JANUARY / FEBRUARY 2024 # 95

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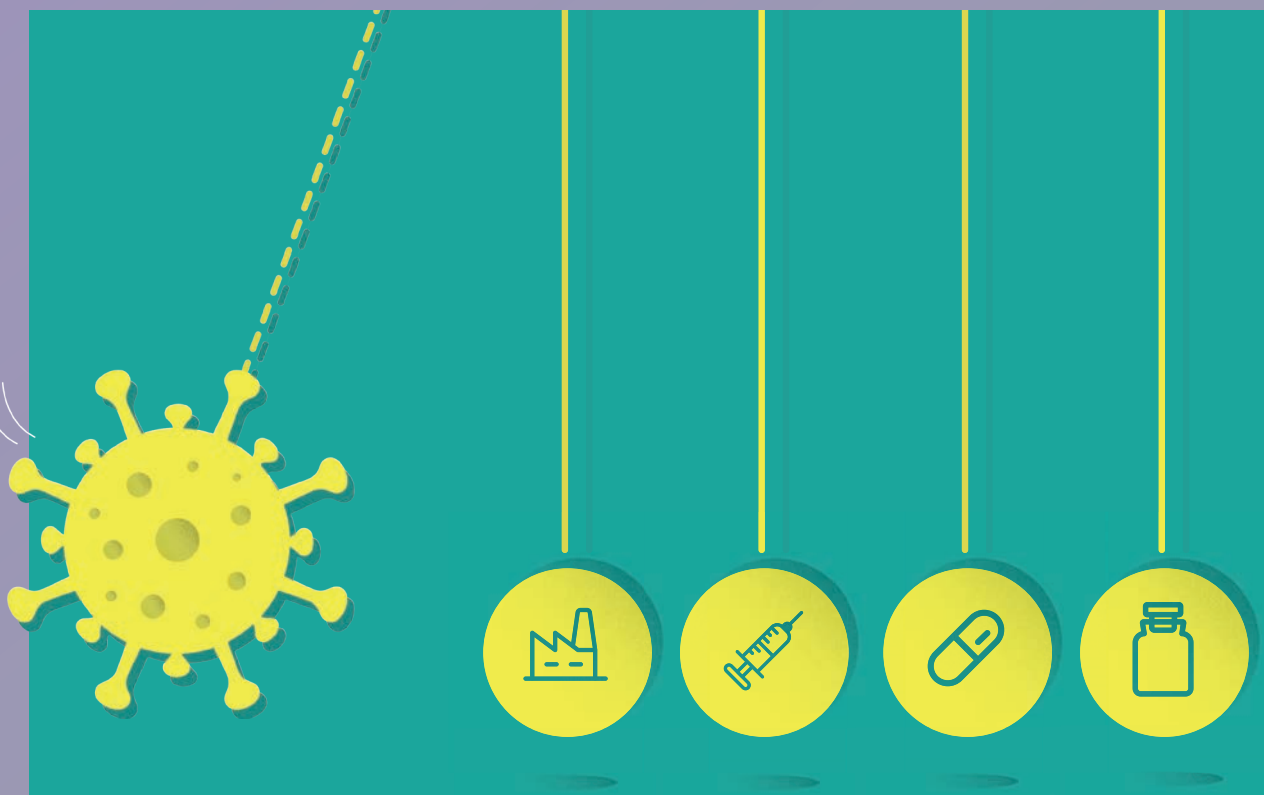

The COVID-19 Knock-On Effect

After supply chain disasters and capacity crunches, we look at how Europe is planning ahead for future emergencies

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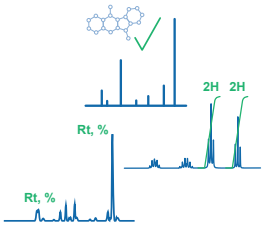
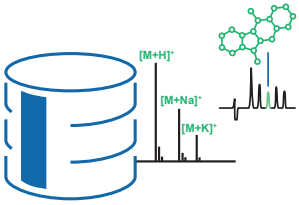


Contextual data storage



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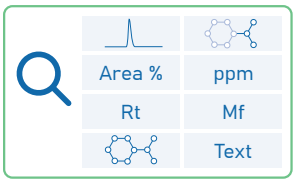

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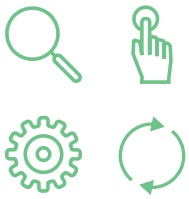
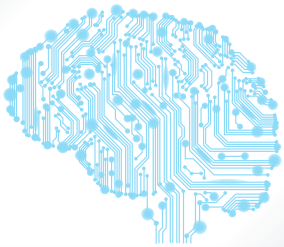
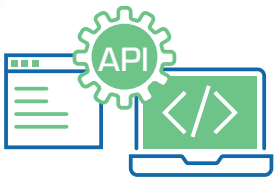


A FAIR-compliant ecosystem



Harmonized, AI/ML-ready data



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Farewell to Aduhelm

But thanks for throwing the spotlight on Alzheimer's disease

In a move that will come as little surprise to anyone, Biogen is discontinuing its development and commercialization of Aduhelm (aducanumab), which includes axing the Envision clinical study. Instead, Biogen will prioritize its more popular child, Leqembi (lecanemab). The company had been looking for potential partners or external financing to support Aduhelm, but has been unable to find a solution. To report the news, Gizmodo chose to run with a rather harsh headline: "It's Finally Over for Aduhelm, the Sketchy Alzheimer's Drug Everyone Hated."

Certainly, the drug's entry into the market might be considered "sketchy" by some. The FDA based its approval on the fact that the drug could reduce amyloid plaques – but, crucially, without evidence it would translate to clinical outcomes for Alzheimer's disease patients. According to reports, at least three members of an FDA advisory panel resigned in protest.

Next, Medicare limited coverage of Aduhelm for patients, and the drug never really gained any traction. At the same time, Biogen and its development partner Eisai doubled down on clinical studies for Leqembi, looking to provide more information to support its use. Their efforts paid off; Leqembi received full FDA approval in July 2023 – and the drug is covered by Medicare under certain conditions. The drug has also been approved in other territories, with a decision in Europe expected in the second quarter of 2024.

Leqembi isn't the only anti-amyloid monoclonal on the block. Eli Lilly is working on donanemab, but the therapies are far from perfect. Leqembi has a black box warning for potentially fatal brain bleeds and trials of donanemab have identified serious side effects.

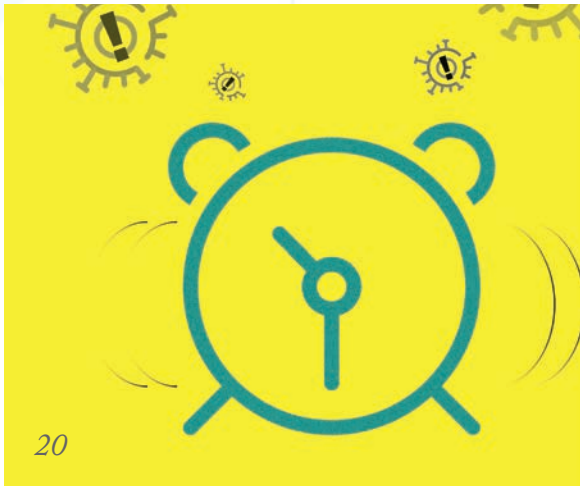
Nevertheless, these therapies represent progress for a disease that has been untouchable for years. Just as COVID-19 reignited interest in innovations against infectious diseases, I hope we will see a similar renewed interest for Alzheimer's disease.

"When searching for new medicines, one breakthrough can be the foundation that triggers future medicines to be developed. Aduhelm was that groundbreaking discovery that paved the way for a new class of drugs and reinvigorated investments in the field," Biogen President and CEO Christopher Viehbacher said in a statement.

Farewell, Aduhelm. May you rest in peace.

Stephanie Vine
Editor

Contents



On The Cover

We continue to feel the effects of the biggest healthcare crisis in modern history, but lessons have been learned.

Feature

Core Topics

NextGen

Business

Sitting Down With

the Medicine Maker

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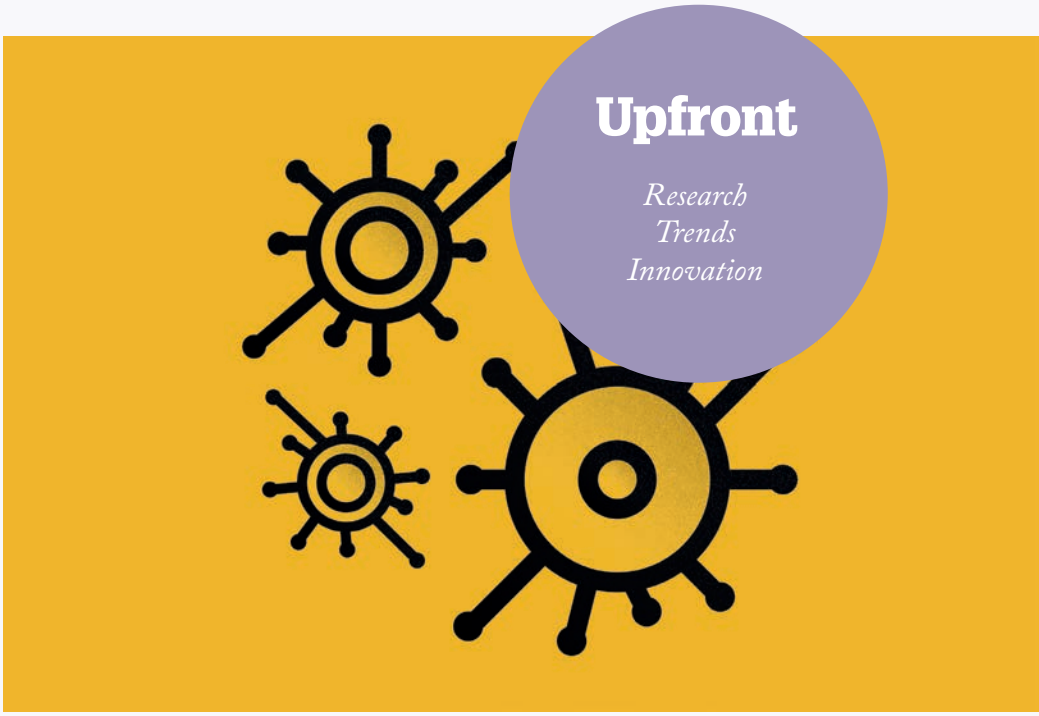


What's Happening with CAR T Therapies?

A look at the FDA's investigation into CAR Ts

Black box warnings are to be added to CAR T therapies currently approved by the FDA because of the risk of secondary T-cell malignancies in patients. The FDA began investigating CAR Ts and T-cell malignancies in November 2023. In Europe, the EMA is also conducting its own investigation.

In letters sent to the affected manufacturers in January 2024, the FDA says, "We consider the serious risk of T cell malignancy to be applicable to all BCMA- and CD19-directed genetically modified autologous T cell immunotherapies." The wording suggests a class-wide warning that could affect future therapies as they come to market.

Writing in The New England Journal of Medicine, Nicole Verdun and Peter Marks from the FDA said, "As of December 31, 2023, the FDA had become aware of 22 cases of T-cell cancers that occurred after treatment with CAR-T products."

Cases have been identified in association with five out of the six currently approved CAR T products, with the cancers generally manifesting within two years after CAR T administration. Verdun and Marks wrote, "In three cases for which genetic sequencing has been performed to date, the CAR transgene has been detected in the malignant clone, which indicates that the CAR-T product was most likely involved in the development of the T-cell cancer."

The CAR T that does not yet seem to be associated with reported cases isTecartus. A few days after the FDA posted its letters mandating a black box warning, it issued an amended letter for Tecartus. The warning acknowledges that T cell malignancies have occurred with CAR T products but removed the mention of Tecartus specifically. However, Tecartus must still include a labeling change with a black box warning that the product can increase the risk of other cancers.

The agency continues to investigate but says that it won't be possible to determine whether the CAR construct triggered the cancer for every single case. It is thought that the risk remains low.

