fighters have been so richly rewarded. Though AstraZeneca enjoyed record revenues of around $37.4 billion in 2021, its COVID-19 vaccine accounted for (only!) $4 billion (2). The winnings are a fraction of Pfizer's pot – and let's not forget the "vaccine linked to blood clots" PR disaster. In some countries, use of the vaccine declined significantly, and it has not yet been approved by the FDA, with plenty of rumors suggesting that the company will be scrapping US plans (3).

Remember Janssen's nameless COVID-19 vaccine? It too was linked to a rare risk of thrombosis with thrombocytopenia syndrome, and in May 2022, the FDA restricted use to individuals for whom other vaccines are not appropriate or to individuals who elect to receive the vaccine because "they would otherwise not receive a COVID-19 vaccine" (4).

Hopes that the single-shot vaccine would become popular with young adults looking to "jab and go" weren't reflected in reality; sales reached $2.39 billion in 2021 (5). What's more, manufacturing issues at CDMO Emergent led to millions of vaccine doses being discarded. Emergent is now pushing for a payment of $420 million after J&J terminated their contract (6).

The COVID-19 pandemic perfectly highlights the enormous risks and rewards inherent in drug development. The world needs pharma companies to step up with answers to global health issues – but it's no wonder the majority of companies remain so risk-averse.

Stephanie Sutton
Editor



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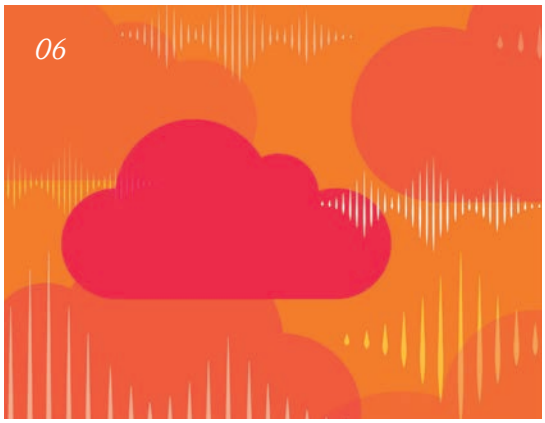

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Mycetoma patients awaiting diagnosis and treatment at the Mycetoma Research Center in Khartoum, Sudan.

Credit: Lameck Ododo – DNDi

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the Medicine Maker

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Feel free to contact any one of us:
first.lastname@texerepublishing.com

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Change of address info@themedicinemaker.com
Tracey Nicholls, The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@themedicinemaker.com

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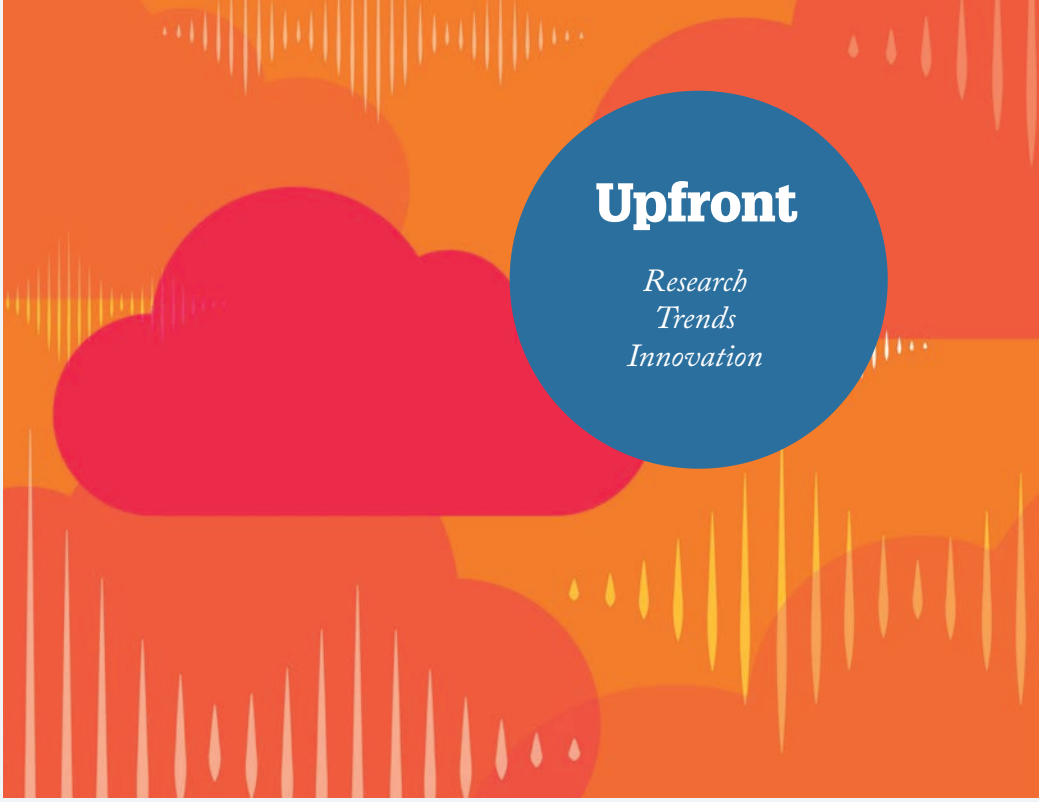

The Pills Are Alive...

...with the Sounds of Sanofi

You've heard of chamber music, lounge music, and elevator music. Now prepare to meet… lab music. And by "lab" we don't mean Dr. Dre's recording studio, we're talking actual laboratories – the pharmaceutical laboratories of Sanofi, to be precise.

In April, SoundCloud account "The Sounds of Sanofi" dropped its very first track: Stir, Stir, Stir, followed by five more with titles connoting everything from studio-era technicolor Hollywood (The Sound of Solution), to postwar dad rock (Tornado in a Test Tube), all the way to 90s euroclub dancefloors (Mix to the Max) (1).

But the Sounds of Sanofi are a little more austere than their titles suggest. Every track is a recording of Sanofi lab equipment at work, with no accompaniment. No drums, no power chords, and no patented Sanofi saxophone. Sanofi have pitched their tracks into a very 21st century genre: ASMR, which stands for "autonomous sensory meridian response" – the practice of producing sounds that trigger a shiver down their spine or a strange (and for some, quite satisfying) sensation. One @SanofiUS tweet tagged #InternationalASMR day, while another noted that the Sounds of Sanofi can help people "destress and unwind" for Stress Awareness Month.

Seems like a prank? A belated April Fool's jest? Think again. Speaking to Endpoints (2), Sanofi's Stefan Roehr (Head North America Supply Chain, Distribution, and Logistics) comes off as sincere, explaining that "providing some type of de-stressing sound" was "really the goal and the intention" of the project, adding that a search is on at Sanofi to find more tickly little sounds "upstream and downstream" across clinical development.

Roehr didn't leave it there though, expanding further, "CEO Paul Hudson says that we're chasing the miracles of science and this innovation and the things that we're doing really capitalizes on that idea and that movement."

While you attempt to interpret that gnomic utterance, keep an eye on the Sanofi TikTok. More aesthetic audio ambience may well be floating down the (gently whirring) pipeline.

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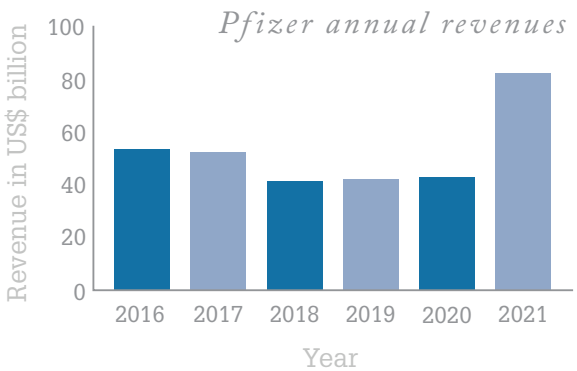
INFOGRAPHIC

Evaluating Pfizer's Revenues Post-Pandemic

Pre-pandemic, Pfizer was staring down the patent cliff with shrinking profits, but Comirnaty has provided a significant financial boost



Top selling Pfizer products in 2021

- Comirnaty: **$36.8 billion**
- Eliquis: **$6 billion**
- Ibrance: **$5.4 billion**

BUSINESS-IN-BRIEF

Monkeypox vaccine orders, cell therapy movie stars, and warning letters for cannabinoids…What's new in pharma this month?

- The US government's Biomedical Advanced Research and Development Authority (BARDA) has ordered an additional half million monkeypox vaccines from Copenhagen's Bavarian Nordic. The order will bring the American government's total stock of the Nordin's liquid-frozen JYNNEOS vaccine to almost 2 million, following a previous order of 1.4 million.
- A report from PhRMA has tallied over 500 medicines for blood disorders currently in development in the US. Of the 549 counted, 173 are for lymphoma, 159 for leukaemia, and 82 for multiple myeloma. The report directly remarks on the strong presence of gene therapies in the tally.
- The FDA is looking to empower consumers to self-treat certain common conditions and improve public health by increasing the range of marketed nonprescription drugs. A proposed rule has been published: Nonprescription Drug Product With an Additional Condition for Nonprescription Use.

- Advanced therapy stars Bruce Levine and Carl June hit the red carpet at New York's Tribeca Film Festival, at the screening of Of Medicine and Miracles – a documentary on the first ever CAR T therapy. The film tells the story of their treatment of six-year-old leukemia patient Emily Whitehead.
- Driven by concern over false claims of health benefits against serious illnesses and packaging designed to appeal to children, the FDA has sent warning letters to five companies for selling products labeled to contain delta-8 THC in ways that breach America's Federal Food, Drug, and Cosmetic Act of 1938.

Farewell, Amfepramone

Propensity for risky misuse spells doom for range of anti-obesity drugs in Europe

Amfepramone obesity medicines – which work by helping to reduce hunger – are to be withdrawn from the EU market following a recommendation from the EMA's PRAC safety committee (1), which says the drugs are often used for longer than the recommended 3-month period. Prolonged use can increase side effects such as high blood pressure.

Although amfepramone obesity medicines are indicated for the short-term management of obesity, the EMA says there is limited efficacy as the patients usually regain weight after finishing the treatment. A statement from the EMA says that the committee did consider introducing further measures to minimize risk, but "could not identify any that would be sufficiently effective." It's also worth adding that other obesity treatment options are available.

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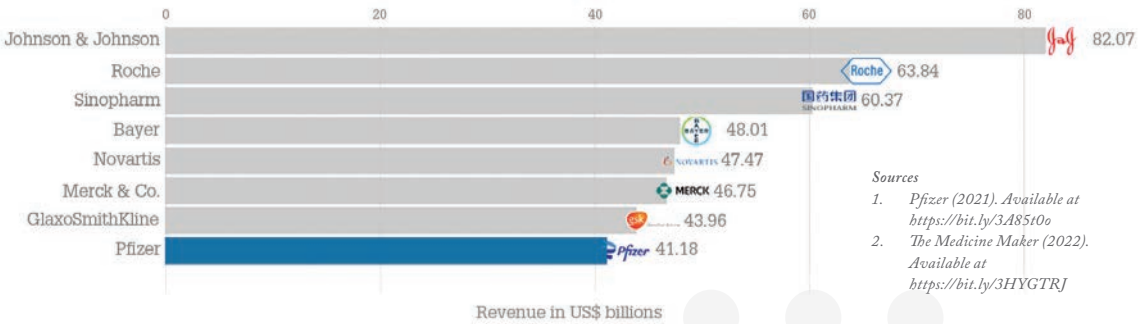
Pfizer's revenue in 2019 relative to other big pharma companies



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Around **1.4 billion** patients used Pfizer medicines in 2021 – that's roughly **1 in 6** people on the planet

Believe the Hype

Could this rectal cancer drug be the real deal? Results from a small trial are highly promising

"Doctors left shocked after clinical trial for cancer drug cures the disease in every participant." It reads like classic consumer media, doesn't it? We're all used to rolling our eyes at bombastic headlines like this; the kind that latch all-too-quickly onto new treatments and set patients up for near-inevitable disappointment.

But, in this case, you can dispense with your cynicism because the results genuinely seem exciting.

For the last two years, Memorial Sloan Kettering Cancer Center has been investigating an immunotherapy involving GSK's checkpoint inhibitor dostarlimab (Jemperli – approved by the EMA and FDA in 2021 for endometrial cancer). The results were recently published (1); tumors in all 12 patients in the trial disappeared – a complete clinical response without the need for surgery or chemotherapy. Follow up ranged from 6 to 25 months – and enrolment in the trial continues. Since the study was published, two more patients have also become tumor-free.

However, the treatment is only applicable to a niche group of patients with stage 2 or 3 rectal tumors that have a specific genetic makeup known as mismatch repair-deficient (MMRd). Only around 5–10 percent of rectal cancer patients fall into this category.

In a statement, Andrea Cercek, a medical oncologist at the center, said, "It's incredibly rewarding to get these happy tears and happy emails from the patients in this study who finish treatment and realize, 'Oh my God, I get to keep all my normal body functions that I feared I might lose to radiation or surgery.'"

The investigators are (understandably!) very excited and are encouraging rectal cancer sufferers to find out if their tumor is MMRd (2). The team is also investigating if the same method could help other cancers, and has already started to enroll patients with stomach, prostrate, and pancreatic cancers.

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Paralyze the Parasite

A new method for muting malaria turns one of the parasite's proteins into a self-destruction device

"Imagine a stealth weapon that can be used to launch a self-destruct attack on your vehicle – slamming on the brakes and cutting the engine," says Leann Tilley of The University of Melbourne (1). No, she doesn't work in the War Studies department; Tilley is a scientist at the university's Bio21 Institute, and co-author of a recent paper that describes a new means for combating malaria (2).

The paper describes the application of ML901 – a compound able to hijack and shut down the malaria parasite without damaging its mammalian host. ML901 enters the malaria parasite aboard an amino acid then seals its doom by breaking the parasite's protein production engine.

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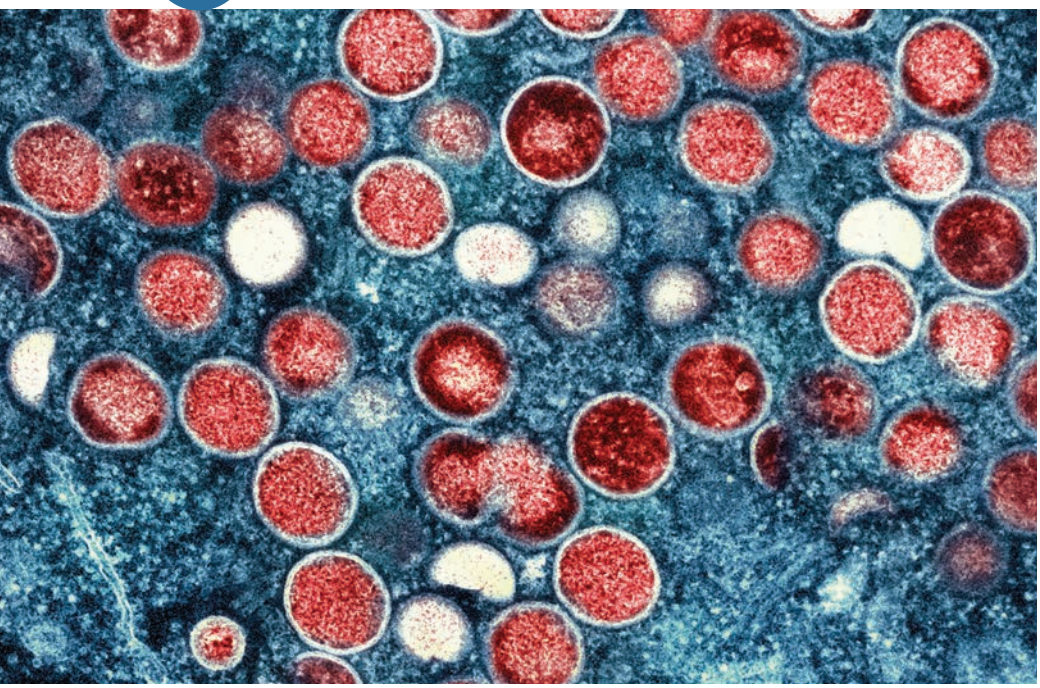
IMAGE OF THE MONTH



Paint Your Enemy

An electron micrograph image of monkeypox virus particles, cultivated in the lab and digitally colorized in striking red against an icy blue backdrop.

Credit: NIAID (2022) <https://bit.ly/monkpx>

Would you like your photo featured in Image of the Month?
Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"Ahmed was a Co-PI for the clinical studies that we were conducting in Sudan, and since then he has been my teacher and friend. He's the one who taught me more about leishmaniasis. We've managed to develop a very good relationship – now he knows my family, and I know his family."

The DNDi's Simon Bolo on working with the University of Khartoum's Ahmed Musa in the Leishmaniasis East Africa Platform (find more on page 21)

Linezolid Lives Again

Research in the global south finds merit in a drug once considered too risky for use

A study spanning South Africa, Peru, Brazil, Iran, and Uganda – funded by the Australian National Health and the Medical Research Council – has found that a multidrug-resistant tuberculosis drug that was previously considered unsafe for pregnant women can actually produce favorable outcomes (1).

Of the 275 women treated with the antibiotic drug, Linezolid, 72.5 percent were cured or completed the treatment, and 73.2 gave birth to healthy babies. In the other 26.8 percent of births, the scientists concluded that the disease and not the drug was responsible for adverse outcomes, such as stillbirth, pregnancy loss, and low birthweight.

The researchers also advised further investigation into the health risks posed by long term use of the drug, which range from digestion and hearing loss to mental health disorders.