Reference

1. *N Verdun, P Marks, NEJM (2024). DOI: 10.1056/NEJMp2400209*

TIMELINE

A Brief History of CAR T Approvals

As the FDA asks for black box warnings for CAR Ts, we look back on how approvals have unfolded since 2017

March 2017

Novartis and Kite submit BLAs to FDA for their respective CAR T therapies (Kymriah and Yescarta)

August 2017

Kymriah (tisagenlecleucel; Novartis) approved by FDA for B-cell precursor acute lymphoblastic leukemia

October 2017

Yescarta (axicabtagene ciloleucel; Kite) approved by FDA for relapsed or refractory large B-cell lymphoma

August 2018

First CAR Ts approved in Europe (Kymriah & Yescarta)

DRUG APPROVALS - IN-BRIEF

The first drug approvals of 2024 are in, including a first-in-class treatment, novel antibiotic, and more

- Ligand Pharmaceuticals' Zelsuvmi (berdazimer topical gel, 10.3%) – approved by the FDA as a first-in-class treatment for the skin infection molluscum contagiosum. The drug is a nitric oxide releasing agent but its mechanism of action is unknown. It is the only topical prescribed medicine for the infection that can be applied at home.
- Sanofi and Regeneron's Dupixent (dupilumab) – approved by the FDA for children aged 1 year and above with eosinophilic esophagitis. The approval extends the drug's initial indication for patients aged 12 years and older. There are currently no other medicines approved for the condition, which can severely impact a child's ability to eat.
- GSK's Omjjara (momelotinib) – received marketing authorization from the European Commission for treating splenomegaly (enlarged spleen) or symptoms in myelofibrosis patients with moderate to severe anaemia. The drug is an oral JAK1/JAK2 and activin A receptor type 1 inhibitor. It was approved by the FDA in September 2023.
- Advanz Pharma's Exblifep (cefepime/enmetazobactam) – positive opinion from the EMA CHMP for treating complicated urinary tract infections caused by gram negative bacteria. Cefepime is a fourth generation cephalosporin cefepime designed to have enhanced efficacy against resistant bacteria, while enmetazobactam is a novel extended-spectrum-lactamase inhibitor (part of the penicillanic acid sulfone class).
- Recent rejections – Defender Pharmaceuticals gets FDA complete response letter from FDA for motion sickness gel; EMA CHMP recommends refusing marketing authorizations for cerebral adrenoleukodystrophy treatment leriglitazone from Minoryx and Neurapharm, and Apellis Pharmaceuticals' intravitreal pegcetacoplan for treating geographic atrophy.

Importation Tension

As the Sunshine State looks to import medicines to lower costs for Floridians, what of ongoing shortages for Canadians?

The FDA has authorized Florida's plans to import certain prescription drugs from Canada for the next two years, if doing so will lead to lower costs.

Canada, however, is not happy with the arrangement and has introduced a new regulation. Like many countries, Canada is currently experiencing a high number of drug shortages. The new regulation will "prohibit certain drugs intended for the Canadian market from being sold for consumption outside of Canada if that sale could cause, or worsen, a drug shortage in Canada. This includes all drugs that are eligible for bulk importation to the US, including those identified in Florida's bulk importation plan, or any other US state's future importation programs."

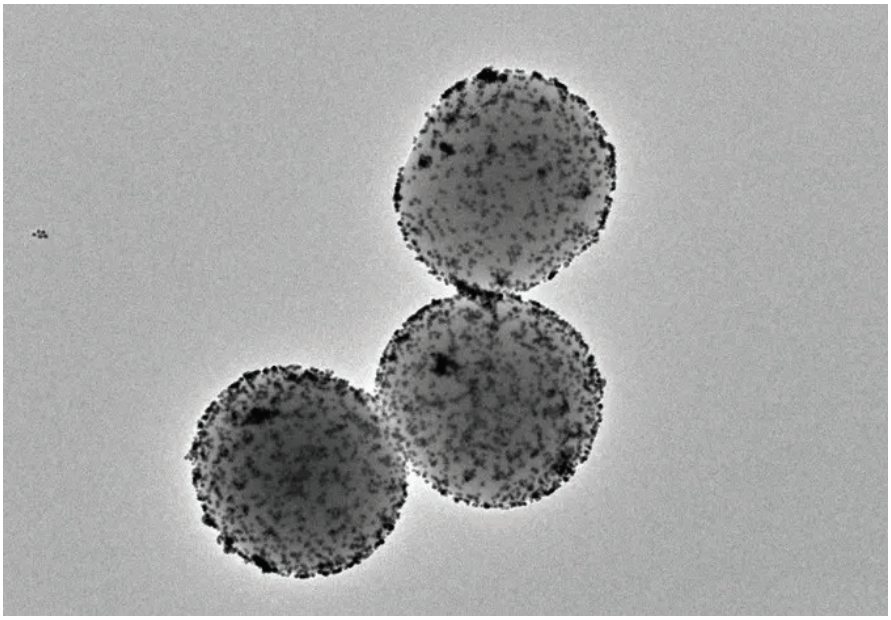
Health Canada says it will be monitoring the Canadian drug supply to ensure that rules are followed.

Other stakeholders also disapprove of the FDA plans, with PhRMA describing the plan as "reckless" because of safety concerns.

July 2020	*February 2021*	*March 2021*	*February 2022*	*November 2023*	*January 2024*
Tecartus (brexucabtagene autoleucel; Gilead) approved by FDA for relapsed or refractory mantle cell lymphoma	Breyanzi (lisocabtagene maraleucel; BMS) approved by FDA for relapsed or refractory large B-cell lymphoma	Abecma (idecabtagene vicleucel; BMS) approved by FDA for relapsed or refractory multiple myeloma	Carvykti (ciltacabtagene autoleucel; Janssen) approbed by FDA for relapsed or refractory multiple myeloma	FDA announces review of CAR T cell immunotherapies	FDA requests black box warning for approved CAR Ts

Bladder Runner

Self-propelled nanoparticles can reduce tumors in the bladder by 90 percent



Institute for Bioengineering of Catalonia (IBEC)

"It's a shame she won't live. But then again, who does?" said Officer Gaff at the end of 1982's Blade Runner. But for bladder cancer patients, sci-fi-esque technology may bring hope of life. Specifically, a team at the Institute for Bioengineering of Catalonia (IBEC) has developed urea-powered nanobots that deliver radionuclide therapy exactly where it's needed.

The nanoparticles consist of a porous silica sphere, which carries various components with specific functions on its surface. Among these are urease, which enables the nanoparticle to propel itself; and radioactive iodine for localized treatment of tumors. In vivo studies in mouse models have shown a 90 percent reduction in tumor volume, which could lead to fewer hospital visits, shorter hospital stays, and a huge reduction in the burden placed upon healthcare institutions.

"Treating tumor-bearing mice with intravesically administered radio-iodinated nanobots for radionuclide therapy resulted in a tumor size reduction of about 90 percent, positioning nanobots as efficient delivery nanosystems for bladder cancer therapy," write the study authors (1).

The nanorobots broke down the extracellular matrix of the tumor by increasing the pH through their self-propelling chemical reaction, favoring greater tumor penetration and achieving preferential accumulation.

According to the WHO International Agency for Research on Cancer, bladder cancer is the 10th most common cancer type, with 600,000 new diagnoses and 200,000 deaths each year (2). Bladder cancer tumors also have an alarmingly high recurrence rate – and though current treatments display good survival rates, therapeutic efficacy is relatively low.

The use of nanorobots delivering therapeutic agents directly to the tumor represent an ongoing means of study for the IBEC engineers, who hope that recurrence levels can be reduced as drastically as the tumor volumes themselves.

Reference

1. *S Sanchez et al, "Urease-powered nanobots for radionuclide bladder cancer therapy", Nat. Nanotechnol. (2024) DOI: 10.1038/s41565-023-01577-y*
2. *"Bladder Cancer", IARC. Available at : https://bit.ly/4900oFC*

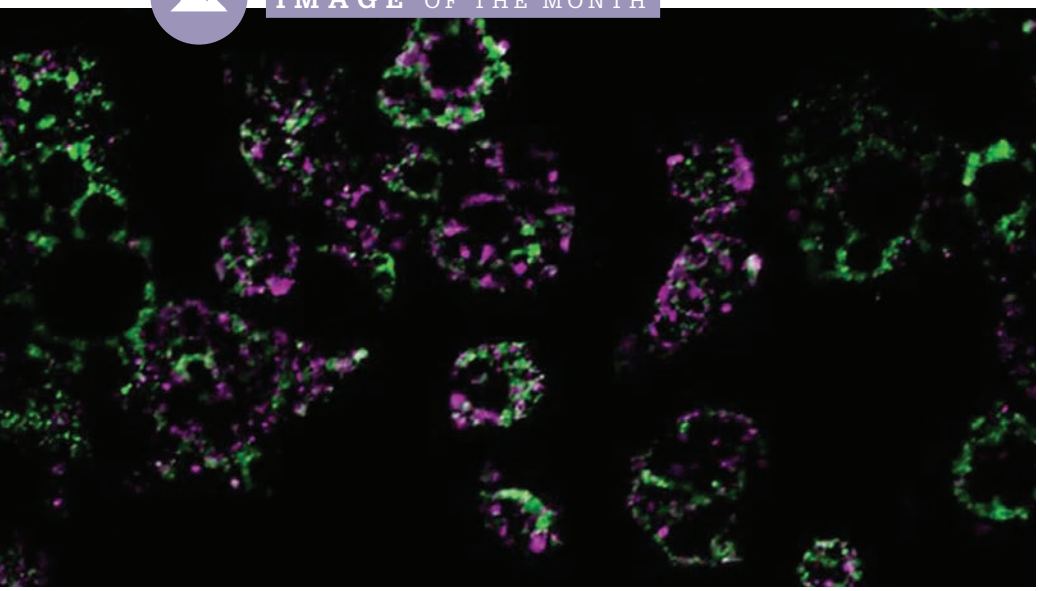
Meet the African Medicines Agency

EMA to contribute expertise and support to African Medicines Agency

Efforts to create an African Medicines Agency (AMA) to improve access to safe and effective medicines in Africa have been ongoing for some time. The AMA Treaty was adopted by the African Union Assembly in February 2019. Now, the EMA has offered its support to the cause. With a grant of ten million euros from the European Commission, the EMA will work with various international stakeholders to help establish the AMA by sharing its own experiences, offering training, mobilizing experts, and assisting in setting up the governance, scientific and administrative processes. The EMA will also be looking to coordinate efforts between its own regulatory networks, and those in Africa and internationally.

According to the EMA, "To date, 27 countries have ratified the AMA treaty, and more AU members are expected to complete the process in the coming months. The creation of AMA is a unique opportunity to facilitate the regulation and oversight of key medicines at a continental level, promoting collaboration among African countries and regions."

IMAGE OF THE MONTH



Fatty fireworks

With the number of drug development projects targeting lifestyle diseases increasing, University of California San Diego researchers show how obesity dismantles mitochondria, resulting in weight gain.

Credit: UC San Diego Health Sciences

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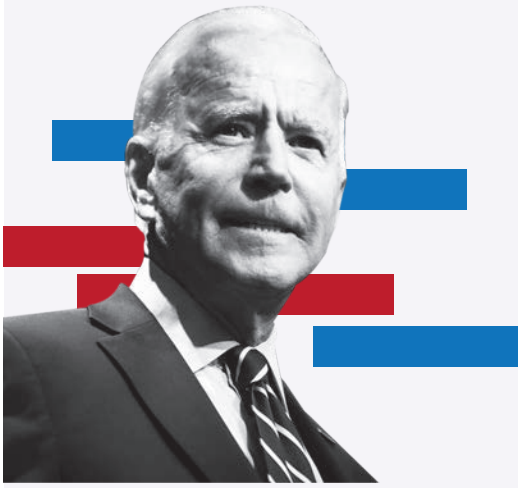
QUOTE of the month

"With more than 27,000 doses of the six approved products having been administered in the United States, the overall rate of T-cell cancers among people receiving CAR T therapies appears to be quite low."

Nicole Verdun and Peter Marks from the FDA writing on the CAR T black box situation (NEJM (2024). DOI: 10.1056/NEJMp2400209)



Let the Negotiations Begin

First round of offers sent as part of US Drug Price Negotiation Program

Offers have been sent out for the first 10 prescription drugs selected for the Medicare Drug Price Negotiation Program. Department of Health and Human Services Secretary Xavier Becerra described it as a "historic" "milestone" that could put "an end to exorbitant price gouging."

Members of PhRMA, however, have criticized the Biden-Harris administration, accusing them of playing politics at a delicate time. Senior Vice President of Public Affairs at PhRMA Alex Schriver said, "This continues to be an exercise to win political points on the campaign trail rather than do what's in the best interest of patients. Government bureaucrats are operating behind closed doors to set medicine prices without disclosing for months how they arrived at the price or how much patient and provider input was used. This lack of transparency and unchecked authority will have lasting consequences."

In My View

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

Never Break the Chain

How do we prevent criminals from reusing primary packaging for counterfeit medicines? Labeling solutions and other creative concepts can help

By Nadine Lampka, Senior Product Manager Pharma-Security, Schreiner MediPharm

Since the EU's Falsified Medicines Directive became effective in February 2019, tampering with secondary medicine packaging has become more difficult. But what about primary containers, such as vials, syringes, and autoinjectors?

Illegal medicines inflict considerable damage on the pharmaceutical industry, posing a massive risk to patient safety. Operation Shield III, conducted between April and October 2022 by Europol, the European Agency for Law Enforcement Cooperation, once again revealed the magnitude of this issue. Authorities seized massive amounts of misused, falsified or counterfeit medicines, doping substances, counterfeit COVID-19 vaccines, sanitary products, and medical devices worth over 40 million euros. Twenty eight European countries were involved in the operation and 59 criminal groups were dismantled.

The Falsified Medicines Directive requires pharmaceutical manufacturers to include an individual serial 2D code (data matrix) on the secondary packaging of prescription drugs, as well as tamper-evident feature, such as a closure seal that indicates the integrity of packaging. Special folding box designs, glue dots, and various seal solutions with irreversible void-effects have all become established as reliable first-opening indicators.