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In My View

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

A Tale of Two Continents

How discussions between the European and African Unions have culminated in a new deal for African vaccine production

By Stavros Nicolaou, Group Senior Executive, Strategic Trade at Aspen Pharma Group

In my country South Africa, we seem to be moving through the final stages of our Omicron wave. However, this doesn't mean we've reached the end. Experts have predicted a fifth wave in the winter months, possibly to be sparked by a new variant, which will hopefully continue the downward trend of lower virulence experienced with Omicorn.

And even when the COVID-19 pandemic is over, we will still need to be prepared for future pandemics. Letting our guard down once COVID-19 is "over" would be foolhardy; you cannot plan for pandemics at the onset; you need to plan between them. Preparedness is crucial – everywhere. Here in Africa we are seeing various moves toward this level of preparedness, but bolstering the strength of our healthcare system remains an ongoing challenge.

Just recently, representatives from the EU and the African Union convened in Brussels for the sixth EU–AU summit (1). Naturally, they hit on a wide range of topics, including two dedicated sessions on vaccines, which resulted in the various parties releasing a highly significant joint statement: "Learning from the current health crisis, we are committed to supporting fully-fledged African health sovereignty, in order for the continent to respond to future public health emergencies."

I believe that "sovereignty" is an enormously important keyword here. To date, Africa has received only 4 percent or less of the global vaccine rollout. At the time of writing, only 18 percent of the continent has been vaccinated. African vaccination programs commenced rather late in the pandemic, and found themselves dependent on Indian vaccine manufacturers – a dependence that became a problem when the Indian government imposed export restrictions.

The lesson that I – and many others in Africa – have taken away from these past 24 months is that we need to focus on using local capacity to solve local problems. We've found that the rest of the world will look after itself first – understandably – and only move to help others once it finds itself with a sizable oversupply of vaccines.

Of course, your local capacities are only as good as your multilateral procurement agencies. Far too many times, I've seen facilities open in Africa to meet an initial demand, only to run into security-of-supply problems further down the line. If there's no demand, the facilities shut down and become white elephants.

We must do a little swimming against the tide. Right now, the African continent's import/export model more or less boils down to the export of raw materials – especially rare metals – and the import of more advanced products. Consider mobile telephones as an example; their production is dependent on metals often sourced from Africa, but those same raw materials are used in advanced manufacturing on other continents and sold back to Africa at prices significantly higher than the collective cost of the raw materials.

It's no surprise then that Africa imports 99 percent of its vaccine requirements, and produces only 1 percent "in house." Zooming further out, we can see the real absurdity of the situation. Africa has, by far, the worst disease burden of any continent. Africa suffers from both non-communicable and communicable diseases, but the continent continues to import almost all of its medicine requirements. This is counterintuitive.

The answer is localization, but localization depends on access to scarce technologies. The problem of access can be solved by technology transfers and IP transfers. This is what happened with HIV; we managed to bring generic antiretroviral products to market via voluntary licensing.

"The lesson that I – and many others in Africa – have taken away from these past 24 months is that we need to focus on using local capacity to solve local problems."

In the case of COVID-19 and the pandemics of the future, I have some views on how to remedy Africa's pharmaceutical conundrum. My employer, Aspen, is collaborating with Johnson and Johnson (J&J) and others to commence vaccine production in Africa. Aspen had already built up significant sterile capacity and capability over the years, running from the city of Gqeberha (formerly Port Elizabeth) as the largest supplier of general anesthetics outside of the US. At the onset of the pandemic, we became a major supplier of muscle relaxants and anesthetics to Europe because we were working to meet a demand that was surging in response to mass-hospitalizations that came first in Italy and France, and then Spain. General anesthetics and muscle relaxers are used to ventilate patients.

The pandemic spurred our collaboration with J&J, which began as a contract manufacturing agreement; we would manufacture their vaccine and they would determine its allocation and distribution. They transferred their technology to us in October 2020 (to enable the contract manufacturing to take place), and production began in March 2021. To date, we have produced around 180 million doses for and on behalf of J&J, the majority of which have either been used or bought by Africa.

This partnership was certainly a positive development and led to the next step, which was the conclusion of a licensing agreement between Aspen and J&J, whereby J&J licensed its IP to Aspen, which leads to vaccine autonomy.

That in turn led numerous African leaders to engage in extensive discussions with the EU, the World Bank, the World Trade Organization, World Health Organization, and other important multilateral organizations. Leaders from Africa included South Africa's President Cyril Ramaphosa (who also happens to be the African Union's COVID-19 champion) and various leading figures who serve on the African Vaccine Acquisition Task Team and the Africa Center for Disease Control and Prevention.

The conversations led to a new licensing agreement between Aspen and J&J, announced in November 2021, which grants Aspen access to the IP for the Janssen COVID-19 vaccine, so we can produce it under a name of our own choosing (Aspenovax). Essentially, the deal gives Aspen the ability and capacity to produce its own vaccine and to allocate and distribute into African markets, which in turn grants Africa greater security of supply and greater vaccine autonomy. Once this is achieved, the likes of Indian export restrictions during pandemics become less of a headache and less able to induce crises.

More recently, we've made a more strictly Euro-African collaboration with two German companies: Siemens and DEG. The German government also got involved here – in fact, it was the German Federal Ministry for Economic Cooperation and Development that commissioned DEG to invest in our capacities, as part of a general recognition of the uneven distribution of vaccines globally, and a need for European players to help in addressing the issue.

In short, Aspen has received digital technology that enables people on our production lines to more readily discard potentially defective products. The vaccine product is highly temperature sensitive, so if it is moved outside of safely controlled temperature levels then it's important that we catch it as soon as possible. The new technology provides alerts that help us do that. The German government is also helping to fund the training necessary to use the new technology.

I may have made this all sound very easy, however I can assure you this is not the case. Licensing technology can be a very complex and tense issue. To be willing to license away your IP, you really need to trust the licensee. If the licensees don't have the necessary expertise, capability, and competence, then the R&D based companies won't feel comfortable. In this case, J&J made a concerted effort to find the most competent players on the continent. I'm proud that they settled on Aspen.

Speaking of trust and pride, I'll add that Aspen and its capabilities don't exist in a vacuum. We are proof that Africa has expertise. To help the story of Aspenovax become part of a continuing pattern and not just a one-off story, Africa needs more champions. I hope future endeavors will better prepare the continent for the next pandemic.

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The Best of Both Worlds

Academia-industry collaboration doesn't have to be difficult; we just need to appreciate one another's differences

By Viktoria Gessner, Chair of Inorganic Chemistry at Ruhr-University Bochum, and Angelino Doppiu, Global Technology Director at Umicore, Hanau, Germany

Scientific endeavor across almost every sector of industry relies on collaboration. Whether it's the development of a lifesaving new drug or the creation of a novel sustainable reaction pathway for use in drug manufacturing, cooperation often plays a key role. Collaboration between industry and academia is particularly important in a number of industry sectors. By collaborating with academic colleagues, businesses can grow their capabilities, gain access to powerful new technologies, and explore a different kind of creative thinking to what lies within their own four walls. But despite the best intentions by both parties, maintaining positive relationships between academia and industry can be challenging. Here, we briefly outline our top collaboration tips, based on experience from a collaboration between Umicore and Ruhr-Bochum University, Germany, on ligand and catalyst technologies (1).

With such different backgrounds, it's natural for industry and academia to hold distinct priorities. This can lead to tension, even within tasks as simple as choosing a publishing route for project results; academics may have preferred journals for example! Our first piece of advice: do not ignore the differences, acknowledge and embrace them.

Each party will be hoping to derive different benefits from a project and, at any point, unforeseen issues may change priorities for one or both parties. With any collaboration, you must be flexible and understanding. Take the differences in attitudes on board and appreciate that it's natural to have contrasting concerns and opinions. This type of mindset can reduce tension by ensuring that all communication comes from a place of understanding.

To more practically demonstrate flexibility, companies can allow researchers a level of freedom in the research routes they take. Though it can be tempting for a company to set out exactly what they require, serendipity often plays a role in discovery. By giving universities a broad remit on what they want to investigate – and trusting their expertise – unforeseen innovation can arise. You'll also be reaping the benefits of what academics tend to do best: create. A flexible approach to rules and guidelines can also be beneficial when it comes to addressing the inevitable changes (and unforeseen challenges) every project faces.

For the duration of an academia-industry relationship, active cooperation is also key. Though the two parties may work together naturally, actively engaging with the relationship allows

"In our view, academia–industry collaboration is a fertile opportunity to drive new product pipelines and bring cutting-edge innovations to market. By combining the expertise of both parties, the best of both worlds can be achieved."

you to develop a greater level of trust and get more out of the partnership. For example, academics have the opportunity to gain a viewpoint on the current industry landscape, which can be of great value as individuals in positions that normally lack such insight. Academics can also speak at conferences and publish results in peer-reviewed journals, which can accelerate career growth. The industry partner can also offer resources (such as chemicals or lab equipment) relevant to not only the collaboration, but other projects as well. This can go a long way toward establishing trust and faith between the institutions.

Perhaps the top piece of advice that we can give is to consider communication. The foundation of any professional relationship is a strong line of communication – and a lack of it, therefore, is a common cause for relationship breakdown. Without open communication, it's easy for researchers to choose industrially irrelevant research pathways – but with it, collaborators can foster innovation, improve understanding, and even explore new research avenues and commercial applications. Only by maintaining strong communication through check-ins and discussions can this potential be accessed.

We recommend maintaining discussions across several platforms – calls, meetings, and emails are a few such examples. You should also aim to communicate regularly; long periods without communication increase the chances that a project will become misaligned on either end. To avoid this, it's important to define clear goals, targets, and expectations when initially setting out the project. Both parties should know what they're getting into from the very beginning. And it's not just about a partnership between two people, or even two research groups; companies should maintain positive relationships with not just researchers, but research institutes as well. Forging well-rounded professional relationships is the key to success in long-term collaboration.

In our view, academia-industry collaboration is a fertile opportunity to drive new product pipelines and bring cutting-edge innovations to market. By combining the expertise of both parties, the best of both worlds can be achieved and your company's offerings expanded. Furthermore, by maintaining the pillars of cooperation, flexibility, and communication, you can ensure that both sides of the relationship are getting the most out of it.

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NÜRNBERG MESSE

The Early Bird Gets the...

All decisions have a ripple effect throughout your cell sourcing supply chain; you must adopt a commercial mentality right from the start

By Joy Aho, Senior Product Manager at Be The Match BioTherapies

When it comes to your supply chain for cell sourcing, you must embrace a commercial mindset whatever phase of development your cell or gene therapy is in. And that means starting with the end goal in mind and working in reverse. Why is this important? With the anticipated trajectory of cell and gene therapy development and approvals, you need a resilient cell sourcing infrastructure from the start, including suppliers that can meet your long-term demand.

What does this mean in practice? Let's look at each step of the supply chain in reverse starting with the patients who will receive the therapy. First of all, you need to think about your indication. The supply chain for a cell therapy treating a rare disease has far different needs than one that will be delivered to thousands of patients per year. Equally important is where the patients will be treated. Here, I'm specifically referring to the country where the therapy will be delivered. Different countries have different regulatory requirements for starting material collection and manufacturing. If you expect your therapy to have international distribution, you need to think beyond where your initial clinical trials take place. This is particularly important for allogeneic therapies (where the same starting material may be used to create therapies for multiple patients).

Consider the following scenario. You collect starting material for your allogeneic cell bank in a manner that is compliant with FDA regulations in the US. Later, you decide you want to distribute your therapy in Australia. The US and Australia have different regulations when it comes to donor screening and product testing for use as allogeneic cellular source material. The differing regulations could render your FDA-only compliant material ineligible in Australia.

You can avoid this by thinking about distribution – and varying global regulations – from the start.

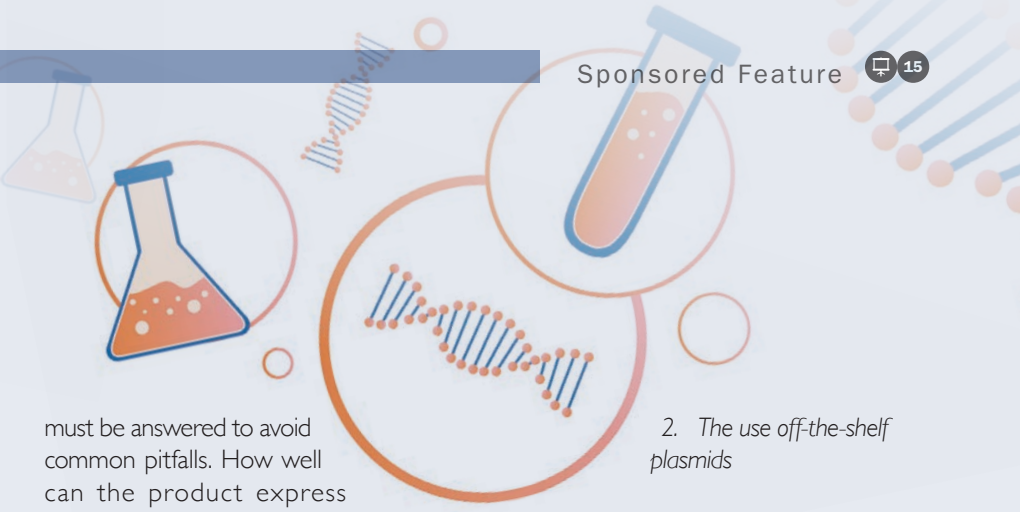
Next, what type of cells will you use as your therapy starting material? This decision impacts how you transport the material. Some cell types are very sensitive to cryopreservation so fresh shipments are necessary, but regardless of method (cryopreserved or fresh), you need to keep an eye on your vendor and make sure they know what they are doing when it comes to moving time-sensitive starting material or cell therapies around the globe. Numerous obstacles can stand in the way of a product delivery – from weather delays to a global pandemic… You need to make sure your vendor is up to the job.

The decisions you make upfront, such as fresh versus cryo, will also impact which apheresis centers can collect for your therapy. Different centers have different cell processing capabilities. And that's also true for capabilities beyond cryopreservation, which is why you need to determine the requirements for your protocol as early as possible; not doing so will cost you development time – and your ability to scale up collections quickly.

Finally, for allogeneic cell therapies, you must know the donor attributes that are critical to the safety and efficacy of the end product as you develop a cell bank that can meet the needs of future patients once your therapy is commercially approved. The more requirements you put on donor characteristics, the larger your donor pool needs to be. Each donor attribute eliminates some portion of the donor population – and the size of the donor pool you need may surprise you. Therefore, it is essential to ensure that the supplier you select to provide allogeneic starting material has a donor pool large enough to meet your needs – especially as you scale.

I worked with our team on an analysis of frequency data for different genetic types within our donor registry to learn the starting pool size needed for 10 qualified HLA-matched donors for a therapy. In the case of the fiftieth most common HLA genotype for donors who self-reported being Hispanic or Latino (which may not seem common but is out of 462,000 genotypes), the donor pool would need to be over 600,000. And, that's before taking other demographics, such as age or sex, into account.

I hope I've persuaded you of the extreme importance of keeping future commercial scale in mind. By adopting a commercial mindset, you can think about your potential needs from a clinical and commercial standpoint from the very beginning. And that's the mindset you need to help set your therapy up for success.



The Cell and Gene Endgame

For effective and efficient cell and gene therapy manufacture, companies need to make better plasmid design decisions with the end goal in mind: commercialization

Viral vectors are nothing short of game-changers when it comes to modern therapeutics. From vaccines to gene therapies, they have the potential to address disease in a way that wouldn't have been possible just a decade ago. However, although viral vectors are used to develop a range of therapeutics, several considerations are vital to ensuring ultimate clinical success.

Plasmid DNA is the critical starting material in a transient transfection production system, which is still the preferred route of vector production. Plasmid DNA defines the functionality and safety of finished therapeutic products – carrying the genetic code for the final therapeutic gene and coding for the vector capsid. Simply put, plasmid DNA is the backbone of viral vector development.

But when and how should companies approach plasmid selection and design?

Plasmid DNA will, of course, be used during the early stages of development. But before steaming ahead, companies should consider how their initial choices on selection and design will impact future stages in the clinical development process. As commercialization represents the route to the patient, investing sufficient time to assess how these early decisions affect this crucial endgame of product development is essential for clinical success.

Better by design

Manufacturing plasmids can be time- and resource-intensive. Before creating plasmids that elicit therapeutic benefits and achieve efficient delivery, several key questions must be answered to avoid common pitfalls. How well can the product express genes? Are the right cell types targeted by the product? How safe is it? Who owns the IP and what potential royalties must be considered?

Companies developing therapeutics need to consider these questions and address them early on to identify how their products will be used before they move into manufacturing in-house or with an outsourcing partner for their manufacture and scale-up.

Here are two points that developers must evaluate:

1. *The ability to produce stable plasmids at scale*

In viral vector production, plasmid yield is of paramount importance. When working with gene of interest plasmids such as those for AAV or Lentivirus, a major consideration is regions such as inverted terminal repeats (ITRs) in AAV's or Long Terminal Repeats (LTRs) in Lentivirus. These regions are challenging to work with because of their poor stability, which impacts viral vector producing efficiency. Sequencing the plasmid at multiple production stages, prior to production and during production, allows developers to confirm there are no mutations during plasmid development. Modification and repair strategies that improve the overall efficiency and productivity of plasmid production often greatly improve transfection efficiency and vector productivity, further reducing cost. Additionally, changing vector design late in programs presents cost, timelines, and regulatory issues that are better to avoid.

2. *The use off-the-shelf plasmids*

Another consideration early on is the use of standard off-the-shelf plasmids, such as the pHelper and Rep/Cap plasmid required for AAV production, and equivalent plasmids for lentivirus production. These standard catalog plasmids offer the advantage of being immediately available, reducing development costs and simplifying supply chains.

As a leading cell and gene outsourcing partner, Charles River knows how important it is for developers to save time, accelerating the transition to the clinic, but this must be balanced with taking the right steps for successful clinical development. From many years of guiding clients, our team knows how important guiding plasmid selection is to preventing issues later. Furthermore, our robust in-house testing capability allows for reduced time between production stages, from plasmid to vector and beyond. These overall time savings allows developers to focus on their cutting-edge science that drives innovation. The better by design approach the team takes supports companies to take the right steps, the first time – because funding is limited and patients are waiting.

Should you require guidance in determining an appropriate plasmid or vector design for your specific cell or gene therapy – or if you need assistance with development and manufacturing – contact Lara Peacock, Marketing Manager, CGT CDMO: lara.peacock@crl.com

For more information on cell and gene therapy manufacture and the importance of plasmid design decisions visit https://bit.ly/3zsXeM4

Medicine Makers *Without Borders*

CURATED HIGHLIGHTS FROM OUR SIX-PART PODCAST SERIES ON THE INCREDIBLE WORK OF THE DRUGS FOR NEGLECTED DISEASES INITIATIVE (DNDI)

By Angus Stewart

In the summer of 2021, I found myself grappling with an article about a new drug treatment for hepatitis B in Malaysia, developed through a partnership between the Malaysian Ministry of Health and an organization with which I was unfamiliar: the Drugs for Neglected Diseases initiative (DNDi).

I learned that DNDi is an international organization focused on discovering and launching medicines for diseases that most pharma companies following a conventional "IP and profits" business model would not touch. I learned that DNDi focuses its efforts in the global south, especially in Africa and Southeast Asia.

I ended up so enamored with DNDi that I wanted to run a podcast series on them. DNDi were keen to participate, and, while working to set up interviews, I soon found that DNDi's collaborators were also flush with enthusiasm – everybody wanted to get the message out. The stars were aligned!

The podcast – "DNDi: Medicine Makers Without Borders" – aired its first episode on April 4, 2022, and ran a new episode every two weeks until hitting its sixth and final episode in early June. Though it was a short series, we covered a lot of ground. I spoke to leaders in AI and open science, as well as DNDi-partnered doctors who are fighting hard against neglected diseases that plague the global south, such as mycetoma and leishmaniasis.

In this feature, I share curated transcripts from some of the series' best moments. You'll also find a kind retrospective on the series from "friend-of-the-pod" Ben Perry – DNDi's Discovery Open Innovation Leader, who featured in two of our episodes and did a great deal of work behind the scenes to help make this series happen. Thank you, Ben!

If you would like to escape the pages and listen to this series on your smartphone or other data-devouring device then just search for "Medicine Makers Without Borders" and you'll find us. You can listen via our website or – better yet – subscribe on your favorite podcast provider. From Apple Podcasts and Audible to Player FM and Podbay, we're on all of them!

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the episodes

1. WHO ARE THE DNDI?

with Bernard Pécoul

All things have their beginning, and no change arrives devoid of a cause. Accordingly, we kicked off our mini-series with a very special guest: DNDi's founder and fearless leader, Bernard Pécoul. He discusses the organization's origins, its mission, and how it aims to challenge and change the status quo.

***Bernard Pécoul** is the Executive Director of the Drugs for Neglected Diseases initiative*

2. NEGLECTED DISEASES AND HOW TO BEAT THEM

with Wendy van de Sande and Ahmed Fahal

Episode 2 looks at the DNDi's work on mycetoma – an infection that slowly inflicts disfigurement and disability on patients in rural, often isolated, and underserved regions in the global south.

***Wendy van de Sande** is an Associate Professor in Medical Microbiology and Infectious Diseases at the Erasmus University Medical Center in Rotterdam*
***Ahmed Fahal** is a Professor of Surgery at the University of Khartoum, Sudan*

3. OPEN SOURCE, OPEN SCIENCE

with Ben Perry, Andrea Vernall, and Aaron Mothersole

We turn to open source. First, we talk to Ben Perry and Andrea Vernall about DNDi's Open Synthesis Network for drug discovery, and then we venture into the academy to speak with one of the students contributing to the Network. Turns out there's some truth to the old maxim: "information wants to be free, man!"

***Ben Perry** is the Discovery Open Innovation Leader for DNDi. He can be found on Twitter at @MrBenGP*
***Andrea Vernall** is a Senior Lecturer in the School of Pharmacy at the University of Otago*
***Aaron Mothersole** is an MRes Drug Discovery and Development Researcher at Imperial College London*

4. THE CUTTING EDGE

with Ben Perry, Pushmeet Kohli, and Alpha Lee

Here, we continue our focus on digital as we look at DNDi's use of next-gen digital projects in open science. This episode is a bit of a two-parter. In our first interview, we talk with Pushmeet Kohli from Google's DeepMind. Then, we talk with Alpha Lee of the University of Cambridge about his role in the COVID Moonshot. Also joining us (for a second time!) is the DNDi's own Ben Perry!

***Pushmeet Kohli** is Head of Research in AI for Science, Reliable and Trustworthy AI at DeepMind. He can be found on Twitter at @pushmeet*
***Alpha Lee** is a Winton Advanced Fellow and Royal Society University Research Fellow (from Sept 2020) in the Department of Physics at the University of Cambridge. His research group lives online at alpha-lee.com*

5. A LEAP OF FAITH

with Simon Bolo and Ahmed Musa

We look at the Leishmaniasis East Africa Platform, also known as LEAP. Talking us through this interconnected, collaborative network are two LEAP members: Ahmed Musa of Khartoum University and Simon Bolo of DNDi Africa. This is a fascinating discussion on many of the serious hurdles faced by medical professionals working in the region.

***Ahmed Musa** is a Professor of Immunology and Infectious Diseases at the Institute of Endemic Diseases in the University of Khartoum*
***Simon Bolo** is Head of Leishmaniasis Access for DNDi Africa. He can be found on Twitter at @BoloSimon*

6. DENGUE, AND THE FUTURE OF DNDI

with Panisadee Avirutnan and Isabela Ribeiro

No existing medicine can defeat dengue. It's one of the top ten threats to global public health, and as the effects of global warming begin to bite, the stage is set for its spread outward from the tropics. This looks like a job for medicine makers without borders.

Panisadee Avirutnan of Mahidol University and the DNDi's own Isebela Ribeiro walk listeners through DNDi's opening gambit against this neglected, climate-sensitive disease. Can the nonprofit model stop dengue in its tracks?

***Panisadee Avirutnan** is an Associate Professor in the Department of Immunology at Mahidol University in Bangkok*
***Isabela Ribeiro** is the Director of DNDi's Viral Diseases Cluster*

Bernard Pécoul, Executive Director of the DNDi

WORDS WITH THE FEARLESS LEADER

WHERE DID DNDI COME FROM – AND WHERE IS IT GOING?

Tell us a little about yourself…

I'm a medical doctor, and I've been the Executive Director of the DNDi since I created it in 2003. Prior to that, I spent 20 years in different positions at Médecins Sans Frontières (MSF).

In one sentence, what is DNDi?

We try to bring the best science to the most neglected populations.

And, in as many sentences as you like, what's the origin story of DNDi?

We were born out of the frustration of MSF doctors like me, who were unable to give patients the proper treatment for severe diseases. Typically these were neglected tropical diseases, such as sleeping sickness, leishmaniasis, and Chagas disease.

Addressing that problem was the basis for our new initiative. It began as a working group, then became a nonprofit organization. Our mission was to bring together players from the public and private sectors to collaborate on research, development, and innovation for neglected diseases. Since then, we're worked to put in place a portfolio of research and development that can deliver new treatments for populations facing those diseases.

Does DNDi challenge the status quo of drug development?

Yes! We throw down this challenge to help populations who live outside of the profitable market. Neglected diseases affect poor people, and the current system under which pharma operates has no interest in poor people. This disregard is most striking in low- and middle-income countries, but more and more gaps are opening up in high income countries too. We have to challenge this system. We need to see patient needs driving innovation, not profit.

Speaking of profit, how do you persuade for-profit partners to work with you?

Let's take the example of our collaboration with Sanofi. It was on malaria, working to combine two existing drugs into a new medication. Through collaboration with academia and a small biotech we had secured our formulation, and we then went to Sanofi in search of an industry partner who could help us with scale up and distribution – cheaply – in Africa. We needed it to be affordable – less than $1 for three days of treatment. This aspect was fundamental.

Sanofi accepted our offer and adopted a "no profit, no loss" model. Thanks to that, we were able to get this treatment to 7.1 million people at a price of 70 cents. And, in fact, this was a good deal for Sanofi too. It was good for their reputation, and it also allowed them to establish a presence inside an African country – maybe not a big attractive market today, but one day it could be.

Of all the changes that DNDi has brought about, which ones make you feel most proud?

We have made great headway on sleeping sickness. When we started, we were still using arsenic to treat these patients. Access to safe and effective treatment was a major issue. Thanks to our efforts, access is opening up. We have achieved similar progress in leishmaniasis and other diseases too.

I'm also very proud of the partnerships we've developed with players in the private sector. These have been not only with big companies, but also with biotechs and generics companies based in countries such as India, Egypt, Argentina, and Malaysia. Alongside partnerships with governments, public sector institutions, and the academic sector, we've built up a very solid index of partnerships.

Are there any areas where you are forging ahead?

Antimicrobial resistance! We incubated a new organization, called GARDP, that is now working on responding to the needs of patients affected by antimicrobial resistance. They don't quite follow the usual DNDi model. In neglected tropical diseases, your mission is to treat more people. When it comes to protecting existing antibiotics, less treatment is the goal! Additionally, though, you need to develop new antibiotics. But in terms of building partnerships to develop innovation, GARDP and DNDi use – and need – the same model.

What are the biggest challenges that you regularly face in your work?

The central challenge is securing the resources necessary to conduct research and development for extremely neglected populations. The ways to go about doing this are not obvious, and are often riddled with faults. Early on, DNDi's founding staff opted to diversify our resources because we did not want to end up dependent on a single source. In fact, according to the strategy we formulated, we did not want a single contributor providing more than 25 percent of our resources. This is a good rule to stick to, but it does create work. We need to constantly renew and review the full range of our relationships. We receive funding from governments, from private foundations, and from private individuals. It's not easy because our focus isn't one that tends to spontaneously attract interest from these groups.

What's the biggest surprise from your time with DNDi?

When we first set up DNDi, we were really not sure that we would ever be able to attract private sector partners. Since then, we have built trusting, solid partnerships with private sector partners, and that has been a great and pleasant surprise. The second kind of positive surprise I'd mention is the capacity and enthusiasm from partners working in very difficult settings. For example, in the Republic of Congo we are setting up very intricate projects in very difficult settings. The motivation and talent our partners in those countries have shown while implementing complex science in difficult conditions has been a wonderful surprise.

What can we expect from DNDi in the years ahead?

We are quite ambitious! We just reviewed our strategic plan for up to 2028, which will also be our 25th anniversary. By that year, we aim to have delivered 25 new treatments for neglected populations. Given that we only have 9 treatments so far this might seem ambitious, but we are confident. We have several treatments very near the end of the pipeline, and are expecting approvals from the authorities in various countries.

What lesson have you learned with DNDi that everyone should learn in their lifetime?

You have to keep the patient's needs at the center of all your decisions. When you have to make a choice and set your priorities in terms of resources and action, you must always put in front of you the needs of the patients. This philosophy is central to our vision. But it's also something that you need to implement on a day-to-day basis – it's not something that runs passively in the background. You need to hold these images in your mind: people in very difficult situations, not receiving the treatment that they need.

Sample collecting.

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A LEAP OF FAITH

TWO FRIENDS, TWO COUNTRIES; ONE DISEASE, ONE NETWORK TO FIGHT IT

In episode 5 of DNDi: Medicine Makers Without Borders we looked at LEAP, the Leishmaniasis East Africa Platform. Our guests were two LEAP members who first met as colleagues and later became firm friends: Ahmed Musa (Professor of Immunology and Infectious Diseases, Institute of Endemic diseases, University of Khartoum, Sudan) and Simon Bolo (Head of Leishmaniasis Access, DNDi). This fascinating discussion covered many of the serious hurdles faced by medical professionals working in the region.

Tell us about LEAP…

SB: It is a clinical research network of leishmaniasis experts in Eastern African countries. It was founded in Sudan in 2003 and has 60 members from 20 different institutions.

AM: The P in LEAP stands for "platform," and it is a platform because it allows us to reach the neediest people who are afflicted by leishmaniasis. Perhaps just as importantly, it also serves as a platform for building strong South–South cooperation. Besides the mandate to combat leishmaniasis, we want to create publicity and build a model for fighting diseases that do not recognize political boundaries.

Speaking of networks, you two have a history…

SB: That's right. I met Professor Musa in 2005, when I joined DNDi. Part of my job then involved working with local partners on financial management of our clinical trials in the region. At that time Ahmed was a Co-PI for the clinical studies that we were conducting in Sudan, and since then he has been my teacher and friend.

He's the one who taught me more about leishmaniasis. We've managed to develop a very good relationship – now he knows my family, and I know his family. This has really been very helpful, especially in networking and in specifically delivering the objectives of alleviating suffering for leishmaniasis patients.

What harm is leishmaniasis doing in East Africa?

AM: It often afflicts areas that are remote or not easily

accessible, and where health facilities are often unavailable or inadequate. The people most likely to be infected are generally poor, and live in villages far from roads and healthcare centers. These patients often die before ever receiving treatment. Some may be able to attend certain remote facilities, but traveling this distance is not easy. In many cases, it is simply too late. Even if the patient does reach the facility, they may still succumb to the illness due to the absence of antileishmanial drugs. Many choose to simply stay at home until they die.

There are knock-on social and economic effects too: decline of school attendance, loss of crops and livestock, and increasing poverty.

What work has been completed with LEAP?

SB: As LEAP we've conducted ten clinical trials, and we've been able to recommend a first-line treatment for visceral leishmaniasis in the Eastern African region: sodium stibogluconate, in combination with paromomycin.

Another of our clinical studies – completed just last year – proposes the first oral treatment for visceral leishmaniasis in the region. This one brings in a drug called miltefosine in combination with paromomycin, and is going to be a game changer. Beyond reducing the hospital stay for patients, it will also remove the toxicity associated with sodium stibogluconate, one of the current drugs.

On top of that, we've improved the infrastructure for conducting clinical trials in the region. We started with Ethiopia, where we built our first leishmaniasis research and training center in a place called Gondar, and then another in the south of the country. In Sudan, we built two facilities in Doka and Umelkher, and we've also been able to build clinical trial capacities for healthcare workers.

AM: Simon mentioned the work we have done to build clinical trial infrastructure, and to that I'll add that we built these centers in the heart of endemic areas to facilitate recruitment and quickly arrive at the outcome through cost-effective clinical trials.

In addition, our presence in the endemic areas has positively influenced the villages regarding education, health awareness, and understanding of the basics of research ethics. Our mission is not only to deal with leishmaniasis, but to treat patients with malaria, scabies, leprosy, and other diseases that are co-endemic in the area.

At the level of government and regulation, we are now harmonizing the treatment guidelines. We're working on this because we have conducted clinical trials to help develop and provide combination therapy for a full set of East African countries. That means that we have to harmonize the treatment guidelines, and also harmonize the regulations in Eastern Africa – because there are differences in the regulations, approvals, and so on.

What challenges do you face in your work?

SB: The operational challenges for conducting clinical trials in endemic areas are serious. These include research capacity, different regulatory and cultural environments, and high staff turnover. We also face serious logistical problems in terms of moving drugs into the Eastern African region. We have customs barriers, high taxes, and of course there are the problems of geography and climate that impact the disease. We also face slow recruitment for our clinical trials because some of our patients are nomadic. And, most importantly, we have the post-registration issues around policy change. These are sometimes very slow in terms of adoption by either the World Health Organization or the various countries involved.

AM: Majority-illiteracy in endemic areas is another problem that we face. At first, it negatively affected our patients' acceptance of clinical trials and research. Since then, we have been explaining and building their understanding of our research and drug development, and that has helped.

The other serious problem with endemic areas is their extreme distance from major centers of population and infrastructure, like Khartoum in Sudan. Transferring patients can take days, and the internet is a nightmare. Once, when I was unable to write emails or even make calls, I would make regular trips from the hospital I was working to a nearby hill to speak with colleagues in Kenya and Geneva. One evening on that hill, I was bitten by a snake – all to secure a half-decent internet connection!

Simon mentioned staff turnover, and it is indeed another nightmare. Brain drain is the problem. Few of our medical doctors are interested in research and treatment for leishmaniasis. We commit to mentoring them and sending them abroad for specialized training, but upon being sent they tend to stay! This is how we lose so many of our doctors to Europe, the Gulf states, and so on. To return and retain them in Eastern Africa, we need to give them decent salaries and we need to prepare solid infrastructure for basic biology and conducting clinical medical research at good standards.

And that's where this excerpt ends! If you're hooked, then you can listen to the rest in DNDi: Medicine Makers Without Borders Ep 5 – A Leap of Faith. In the episode, you'll hear Simon Bolo and Ahmed Musa go on to talk in detail about financial sustainability, expanding the LEAP Network's capabilities, and reaching out to nomadic communities.