In some healthcare settings, however, secondary packaging materials may be disposed of and the primary containers stored elsewhere until the medicines are dispensed. An integrity check of the container prior to its first use would be essential in this case — but the EU Directive only addresses secondary packaging.

Counterfeiters have been known to search for empty, original medicine bottles or vials in waste containers, refill them with counterfeit substitutes and sell them as supposed originals. Thus, to achieve comprehensive product and patient safety as the result of a consistently secured supply chain, appropriate security solutions should also be implemented for primary packaging.

Various security concepts exist to help ensure the integrity of primary containers. For glass vials, for example, a security label can be wrapped around the vial up to the level of the cap. Before opening, a tear strip has to be peeled off, which indicates that the label has been opened, and a covert warning message becomes visible. The first-opening indication can also be further enhanced by an optional void effect, where previously invisible lettering or symbols irreversibly separate from an indicator field. Afterwards, it is no longer possible to unnoticeably reuse the container. This type of tamper-evident label is suited particularly for small vials and can be equipped with an inspection window. Special labeling materials are also usually available that can protect

the medicine in the container against UV or other light rays by selecting a special label material.

Label-based sealing solutions with first-opening indication can also be used for prefilled syringes. For example, a specialty label that wraps around the entire cap and syringe barrel can secure the integrity of the syringe until the injection is performed. Opening the label activates a first-opening indication and special security die-cuts result in partial destruction of the label to prevent reclosing. Covert warning messages can also be added.

Another example for luer-lock syringes is a label plus cap. Initially, the differences between the radii of the syringe body and the closure cap are equalized by means of a special cap adapter placed on top of the syringe closure. Subsequently, a label with an integrated perforation for tamper evidence is applied to the syringe body and cap adapter so that it firmly wraps around both elements. Since the adapter interlocks with the original closure of the cap, the syringe can be opened in a single move as usual. This purposefully destroys the label, which thus clearly and irreversibly indicates that the syringe has been opened. The larger circumference of the adapter compared with the original syringe closure makes it easier for the user to open the cap. In addition, this concept helps ensure the sterility and integrity of the luer-lock syringe up until its use.

And what about the autoinjectors used in homecare settings? Self-medication is increasing and patients need to be able to easily and quickly check their injection aids for integrity and authenticity. Near field communication (NFC) chips can be integrated into smart labels, which can be applied to primary containers during production and serve as digital tamper evidence. They can be read using a smartphone app. NFC labels can be applied so that they wrap around the autoinjector, including the cap. Before pulling off the autoinjector cap, the user checks if the product is an original; after reading the chip, the app will show a respective confirmation. After opening the cap and another reading of the chip, a warning message will appear indicating that the product has been opened. If this warning message appears before the patient has opened the device for the first time, this indicates a potential tampering attempt. In addition to the first-opening indicator function, the chip can be also used for further features. For example, pharmaceutical manufacturers may integrate interactive applications, such as product information or demo videos. Geo tracking features can also be added to detect potential gray market activities in local markets.

Both analog and digital security solutions provide comprehensive tamper evidence for primary containers and injection aids, assisting healthcare professionals and patients in readily detecting previously opened containers as part of their daily routines. However, in the context of a secure supply chain, such solutions are inadequate because, in addition to product identity and integrity, the authenticity of a product must be ensured.

In my view, comprehensive protection against counterfeiting and tampering can only be guaranteed by a combination of different features. For instance, analog authentication features, such as holograms, thermo-chromatic effects, or a perforation preventing undetected re-capping, can be integrated into a label in addition to an NFC chip. Ideally, integrated security concepts should combine several security technologies in a multi-layered approach addressing different user groups within the supply chain.

End-to-end supply chain integrity plays a major role for the pharmaceutical industry, by embracing appropriate security concepts, stakeholders can verify both secondary and primary packaging.

Pharma's Portal to the Lab of the Future

Labs of the future will use VR, AR, AI and more. But we must overcome the barriers of implementation, including cultural resistance

By Becky Upton, President, the Pistoia Alliance

The Pistoia Alliance was founded more than 15 years ago as a not-for-profit with the mission to lower barriers to innovation in the life sciences through pre-competitive collaboration. Core to this mission is working with our member organizations to overcome common obstacles that are holding back technological innovation in our industry. We know that adopting new technologies in R&D and proving their value is both a huge undertaking and a great expense. By working together, we

are able to break down silos and remove the interoperability problems often created when companies choose to "go it alone," allowing our members to integrate emerging innovations more seamlessly and continue delivering life-changing therapies to patients.

The "lab of the future" is one such area where we are keen to see more innovation. To see how our members are progressing with integrating new technologies into the lab, we worked with the Lab of the Future Congress to survey experts from top pharma companies, medium enterprises, startups, and beyond. Our survey reveals which technologies are top of the investment agenda, what organizations are struggling with, and how we can help make the tech of tomorrow a reality in the labs of today. Over half the experts we surveyed said their labs are already using robotics; 40 percent said they expect to be using virtual reality, augmented reality, and wearables in the next two years. AI and machine learning also feature highly in the adoption curve, with AI seen as being able to significantly accelerate existing workflows in small molecule discovery and lead optimization for new drug candidates. Given this proven potential, it's not surprising that AI and ML topped the list as the technology most companies (60 percent) plan on investing in during the next two years.

Underpinning the successful use of any new technology in the lab, however, is the need to establish a foundational data backbone. What does that mean? Well, all the behind-the-scenes, less headline-grabbing systems and data science techniques that are critical to unlocking the benefits of AI and machine learning. For example, cloud technologies that provide storage space and computer capacity are being invested in by more than half of companies, while 60 percent expect to be using laboratory information management systems (LIMS) in the next two years to digitally capture and share methods and results. Such foundational data management technologies can lay the groundwork for more hyped-up technologies, such as generative AI. After all, companies must learn to walk before they can run.

"Underpinning the successful use of any new technology in the lab, however, is the need to establish a foundational data backbone."

Despite encouraging investment in foundational data technologies, the survey also revealed there are still significant data quality and management challenges that prevent companies from realizing a return on their investments. For example, data silos were cited as barriers by 66 percent of respondents, followed by unstructured data (58 percent), and lack of metadata standardization (42 percent). These insights suggest research environments continue to be what we call "unFAIR" (findable, accessible, interoperable, reusable), preventing data from moving freely through the research environment – and thus leading to longer, more costly workflows.

The other barrier called out by almost half of respondents was cultural resistance – specifically, hesitancy over data sharing. And that's despite the industry now generally acknowledging that sharing expertise is essential for overcoming regulatory and ethical hurdles, mitigating risk, and preventing duplication of costly R&D work. A third of our experts also pointed to a lack of proven business cases for senior stakeholders, such as time saved by using LIMS, or number of new targets identified by AI. Though labs continue to adopt new technologies at pace, measuring and proving the value of technology with such tangible business case studies is important for fuelling further investment.

The good news is there are some steps that can be taken to overcome common barriers and ensure researchers, investors, and patients can all reap the benefits of more efficient drug discovery brought about by technology. Some of the resources and actions our respondents called for include:

- Best practice use cases that demonstrate the value of AI (55 percent) and FAIR implementation (43 percent).
- Data governance principles/ frameworks for AI (32 percent) and FAIR implementation(40 percent).
- AI algorithm skills training (38 percent).
- Management of data standards and ontologies for FAIR Implementation (42 percent).
- Maturity models to benchmark FAIR implementation against other companies (31 percent).

What all our experts' suggestions have in common is a clear need to collaborate, share knowledge, and share risk. If companies come together, the industry can collectively reap the benefits of the labs of the future – improving the accuracy and reproducibility of research, preventing duplicated efforts, reducing long term costs, and more besides.

Since its inception, the Pistoia Alliance has been making headway on some of the above suggestions through our member-led projects and new training initiatives. We are shaped by the priorities of the life sciences community and our members, and we invite organizations to bring ideas to us today so we can realize the journey to the lab of the future together.

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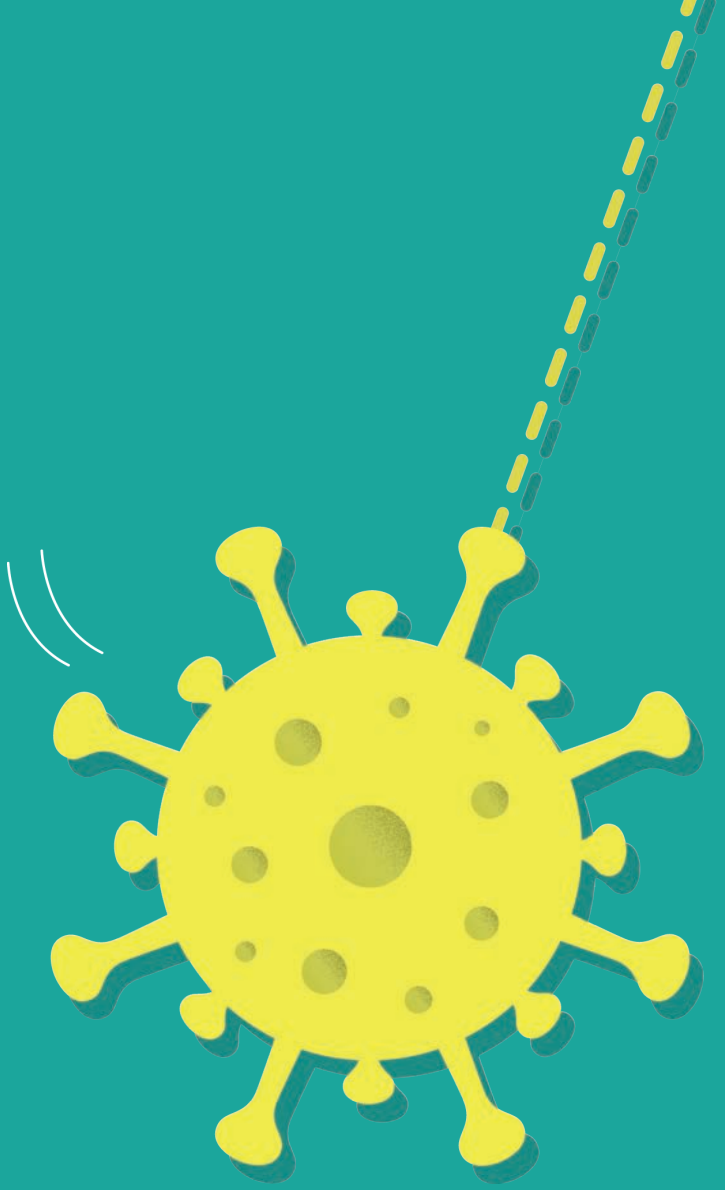
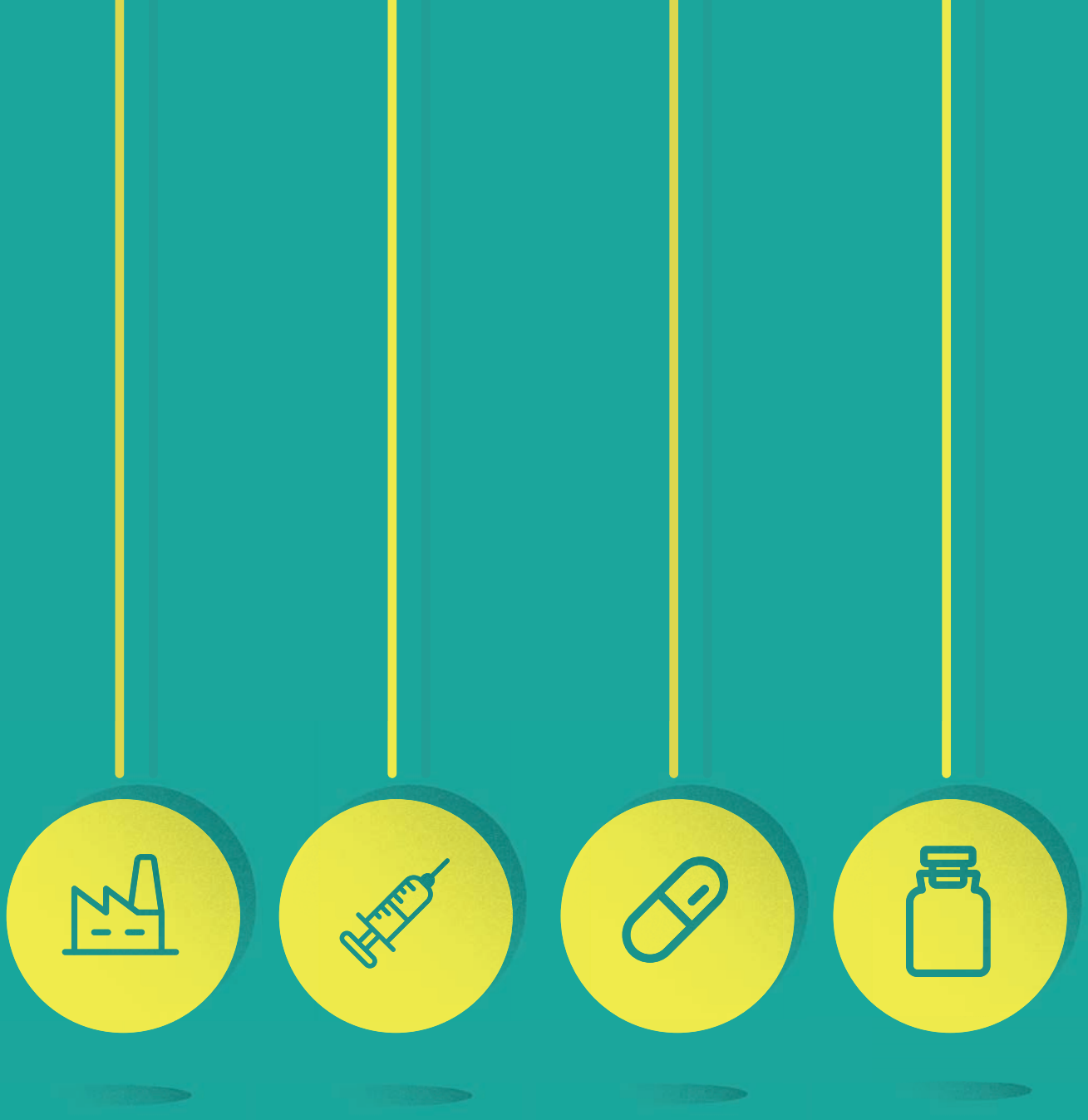


Kinetic Lessons: THE KNOCK-ON IMPACT FROM COVID-19



We continue to feel the effects of the biggest healthcare crisis in modern history, but lessons have been learned. In Europe, the European Commission has already struck deals to ensure manufacturing capacity for future emergencies.