HOW WE CAME TO START THE OPEN SYNTHESIS NETWORK

NOTHING HAPPENS IN A VACUUM – AND ESPECIALLY NOT COLLABORATIVE, OPEN SCIENCE

By Ben Perry

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Prior to joining DNDi, I'd spent a lot of time working in and thinking about the strengths and weaknesses of regional academic drug discovery ecosystems. I'd noticed how the lack of early engagement with chemists resulted in a lack of high quality innovations meriting further investment and, in turn, successful spin out companies. I'd imagined a somewhat utopian situation in which academic drug discovery projects, often led by biology and medical faculty, could somehow formally tap into the wealth of talent and resources found in academic chemistry labs and teaching facilities to give their projects a head start. In return, the students, PhD candidates, and postdocs in these institutions would get the chance to expand their scientific knowledge and horizons by engaging with colleagues in other scientific disciplines. I knew that if I'd had such a chance as a chemistry PhD student, I'd have jumped at the chance.

A couple of months after joining DNDi, I happened to bring this idea up during a coffee break with Rob Don, the then Discovery Director. It turned out that not only had Rob had the exact same idea, but that he'd followed it through further than I had; DNDi had the missing piece of the puzzle to make this idea a reality. This missing piece was a recognition of the fact that not-for-profit neglected tropical disease research does not have to depend on the IP, patents, and complex revenue sharing agreements which are so often a sticking point when it comes to drug discovery collaboration with a commercial potential. Furthermore, DNDi had engaged an MBA student in the UK to write a dissertation on the concept, interviewing chemistry faculty from across the UK for feedback. I read this report with interest, and was amazed to see that so many high profile professors from my field of synthetic chemistry not only approved of the concept, but seemed more than eager to engage. With the support of Rob, I decided to try to make the concept a reality.

We approached a handful of "reliable" partner universities in the UK, US, and India whom we knew would be either enthusiastic about the idea, or guaranteed to be capable of executing it, or both. Every one of them agreed to participate in a trial run of what we were now terming the Open Synthesis Network. We would effectively crowdsource chemistry students' lab efforts to make molecules for an ongoing DNDi drug discovery project. We selected a project that was both useful to DNDi and had no major urgency: a project attempting to find a "back-up molecule" to a recently nominated candidate for visceral leishmaniasis. We knew the synthetic routes relatively well, we knew how to design interesting new molecules, and we had stocks of chemicals already in house. We designed a list of compounds and asked the teaching staff and professors at the institutions how to integrate the synthesis of these compounds into the students' lab classes. We literally sold it as "instead of 30 students all making aspirin which ends up straight in the incinerator after the lab session, how about those 30 students each make one entirely new, never-before-seen molecule, which we'll test and then share the data into the public domain, along with acknowledgement of the students' effort."

The project took off, with each university incorporating the challenge differently in their curriculum; some as small projects for budding Master's students, others as projects for large, intensive end-of-year practical undergrad labs, and others as part time challenges for their PhDs and postdocs.

Within two years we had over 100 new molecules made, and some of these clearly outclassed the original candidate molecule in terms of anti-parasitic potency. Furthermore, every single university reported a significant uptick in student engagement and satisfaction and the professors thanked us for taking some of their workload off their plate. It was effectively a win-win-win situation, which I've since learned is the key to building collaborations in the DNDi virtual pharma space – approach every collaboration and problem solving opportunity with your thoughts focused on how to make the interaction a "win" for everyone concerned.

A DeepMind employee at work

Credit: DeepMind

MEET THE PROTEIN DECODER

DEEPMIND'S PUSHMEET KOHLI LAYS OUT THE CONNECTIVE TISSUE BETWEEN DNDI AND ONE OF GOOGLE'S MOST FUTURISTIC AI ASSETS

Ask any literary sci-fi fan to name the greatest fictional supercomputer and they might nominate Douglas Adams' Deep Thought, most famous for calculating the answer to the question of life, the universe, and everything. (The answer: 42).

The first AI celebrities certainly seemed just as far-removed from the humdrum concerns of hard science. A nonfictional namesake of Deep Thought won the World Computer Chess Championship in 1989, and as far into the "future" as 2017, AI superstardom remained bogged down in board games. But when Google-owned DeepMind's AlphaGo defeated 18-world-title-holder Lee Sedol in Seoul (and next year, trumped world Go champion Ke Jie in the ancient canal town of Wuzhen), something changed.

Specifically, DeepMind started applying its AI to "real world" scientific problems, like predicting protein structures. Today, just like DNDi, DeepMind participates in open science. Its enormous AlphaFold Protein Structure Database was published online without paywalls in the summer of 2021. So perhaps its collaboration with the DNDi's Open Synthesis network should come as no surprise.

In Ep 4 of our podcast, we spoke to DeepMind's Head of AI for Science, Pushmeet Kohli, to learn more about the bonds these two incredible organizations are forming.

How did AlphaFold come into being?

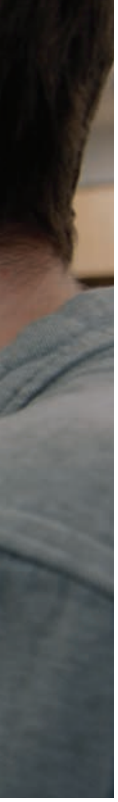
DeepMind's mission is solving intelligence to benefit science and humanity. In the past, we've showcased our AI performing feats like automatically learning to play Atari Games. Many listeners will have heard of AlphaGo's triumphs over the world's best Go players. But in the last few years, we have started to apply our breakthrough AI research in the natural sciences. This led to the science program that I manage, which covers structural biology, quantum chemistry, problems in physics, pure mathematics, and more.

We're looking at all of the problems in these fields from a scientific perspective, so in some ways we might nowadays call DeepMind a science company, both in terms of our focus on science applications and our scientific approach to asking and answering questions like, "What is intelligence? How can you recreate it? How can you make a machine intelligent?"

And how did DeepMind's collaboration with DNDi begin?

The basic operation of any disease involves certain processes within the body in which proteins are involved and interacting. As a medicine maker, you may wish to break or otherwise intervene in those interactions. But to do that, you'll want to understand the structure of the proteins involved. This could help you, for example, build a small molecule that binds to a particular protein.

This is the essence of the collaboration between DNDi and DeepMind. We want to zoom in on the proteins that are involved in some of these extremely problematic diseases,



and consider the support we can offer using our structure-predicting technology.

What marks AlphaFold as "cutting edge"?

Very early on, we knew that the results provided by AlphaFold would create a very broad impact. Protein structure predictions are not only useful for understanding diseases and small molecules; they are like the roots of a tree. If you solve these 'root node problems', you unlock so many other solutions to so many other problems in everything from drug discovery to plastic pollution in the oceans. We realized that we wanted to help make significant and dramatic improvements, and we wanted to make them in the most responsible way.

To that end, we openly published our AlphaFold Protein Structure Database in partnership with the European Molecular Biology Laboratory. Previously, scientists working in any given drug development program who needed to develop a small molecule but didn't know its structure would have to go through years of research. Often, they would have to isolate the protein and then send it to special facilities only available in certain labs in certain countries. Even then, success would not be guaranteed.

AlphaFold sidesteps that problem and accelerates the process. With the means to accurately predict these structures and make them accessible everywhere, we can really do something to help researchers working on neglected diseases – especially those in developing countries, who might not have access to the facilities they would otherwise need.

DeepMind and AlphaFold have blown a lot of minds. How about yours?

One of the great and unique things about DeepMind is its belief in the multidisciplinary approach. It's something I knew about even before I joined them. DeepMind also thinks in the long term, and does not shy away from ambitious goals. I feel one of the biggest lessons I've learned from AlphaFold is that with the right approach we can do amazing things that many people dismiss as either impossible, or lying decades beyond our reach.

The highlights end here, but the content does not! To listen to the full interview with Pushmeet tune in to DNDi: Medicine Makers Without Borders Ep 4 – The Cutting Edge.

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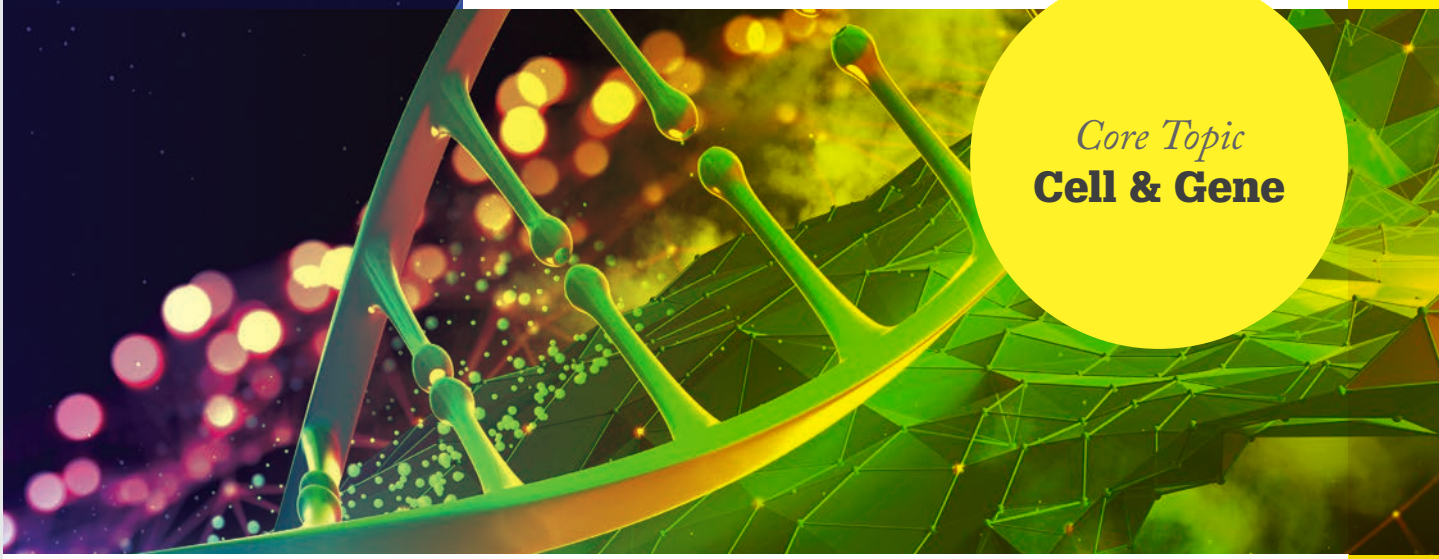

Core Topic
Cell & Gene

Welcome to the hotel Caliphagia. Dysphagia is unpleasant, as many head and neck cancer patients are aware. Fortunately, Californian scientists are on the case. The California Institute for Regenerative Medicine will invest US$11 million into an autologous cell therapy that, if successful, will strengthen patients' tongue strength and ability to swallow. A phase II trial of the therapy is currently being conducted by Peter Belafsky, the director of the UC Davis Health Center for Voice and Swallowing. The treatment takes autologous muscle-derived progenitor cells from the patient, and injects them into the patient's tongue.

It all ads up. Google has lifted its ban on advertisements for cell and gene therapies in the US. A policy update says, effective from July 11 2022, Google Ads will "permit the promotion of FDA-licensed or approved cell or gene therapies in the United States by entities that hold the relevant FDA-issued license or approval to market that product." Advertising for advanced therapies without the all-important nod from the FDA will not be permitted. The update also says that Google intends to "clarify its policy language" to allow purely informational cell and gene therapy ads outside the US.

A Penn partnership. Penn Medicine and the Children's Hospital of Philadelphia (CHOP) have announced a plan to facilitate CAR T therapy research in Costa Rica. The two CAR T champions have each signed an agreement with the Costa Rican Social Security Fund, which manages the majority of the public health sector in the Central American country. Penn's press statement on the deal uses the word "equity" three times – emphasizing the disparity in development between Costa Rica and the US. CHOP doctor Stephan A Grupp remarked the deal could prove a model for aiding other middle income countries worldwide.

The bluer the birdie. Strawberries and cream. Midsummer sunshine and scorching hot tarmac. Healthcare pricing controversy and the US. All classic combos. The US pricing watchdog, ICER, recently partook in that fine tradition by giving a thumbs up to beti-cell, a gene therapy from bluebird bio. The spicy bit? Beti-cell has a price tag of US$2.1 million, which ICER is okay with, on the grounds that: "Traditional cost-effectiveness modeling finds that this new treatment meets commonly accepted value thresholds at a cumulative price of $2.1 million with an 80 percent payback option for patients who do not achieve and maintain transfusion independence over a five-year period."

IN OTHER NEWS

London's Science Museum exhibit "Cancer Revolution: Science, innovation and hope" uses palette of art, artifacts, personal accounts, and Lego to paint a history of cancer treatment – right up to and including the emergence of advanced therapy

Findings by Harvard University researchers show fat-based Schwann stem cells work as substitutes for neural stem cells; opens possible new means for treating sensory apparatus

Scientists across multiple PRC universities find C3aR costimulation boosts CAR T-cell effectiveness, with particular improvements against leukemia

CDMO Forge Biologics announces Scientific and Manufacturing Advisory Board, pulling in five big-name experts from industry and academia

Survey in Japan captures attitudes towards gene editing human embryos; patients and families positive on clinical use while doctors cautious

Champions of Cell and Gene Therapy

How do we ensure that not only the rich benefit from cell and gene therapy?

Dave Seaward

Edwin Stone

In our ongoing series, we give cell and gene therapy champions the opportunity to answer a question on a hot topic. This time, we asked, "How do we ensure that not only the rich benefit from cell and gene therapy?"

Do you want to vote on the next question? Sign up for our Cell and Gene newsletter at: https://bit.ly/TMM-CG

Dave Seaward of 3P innovation says:

One word: automation

To answer this question, it may be worth considering an analogy from the early years of the automotive sector. Before the introduction of the moving assembly line in 1908, the Ford Model T was priced at $825. By 1925, after Ford had revolutionized the method of manufacture, it was priced at $260. At the same time, Ford's employees saw their weekly working hours shrink and their wages rise.

During this period, the British company Rolls-Royce employed large teams of highly skilled artisans to hand craft their Silver Ghost chassis. We should remember that, while Ford produced complete cars, Rolls-Royce only produced a chassis and engine. They left it to other companies to produce the coachwork. Over a two-decade period, Ford produced around 16 million cars. How many Rolls-Royces? Eight thousand.

Cell and gene production is currently analogous to those beautifully hand crafted Rolls-Royces – and the highly skilled laboratory technicians and PhD graduates are the "highly skilled artisans."

Cell and gene therapies are revolutionizing the treatment of many life-limiting diseases, but the growth of this nascent industry is constrained by a worldwide lack of skilled staff for their development and manufacture. Throughout human history, automation has reduced the costs of goods by reducing the number and skill level of operators. Automation has also improved the consistency of the product (with reductions in faults and scrap) and, in many cases, it performs tasks that humans simply cannot.

Cars revolutionized transport and Ford revolutionized their manufacture. Today, we need a "Ford" of cell and gene. And that's why the new paradigm will almost certainly include significant automation – both physical and digital.

Edwin Stone of TTP says:

Reform the structure

The cell and gene therapy industry has some structural challenges. Currently, the eco-system is fragmented. Early stage developers often call on CMOs to make therapies that are then acquired by big pharma. Equipment companies develop systems and sell consumables into this ecosystem, trying to respond to not only shifting requirements as a therapy moves through the pipeline, but also to demands that change over time in a fast-moving field. All this comes before we consider payers, regulators, logistics, local governments, and the multitude of other interested parties. Each stakeholder wants a seat at the table, but, at present, there are many opportunities for objectives and motivations to misalign.

One solution is massive vertical integration. Everywhere from mobile phones to ophthalmics, vertical integration has helped drive down prices and increase access. But this approach is not without flaws, especially when a limited number of players become too dominant. The alternative is deep collaboration. Here, our field's greatest strength is the alignment of our core motivation: the desire to bring therapies to as many patients as possible.

So how can we deepen collaboration? Grand solutions may seem attractive, but achievements built from small, stacked bricks are the better bet. We are in an industry that is simultaneously innovative and cautious. Standardization in everything – from shipping though digitization and even into fluidic connectivity – could greatly simplify new therapies' entry to market. We should also look at how creative use of payer models can be used to lower the cost of entry. Finally, we need to analyze and develop the talent pool to meet the needs of the industry. Unless we all invest in growing that pool, we will be stuck as a boutique industry for the few.

Despite every hurdle, I am confident that our field has the people, motivation, and resources to solve all of the above, and make good on the incredible promise that we all know lies in cell and gene therapy.

Jason C Foster of Ori Biotech says:

Yesterday's answers cannot solve today's problems

It is well known across the cell and gene sector that we must tackle the high costs


Jason C Foster


Rob Collison

and inability to treat large numbers of patients. Current manufacturing practices and technologies can only practically address small production volumes. Until these manufacturing challenges are solved, prices will remain above society's ability to pay for them, and these products will remain all but inaccessible for patients. These challenges have been discussed across the sector for many years, but no real solutions have been presented.

Researchers and therapy developers are currently using an old pharma playbook approach; requiring them to chase milestones set by investors that value approvals over affordability and accessibility. This leads to cell and gene therapy programs that are rushed into the clinic without the ability to have a parallel focus on incorporating and developing systems that create robust, scalable manufacturing processes through development into commercialization. Following this out-of-date strategy has led to repeated commercial challenges in numerous products, including Skysona and Zynteglo in Europe (US still TBD) (1), as well as several commercial cell therapy products that are exhibiting signs of trouble with declining volumes (Kymriah -16 percent year over year (2)) and/or significant publicized manufacturing challenges (Abecma) (3).