The WHO declared the COVID-19 pandemic officially over in May 2023, but the disease continues to make media headlines. In the UK, for example, an outbreak of COVID-19 caused severe flight cancellations in late September at the country's second biggest airport. In the US, cases have risen over winter, which has triggered the government to re-introduce free at-home testing. Meanwhile, the EU is reportedly talking with Moderna about a new supply deal because of concerns over rising cases.

COVID-19 has sometimes been referred to as a "black swan" event, although this description is something that has irritated Nassim Nicholas Taleb (who coined the term "black swan" in his 2007 best selling book with the same title). He said, "black swan" should not be a "cliché for any bad thing that surprises us" and pointed out that many had predicted the dangers of COVID-19 in January 2020, but no action was taken. Perhaps smaller pandemics had lulled the world into a false sense of security.

"In recent years we've experienced SARS, MERS, and Ebola, but otherwise, the world hasn't experienced a global health emergency on the scale of COVID-19 since the 1918 influenza outbreak," says Drew Burch, Executive Vice President of Nucleic Acid Products at TriLink BioTechnologies. "We have learned how quickly a pandemic can begin and spread in the modern world."

Although the world was unprepared for COVID-19, lessons appear to have been learned, with actions already being taken to prepare for the next pandemic, whenever and whatever it may be. According to researchers, the chance of a pandemic in any given year is around two percent, but climate change's effect on animal habitats is also increasing the risk of zoonotic and mosquito borne diseases. Over 50 percent of infectious diseases have reportedly been aggravated by climate change. And that means that the world – and the pharma industry – must be ready.

"The chance of a pandemic in any given year is around two percent, but climate change's effect on animal habitats is also increasing the risk of zoonotic and mosquito borne diseases."

INVESTING *in* PREPAREDNESS

In June 2023, the European Commission struck deals with several European drug makers under its EU4Health program to reserve vaccine manufacturing capacity for up to 325 million doses per year in the case of a public health emergency. This network of capacity is called the EU FAB network and will, according to the EC, "close the gap between manufacturing and scaling up of vaccine production, while ensuring the capacity of the industry to produce life-saving medicines." So far, the manufacturing contractors involved include Bilthoven Biologicals, Laboratorios Hippra, CZ Vaccines and Laboratorio Reig Jofre SA, and Pfizer subsidiaries in Ireland and Belgium.

"I am extremely happy to hear that the EU has struck a deal with European drug makers to reserve the capacity to develop a vaccine for future global health emergencies. I'm also delighted to say that Bilthoven Biologics (the Netherlands), which is a subsidiary of Serum Institute of India, is one of the drug makers selected by the EC! The industry was not ready for the COVID-19 pandemic and the need to supply vaccines to the world, but lessons have been learned," says Kedar Gokhale, Executive Director at the Serum Institute of India.

The deal has been welcomed by many in the industry. It should also be noted that companies outside of the network are also taking steps to be able to quickly increase production if required. Thomas Zimmer, Vice President of European Operations at ISPE, says, "It is impossible to know the modality or magnitude of the next pandemic, so we cannot predict if the reserve capacity is fit for use to receive the new process demands. However, the National Competition Authorities (NCAs) and EMA, based on Health Emergency Preparedness and Response (HERA) recommendation, have also started implementing proactive actions with marketing authorization holders to set up measures to increase their production. We also understand that the EC, EMA, and NCAs, in conjunction with manufacturing companies, will monitor demand and supply to anticipate and react to potential events."

This monitoring and communication will be key to any future responses. Zimmer continues, "The COVID-19 pandemic revealed a lot of bottlenecks, but early actions could give enough time to have sufficient manufacturing capacity. EC

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actions are going in the right direction to provide the industry with relevant information on the demand, which allows better responses from manufacturers. This is similar to the existing arrangements for flu vaccines with a production to supply patients from September onwards. Since the pandemic, we have been informed that several fill-and-finish manufacturing sites have increased capacity and are available to supply. Emerging countries have also arranged the introduction of new capacity and facilities."

GOING LOCAL

For many countries, local production has become a key priority. COVID-19 drastically affected supply chains. Burch explains, "Organizations were able to prioritize and obtain supply for development, but restrictions between national borders stood in the way of obtaining necessary materials. In addition, backlogs in production equipment occurred, slowing down vaccine production."

Prior to the pandemic, there had been a trend in the pharma industry towards a lean, just-in-time supply chain – much less effective in an emergency. "Just-in-time inventory is perfect when everything is business as usual," says Burch. "However, in pandemic preparedness, you must plan for the unplanned and extend flexibility. For example, many companies now stockpile certain raw materials to provide flexibility. Since mRNA offers the opportunity to develop a new vaccine faster and uses a common set of raw materials regardless of the vaccine target, it can be a particularly valuable approach."

It also became all too clear that some countries were better positioned than others to weather the challenge. Gokhale says, "During the pandemic, resource availability was a concern and building new facilities in a short time was not feasible. The main major lesson learned from the pandemic is that every continent should be ready with additional reserve manufacturing capacity at a different vaccine platform so that millions of doses can be rolled out quickly – and at affordable prices."

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Developing countries dependent on imports were extremely vulnerable to shortages of both medicines and medicine supplies. But even in territories with well-established and robust supply chains, like Europe, there were issues. Relationships between the UK and the EU became strained over supplies of AstraZeneca's COVID-19 vaccine. When AstraZeneca came up short in its deliveries to the EU, the EU asked for doses of the vaccine to be sent from the UK – leading to a very public war of words and the EU threatening to block exports of vaccines to the UK.

"The pandemic strained international cooperation, which challenged supply chains and impeded the global health response," Burch adds. "The EC's involvement helps remove that roadblock by securing internal supply and infrastructure. However, it's important to note that the capacity for responding to a pandemic depends on the drug that can be useful in that specific pandemic. Early in the pandemic, when we thought certain medicines might be useful, there was a scramble to address the capacity of those medicines. As it turned out, mRNA vaccines became the most popular approach, which drove the need for new production processes. In short, sometimes we can leverage existing capacity and sometimes we cannot. What we can do is try our best to be prepared for the unexpected. The good news about mRNA technology is that it can be adapted incredibly quickly to new pathogens."

The PROMISE *of* mRNA

The EU FAB network covers mRNA, vector-based, and protein-based vaccines, but mRNA is perhaps viewed by many as the golden child after COVID-19 successes. So great was the impact of mRNA that it led to the 2023 Nobel Prize in Medicine being awarded to Katalin Karikó and Drew Weissman, whose technology is used in the Pfizer/BioNTech and Moderna COVID-19 vaccines. Karikó and Weissman discovered nucleoside base modifications that allowed mRNA

to be used in vaccines, as well as other therapeutics.

Burch says, "mRNA fully demonstrated its effectiveness and its speed of development during the pandemic; it was less than a year from the genetic sequence of SARS-CoV-2 to receiving emergency approval. As we progress out of the pandemic, we know we have the ability to design a response to a new threat quickly and adjust the regulatory pathways. The technology has not only been validated by governmental approvals, but also via the billions of people that have received the vaccine. A lot of capital and investment is now flowing into the mRNA sector."

And the science of mRNA continues to advance. Burch points to new LNP and other delivery technologies, as well as capping innovations that are improving yields and speeding up manufacturing.

Zimmer agrees that mRNA has great potential: "mRNA has been a real game changer in the vaccines field. For many years prior to the pandemic, companies were testing mRNA anti-cancer drugs in low volumes. They were able to use this prior knowledge and technology for the pandemic. Now, the world of mRNA is continuing to develop products. Similar breakthroughs can be expected in other therapeutic sectors. In particular, the scope for mRNA cancer vaccines is vast, such as individualized mRNA cancer vaccines to target solid tumors."

Burch adds, "An era of therapies based on an understanding of nucleic acids is underway, and mRNA has a huge role to play. The industry has witnessed incredible efficacy and safety, not only in the billions of people who have taken the COVID-19 vaccine, but in clinical trials for other infectious diseases, cancers, and other indications."

"An era of therapies based on an understanding of nucleic acids is underway, and mRNA has a huge role to play."

BEING READY

The drug development industry truly shined during the COVID-19 pandemic. Although there were challenges in supply chains and other areas, close collaboration between all stakeholders led to the development and deployment of vaccines across the globe in record timeframes – with millions of lives saved.

Zimmer says, "Regulatory agencies worldwide demonstrated extreme speed and flexibility in approving new vaccines and treatments, while respecting all requirements for drug safety and quality assurance. Close collaboration and communication was essential to the pandemic response – and will be for future pandemics and emergencies too."

Following the COVID-19 pandemic, the world has a greater appreciation for innovation and science. And the industry, itself, has a greater appreciation for the importance of supply chains – and how much experience, reliability, and relationships all matter.

Although the European Commission's initiative is a positive step in pandemic preparedness, it isn't an automatic route to success. There's still a great deal to discuss – and lead times to plan for. "The European Commission initiative shows the enormous cost and long lead times necessary to develop such strategies," says Zimmer. "Multiple stakeholders (manufacturers, supply chain, regulators, and so on) must work together to develop business cases to achieve the goals. Some contract manufacturing organizations may have some capacity and could provide additional production capacity too. There is also a need to anticipate requirements for common components, such as vials, stoppers, and caps. Here, standardization of such components would be a great help. Increasing capacity by introducing more shifts is an obvious strategy; however, for aseptically produced injectable products, there will be a long lead time to train additional staff. Timescales like this need to be factored into future strategies."

Preparing for a pandemic goes beyond looking for therapeutic interventions. Burch points out the need for greater knowledge in prevention tactics. "What can be done to avoid spreading the pathogen? Is it isolation, masking, or washing? The best course of action can vary depending on the pathogen and the mode of transmission. It is also important to consider the role of education and frameworks for international cooperation. When there is a lack of trust in the institutions, it is difficult to have successful widespread prevention or response."

Zimmer adds that we can also learn from other global health emergencies, such as drug shortages. "Drug shortages have been an increasing problem for years. We still don't have the problems under control – in fact, it's getting worse! However, a number of learnings have emerged: multi-stakeholder management is needed to ensure the complexity of the problem is understood, there are numerous root causes (it is never monocausal!), and there is not one simple solution. All of this can also apply to pandemic preparedness."

A TERRIFYING AWAKENING

Contact with the sharp end of reality eliminates our assumptions and exposes our weaknesses. Contact with COVID-19 has done the same for pharma and healthcare

By Rainer Lichtenberger President & CEO, Atriva Therapeutics

By virtue of working in infectious disease, the realization of the severity of COVID-19 came quickly to my colleagues and I. We had just been to China in November 2019 to scout for investors. When we first heard about lockdowns there early the following year, we were in San Francisco, at the JP Morgan Healthcare conference and had plans to fly back to China after the meeting. Those plans changed and we traveled back to Germany to investigate whether our pandemic asset – which we already knew worked against SARS-CoV-1 – could also work for SARS-CoV-2.