Providing therapy developers and academic researchers the ability to focus on manufacturability early in their programs and in parallel with preclinical work is critical to overcoming these challenges. We as an industry need manufacturing platforms that have a digital-first approach and provide flexibility in the early phases and scalability in the commercial phase. This inherent scalability will enable development programs to seamlessly transition from preclinical process discovery into clinical trials, and from clinical trials efficiently onto the market at commercial scale. Such digitally native systems will exponentially reduce costs and help ensure that these therapies can benefit all patients in need.

Rob Collison of Cambridge Consultants says:

It's about more than cutting costs

Great question! It is vital that we strive to democratize the availability of these therapies, and, for me, the answer lies in three key strands: reducing costs, providing better access, and conceiving new payment options.

Let's start with costs. They can be reduced significantly through manufacturing innovations that incorporate automation, AI/machine learning, and other emerging technologies to allow the scaling out and scaling up of therapies with reduced labor and minimized controlled environments – both of which are key cost drivers. Such innovations will allow biopharma companies to develop robust manufacturing platforms that produce multiple therapies – each for a wider range of clinical indications – and benefit from economies of scale. I envision a plug-and-play model that uses the same process and has the ability to modify cell types, viral vectors, and/or genetic modifications; for example, a CAR platform that is able to produce CAR T, CAR NK, and CAR M for varying targets, such as CD19, BCMA, and so on.

Turning to improved access, we'll need new hospitals and treatment centers in economically diverse areas, equipped with specialized resources and trained clinicians. Hospital systems – benefiting from government subsidies or directly from biopharma – will need to invest to provide greater local access. Individuals on low incomes may not have the means to travel and access currently limited treatment facilities.

Finally, I see unique payment models from both healthcare and biopharma as an option to serve broader populations. Government/socialized healthcare and insurance providers need to evaluate the upfront costs of curative cell and gene therapies versus the total long-term costs of treatment and medication. New reimbursement strategies could then be implemented. Perhaps biopharma will develop a performance-based payment approach, recouping costs through recurring income based on therapy performance and longevity rather than a single initial price. This could reduce the barrier to entry for cell and gene therapies by defraying costs.

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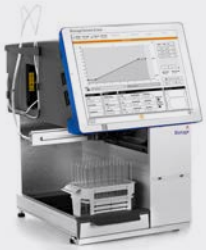

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Core Topic
Bioprocessing

FDA limits Janssen vaccine. The FDA has limited use of Janssen's COVID-19 vaccine to individuals over the age of 18 years of age where other authorized COVID-19 vaccines are "not accessible or clinically appropriate." Individuals can also elect to receive the vaccine in certain circumstances. The FDA decision is based on the risk of thrombosis with thrombocytopenia syndrome (TTS). "Our action reflects our updated analysis of the risk of TTS following administration of this vaccine and limits the use of the vaccine to certain individuals," said Peter Marks, director of the FDA's Center for Biologics Evaluation and Research.

Fast and furious partnership. Sanofi has partnered with McLaren Racing to "accelerate efficiency and performance in support of the company's ambition to attain world-class standards of manufacturing excellence." The collaboration builds on a successful pilot from 2021 and will now expand to more than 100 of Sanofi's production lines. Sanofi isn't the first pharma company to collaborate with McLaren. McLaren uses digital and analytical expertise with the aim of anticipating and resolving issues before they happen. Modeling and simulation are key tools in the McLaren tool kit – and biotech companies are just as eager to reach the checkered flag first!

RSV vaccine on the way? A handful of big pharma companies have been racing to bring the world's first respiratory syncytial virus (RSV) vaccine to market – and we may have a winner. GSK has received positive results from its phase III RSV trial of candidate AReSVi 006, which involved around 25,000 participants. Details about the efficacy haven't been revealed but GSK claims the vaccine showed "statistically significant and clinically meaningful efficacy in adults aged 60 years and above." The magnitude of effect was also "consistent across RSV A and B strains, key secondary endpoints and in those aged 70 years and above." GSK is looking to make a regulatory submission in the second half of 2022.

Stamp of EU quality. The EMA's CHMP has recommended two Novo Nordisk insulins – Actrapid and Insulatard – for use outside of the EU in certain low- and middle-income countries, under the "EU Medicines for all" regulatory procedure. The insulins were assessed by experts from the EMA and WHO, as well as experts from the target countries. Novo Nordisk has performed an assessment of the insulins to include storage without refrigeration when used in countries outside of the EU. They can be stored at temperatures up to 30°C for four weeks.

IN OTHER NEWS

NIBRT, Kerry Group and ValitaCell announce partnership to study properties of protein hydrolysates in cell culture media during commercial manufacture

Waters opens innovation and research laboratory at University of Delaware; brings together students, faculty and Waters experts to address challenges in biopharma

Sartorius invests 20 million euros and expands manufacturing site in Tunisia to increase production of fluid management technologies for biopharma

Roche's crenezumab does not achieve statistically significant results in Alzheimer's trial. Crenezumab was designed to neutralize neurotoxic oligomers (a form of beta-amyloid).

Novo Nordisk reports positive results from ONWARDS 1 and 6 trials for once-weekly insulin icodec

Credit: Fearedlion123 / Wikimedia Commons

The Final Frontier for Regenerative Medicine

What will drug development look like aboard a new commercial space station?

By Stephanie Sutton

Space stations are cool. Regenerative medicine is cool. Combine the two, and the coolness goes into overdrive.

The RegenMed Development Organization (ReMDO), the Wake Forest Institute of Regenerative Medicine (WFIRM), and Axiom Space have established a partnership to "advance in-space regenerative medicine biomanufacturing."

It's very early days – so early that the space station where the research will take place hasn't been completed yet – but it's still an intriguing project. And Axiom Space has demonstrated its clear commitment.

Axiom is a private spaceflight company with ambitions to operate the world's first commercial space station, which will initially be attached to the International Space Station (ISS). Axiom's first private mission – "Axiom Mission 1" – took place in April and was the first private trip to the ISS.

According to a press statement from Axiom, the mission supported "26 science payloads and technology demonstrations that had been curated with leading academic and research partners around the globe, including the Mayo Clinic, Montreal Children's Hospital, Cleveland Clinic, and the Ramon Foundation." They also added that the astronauts from the trip served as "research subjects to better understand the impacts of microgravity on the human body, as well as methods for maintaining connectedness to loved ones on Earth during space travel."

The station Axiom is proposing to ultimately build is called Axiom Hub One and is being designed to include crew quarters, as well as research and manufacturing capabilities. Construction is in progress and launch is planned for 2024.

Why conduct research in space? Axiom points to the benefits of researching aging in space by claiming (1), "Spaceflight offers aging researchers a distinct research model in which to test new ideas that may uncover meaningful discoveries." The company explains that spaceflight can accelerate aging, as many returning astronauts experience symptoms similar to those seen in the elderly, such as decreased cone density, reduced cardiovascular capacity, and immune dysfunction – to name just a few.

ReMDO and WFIRM have not yet given details about the exact work they are planning, and since it is such a new "frontier" it will likely take time before we really understand the biomedical benefits that can come from researching medicines in space. However, one area that WFIRM is interested in is developing treatments for conditions that affect humans who have been exposed to space travel.

If astronauts are ever to be sent for long-term missions – for example, trips to Mars – they will likely need medicines. Moreover, space is a grueling environment that can cause numerous health issues in astronauts. Back in 2020, I spoke with Phil Williams from the University of Nottingham about his work on an "astropharmacy." He had a lot to tell me about spaceflight, the human body, and medicines (2). For example: "This environment causes redistribution of fluids in the body, in particular the blood, which is no longer pulled towards the feet and away from the head. The body compensates for this unnatural pooling in the upper half of the body by then reducing the volume of the blood. These changes in fluid distribution and blood volume all cause immediate changes to pharmacokinetics/pharmacodynamics. Studies on the SpaceLab (the laboratory that flew in the bay of the Space Shuttle), for example, have shown that the rate of absorption (measured in saliva) of paracetamol and scopolamine/dexedrine from tablets were double after one day of space flight, and almost halved after two. Longer term changes caused by microgravity include muscle atrophy, insulin receptor desensitization (astronauts can be clinically diabetic after 30 days of spaceflight), retinopathy, and decalcification of bone (and the consequent deposition of calcium elsewhere, often as kidney stones)."

If you want to know more, you can read the article from Williams on our website.

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Towards Better Biosimilar Access

Offering originator alternatives sounds great on paper – but what about in practice?

Featuring Steven Selde, Director of the Biosimilars Council, Association for Accessible Medicines, USA

What's going right with biosimilars in terms of access to medicines – and what's going wrong?

Biosimilars represent new access to care for patients. Even in the face of adoption challenges, biosimilars have provided new access to more than 10 million days of therapy.

But too many patients still lack access to biosimilars as a result of pharmacy benefit managers' (PBM) formulary decisions in favor of higher-cost brand drugs with high rebates. The Health and Human Services Office of Inspector General highlighted this challenge in Medicare Part D, noting that many formularies did not include biosimilars, and those that did often failed to encourage biosimilar adoption.

How can companies ensure biosimilars are fairly priced?

Biosimilars are bringing important and meaningful price competition to the market. We've seen price decreases across the board once biosimilar competition begins. Every market is different but, according to Medicare data, the average biosimilar price is almost half what the reference biologic's price was at the time of biosimilar launch. Additionally, the brand price is more than a quarter lower than when it was first subject to biosimilar competition. If policymakers ensure coverage and reimbursement policies are aligned to support greater adoption of these lower price options, this robust price competition will continue.

What are the biggest challenges biosimilars face in coming to market, particularly in the US?

It was only in 2010 that Congress authorized the US FDA to create a pathway to review and approve biosimilars, making this a fairly new product with evolving market dynamics. To date, biosimilar development and marketing have faced two main challenges.

The first challenge is education. Biosimilars have faced significant brand-initiated misinformation and disparagement campaigns that sow doubts in patients' and providers' minds. To aid patients and healthcare professionals, the Biosimilars Council has developed a variety of educational resources. The FDA also has a host of resources, and most recently published medical degree curriculum materials to help educate students in medical, nursing, physician assistant, and pharmacy programs, as well as practicing healthcare professionals. The work that the agency and some health care professional groups have done to educate providers and patients on biosimilars is crucial and must be continued.

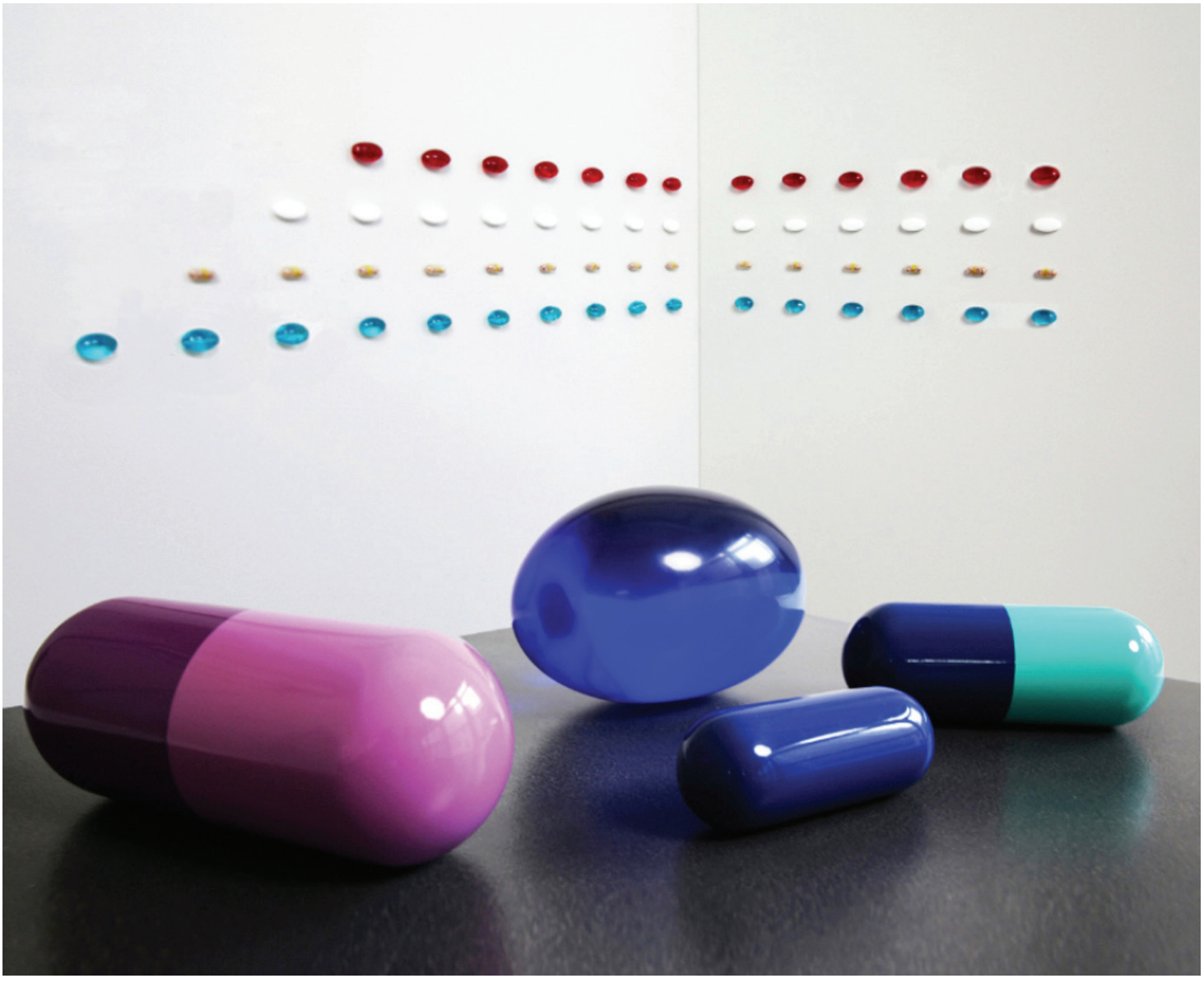
Second, as previously mentioned, biosimilars have been hindered by drug reimbursement and formulary design policies. For example, an IQVIA study highlighted that biosimilar adoption was greater when the relative reimbursement was higher for the biosimilar. The study also observed that providers in the oncology care model, which holds providers accountable for the total cost of care, used biosimilars more often than other providers. PBM formulary design is too often swayed in favor of high-cost, high-rebate brand drugs.

Congress can address these challenges through some straightforward bipartisan proposals. In Medicare Part B, Congress can increase the add-on payment for providers when they use a biosimilar or direct Centers for Medicare & Medicaid Services to create a shared savings demonstration program. Under these programs, providers would choose the right medicine for their patient but receive higher reimbursement when they use the lower-cost option.

Congress can also update the Medicare Part D program to better encourage health plans that prioritize lower-cost medicines such as biosimilars. Not only would these proposals mean lower costs for taxpayers, but they would also mean lower out-of-pocket costs for patients. Addressing these respective challenges would result in billions of dollars in savings for all.

Are you optimistic about the future?

Yes, biosimilars have clearly established their value proposition, and we will see this grow in future years. For instance, beginning next year, it is likely that patients will have access to more than seven biosimilar versions of the best-selling drug Humira. IQVIA projects that biosimilars will generate more than US$130 billion in savings by 2025. But I believe there are greater savings to be realized if policymakers take action on these issues.



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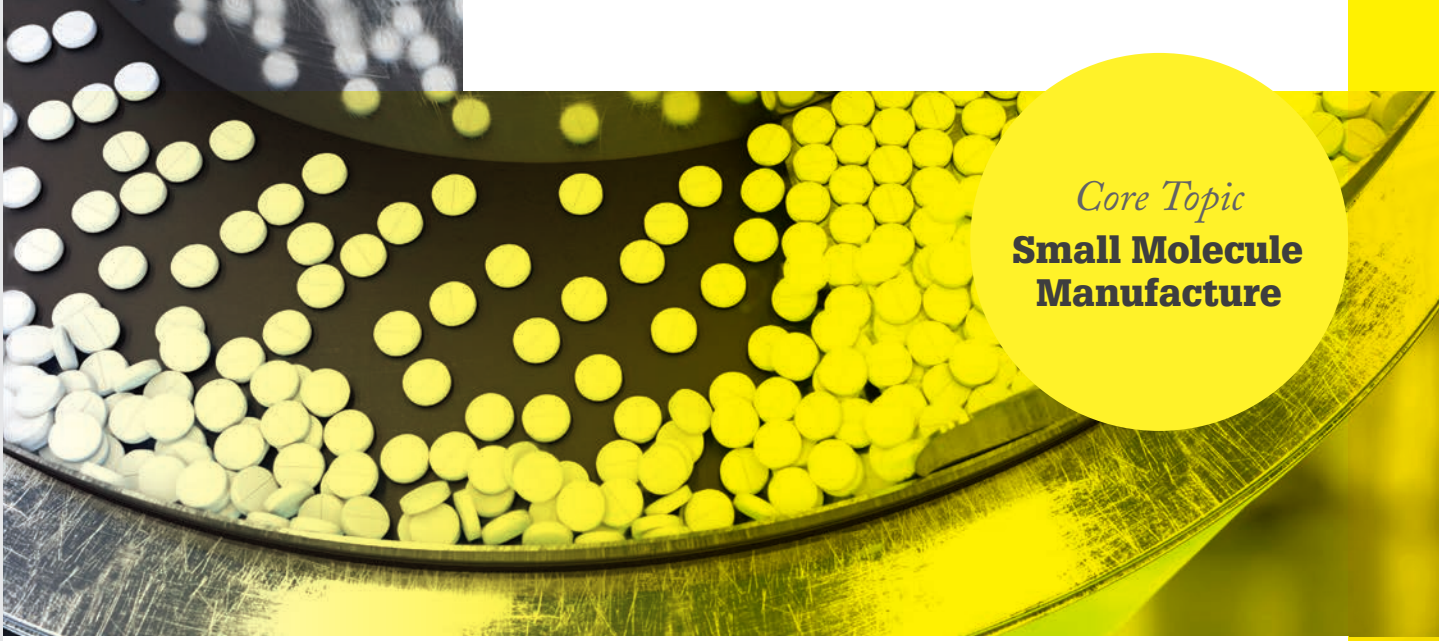


Core Topic

Small Molecule Manufacture

Hair-raising breakthrough. The FDA has approved the first medicine for severe alopecia areta: Eli Lilly's Olimiant (baricitinib). Studies showed that the once-a-day pill caused regrowth in both its 2 mg and 4 mg formulations. "People with alopecia areata, dermatologists, and other healthcare providers have been looking forward to this day when there is an FDA-approved systemic medicine for this often-devastating disease. Alopecia areata causes unpredictable hair loss that can be patchy or complete, and it affects people of all ages and ethnicities," Brett King, associate professor of dermatology at Yale School of Medicine and lead investigator behind the trial, said in a statement.