BURNING LIMELIGHT

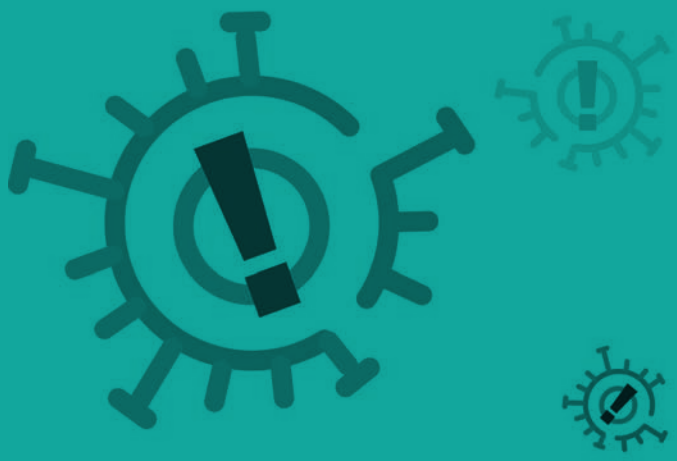
The COVID-19 pandemic was a perfect storm, but also a perfect opportunity. It was a chance for public health officials, pharma executives, and life science researchers to show the significance of global health. Without the rapid collaborations between companies such as Pfizer and BioNTech to find a vaccine, the willingness of researchers to work tirelessly and the candor of public officials, societies would not have been able to respond to the COVID-19 crisis as swiftly as they did. But to win the longer game of pandemic preparedness for the next crisis, we need to focus on the aspects of the response that were less successful.

One area that lacked a robust response was the development of effective therapeutics. I would argue that a weakness of the new mRNA vaccines is that they are not a one-shot solution. Luckily, COVID-19 morphed into Omicron – a relatively tame house pet compared with its first fatal iterations. Without this attenuation, the lack of effective therapeutics would have proven disastrous. We will certainly need them in the future; COVID-19 has intensified a pre-existing debate about the future of megacities and whether the concentration of so much population and economic activity in a few large centers is desirable. While it may take some time to resolve that question, expediting infectious disease therapeutics could be more feasible.

Testing, Testing…

Testing and diagnostics must not be neglected – and fortunately the industry was able to provide a supply of test kits sufficient for mass regular testing. There were certainly regional and geographic inequalities in this supply, but I would put this down to organizational problems that lie outside the hard sciences. I would hope that the wealthy nations of the EU, the US, and other wealthy countries can contribute to making the entire world better prepared for the next pandemic. This mission is not just about science and technology; it is about mankind's ability to pounce on an emerging virus absolutely anywhere, and shut it down before it is able to spread everywhere.

Recent improvements in testing and diagnostics, brought on by the urgency of the pandemic, can help us here. My company is currently running a study on a test kit that covers SARS, influenza, and RSV. These kits can be made available at the hospital, and can check the patient's viral state at the bedside within a few minutes. Two years ago, this would not have been possible – the wait for a readout would have taken at least 48 hours. Advances like this demonstrate why we need to keep on investing serious money into pandemic preparation. Especially within Germany and the European Union, I see a need for political activity to keep attention and resources directed toward improving our anti-pandemic infrastructure.



To start, we need blueprints of emerging and potential viruses so that we can develop broad-acting antivirals that could serve as an early defense line, protecting our hospitals and national healthcare systems from collapse, as they came so close to doing in 2020 and 2021.

Next, we need to develop drugs with more specificity. Pfizer's Paxlovid was a good example, although its importance has since diminished because of its poor effectiveness against Omicron. That's not Pfizer's fault – it's simply down to the variability of the virus and the specificity of the drug. And that's why drugs that target host cells are ideal; they can make use of the commonalities of an entire class of viruses and target their signaling pathways.

ONE SPECIES

International collaboration will again be the only way through future pandemics. Thankfully, during the COVID-19 crisis, we did not see any Western countries attempt to "go it alone" in terms of science, technology, or information. In more autocratic countries the story is a little different. We should bear in mind that an authoritarian government not prone to acknowledging its own errors might run into political turmoil if it, say, admitted that its systems might not be able to cope with a given disease. We saw this with China's unswerving and long-term adherence to a "zero COVID" policy.

Nation states aside, we've seen some excellent examples of corporate cooperation. The way that BioNTech and Pfizer collaborated to develop their vaccine was very successful – and it was fast. They took joint risks, and that is something other pharma companies could learn from. The willingness of big pharma companies to engage quickly with the pandemic was admirable. These companies are "supertankers" – they're not traditionally or structurally inclined toward rapid maneuvers.

As well as preparing for the next pandemic, it would also be beneficial if big pharma could apply the collaborative mindset from COVID-19 to other important areas. I think both the public and the private sector need to turn their attention to the antibiotic resistance crisis. The antibiotics that we have are no longer sufficient to fight multi-resistant bacterial strains. It is on governments to bring about affordable

pricing, and it is on pharmaceutical companies and their investors to target more than just the most attractive markets, like oncology. All too often, these companies simply jump onto one bandwagon; we need more companies who will be the first to jumpstart an alternative bandwagon. Once it starts moving, we can get somewhere.

FOOL ME ONCE...

I believe the knowledge we need to take away from this first pandemic of the 21st century can be distilled into three main lessons that we must internalize and act upon.

The first lesson is about learning itself; we must learn from pandemics not commercially, but socially – as societies, institutions, and countries rather than as industries and companies. We can see a good example in the US, where they have established a good model for institutions and data at the federal level. We should try to emulate this on a pan-national basis in the EU. We have the money to do it, but right now that is not the issue – the problem is the complexity of the organization. Hierarchical government structures won't serve us well in the face of a pandemic – instead we need speed and expertise.

The second lesson is that we must adequately fund our health systems. We need to know that they will not be immediately overwhelmed in the first wave of the next pandemic. We should not be designing health systems as money makers. Instead, we should be setting them up to serve the people and society. Ideally, they should be fully funded by taxes. We have seen that the societies with the priorities I have described generally had the best pandemic responses. It is expensive, but it pays off. Ideally, we need a good mix of entrepreneurial leadership combined with proactive governance and public institutions.

The third (and final lesson here) is that we need to look to and assist the poorer countries of the world. If we only pay attention to the West, plus a selection of rich Asian countries, the next pandemic will sweep across the world just like COVID-19 did. We need to build up more efficient global structures – and quickly. We can't succeed as a fragmented species, no matter how sophisticated our science and technology may become – this is my firm conviction.

The Origins of Atriva

In 2001, an article by the future scientific founders of my company, Atriva, was acknowledged in Nature Infectious Disease under the headline "Inhibiting RAF and fighting 'flu." It was the first published discovery on the means by which host cells target infectious diseases and how antiviral therapies could be used to fight viral diseases, such as influenza or COVID-19. Our founders had been working in this area for more than 25 years.

In 2015, I left the company that I was leading at the time and, via existing industry networks, I became involved with the scientific founders. Together we founded Atriva Therapeutics. We set the company up in Tübingen, Germany, because of the biotech-friendly ecosystem in the city, the infrastructure, and the centuries-long spirit of industry and entrepreneurship in the surrounding state of Baden-Württemberg. We received €25,000 in support from the regional biotech hub and, with an additional €100,000 that the founders injected into the company, we survived our first year.

Following this, we received our first venture financing. And then the serious work began as we worked to find cures for the next influenza pandemic. When COVID-19 arose, we trained our sights on it.

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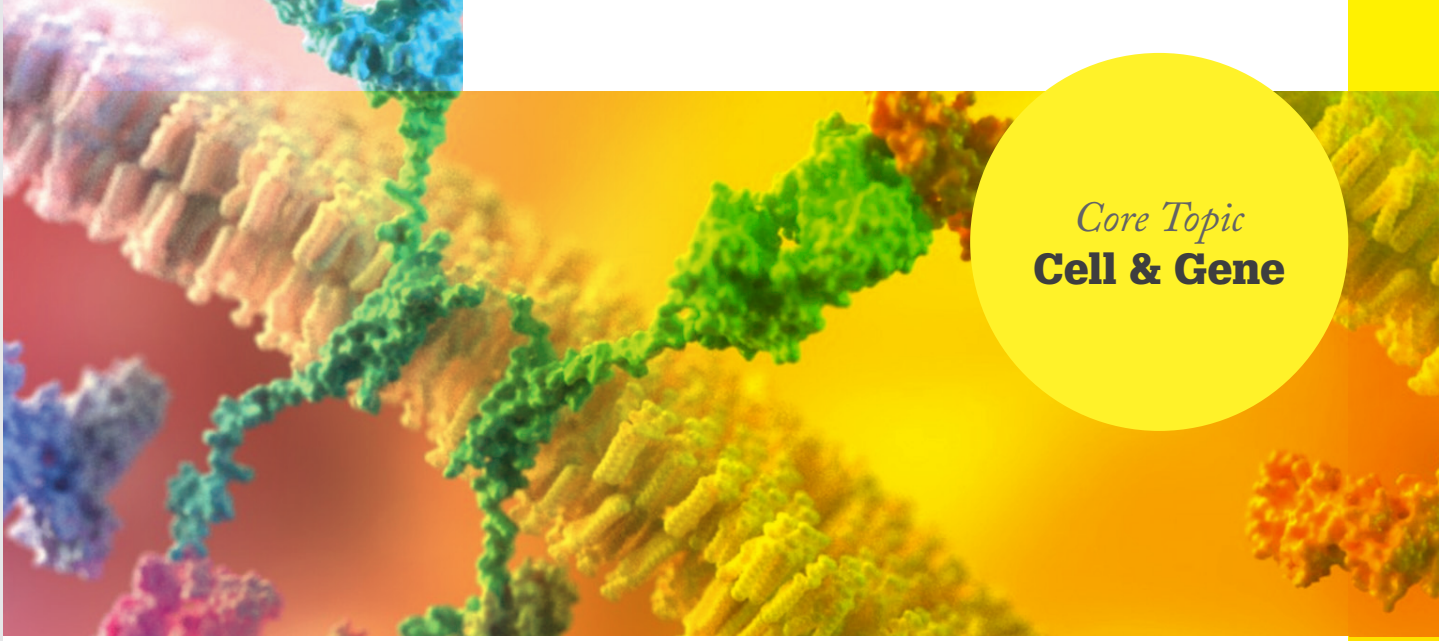

Core Topic
Cell & Gene

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Sickle cell focus. The Biden-Harris Administration has chosen sickle cell disease as the initial focus of the Cell and Gene Therapy Access Model. The model is part of broader efforts to lower drug costs, enhance health outcomes, and expand access to cell and gene therapies. "The goal of the Cell and Gene Therapy Access Model is to increase access to innovative cell and gene therapies for people with Medicaid by making it easier for states to pay for these therapies," said Liz Fowler, CMS Deputy Administrator and Director of the CMS Innovation Center. "By negotiating with manufacturers on behalf of states, CMS can ease the administrative burden on state Medicaid programs."

In-body editing. Most approved gene therapies modify cells outside the body before reinfusing them into patients, but a new approach suggests in-body gene editing could eliminate the need for bone marrow destruction. Developed by researchers at UC Berkeley, the method involves wrapping Cas9 editing proteins and guide RNAs in a membrane bubble decorated with monoclonal antibodies that target specific types of blood cells. First trialed in mice equipped with a humanized immune system, the team turned their human T-cells into CAR T-cells able to home in on and eliminate B cells.

Lifetime of achievement. Jeffrey Chamberlain, Professor of Gene Therapy at the University of Washington, has received the Muscular Dystrophy Association's (MDA) 2024 Legacy Award for Achievement in Research. Sharon Hesterlee, Chief Research Officer at MDA, said: "He received our first ever gene therapy award 25 years ago and has continued making major contributions ever since, including the development of the miniaturized gene used in several ongoing clinical trials for Duchenne muscular dystrophy. Just last year we funded a new study for Dr. Chamberlain to make this miniaturized gene product less visible to the immune system and, in a separate project, to develop a way to deliver a full-sized gene for Duchenne."

Apheresis alternative. Kyverna Therapeutics has described a proprietary manufacturing process – Ingenui-T – that uses less than 300 ml of whole blood from a blood draw for the collection of T cells from patients undergoing CAR-T therapy. The goal is to lower production costs and offer a "less invasive" alternative to apheresis. Ingenui-T uses the same fully human anti-CD19 CAR construct as the company's investigational KYV-101 cell therapy targeting B-cell-driven autoimmune diseases. The authors of the study (doi: 10.1101/2024.01.24.576713) write, "Importantly, the Ingenui-T platform yields CAR T-cells with a potent functional profile and a less differentiated phenotype compared to CAR T-cells generated from a more conventional manufacturing process that uses apheresis-derived cellular starting material."