Slap on the wrist. The FDA has issued a warning letter to US biotech, Althera, for producing false and misleading claims about its drug developed to treat hyperlipidemia. The company elected to misrepresent information regarding the drug's safety profile. Responding to this concerning activity, the FDA penned a letter outlining its qualms – particularly stressing the fact that patients should be privy to information that is "truthful and non-misleading […] regarding the risk and expectation benefits of a cholesterol-lowering product."

Ending the discussion. After months of deliberation, the World Trade Organization has lifted intellectual property rights to COVID-19 interventions. The TRIPS waiver was subject to much scrutiny in industry circles, with trade organizations expressing concern about the loss of companies' IP. In a statement, IFPMA Director-General, Thomas Cueni said, "The conversations on an intellectual property waiver have been challenging from the beginning, with disregard to evidence and facts. The decision is a disservice to the scientists that left no stone unturned and undermines manufacturing partnerships on every continent. The single biggest factor affecting vaccine scarcity is not intellectual property, but trade."

Environmental awareness. A report published by the UK's OECD provides guidance on minimizing household pharmaceutical waste. Though there are now more efforts than before to counter the impact of the pharma industry on the environment, there are still issues that need to be addressed. The document encourages companies across industries to find ways to reduce the volume of expired products in circulation, employ environmentally friendly collection methods for pharmaceutical waste, and create campaigns to raise awareness about appropriate methods for waste disposal.

IN OTHER NEWS

Researchers at Bielefeld University have developed a new method to examine drug interactions in liver tissue

Piramal Pharma expands its API development capacity in its Digwal, India site and invests in novel manufacturing tools

American think tank, Brookings Institute, publishes report outlining how FDA can increase generics competition

As inflation continues to soar, industry organization, Medicines for Europe releases open letter requesting EU support with medicine supply chain

EMA to suspend over 100 drugs after revealing integrity issues in data provided by India-based CRO, Sychron Research Services

Clinical Trials: Getting Smart with Pill Dispensing

Is it possible to improve clinical trials with smart packaging and devices?

In 2019, we spoke to James Burnstone, Chief Executive Officer at Pill Connect, about the company's proprietary pill dispensing solution. Helping to combat medical non-adherence, their smart pack was designed to monitor, learn, and predict behaviors that caused patients to forgo their medication. The technology also curbed abuse by only allowing patients to dispense their medicine after a notification from the mobile app developed to accompany it. But in the three years since our last discussion, what has changed for the company? Burnstone sat down with us to fill in the blanks and explain how their updated dispenser technology will help track the use of solid dosage forms in clinical trials.

Why do solid dose trials suffer from a lack of patient adherence?

At its core, it's a human problem: we forget, we get busy, and sometimes we intentionally choose to not do something. I'm very aware of this myself as an asthma sufferer who got many more reliever inhaler prescriptions than preventers!

It happens in trials, too, so it's important for pharma companies to account for it. That's where we hope to help. Our aim is to provide complete monitoring of what participants are doing in a trial. With that information, you can see where and when adherence is a problem and address it with human intervention. Our dispenser then continues to record whether this has an effect.

One reason for poor adherence is the traditional approach of monitoring solid dose adherence via pill counts. These are unreliable, retrospective, and participants can choose to censor them, which is a problem because it hides useful information – we don't have a clear sense of why the participant does not want to take the drug…

I also think there's more of a disconnect between taking a solid oral drug and "seeing" a response. This is where participant engagement and well-delivered education is important to ensure the participants know why they are taking the drug. This is especially necessary with complex dosing regimens, but should be provided alongside any prescription.

Since the last time we spoke, what has changed for Pill Connect?

Drawing on the results of our usability studies in 2019, along with industry feedback and input from patient involvement groups, we developed an updated version of our dispenser.

It can be easy to see a problem in the clinical world and say that a technology can instantly solve it. However, delivery, usability, and integration with other systems will dictate whether it really has a positive impact on patients and healthcare providers. We certainly saw this and, although our early dispenser met a clinical need, we had work to do to address usability.

As a result, we separated the device and phone. Patients can use the dispenser like a normal bottle (though with a button that delivers their dose) and the dosing data, which is useful for the clinical

team, is collected automatically in the background. This frictionless approach to adherence monitoring is important if you want patients to engage with your solution.

Another major change was to make the product more sustainable. We did this by making the product an add-on to the patient's normal bottle. As such, it can be removed and reattached, so patients may only need a single Pill Connect dispenser for multiple years of use, preventing unnecessary waste.

The dispenser recently completed a pilot with a pharma company and we're about to conclude our feasibility study for patients taking tuberculosis (TB) medicines.

What lessons does the industry still need to learn about clinical trials?

Future clinical trials must factor in resilience to major disruptions whilst providing participants with more choice. This is where decentralized clinical trials (DCTs) or hybrid trials can provide a solution. It's a path pharma has been looking to take for some time – and some companies did it decades ago – but the trend has now accelerated. I imagine that trial participants themselves will increasingly expect to have the ability to take part in trials without the burden of regular travel to sites. Telemedicine and digital health technologies (DHTs) can make this possible. However, there are still major challenges and implementations for different conditions may require different solutions.

What types of issues might arise?

In my opinion, DCTs introduce new challenges when it comes to medical adherence. If a DCT has fewer site visits, participants go longer without having their adherence checked manually (pill count) and may struggle to get dosing questions answered quickly. Adherence can also be affected by engagement, which may decline if the participant's involvement with the trial is reduced.

Therefore, remote adherence monitoring tools may be a key component to facilitating well-run DCTs. It is particularly important that the tools work in real time so that changes or problems with adherence can be identified early on – before the next site visit.

Furthermore, monitoring when the participant dispenses is a key marker for engagement and showing that patients understand the regimen. We want to highlight straight away if a participant has altered their behaviors so that the change can be addressed before it leads to disengagement and poor adherence.

What about DHTs?

On paper, DHTs should clearly improve efficiencies, but I think the levels of engagement need to be accurately measured and accounted for if you're using remotely provided data to make a serious clinical decision. Any new technology used in a trial can have negative effects on recruitment or retention, which is why a lot of work must be done to address usability. There's also data privacy and protection of blinding, which must be considered from the generation of the data to the various transmission and storage points it goes through. We've found that the best way to identify and manage these risks is early engagement with sponsors and companies running trials.

Where must the industry go next to overcome clinical trial challenges?

Recent FDA draft guidelines on DHTs discuss the need for early collaboration between sponsors and DHT manufacturers with a focus on usability – but this requires involvement from participants. The problems and inefficiencies DHTs want to solve are clear; it's the application and implementation that manufacturers need to ensure they've considered in their design.

There are a lot of pilots and collaborations going on but, to move past these early stages, we need to show real evidence of the solutions' clinical value. This will require sponsors to show innovation and agility while protecting their products and participants.

Finally, I hope that DCTs will allow for much-improved diversity in trial participation among people who have never taken part before. Anyone expecting to deliver a meaningful DHT needs to ensure that their product does not exclude anyone or limit recruitment. Requiring the participant to use a phone to dispense, for example, was a major limitation.

What's next for Pill Connect?

Since 2019, we've continued to work with University Medical Center Groningen and we've been running a clinical trial to measure whether our device can supplement directly observed therapy for patients taking TB medicines. We hope to have the results out soon and we're already planning a follow-up in a TB-prevalent country.

We're currently validating our new dispenser, which we plan to launch later this year as a remote monitoring tool for clinical trials. We're also evaluating how the dispenser could be combined with intelligent clinical platforms to provide a digital therapeutic solution in conditions where unknown non-adherence can quickly lead to unnecessary hospitalizations.

So watch this space!

End-to-End Sterility Assurance with the new SCHOTT iQ® Integribag

High-value ready-to-use (RTU) drug delivery and containment solutions, eliminate the need for pharma companies to wash and sterilize their containers before filling. Hence, it provides peace of mind and allows pharma companies to focus on their core competency of developing and manufacturing drugs. However, uncontrolled process steps, such as handling and transporting RTU containers to ISO 5 (Grade A) cleanroom zones, pose a contamination risk and can be difficult to manage. To reduce the risk of contamination and human errors, interest is growing in continuous improvement of fill-and-finish processes and the preceding transfer steps into the aseptic zone.

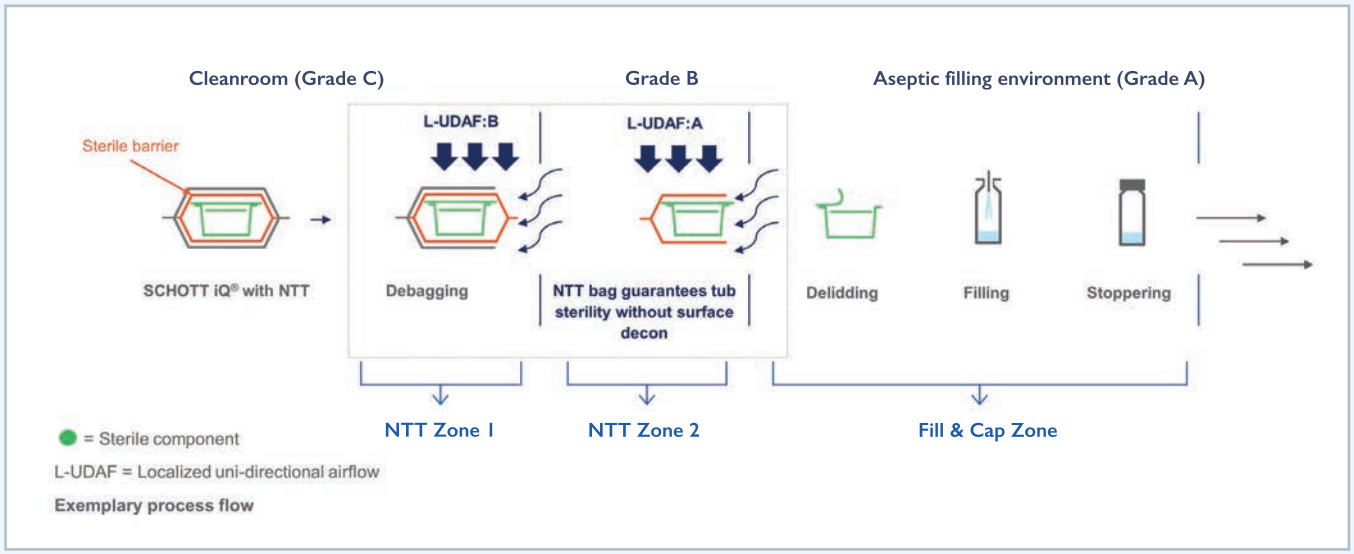
"Regulatory requirements are becoming increasingly stricter, and contamination control becomes more important, not only with highly automated systems," explains Dr. Robert Lindner, Global Product Manager at SCHOTT Pharmaceutical Systems.

In line with optimized fill-and-finish processes, improvements can be made in RTU packaging. SCHOTT followed a quality-by-design approach to overcome the limitations of current RTU options with superior materials and a design that ensures sterility protection and seal integrity. The result is the all-new SCHOTT iQ® Integribag. Pharma companies and contract manufacturing organizations (CMOs) can order containment solutions from the SCHOTT iQ® platform with the specially designed bag system. Unlike currently marketed RTU systems, this No-Touch-Transfer (NTT) solution shifts the sterile barrier to encompass the outside of the tub and Tyvek® seal layer even after handling and transport.

SCHOTT iQ® containers ordered with the SCHOTT iQ® Integribag packaging option help pharma companies and CMOs improve risk management by relying on an enhanced secure sterile barrier with a tamper-evident seal.

Sterility protection

Current RTU containers typically arrive in a double-bag system. The outer header bag features a transparent window and five seals: top, bottom, two sides, and window. In this setup, the sterile barrier is on the tub/Tyvek® level and protects the inside of the sealed tub holding the containers and the Tyvek® inlay. To reduce contamination risks during debagging and transfer into ISO 5 (Grade A) filling zones, some pharma companies add a decontamination step, such as E-beam, vaporized hydrogen peroxide or ultraviolet (UV) irradiation or manual disinfection with alcohol wipes. However, despite these practices, failure to disinfect materials before introducing them into the ISO 5 (Grade A) aseptic processing area is a fault commonly noted by FDA inspectors (1). Furthermore, each decontamination option has disadvantages. E-beam treatment comes with high capital and operating expenses, generates ozone and requires staff with



radiation safety management expertise. Hydrogen peroxide is a batch process, might leave harmful residuals, and also requires a high capital outlay. Ultraviolet irradiation is sensitive to shadowing, not particularly compatible with tub handling, and requires frequent replacement of the light source. The manual process using alcohol wipes is difficult to validate and leaves residuals.

Based on a quality-by-design approach to enhance sterile integrity, the robust SCHOTT iQ® Integribag double-bag system supports NTT and eliminates the need for a decontamination step as well as the expenditure of related time and resources. The design features two separate bags, each consisting of a Tyvek® component in the front and a blue-colored laminate on the back. The intricate combination of layers of industry-leading materials and outstanding production processes provide an improved physical barrier and enhanced safety. More importantly, the qualified double-bag design assures end-to-end sterility and moves sterility protection beyond the inside of the tub to the outside of the tub and the inner bag of the dual-bag packaging (2).

The protective qualities of the SCHOTT iQ® Integribag system depend on multilayer materials. The laminate minimizes the risk of pinholes, and the highly durable Tyvek® material offers the strongest puncture resistance among commonly used healthcare packaging materials. Sturdier bags lessen the chances of damage during transport and handling, thereby protecting the tub of sterile components from contamination, strengthening risk management and enhancing patient safety.

Seal integrity

To create a solid and protective bag, the Tyvek® material and the blue-colored laminate are fused to form a solid seam seal. The unique blue color in the seam area enables easy confirmation of seal integrity. Complete, integral seals display a consistent shade of blue. Seal lines that exhibit spotting, fading or unevenness indicate bag integrity could be compromised. By adding this visual feature, pharma manufacturers and CMOs don't have to rely solely on Quality Sterilization Certificates to ensure component sterility. Visual inspection techniques easily confirm package integrity and product safety.

Conclusion

One of the most critical steps in aseptic fill-and-finish is the introduction of the container into the aseptic core. Thus, flexible fill-and-finish processes require sterile packaging. However, standard solutions pose the risk of contamination during transport and transfer into the aseptic environment. The robust SCHOTT iQ® Integribag system significantly improves component sterility assurance compared to industry-standard packaging by reducing the chance of seal failure and substrate damage, punctures and pinholes. Additionally, the sterile barrier is shifted to the innermost bag, so that the exterior of the tub and Tyvek® are sterile. The system is compatible with all SCHOTT iQ® containers and supports NTT fill-and-finish operations.

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Business

Economic drivers
Emerging trends
Business strategies

Kyiv: Escape and Return

Ukraine is proving to be a crisis-resistant country – and Kyiv-based drug discovery CRO Enamine is finding itself just as resilient

At the onset of the Russian invasion of Ukraine, we spoke to MedChemica's Ed Griffen about his company's COVID-19 Moonshot partnership with Enamine, a major player in international drug discovery collaborations. Here, we speak with Oleksandr Grygorenko, a consulting scientist, and Ivan Kondratov, head of medicinal chemistry – both at Enamine – about the history of modern Ukrainian life sciences, the origins of Enamine, and where the company stands now as the Russia–Ukraine war continues.

The situation in Ukraine is changing rapidly. For context, this interview was recorded on March 29, shortly before Russian forces retreated from Kyiv. A few days later, Enamine resumed operations. In late April, they successfully relocated their collection of screening compounds to western Ukraine. However, at the time of publishing, a new airstrike struck Kyiv.

Prior to the invasion, what was Enamine's story?

Ivan Kondratov: We were founded in 1991, immediately after the collapse of the USSR. The times presented us with an interesting situation. Under the USSR, there was a great deal of chemistry work ongoing in Ukraine. However, that work was all done by Soviet scientists, which means it was firewalled – in a sense – from the Western world. At that time, we saw a great deal of interest in the compounds produced by Soviet scientists working not only in pharmaceutical companies, but also in agro-chemistry and material science.

1991 was also a time of flourishing high-throughput synthesis and screening technology. There was huge demand for libraries with thousands, or even hundreds of thousands, of compounds. Every pharmaceutical company sought opportunities to enlarge its collection and Enamine's founder, Andrey Tolmachov, understood this trend.

Enamine didn't really begin as a "startup" as we understand the term today. There were only a few companies like us operating in post-USSR Russia and Ukraine and it was a golden age of interest in new compounds. Enamine's next move was to open its own "marketplace" for a diverse range of chemical building blocks. This was something new because, prior to this move, all such blocks had to be bought from larger, more traditional companies. Our business model proved successful and really took off in the 2000s and 2010s.

Oleksandr Grygorenko: Enamine became such an influential player in pre-war Ukraine that, these days, most students who graduate from our universities' chemical faculties go on to work for Enamine. That is the sort of presence we have become within the country's chemical and scientific community.

Can you paint us a picture of pharma and the life sciences in Ukraine?

IK: In Ukraine's pharma industry, we do not have huge investors and producers like GSK, Pfizer, or AstraZeneca. We have several companies mostly involved in the production of generics for the domestic market; these companies tend to have no or minimal R&D capabilities. This means that, across the life sciences, Ukraine's main niche in global pharma lies in chemical CROs. Among those domestic CROs, Enamine is the biggest in terms of employees, cash flow, products, and so on.

At Enamine, our usual role is to support drug discovery up to the preclinical stage. Unfortunately, we have not yet achieved GMP and therefore cannot manufacture APIs – and, even if we could, we would likely find ourselves outcompeted by companies in India and China. That said, we have our niche and our reputation and they work well for us.

Zooming out again to the nation at large, an area where Ukraine is doing well (but could still do better) is academia. On the one hand, we cannot compete with top universities in Western Europe and North America in terms of research impact; on the other hand, Enamine and other Ukrainian companies have a very good relationship with our domestic universities. Together, we've had many publications in high-ranking journals.

Enamine invests a great deal in

investigation and research because results published today can mean compounds synthesized tomorrow. We support research inside Ukraine and also international research projects with some Western partners.

OG: I second this. In Ukrainian life sciences, organic chemistry is perhaps our strongest point.

So far, which projects have you enjoyed most?

IK: We're very proud of our work on the COVID Moonshot targeting the main protease inhibitor of the virus. Pfizer recently developed a drug that uses the same mechanism of action, but the Moonshot project started on this back in March 2020, when the first structure of the target was disclosed.

Along with our friend Frank von Delft – principal beamline scientist at the UK's Diamond Light Source – and his colleagues at Oxford University and other British and European institutions, we organized a consortium to search for a drug that could hit this target protease. As the primary chemical supplier, Enamine supported the COVID Moonshot from the initial search and hits through to the lead optimization campaign and, finally, to securing several very important leads, which we will progress to the preclinical stage.

None of this story is confidential. The COVID Moonshot is an open science project, so you can get access to the full story and all the relevant information on its website. Excellent chemists were involved and interesting results were found. Overall, I'm really glad we were able to participate.

OG: There are a couple of more chemistry-related achievements I'd like to highlight. The first is a project geared toward creating an ultra-large chemical space of compounds. Recently, computational tools able to search billions of compounds have become

R to L: Valentyn Badlo, Olena Tykhoniuk, Andriy Khairulin, Ivan S Kondratov, Anastasiya Yakovenko, and Volodymyr Yarmolchuk

available to researchers. This is excellent news for Enamine, because we are now able to synthesize these billions of compounds on demand. One of the key people behind the tool is Yurii Moroz, CEO of ChemSpace. We're now using this tool to expand and improve our own chemical space and are even combining it with machine learning techniques. It's very exciting.

Second, I want to mention the progress we've made on building block synthesis. Recently, the European Journal of Organic Chemistry published an entire issue dedicated to Enamine's 30th anniversary, featuring articles covering a range of topics across organic chemistry. Organofluorine compounds, lipophilicity and metabolism in saturated ring systems, organoboron building blocks – all of these really tick my boxes.

The Russia–Ukraine conflict has been ongoing in Donbas since 2014. Over the last eight years, did Enamine formulate contingency plans for possible escalations?

IK: The main issue here is the location of our headquarters in Kyiv. All of our production facilities are located there, as well as the main stock of our components, all our labs, and most of our employees. We also have two stocks abroad: one in Riga, Latvia – an EU and NATO member – and one in the US state of New Jersey. This was part of our business strategy, but not actually part of our contingency plan regarding conflict with Russia.

Nobody had considered the possibility that Kyiv might be in danger. All of the problems we anticipated would have taken place in territories near Luhansk and Donetsk. News about the fighting in these border regions may have fizzled out in the international media, but the conflict was constant. Shelling, attacks, movements, and deaths kept happening over time, albeit at varying levels of intensity.

In 2014, we helped many of our colleagues evacuate from Donbas to Kyiv, but it wasn't until late 2021 and early 2022 that we began to consider a possible risk to Kyiv. As Russia ramped up preparations for what we now know was the invasion, many of our customers began to ask how we were responding.

As a result, we began to develop a location in western Ukraine… but, before we had completed it, the invasion began. What had until then been an abstract threat to Kyiv suddenly became very real. We had made some minor plans in areas like cybersecurity; we made sure to protect our servers and back up all of our data on servers outside Ukraine. We had also prepared for problems with electricity supply by purchasing generators. But, ultimately, nobody expected such a sudden and massive attack from Russia.

"If children were the highest priority, then employees were the next highest."

We did not expect missiles and shells. That's why our full response to the crisis is still a work in progress.

When you woke up on February 24, what were the very first moves you made?

IK: First came shock and panic. There was a lack of information. Everything we heard in the media seemed very ambiguous. We would hear that Kyiv was already occupied, then that it was not. That made it difficult to make any concrete decisions.

Our first choice was to tell employees not to come into work that day. Then we said, take care of your families as much as you can. We were unable to make any further recommendations at that time simply because so little information was available. We told our employees that we would accept any decision they made. If they left Kyiv, we would accept it. If they chose to stay, then we recommended that they find a safe place. During that first day, many people chose to get out of the city and keep their families safe. Children's lives were the highest priority.

At the end of February, we tried to set up a network to stay in contact with as many employees as possible. We also sent a payment through to them – a sort of salary to help provide support during a difficult situation. If children were the highest priority, then employees were the next highest.

We then took action to inform our customers about our situation. Essentially, we said, "Sorry; we don't know what's going on, so we are going to pause until Monday and then provide further updates."

Next, we dealt with our facilities. Our chemical labs contain many flammable solvents and gases that could be extremely dangerous in an emergency situation, so we halted all activities and worked to make the buildings safe.

That is how we responded in those first few days.

OG: I remember them well. I was in total shock. It was unreal. I remained in Kyiv for a few days, then moved to the west of Ukraine. The scenes there only continued the sense of unreality. Hordes of people at the stations. Gunshots. Sirens. Air attacks.

It took me about a week to return to a more-or-less normal life in a safer place. Now, I have begun to resume communication with our colleagues from Europe. I'm letting them know that I'm safe and telling them what actions they can take to support Ukraine.

In the longer term, how does the situation look?

IK: In the first 10 days of shock and confusion, I could not even begin to think about long-term plans. Our main wish was to inform people as much as possible. We formed a group of colleagues to spread the word online and secure interviews with the media.

After the first couple of weeks, new confidence began to emerge. It looked like the country would be able to put up a proper defense and that Kyiv would not be occupied quickly – if at all. There was going to be a struggle. By the middle of March, it seemed clear that it would be impossible for the Russians to capture Kyiv. This enabled us to think a little more strategically about the possibility of resuming operations.

Task number one was to refill our Riga and New Jersey stocks with compounds from Kyiv, which was difficult at first. Logistics were problematic. There were many checkpoints along the way and planes were ruled out entirely. Transport over land, by vehicle, was the only option. We seem to have pulled this off, which – if all goes well – is great news for us, because it means we can resume cash flow through sales of these stocks.

As for the safety of our employees, some cracks of light are opening there, too. Universities and institutions, as well as customers and even competitors, have proposed sites for us to relocate our chemists and workplaces. A door is open in Riga, because we already have compounds and a logistics center there, along with a good relationship with the Latvian Institute of Organic Synthesis. All that said, we were not able to relocate many of our chemists here, due to martial law which dictates that men aged between 18 and 60 cannot cross the border, allowing for a small number of exceptions. Thus, we have a small, initial team of ten chemists who have started working there.

We are all itching to return to work. Most of us have been sitting in our homes watching the news and slowly going crazy. We don't intend to resume any dangerous work, but there is some safer, less complex chemistry that we hope to get back to very soon. For employees with families who, quite rightly, wish to remain home, there is lab-free work – reports, updates, white papers – that we can assign to them.

OG: As for my department – research support – we are lucky. Our tasks can be done remotely. We have quite a lot of unpublished work that can be structured into scientific papers. I feel it is important that we maintain our presence in scientific journals and

research. That is what we are working on and we have had quite a few papers accepted; the first were published in early March. Eventually, however, that backlog will run out. Right now, I'm thinking about what useful paperwork we can turn to next.

What message would you like to pass on to readers?

IK: We would like to thank everyone who has shown and provided support to Ukraine. We have received donations to our army, to medical supplies, and to refugees. It has been amazing. We have also organized an Enamine Charity Fund, and were really glad to receive many donations from our customers, partners, and friends from around the world.

We have seen many companies take a very strong position on Russia. Many have ceased collaborations with Russian entities or pulled out of the country entirely. Among the first to react were GSK, AstraZeneca, Novartis, and many smaller biotech companies. It is right that the supply of essential medicines to Russia continues, but we see the halting of many other business activities, such as R&D and investment, as a very good sign. Maybe even more can be done.

I would ask your readers to stop all collaboration with Russian companies or research organizations. To support any Russian organization right now is to indirectly support the Russian state's terrorist actions in Ukraine. As you have heard from our president, Zelensky, we need more weapons, more support, and we need to close the sky. We need more sanctions on Russia, an oil embargo, and all political pressures possible to stop this war.

As well addressing the readership, I would like to say thank you to Enamine's customers for sticking with us. I hope you can see that we are a crisis-resistant company.

OG: I want to thank everyone who has reached out to Enamine. I've received messages of support from many people around the world. They helped me stay calm in an upsetting situation.

So what is to be done? I second Ivan; all collaboration with the aggressor indirectly supports the aggressor. Many big pharma companies have pulled back from Russia, but not all of them. More can be done here.

Many scientific publishers have made their support for Ukraine clear, but I think more can be done here, too. In my opinion, Russian and Belarussian scientists should not be included in the global scientific community as long as this conflict continues. More than 700 Russian universities have supported this aggression and many student organizations have joined them in this support. I understand that there may be a dissenting minority of scientists in Russia, but I do not think their existence justifies treating Russia as a normal partner.

I would also say to readers that, if they want to support Ukraine, they should look to organizations local either to Ukraine or to their own country, because we have seen some worrying behavior from international organizations.

If you are a reader with significant influence, I would suggest putting pressure on the government where you live. Even if you do not have much influence or money, even a small donation or a single post on social media can make a difference. These are all ways to stand with the people of Ukraine.

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NextGen

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The Big Question: Can We Truly Remodel Pharma With AI?

Perhaps the pharmaceutical industry's relationship with artificial intelligence will continue to grow from strength to strength – taking science to hitherto unimagined places. Perhaps algorithms and machine learning platforms will be slowly, subtly, but irreversibly integrated into the world of medicine making… We explore.

By Maryam Mahdi

Welcome to The Big Question – a new series for The Medicine Maker that takes an in-depth look at a hot topic. First up: artificial intelligence (AI).

But why? AI is often touted in pharma circles as a great enabler that could streamline manufacturing processes, cut out the noise in the mountains of data produced and obtained by pharmaceutical companies, and reduce the risk of error. To this end, more and more companies are beginning to explore how they can implement AI technologies.

Our experts had vastly different interpretations and thoughts on the topic. Can AI technologies really help drive the industry to new heights or does the hype outweigh reality? Let's hear their views.

Out With the Old

If the pharma industry wants to move ahead of the curve when it comes to manufacturing, it must do away with the legacy systems that hold it back

By Angelo Stracquatanio, CEO & Co-founder at Apprentice io

The life science industry is shifting toward more complex manufacturing, which can evidently be seen in the development of new biologics and cell and gene therapies. Despite these innovations, the approach to manufacturing critical drugs is stuck in the past; traditional methods – paper-based processes and legacy systems – can't hold up to the demands and pressures of new production methods.

Organizations must seek new ways to scale up and down to suit different batch complexities and sizes, identify how to handle new product introductions, and orchestrate flawless execution across teams and sites. Leading organizations are now embracing technologies, such as cloud computing, augmented reality, and AI, because modern, intelligent systems can bring them up-to-date and help them remain competitive in an ever-changing market.

In particular, AI tools can be used to augment decision-making with data-driven analysis. It can be built into the applications that decision-makers use daily, delivering usable insights that improve outcomes based on the data.

Although some currently available pharma systems can provide historical data, what's currently missing is the ability to make predictions. Using AI, historical data can be analyzed to determine what may happen next and to help with process optimization. Organizations can also build AI models that simulate changes in process data to see how it would impact yield, quality, and efficiency, without having to run extremely time-consuming manual tests. Simply put, AI predictions can speed up these processes as the data

already exists in one central system. In turn, organizations become less reliant on technical teams for data gathering, report analytics, AI modeling, and data requests.

On the shop floor, pharma organizations can even leverage AI to help machines make their own predictions or manage their own preventive measures. Operators can continue with confidence knowing that the shop floor can operate itself to increase speed and efficiency of production.

Though many in the industry are finally seeing the immense benefit of incorporating intelligent technologies and AI into their operations, there are only a few software providers capable of providing systems that are flexible enough to scale up and out with changing methods or deliver on the promise of pharma 4.0 connected systems. Traditional manufacturing technologies cannot easily (if at all) incorporate AI into their applications because of the level of technical expertise required to not only customize the platform, but also properly implement it and manage the AI models.

COVID-19 accelerated the immense uptick in adoption of new technology approaches in pharma, but there are few vendors who can adapt to the industry's changing needs and provide systems that are future-proof.

Perhaps the biggest drawbacks of these tools stem from a lack of understanding in terms of use cases and benefits. In my experience, some simply lack technical knowledge to use these systems effectively. Identifying how to apply this tech can be an issue for customers who aren't sure where to start, especially if those customers are using their own data scientists to maintain AI tools.

And for those who fear that there are risks associated with using AI for automation in such a highly regulated industry? I would remind them that there are guardrails that can be put into place. It's also worth noting that critical decisions will also always require human involvement. Overcoming many of these challenges comes down to appropriate education and support. By providing the right information, we can help each other on our journeys towards modern digitization. If you've not already embarked on your journey, now's the time!

Intelligent technologies, including AI, can increase operating efficiency, ensure process reliability, better track performance, and help you plan for the future. In a constantly changing landscape, the degree of digitalization will be a key differentiator. Even the FDA is investing in its own modernization plan, pushing out legacy systems and encouraging greater adoption of digitalization. In short, pharma needs to adopt new technologies to remain competitive and keep up with demand.

Finding the True Meaning of Disruption

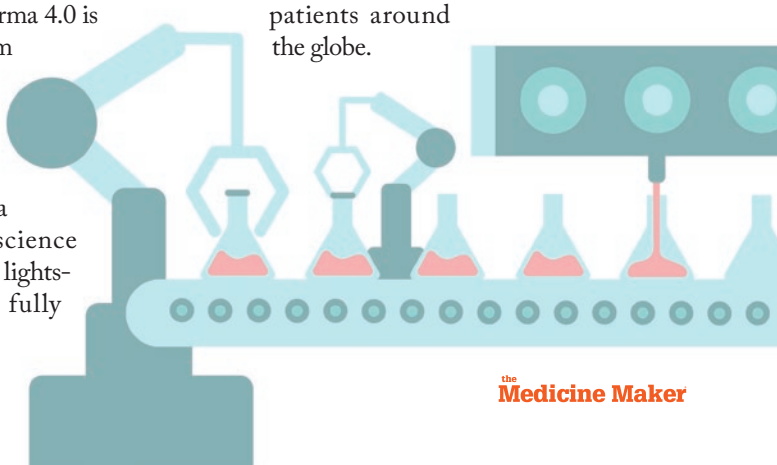
When it comes to innovation, keen and eager companies often describe their work as disruptive. But how many of the innovations making their way onto the drug development and manufacturing scene truly have the capacity to change the industry for the better?

By Noel Maestre is Vice President, Life Sciences at CRB

Disruptive is a term that is overused in the life science industry. It's often applied to marginal technological upgrades or even adapting a tried and true technology to a new application. That said, the current transformation in our industry is both exciting and unknown – and, by definition, disruptive.

Much like the scientific revolution currently being fueled by novel modalities, such as RNA, cell therapy and gene therapy, we are also seeing swift technological advancements. Pharma 4.0 is a complex ecosystem of tools, systems, and technologies that will amplify the industry's capabilities to a degree nearing science fiction. The age of lights-out, cloud-based, fully automated, and self-learning facilities is entering the biopharma industry, and progressing at a rapid pace.

As an industry, we must prepare for the profound changes the next two decades will bring in the form of curative therapies being manufactured in factories and processes that will have little resemblance to the ones we know today. Automation will help us get there. But it is our responsibility to harness the power of this revolution to make cures and therapies accessible to patients around the globe.



Intelligence by Design

AI is finding its place in the pharma industry and companies of all sizes and across therapeutic areas are open to the possibilities its use might bring. Here, we speak to Marcelo Bigal, President and Chief Executive Officer at Ventus Therapeutics, Jo Viney, founder, President and Chief Executive Officer at Seismic Therapeutic, and Tommaso Biancalani, Senior Principal Scientist and Director, AI/ML at Genentech, about their AI journeys and why these systems are so important to the future of R&D.