IN OTHER NEWS

Oxford Biomedica completes acquisition of ABL Europe from Institut Mérieux SA to expand cell and gene therapy CDMO multi viral vector capabilities

Solvias signs long-term agreement with Vertex Pharmaceuticals to perform analytical release testing services for Casgevy

Regeneron creates Regeneron Cell Medicines with acquisition of 2Seventy Bio's pipeline of investigational novel immune cell therapies and clinical manufacturing capabilities

Bluerock Therapeutics licenses iPSC-derived cell therapy OpCT-001 from Fujifilm Cellular Dynamics and Opsis Therapeutics

EXO Biologics launches ExoXpert – a CDMO specializing in exosomes for cell and gene therapies

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Format and Function: Optimizing Gene Therapy Manufacturing Workflows

Gene therapy is a rapidly evolving industry with the potential to transform patients' lives, but promising treatments for a wide range of diseases require optimal cell culture media solutions

By Elpidia Gamez, Senior Manager, Product Management, Thermo Fisher Scientific

Format choice for cell culture media can have a significant logistical impact on gene therapy development. Understanding the suitability of a format for use at commercial scales and making the appropriate choices throughout process development can help streamline operations and reduce the risk of delays.

The use of media in a liquid format is well-established for small-scale gene therapy development because liquid media are ready to use and require few preparation steps. Saving time and reducing in-house workload, the liquid format is ideal for helping developers create a more convenient process.

However, as workflows scale up and liquid media volumes increase, so too do the logistical and financial challenges of shipping and storage. Careful planning and forecasting are required so that media are available when needed and used before expiration. However, liquid media are heavy, which means they can be expensive to ship and challenging to move around facilities. Moreover, large areas of manufacturing facilities may be needed for storage, reducing production space. Using third-party warehousing can lead to substantial additional costs, and storage is further complicated by the relatively short shelf life of liquid media.

Furthermore, while liquid media do not require reconstitution, the addition of supplements can increase complexity by adding to the number of preparation steps.

Because of the challenges associated with liquid media, many companies choose to use dry powder media (DPM). DPM is more compact, saving on storage and shipping costs, and leaves more facility capacity for operations, providing the opportunity for greater productivity. DPM also has a longer shelf life, which allows for the stockpiling of supplies and results in less pressure on accurate forecasting – as well as the reliance on supply chains.

However, standard DPM requires a multistep rehydration process before it can be used, which can add to the in-house workload. The need for manual handling steps during the rehydration process, such as pH and osmolality adjustments, can increase the risk of inconsistency. When using DPM, it is important for developers to have strict quality protocols in place to reduce any process variability.

There is also an alternative option that can bridge the gap between production-ready liquid media and DPM: granulated media formats. Granulated options provide a simpler reconstitution process and lower dust generation without the need for pH or osmolality adjustments, increasing efficiency and reducing the risk of inconsistency. Moreover, supplements can be integrated into a granulated format, effectively resulting in a convenient single-component product.

By providing similar storage and shipping benefits as DPM, alongside

"Granulated options provide a simpler reconstitution process and lower dust generation without the need for pH or osmolality adjustments, increasing efficiency and reducing the risk of inconsistency."

helping support more efficient preparation and improved consistency, granulated media can help many developers reduce operating costs and increase productivity.

Transitioning from liquid to dry powder or granulated media during scale-up can be challenging. Carefully considering the optimal format early during process development is essential to help avoid costly delays, such as reformulation or requalification of a medium.

Choosing an off-the-shelf medium that is available in multiple formats could prepare a workflow for future changes. Similarly, validating that a proprietary formulation is suitable for conversion can help streamline the transition. This validation step can still be beneficial for developers who plan on using liquid media at all scales. Knowing that a formulation can be used in multiple formats means developers have a backup option should they face complications.

That said, using the same format at all stages can support the more rapid progression of the therapy. Liquid, dry powder, and granulated media formats offer a variety of benefits and potential drawbacks, depending on the specific process requirements. The challenge is finding a medium that provides consistent quality and performance in a format that can also help optimize logistics.

Ultimately, developers need to consider scalability, cost-effectiveness, and convenience during process development to find the format that will be most suitable for their current and future needs. By choosing the right format, developers can optimize their development and manufacturing processes to help them accelerate the speed to market for their gene therapy product and confidently meet future demand.

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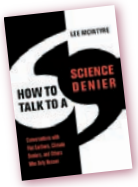

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Core Topic
Bioprocessing

Phase III failure. Gilead's phase III EVOKE-01 study of Trodelvy (sacituzumab govitecan-hziy) versus docetaxel in non-small cell lung cancer failed to meet the primary endpoint of overall survival. However, the company says an improvement was noted in a subgroup of patients non-responsive to last prior anti-PD-(L)1 therapy, and will be looking to further understand how the drug may be able to assist patients with high unmet medical need. "The totality of our data gives us continued confidence in Trodelvy's potential in metastatic NSCLC, and in our broader lung cancer clinical development program," said Merdad Parsey, Gilead's Chief Medical Officer. "Treating metastatic NSCLC that has progressed on or after platinum-based chemotherapy presents significant challenges and the need for safe and effective treatments remains urgent."

Cellular transport. Dirk Görlich, Director at the Max Planck Institute for Multidisciplinary Sciences, has received the Louis-Jeantet Prize for Medicine 2024 for his contributions in understanding how macromolecules are transported in and out of a cell nucleus. In researching how proteins get to the right place, Görlich discovered a new kind of biological matter - the FG phase - and how it affects the transport function of a cell nucleus. "The transport of macromolecules between cytoplasm and nucleus is fundamental for eukaryotic life and also highly relevant for disease," saidHolger Stark, Managing Director of the Max Planck Institute for Multidisciplinary Sciences. "With the discovery of the FG phase, he has opened up a completely new field of research." Görlich has also been working with Scinai Immunotherapeutics on nanosized VHH antibodies.

Third-party headaches. Astellas is the latest pharma company to receive an FDA complete response letter for a new drug because of problems at an unnamed third-party manufacturing facility. The FDA cited no problem with the oncology drug itself (zolbetuximab) and has not requested additional clinical studies. Astellas says it is working with the manufacturer to address the problems. In 2023, Eli Lilly, Checkpoint Therapeutics, Regeneron, and Zeland Pharma all received FDA complete response letters because of problems at third party sites.

Sa-mRNA potential. CSL and Arcturus Therapeutics have reported results of a follow up analysis of their phase III trial of self-amplifying mRNA COVID-19 vaccine, ARCT-154. "The new analysis at 6 months post-vaccination shows that ARCT-154 induces a longer immune response as compared to Comirnaty for both the original Wuhan strain and Omicron BA.4/5 variant and an advantage in antibody persistence," said the companies. The vaccine was approved in Japan in 2023.

IN OTHER NEWS

WuXi Biologics signs research service agreement with BioNTech focusing on mAbs and "next-generation" therapies

Boehringer Ingelheim to further expand Koropi, Greece facility with 120 million euro investment

Rockland launches Nuclease ELISA impurity detection kit for Serratia marcescens endonuclease in manufacturing processes

Corbevax COVID-19 vaccine developed by Texas Children's Hospital and Baylor College of Medicine and licensed to Biological E receives WHO Emergency Use Listing approval

EMA to meet before March 31 to discuss marketing authorization for lecanemab in Europe

Propelling the Promise of mRNA

With mRNA technology scooping the 2023 Nobel Prize for Medicine, demand is growing. Can CDMOs keep up?

Propelled into the limelight by COVID-19, mRNA has emerged as one of the top breakthrough technologies of the century, providing great promise to go beyond infectious disease management and into the realms of curing and preventing cancer, heart disease, muscular dystrophy, and more. With increased demand, drug developers are fighting over partners with the right capabilities and facilities.

Merck recently launched two new GMP-grade mRNA drug substance manufacturing sites in Germany; one in Darmstadt, where the company was founded 355 years ago, and a second in Hamburg, which builds on existing infrastructure and expertise, including the former AmpTec GmbH headquarters.

Here, we speak with Dirk Lange, Head of Life Science Services at Merck, to get his perspective on why mRNA is such an exciting technology for the future of drug development.

What is driving demand for mRNA and investment in new manufacturing facilities?

Over 21,000 molecules are currently in development, but 72 percent of these are owned by emerging biotechs who rely heavily on CDMO partners for technical and regulatory expertise. For mRNA specifically, there are currently over 500 ex-COVID molecules in development (up 54 percent from 2022), with emerging biotechs representing around 80 percent of these. Additionally, the market is expected to grow by over 20 percent in the next four years.

Propelling the promise of mRNA beyond COVID-19 and continuously investing to help bring therapies to patients sooner is a priority for CDMOs. The demand for mRNA and investment in these new facilities is clearly reflected in the mRNA program pipeline, which has grown by 64 percent since February 2022. Additionally, 77 percent of active mRNA programs extend beyond COVID-19.

I have seen a tremendous wave of companies investing and pushing their pipeline in this space, while expressing the need for external partners to navigate this complex landscape.

Where do you see mRNA technology having the most impact?

Owing to success during the pandemic, mRNA as a platform technology is being further explored for vaccine applications for infectious diseases, where the most advanced developments are seen in programs for respiratory syncytial virus, seasonal influenza, and continuous adaptation for emerging COVID-19 variants. But we are also seeing tremendous strides being made in the oncology space – for therapeutic cancer vaccinations, for instance – to treat melanoma, as well as for oncology indications with high unmet medical needs, such as pancreatic cancer.

Notably, mRNA can also be used to fix or replace missing genes and thus potentially cure by targeting the source of the disease, using the patient's own body to produce proteins to fight disease – a unique advantage over conventional biologics or small molecules. For example, we have been working with Simone Spuler of the Max Delbrück Center for Molecular Medicine to advance her research in finding a cure for muscular dystrophy.

mRNA also promises to speed development and bring therapies to patients faster than other traditional modalities – simply by changing the sequence encoded within the mRNA.

How will the Nobel Prize in Medicine for work on mRNA further affect the market?

The Nobel Prize in Medicine award truly underlines the potential of mRNA and shines an even brighter light on mRNA's superpower and unprecedented flexibility. And I'd say the Nobel Prize in Medicine win for mRNA will further strengthen confidence in the technology and, as such, positively affect the market.

What does the future of mRNA manufacturing look like from here?

We are only at the beginning of the mRNA era and there is no blueprint, or one-size-fits-all mRNA manufacturing process established. This means that drug developers should consider partnering with the right manufacturing experts. CDMO services are well-positioned to help shape the future of mRNA manufacturing, from the supply of critical raw materials, to providing expertise in formulation optimization and cGMP manufacturing.

What role will industry 4.0 play in the mRNA treatment development and commercialization?

Integration of industry 4.0 principles and digital technologies significantly amplifies the potential and efficiency of mRNA programs across their entire lifecycle. We already see impacts on several levels, starting from the conception phase with computational sequence optimization, to the application of data-driven design of experiments, prediction models, and digital twins, to analytics and digital data analysis supplementation in the overall process design. Cumulatively, this will enable a more efficient mRNA process that has a positive effect on the trajectory of mRNA programs and clinical outcomes.


"The Nobel Prize in Medicine award truly underlines the potential of mRNA and shines an even brighter light on mRNA's superpower and unprecedented flexibility."

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Core Topic

Small Molecule Manufacture

Potentially potent. Insilico Medicine has announced a new AI-generated preclinical candidate (ISM9682), which the company believes has the potential to be best in class. The molecule is in development to inhibit KIF18A with the aim of addressing chromosomal instability or persistent errors in chromosome segregation during mitosis. It has demonstrated broad anti-tumor activity, potent in vivo efficacy, and has a favorable oral bioavailability. Insilico is examining the potential for numerous cancer indications. This is the 18th preclinical candidate to date that the company has brought forward from its generative AI platform since 2019.

Simplifying synthesis. Tokyo University of Science researchers have developed a method of synthesizing dibenzothiophene S-oxides, involving Suzuki-Miyaura coupling of 2-bromoaryl-substituted sulfinate esters, followed by an intramolecular electrophilic sulfinylation. With details published in Chemical Communications (DOI https://doi.org/10.1039/D3CC05703H), the new method has the potential to simplify the synthesis of a variety of sulfur-containing molecules and is considered a significant step forward in the field of chemical biology with potential applications in various research areas.

Small world. Cycle Pharmaceuticals and Inceptua Group are collaborating to make NITYR (nitisinone) tablets available via a free goods program for eligible patients with hereditary tyrosinemia type 1 (HT-1) and alkaptonuria. Cycle has an existing free goods program with patients with HT-1 in India, Bangladesh, Pakistan, and Sudan. Inceptua will now support the company in expanding the program to include other countries where NITYR is not commercially available, or where the local healthcare system is unable to afford this medication. Potential countries include Argentina, Bangladesh, Brazil, Chile, and Colombia, among others.

Agreed and acquired. Novartis has agreed to acquire MorphoSys AG, subject to customary closing conditions, including the drugs pelabresib and tulmimetostat. Pelabresib, in combination with ruxolitinib, met its primary endpoint of spleen volume reduction in JAK inhibitor-naive myelofibrosis patients. Splenomegaly, disease-associated symptoms, anemia, and bone marrow fibrosis were all improved with this combination. CMO Shreeram Aradhye said, "With the planned acquisition of MorphoSys, we aim to further strengthen our leading pipeline and portfolio in oncology, adding to our capabilities and expertise."