Why are you personally so fascinated by AI?

Biancalani: I'm excited by the recent progress made in the field of "generative models." These are models that are capable of starting from a certain data sample and transforming it in a specific way. The classical examples are the filters on our phones that start with a photo of us and end by making us look older or younger. Can we do the same thing with medicine? For example, can we start from a known drug and ask the AI to transform it into a new one with fewer side effects? This would truly be game-changing in the healthcare space.

Bigal: In my view, small molecule drug discovery is an incredibly challenging pursuit that typically requires years of time, and the design and testing of thousands of molecules. Despite all the rigorous work, we frequently find that empirically identified "optimal" molecules fail in the clinic due to unoptimized potency, selectivity, or pharmacokinetic properties. The challenge of designing molecules that are fully optimized on potency, selectivity, and pharmacological properties is to get the physics right.

If we had the ability to model and determine the precise atomistic quantum physics parameters of protein-small molecule interaction, we could, in principle, design fully optimized molecules de novo with minimal chemical exploration. While this is not possible yet, I am fascinated with the opportunity to harness the power of machine learning and AI to make the dream of fully optimized physics-based drug discovery within our grasp. In theory, a physics-based AI approach could reduce the number of molecules under scrutiny from thousands to hundreds, and speed up the drug discovery process.

Viney: I've spent my entire career in autoimmune disease drug discovery – taking 13 drugs to the clinic at biotech companies. I am personally captivated by AI because I know from experience that developing drugs that target the immune system is difficult. When I began to understand the impact of machine learning to design better biologics and their capacity to advance them faster, I knew this was something I wanted to be a part of!

"AI cannot replace human scientists in target and drug discovery – but it can definitely help them."

How has the use of AI in pharma changed over the years?

Biancalani: I see two main turning points. First, our ability to generate and store data exponentially increased in the last few decades (just consider that any pocket-portable USB stick can now contain many more books than the largest library in the world!). Second, the invention of the graphical processing unit (GPU) gave AI algorithms the power to manipulate large datasets – so-called deep learning.

Bigal: Machine learning has been part of drug discovery for more than two decades, with initial applications predicting physico-chemical properties of molecules and designing small libraries of chemical matter for a given target. In those days, lack of computational power made it challenging to widely apply these approaches to very large data sets, and also largely prevented scientists from even conceiving of other applications that we now see being developed. As Tommaso says, advancements in processing power, particularly with GPUs (driven by the gaming industry), have increased the scale of computational


Tommaso Biancalani


Marcelo Bigal


Jo Viney

possibilities within practical time limits by at least 100-fold. Simultaneously, development of the deep-learning network architectures driven by natural language processing and image recognition has produced new machine-learning capabilities.

Of course, hardware and algorithm development were both required for software development, and thus together they represent a turning point in the application of machine learning to drug discovery. These advancements have led to a renaissance in computation-based drug discovery, revealing the potential for faster identification and optimization of potent and selective drug-like molecules for clinical testing.

I believe that machine learning will have its biggest impact when combined with and used to enhance novel physics-based methodologies for drug discovery and, as an industry, we are aggressively pursuing novel methodologies and algorithms, with the goal of ultimately identifying drug-like molecules completely in silico.

Viney: With all of the many steps and complexities in the drug development process, it has taken some time for drug developers to figure out how to integrate AI and machine learning within the process. AI is an amazingly powerful technology, but it does not stand alone from other analyses, experiments and insights from expert scientists that are key ingredients to discover and develop new medicines.

What are the biggest misconceptions about AI?

Viney: Related to my last point, perhaps one big misconception is that AI can operate as a standalone approach for drug discovery, design and optimization! Creating a new drug is a complex effort that requires many steps and inputs. In my view, AI can serve as a powerful technology so long as it is integrated with human insights that are essential to the process of creating new medicines.

Bigal: I agree with Jo. The biggest misconception about AI is that it can be a panacea applicable to all aspects of drug discovery – solving all challenges by itself. Like any tool or platform, it is well suited to some areas and not others. One fundamental challenge of AI is the need for sufficiently large data sets to train the algorithms. It is necessary that these training sets have far more data points than the query set. If this is not the case, then AI will have little to no impact on the problem. This is particularly acute in drug discovery, where the query set (chemical space) is over 1063, and the data points are many orders of magnitude less than that.

Another misconception is that AI and machine learning are the same thing. Machine learning is a very specific sub-field of AI. In fact, almost everyone doing work in this field is using machine learning (image processing, language processing, text processing, clustering, property prediction, and so on).

AI is not a black box that magically solves any problem it is applied to. It is a diverse set of powerful technologies that requires ingenuity, deep understanding of the problem, and large amounts of quality training data to develop a successful application.

Biancalani: AI cannot replace human scientists in target and drug discovery – but it can definitely help them. Today's datasets are so massive that humans cannot possibly "look" at all this data; we need computational methods to extract relevant patterns and information in an automatic fashion. AI offers the tools for doing just that.

Another common misconception comes from the name "artificial intelligence," which suggests that these algorithms possess (or can eventually exhibit) intelligentia in the same way a human does. This is not correct. These algorithms can perform tasks that were typically performed by humans, but that doesn't make the software "intelligent." For example, a software that allows a vehicle to self-drive is very cool, but doesn't imply that the software "learns" or "thinks" in the same way a human does.

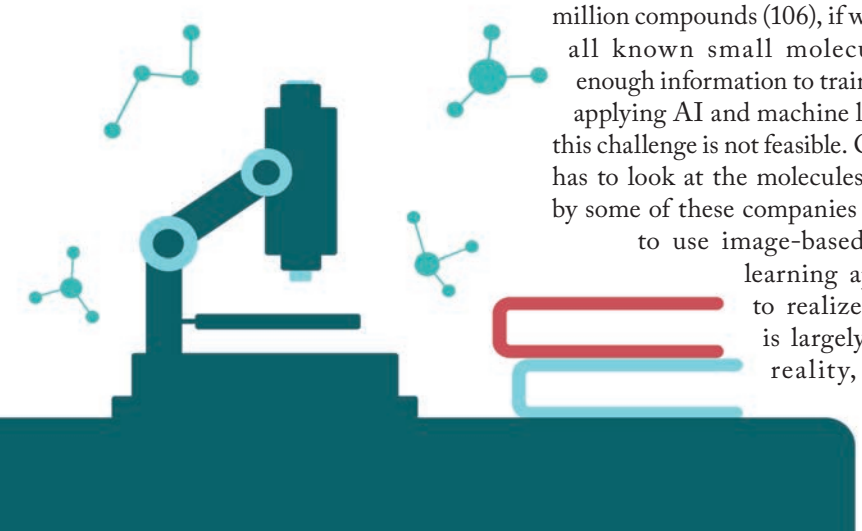
What is the hype versus the reality of AI?

Biancalani: AI is an essential tool or "lever" for R&D and the creation of patient-centric solutions, but it is just one part of the puzzle. There are other critical levers for R&D, including a deeper characterization of human biology,

"The first AI-designed drugs are just beginning to enter the clinic, meaning we really are at the cusp of being able to see the power of the AI approach."

the ability to conduct experiments at exceptionally high resolution and massive scale, and the exploration and application of diverse therapeutic modalities. It's the interplay among these levers that has the potential to deliver a variety of benefits for patients.

AI is a great tool for navigating large datasets and finding insights that can inform the development of better medicines for patients. But we aren't at the stage where AI can create a medicine on its own. We still need scientists to validate these insights in the lab and to test the safety and efficacy of potential medicines in clinical trials.



Viney: The excitement surrounding AI in drug development is palpable, as it has emerged as a powerful new technology that can help us to design better drugs and advance them faster to patients. The reality is that there are a multitude of ways that AI can be integrated in the drug discovery process, and our industry is in the early stages of building new approaches to use AI and machine learning. There is so much potential in the future; AI can make major contributions to how we can improve and accelerate the process of creating new medicines.

Bigal: Many companies and scientists have set out to apply AI and machine learning to the entire drug discovery spectrum, from target identification, small molecule discovery, and optimization, to biomarker discovery and clinical trial design and execution. There has been a huge amount of hype from some of these companies, stating that they will solve all the challenges of drug discovery. However, in reality, many of the areas they claim they can impact do not have large enough training sets for this to be possible. In particular, the application of AI to identify new chemical starting points and optimize affinity of chemical matter using purely image-based approaches is an area where the hype outweighs the reality.

As I mentioned, the theoretical query set of small molecules is thought to be about 1063, yet the training set in the best of circumstances is likely less than a million compounds (106), if we combine all known small molecules with enough information to train on. Thus, applying AI and machine learning to this challenge is not feasible. One simply has to look at the molecules produced by some of these companies purported to use image-based machine learning approaches to realize that this is largely hype. In reality, they are simply making small modifications to pre-existing chemical matter, which a good medicinal chemist could do easily without any computational help.

The challenge of small molecule drug design is a function of physics. The laws of physics are universal and thus applying machine learning approaches to enhance and optimize physics-based parameters requires a far smaller data set to train on. I believe companies pursuing these types of approaches and platforms are the ones that should be able to realize the value of machine learning to this problem.

What advice would you give to others interested in using AI for pharmaceutical R&D?

Bigal: My advice would be to make sure that you understand the problem from the first principles and not just assume that AI can solve it. Find those areas to which AI approaches are best suited, where sufficient training sets exist, and focus on those areas. Drug discovery is an incredibly complex and difficult undertaking; don't assume there is one way to solve the challenges and instead think beyond AI to look for solutions. Importantly, never underestimate the need for experienced drug discovery scientists in your organization. Nothing can replace years of experience and a track record of success in developing drugs that address diseases of high unmet need. AI is only a tool to support those scientists and cannot replace the years of experience and know-how that will remain a critical component for success.

Biancalani: Smaller enterprises, such as startup companies, often have sophisticated AI methods. However, to be successful in leveraging these methods to solve complex problems and accelerate R&D, you need both sophisticated AI and large datasets. Large datasets can be very difficult for a small company to access, but they may be able to

access them through collaborations or partnerships with larger companies like Roche and Genentech.

What will pharma's future relationship with AI look like?

Viney: We have seen a lot of interest throughout the drug industry in AI and machine learning, and pharma companies are exploring different ways that AI can be used for specific drug modalities and in specific therapeutic areas. Like Tommasso says, it is important that companies maintain open dialogue with others who might be potential collaborators, while keenly focusing on advancing their own drug programs and developing drug product candidates to help patients.

The first AI-designed drugs are just beginning to enter the clinic, meaning we really are at the cusp of being able to see the power of the AI approach for accelerating and augmenting drug discovery and development. A decade from now, I hope we will be able to look back and see that this was an exciting time and a major turning point for medicine.

Biancalani: I believe AI can remodel every field where large datasets are present. This is an incredibly exciting time in the healthcare field. We are at an inflection point in drug R&D; science and technology are converging, and computational methods, such as machine learning, will be as essential as biology and chemistry to the future of medicine.

Thanks to this convergence, and the transformative scientific and technological advances in recent years, we have an opportunity to bring multiplicative, rather than incremental, benefits to drug discovery and development – and, most importantly, to patients.

Bigal: I think AI will continue to be a growing part of the pharma industry as we move beyond the hype and identify areas where AI can truly make a difference. With the continuing advancement of algorithms and hardware, we will continue to see innovative scientists think of new ways to apply this toolset.

It is important to remember that the concept of applying AI and machine learning to drug discovery is not new. Many of the concepts have been considered before only to fall by the wayside due to ineffective application, lack of computational power, weakness of algorithms, or the absence of enough data to train on. Though advancements in AI will make application to drug discovery more effective, I do not believe it will completely remodel the industry. At the end of the day, we are developing chemicals that have biological effects in complex organisms. The complexity of the human organism is still far beyond our understanding, and it would be naïve and arrogant to believe we have the knowledge to effectively model this in a computer to the point that it can replace experimental testing and hypothesis-driven science.

AI is an exciting new technology and we are in the hype cycle. Though some of the claims out there are for marketing purposes, there are many areas where the application of AI technology can genuinely increase throughput and efficiency of drug discovery, from target analysis with platforms like AlphaFold 2, to virtual screening of chemical libraries, to processing experimental results with image recognition. As we collect more data on biological interactions in organisms, we can envision AI helping to uncover complex patterns underpinning those interactions that would help us to understand disease mechanisms, select the most effective targets, rapidly identify and develop therapeutic molecules, and quantify effects of genetic variability to personalize treatments.

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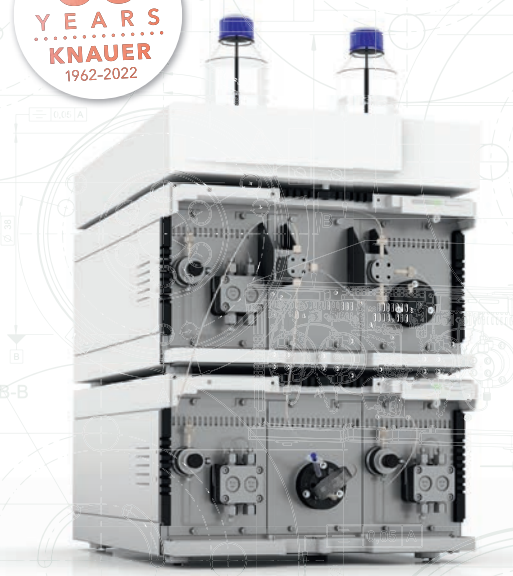

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Changing People's Perspectives

Sitting Down With… Akhil Ravi,
CEO of Aurigene Pharmaceutical Services,
a Dr. Reddy's Laboratories company, India

How did you join Dr. Reddy's?

I studied business before joining McKinsey and Company, where I worked across numerous sectors, including healthcare and other allied sectors. Dr. Reddy's is considered one of the most respected companies in Hyderabad – the city I grew up and lived in. After a few years as a consultant, I had the opportunity to go to Dr. Reddy's, but I had to think about it for a few years!

Eventually, I took the plunge. I knew a few colleagues at Dr. Reddy's, so I spoke with them about the culture, which is very important to me. I worked with a lot of promoter-driven companies in my time at McKinsey and I didn't enjoy that culture. But Dr. Reddy's has a very professional management team, as well as a good reputation in India and globally. Since joining, I've worked in many different roles, including manufacturing, strategy for the active ingredients' division, and leading sales in Europe for that division.

Why do you think working in the pharma industry is so rewarding?

Everyone in the pharma industry has always found the work rewarding, but I think the reason for that has really hit home in the last three years – thanks to the impact we've collectively had across the entire chain of tackling the pandemic – from prevention to cure. We've gained control of the pandemic and we can now prevent severe COVID-19 disease.

When I first joined pharma, I found it a little frustrating because the pace was slow and conservative. You need to talk to many people to even move an inch! I think the pandemic has taught us that we can move faster while still making high-quality, safe medicines.

Many things came together during the pandemic; the industry was leveraging data sets and computational power; governments were prepared to play their part, and supply chains were adjusted to suit the vaccine roll out. Overall, it's really changed the way people and biotechs think about R&D and how we bring medicines to market.

How have you settled into the role of Aurigene's CEO?

It's been a very interesting journey so far with a lot of new opportunities and exposure to diverse areas. To be honest, I was a little surprised when I got the job! I was on vacation last year when I got a call along the lines of: "Hey, you know how this person left? Do you want the role?" There were then many conversations, but gradually I became more comfortable with the idea of leading Aurigene services, which is a contract research, development, and manufacturing subsidiary of Dr. Reddy's.

My division is focused on using cutting-edge science to partner with other companies and bring new medicines to patients. I've had to learn quickly. I've been looking at what works well, and what we need to change. And I've focused on getting the whole team to see the same vision. We have a great opportunity to bring new medicines to the world through our partners and it's important to ensure that friction in our way is removed.

What are the big topics in pharma right now?

First and foremost, our industry is growing! A great deal of money is being pumped into biotechs across the world, and they need contract partners to help them advance their vision. Many of these companies do not have their own labs or manufacturing facilities and need partners. Thus, there is enormous demand for contract partners right now.

Therapeutics are shifting in complexity. Oncology remains a critical space, but CNS is growing. Technology platforms are also changing, across small molecules, biologics, and cell and gene therapies. There are many different potential avenues to grow – and companies will need to make choices. Where do you want to focus and differentiate yourself, and invest your resources?

What's your view on sustainability?

It's a really important area for me. But I'm certainly not alone – I think we're all becoming more aware of the issues. In pharma, we not only need to consider reducing energy and plastic use but also the number of solvents or chemicals used to manufacture medicines and our reliance on animal testing. There are many opportunities to improve, with potential solutions at different stages of maturity.

The industry needs to translate peoples' will to help the planet into company policies – and keep environmental, social, and governance (ESG) goals in mind. Remember, some investors reward companies that perform well on ESG metrics – and other companies may purposefully choose to work with partners who have good ESG. And that means ESG can be rewarding for a business – while also making a big difference to the world.

As an organization, we embarked on our voluntary sustainability disclosures journey in 2004 and have been listed on the Dow Jones Sustainability Index since 2016. We were one of the first companies in India to be listed (we were ninth among the most sustainable pharma companies in the Index in 2021). It's been a very conscious effort and we continuously improved over the years with progress in waste minimization and management, and the establishment of zero-liquid discharge at our manufacturing sites.

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

I would change the perception of the industry. There are many articles and documentaries that demonize the industry. But these are isolated events that do not define the industry as a whole.

In particular, some people also have a poor perception of certain manufacturing facilities in India. To those people I say, please come to our facilities. People often visit us in India and are very surprised by what they see! India's CDMO industry has grown tremendously in the last 10 years and works with almost every top twenty pharma company.

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