IN OTHER NEWS

FDA approves Janssen's Balversa (erdafitinib) for adults with locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations

Imperial College London research finds low and controlled dose of morphine may reduce coughing from idiopathic pulmonary fibrosis

Vicore Pharma Holding signs exclusive licensing agreement with Nippon Shinyaku to develop and commercialize Vicore's drug candidate C21 in Japan

EMA warns of risk of potentially fatal adverse reactions when using Pfizer's Paxlovid in combination with certain immunosuppressants

University of Illinois Urbana-Champaign study confirms acetaminophen use during pregnancy linked to language delays in children

The Sulforaphane Promise

Sulforaphane has therapeutic potential in numerous areas but formulation is key. Can enteric coatings help find the way forward?

By Helen Kuhlman, Chief Business Officer, Evgen Pharma

At Evgen, we have been exploring the anti-cancer properties of sulforaphane. In my view, this is a compound with enormous therapeutic potential backed by a wealth of evidence from pre-clinical research. Our lead asset, SFX-01, has undergone clinical trials in oestrogen-positive (ER+) metastatic breast cancer, and is also being investigated in glioblastoma, under an investigator sponsored study at the Erasmus University Medical Center, supported by a grant awarded to Dr Marjolein Geurts by the KWF Dutch Cancer Society. We've also signed an out-licensing deal with Stalicla SA to collaborate on a clinical program in autism, where Stalicla will use its proprietary DEPI technology to identify autism patients most likely to respond to SFX-01. In this article, I want to give a quick overview about our work with SFX-01 and the progress we have made so far.

Sulforaphane has shown potential benefits in a number of indications including neurodevelopmental disorders, oncology, and inflammatory conditions. Whilst the exact mechanisms are still to be fully elucidated, sulforaphane is known to exert a pleiotropic effect on the immunological response, which is dependent on the cell type/disease status.

A major challenge for the development of sulforaphane as a therapeutic is that it is a transient and highly unstable compound unsuitable for clinical development. The parent compound glucoraphanin originates from cruciferous vegetables, and is enzymatically transformed by myrosinase in the gut into the active sulforaphane. However, we have developed a technology that can synthesize and stabilize sulforaphane and novel proprietary analogues based on sulforaphane.

SFX-01 is a composition of synthetic sulforaphane and alpha-cyclodextrin, which is stable and suitable for clinical research (and hopefully eventual approval as a medicine!). Recently, we conducted a phase Ib trial for a new enteric-coated formulation (developed in partnership with Seda Pharmaceutical Development Services). An enteric coat can delay release of the API, bypass the acid environment of the stomach, and target release to

Sulforaphane can be found in cruciferous vegetables, such as broccoli

certain parts of the intestine where it is absorbed. By utilizing a coating that is sensitive to dissolution at higher pH, the tablet passes through the acidic environment of the stomach and only dissolves in the higher pH of the small intestine where the drug is then taken up. Minimizing API exposure in the stomach can prevent acid/enzymatic degradation of a sensitive drug and make the release profile more consistent between subjects.

The goal of developing a new enteric-coated tablet formulation was to achieve a predictable release profile and minimization of potential gastro-intestinal side effects at higher dosages. Avoiding dissolution of the tablet in the stomach minimizes the time that free sulforaphane is in contact with the acid/enzyme environment of the stomach, minimizing the potential for degradation and irritation of the stomach lining before absorption. The new formulation will replace our previous prototype capsule formulation, and will be suitable for large scale trials and commercial supply.

"Our phase Ib study investigated how sulforaphane released from the enteric-coated tablet formulation was absorbed from the intestine and its effects on the physiology of healthy volunteers."

Our phase Ib study investigated how sulforaphane released from the enteric-coated tablet formulation was absorbed from the intestine and its effects on the physiology of healthy volunteers. The study was a double-blinded, placebo-controlled modular design involving three cohorts of volunteers, each receiving different doses of SFX-01 or matching placebo. And the results were good.

Based on the time course seen, sulforaphane was released by the new enteric-coated tablet beyond the acid environment of the stomach. Total blood levels of sulforaphane (SFN) and SFN-metabolites were confirmed in the micromolar range, where efficacy is seen in vitro. Additional pharmacodynamic exploratory investigation, utilizing mRNA sequencing, showed changes in gene expression after dosing with SFX-01 even in healthy volunteers. No serious adverse events were observed.

Changes in gene expression were measured by mRNA sequencing on participants' blood, for placebo and SFX-01 treated subjects that received 600 mg once daily. The initial analysis identified a large number of significant differentially expressed genes in the SFX-01 treated group, between blood samples taken before the first dose was administered (baseline) and blood samples taken after the first dose timepoint (6 hours after first dose). Further analysis will be undertaken on this large and complex dataset to gain insight into the particular genes identified. More disease-related mechanistic insight will also be provided from future clinical studies in patients.

The future clinical development of SFX-01 is highly exciting. With recent evidence that it augments the effects of radiotherapy and other anti-cancer therapeutics, it has the potential to bring substantial benefit to patients. However, formulation is key to successful drug development and the end goal of improving outcomes for patients – only with effective drug delivery will we be able to gain the exposures necessary to cause effect in target tissues. We believe our new formulation achieves these goals.

NextGen

R&D pipeline
New technology
Future trends

At First Sight

Three companies – Cardinal Health, Regenxbio, and Beacon Therapeutics – help us explore gene therapy development in the ophthalmic space

By Jamie Irvine

Over 100 years of scientific progress separate Gregor Mendel's pea plant-crossing experiments from the moment US scientists Theodore Friedmann and Richard Roblin published their paper "Gene therapy for human genetic disease?" in Science. After they outlined the potential of replacing a disease-causing gene as a form of treatment for genetic disorders, it's no surprise that worldwide debate regarding its therapeutic potential and ethical considerations followed. But as with many facets of life, time reveals all – and their big question was answered. Today, gene therapy research – alongside many scientific and technological developments – is writing a new narrative that shows that disease can be confronted at its root cause.

We've talked about the potential of gene therapy on many occasions in The Medicine Maker, but one area we haven't explored in such detail is its relation to eye disease (a task we typically leave to our sister publication, The Ophthalmologist). There are several factors that make the eye a particularly attractive target for gene therapy, including its accessibility, immune privilege, and well-defined anatomy. And though the implications of gene therapy in this field are huge – and thus research activity is expanding rapidly – there is still so much to learn.

We hear from three companies – Cardinal Health, Regenxbio, and Beacon Therapeutics – who are convinced gene therapy will broaden our treatment modalities against ocular conditions.

Broadening Perspectives with Cardinal Health

Located in Ohio, US, Cardinal Health is a global manufacturer and distributor of medical products, providing performance and data solutions for healthcare facilities to nearly 90 percent of US hospitals. The company has assisted numerous biopharma companies in establishing their own advanced therapies – the likes of which date back to the first CAR-T therapies of 2017. Covering clinical development to commercialization, their expertise in this field is widespread. Accordingly, we asked Fran Gregory, Vice President of Emerging Therapies at Cardinal Health, to give us a broad overview of the field – from challenges to future prospects.

What are the scientific challenges of developing gene therapies for ophthalmic conditions?

Most retinal or ocular treatments on the market – or in development – target a specific genetic marker or mutation. However, the human genome is complex; there are many potential genetic mutations that could lead to ocular dysfunction. This makes identification of the dysfunctional, over-expressed, or under-expressed gene necessary for effective therapeutic intervention. As you can imagine, however, this is easier said than done.

There are millions of potential genetic mutations that lead to eye disease, and gene therapies cannot work for all patients. Only if the patient has the specific gene mutation contributing to their condition can the treatment work – but, even in such ideal circumstances, complications can occur. Ensuring gene therapies have the intended result is crucial. With substantial costs, repeated treatment is not a feasible option. Companies must achieve effective and durable responses that can for last years, or better yet, a lifetime.

"There are millions of potential genetic mutations that lead to eye disease, and gene therapies cannot work for all patients."

Why is gene therapy significant for ophthalmology?

The first ophthalmic gene therapy was approved by the FDA in 2017. Though this treatment is limited to a highly specific gene mutation involved in Leber's hereditary optic neuropathy, it's a one-time therapeutic with the potential to restore the visual cycle entirely. Existing treatments for ophthalmic indications (i.e., macular edema, diabetic retinopathy, and wet age-related macular degeneration) belong to a class of medications called VEGF inhibitors. These treatments are injected into the eye several times a year, slowing the progression of disease or vision loss for patients who adhere to the dosing regimens.

With at least 25 treatments in phase I-III clinical trials, the advanced medicine pipeline is full of potential treatments for ocular conditions. The excitement for gene therapy is palpable, and for patients with genetic or inherited ocular conditions who have never before had treatment options, the future is promising.

What concerns do ophthalmology companies face in developing gene therapies?

Scientific challenges and population health considerations are at the forefront of company concerns. Since I've already discussed various scientific issues, let's move on to the latter – we must think about overall population health. Who needs the treatment; can we identify them; and can we get the final product to the patients that can benefit from it.

All gene therapies in development treat a very specific gene, meaning that we must identify that genetic defect in every patient prior to treatment. If one is not already available today, a genetic test must become a standard-of-care. Once the patient's genetic profile is understood, then the product must be an exact match for that patient. Finally, training the physician to identify genetic ocular conditions, perform the genetic testing needed, and refer the patient for gene therapy is another area of consideration. In an ideal world, physicians should be trained to perform ophthalmic surgery and be certified by the manufacturer to administer gene therapy.

Is there enough focus on developing advanced medicines for ophthalmic conditions? Or do indications like oncology take up most of the research effort?

There is certain positive evolution, based on the pipeline alone. This evolution doesn't necessarily undermine oncology, but shows the space is more inclusive of additional therapeutic areas. While oncology will continue to have a presence (rightfully so), we will begin to see more therapies move along the development pathway for other, sometimes more prevalent conditions. Based on the gene therapy pipeline overtime, the percentage of non-oncology indications being studied will be short of 50 percent in the next 3–5 years.

Where should the priorities lie for the future growth of advanced medicine?

We're only just starting to prove that these treatments are safe, effective and durable; gene therapy is in its infancy. Over time, it will be crucial to devise scalable manufacturing solutions and delivery methods of the gene therapy, all while assessing how impactful a single treatment could be. For example, the gene therapies in phase III and on the market all target a single gene, limiting broad population impact. Priorities, therefore, should be in manufacturing efficiency, development of new, potentially more cost-effective delivery methods, and broadening population impact.

Focusing on Wet AMD with Regenxbio

Regenxbio is a clinical-stage biotechnology company with a mission to improve lives through the curative potential of gene therapy. They got their start in 2009 by acquiring the rights to the NAV technology platform, which encompasses over 100 AAV vectors. With this step, they played an important role in reviving the AAV gene therapy field and helping set its current course towards producing one-time potential curative treatments for diseases of the eye, muscle, and brain. Indeed, they have a pipeline of investigational AAV-based therapeutics focused on retinal, neuromuscular, and neurodegenerative diseases – including late-stage programs.

But, we wanted to learn more about a specific condition, namely wet age-related macular degeneration (AMD). Wet AMD occurs when abnormal blood vessels grow into the macula which leak blood or fluid, leading to scarring of the macula causing rapid loss of central vision. How could gene therapy be used to treat this condition? Steve Pakola, Chief Medical Officer at Regenxbio, has the answers.

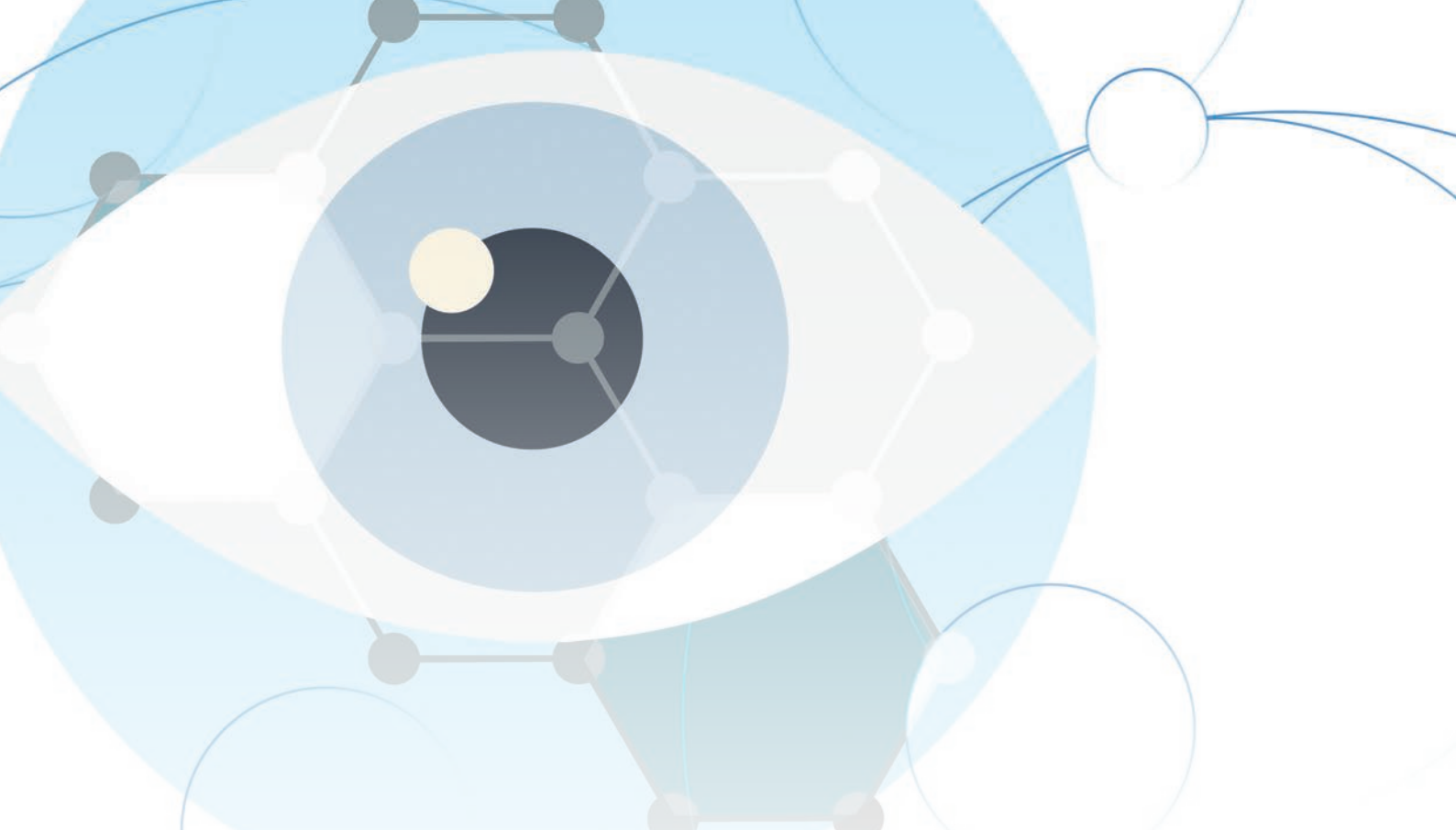
What are the limitations of current treatments for retinal diseases – and wet AMD specifically?

Nobody enjoys injections to their eyes – nor do they enjoy the frequent visits needed to administer them. Most wet AMD patients need to receive injections that block vascular endothelial growth factor (VEGF) into the eye every four to 16 weeks indefinitely. Although these treatments have been shown to work in clinical trials, the requirement of frequent injections can place a heavy burden on patients and families alike.

What is your approach?

The wet AMD patient population is expected to increase to 5.7 million in the US, EU, and Japan in the next five years. So a one-time treatment that uses gene therapy to deliver sustained anti-VEGF activity is exciting to say the least.

ABBV-RGX-314 is an investigational one-time AAV therapeutic that we are developing in collaboration with AbbVie for wet AMD, diabetic retinopathy (DR), and other chronic retinal conditions. It uses the NAV AAV8 vector to deliver a gene encoding a therapeutic antibody fragment to inhibit VEGF. Two separate routes of administration of ABBV-RGX-314 are currently being evaluated – a subretinal delivery procedure and a



targeted, in-office administration to the suprachoroidal space.

ABBV-RGX-314 is involved in several clinical trials. For treatment of wet AMD delivered to the subretinal space, enrollment in phase III trials is ongoing. These are expected to support global regulatory submissions with the FDA and the EMA in late 2025, through the first half of 2026. To date, this is the largest gene therapy pivotal program ever executed.

For wet AMD treatment delivered to the suprachoroidal space, positive interim data from our phase II AAVIATE trial was presented earlier this year, showing improved stable visual acuity and retinal thickness.

And we expect to report additional interim data at upcoming medical meetings. For treatment of diabetic retinopathy delivered to the suprachoroidal space, positive interim data from our phase II ALTITUDE trial was also presented this year; again, we expect to report additional interim data at upcoming medical meetings.

Simply put, after one administration of ABBV-RGX-314, the eye will have what it needs to make its own anti-VEGF instead of relying on regular injections. In essence, our ABBV-RGX-314 candidate aims to turn the body into its own drug factory, eliminating the need for repeated treatment with injected therapies.

RGX-381, another candidate in our retinal portfolio, is an investigational one-time AAV therapeutic for the ocular manifestations of late-infantile neuronal ceroid lipofuscinosis Type 2 – or CLN2 disease, which is a form of Batten disease (a condition characterized by seizures, vision loss, problems with thinking and movement, and eventually death). It uses the NAV AAV9 vector to deliver the TPP1 gene directly to the retina. We recently announced the dosing of the first patient in the phase I/II trial of RGX-381, and we expect initial data to be shared in 2024.

If gene therapy is to be more widely used in ophthalmology, what challenges need to be overcome?

An important consideration in ophthalmology drug development is demonstrating the ability to treat both eyes in diseases that affect both eyes, such as VEGF-driven retinopathies. We are starting to address this issue in the clinic, with the goal of demonstrating similar safety and efficacy when treating the second eye of patients with wet AMD.

Another potential challenge with common diseases is having the capacity to manufacture sufficient doses for large numbers of patients. Again, we hope to address this through the addition of a specialized manufacturing facility that will enable us to boost manufacturing of NAV technology-based AAV vectors at scales up to 2,000 liters. The facility will implement our NAVXpress platform suspension cell culture process, which can increase product purity and yield.

Evidently, you see a significant role for gene therapy in retinal disease treatment in the future…

We are running the largest ever gene therapy program – not just in the field of retinal diseases but for any indication. The lessons we learn during the treatment of these patients will help inform future development of other gene therapies for retinal disorders. We are also the first company ever to evaluate gene therapy delivery via the suprachoroidal space, allowing for in-

"Diseases of the eye are actually a solid target for gene therapies."

office delivery to a compartmentalized space close to the target tissue and thereby limiting exposure to other ocular tissues, including anterior eye structures. We believe that there is tremendous potential for our gene therapies to become a new standard of care to treat and prevent progression of vision threatening diabetic retinopathy.

New Beginnings with Beacon Therapeutics

Let's say you're a new company starting off in the ophthalmic space, what do you do? Take things slowly, limit your expertise to one treatment, or attack the market with numerous preclinical programs across multiple indications. Beacon Therapeutics – thanks to support from Syncona and additional investors – chose the latter. Targeting X-linked retinitis pigmentosa, dry age-related macular degeneration, and cone-rod dystrophy, Beacon is banking on a diverse pipeline to pave their route to approval.

We were joined by both Dave Fellows, CEO, and Nadia Waheed, Chief Medical Officer at Beacon Therapeutics to find out more.

What indications are you focusing on for gene therapy?

At the forefront of our clinical programs is AGTC-501 – a late-stage development candidate we're using to treat X-linked retinitis pigmentosa (XLRP). XLRP is an inherited monogenic disorder that causes progressive vision loss in boys and young men, affecting approximately one in 40,000 young males. Since the condition is commonly caused by mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene, AGTC-501 was designed to directly counteract this. Our drug expresses the full-length protein of the RPGR, thereby addressing the complement of photoreceptor damage caused by XLRP, including both rod and cone loss.

We are also working on two additional preclinical programs. Our first preclinical asset is an intravitreally (IVT) delivered novel AAV based program for dry age-related macular degeneration (dry AMD). Approximately 200 million people worldwide are living with age-related macular degeneration (AMD), and this is expected to grow to 288 million by 2040. Dry AMD accounts for around 9 out of 10 cases. It is a leading cause of irreversible vision loss in people over 60 if left untreated. The second preclinical asset targets cone-rod dystrophy (CRD), which is caused by a null mutation in the Cadherin Related Family Member 1 (CDHR1) gene. This program was licensed from the laboratory of Robert MacLaren, Professor of Ophthalmology at the University of Oxford.

Many ophthalmic therapies require surgery to be delivered. XLRP is a rare disease with no current treatment or cure and the individuals suffering tend to be more tolerant of the necessary surgical procedure. However, with a more prevalent disease, such as dry AMD, a less invasive procedure is preferable. IVT delivery requires less clinician training and can be delivered in clinic rather than via surgery, making treatment more accessible to both patients and health care providers alike.

These programs represent just the start of what we hope to achieve.

When it comes to commercialization of advanced therapies, what hurdles do you face?

A comprehensive clinical development strategy and program are essential in overcoming the demands of commercialization. We're currently building a surgical training program and optimizing surgical procedures, while defining patient populations most likely to benefit from our therapies.

The manufacturing of advanced therapies, like the adeno-associated virus (AAV) platform we use, can be more complicated than other pharmaceutical modalities. Accordingly, we invested in building our own manufacturing facility in Florida to transfer the knowledge and know-how we've gained during process development for delivering commercial products for patients. The facility will be split into two parts: a biotech accelerator featuring office space with wet and dry labs for product development by companies; and manufacturing space to make small batches of the companies' products for use in clinical trials.

How challenging is it to develop ophthalmic gene therapies?

Ophthalmic treatments can make people feel squeamish, but diseases of the eye are actually a solid target for gene therapies – partly due to their potential for efficient delivery, as well as the lower risk of adverse immune responses. In fact, the reasons behind the rapid rise of gene therapy in this space is owed to three main characteristics. First, the eye is easily accessible for treatment via injections and surgical interventions. Second, an immune-privileged status means the eye can accommodate the antigenicity of a viral vector. And third, the tight blood-ocular barrier prevents other organs from unwanted contamination.

Business

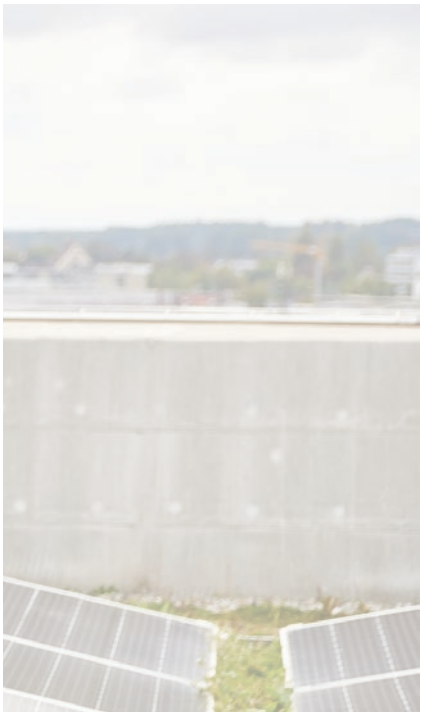
Economic drivers
Emerging trends
Business strategies

Being Mindful of the World

From renewable energy to bicycle schemes and more; here are just a few examples of how a pharma business can be more sustainable

No matter how much we talk about our concerns for the environment or potential mitigating sustainability strategies, making real progress is challenging. But no one wants to be seen to be standing still – so, in recent years, numerous major international businesses have been called out for greenwashing (marketing sustainability as a major focus without taking any concrete action).

In the pharma industry, I'm pleased



to say there are numerous examples of successful sustainability strategies. In 2022, a number of pharma CEOs (including AstraZeneca, Roche, GSK, Novo Nordisk, among others) announced joint action to help accelerate the move towards net zero health systems. Indeed, The Medicine Maker Company of the Year Awards 2023 saw GSK crowned by readers as one of the top companies for smart sustainability strategies.

But it's not just big pharma that is investing in sustainability. In 2021, aseptic filling and packaging CDMO Vetter announced that all of its corporate sites were carbon-neutral. According to Vetter, "Sustainability today means keeping an eye on how our actions impact society, the economy, and ecology, and refers to the holistic responsibility that a company is prepared to assume in all spheres of life, as it stays mindful of the finite nature of resources."

In 2022, the company won awards for climate engagement, sustainable impact, climate mobility, leadership, working conditions, and for improving bicycle and pedestrian traffic – among others. We spoke with Henryk Badack, Senior Vice President Technical Service and Internal Project Management at Vetter, to learn more about the company's sustainability work.

When did Vetter decide to make sustainability a core part of its business strategy?

The topic of sustainability is not new to Vetter. I have been with Vetter for over 20 years and during this time the company has always had a long-term plan in sustainability. None of this has ever been about just obtaining a green label; it's because a sustainable strategy is a good business strategy for both external and internal stakeholders.

From an external point of view, we – as a CDMO – are a very important part of the value stream and the supply chain of our customers. We are in the scope three calculation of our customers, which means that customers expect us to work on sustainability and reduce our carbon footprint. If we can reduce our carbon footprint, we also reduce the carbon footprint of our customers. Customers need their CDMO partners to be transparent. In addition, when comparing different service providers, customers will also strongly consider sustainability when deciding future business relationships.

From an internal perspective, our employees rely on us, and they want us to be prepared for the future because they want their jobs to be safe. They also want good working conditions. We are one of the biggest players in this region, so employees, their families, and communities rely on us. In addition, there are many local partners and suppliers who rely on us too. We've always believed in the three Ps: planet, people, and progress, and our sustainability strategy is rooted in our core philosophy to be a reliable and responsible company in this region – something that both our management and the family that owns Vetter are aligned on. Without their support and commitment, we wouldn't be so successful.

In 2011, we adopted a truly holistic sustainability program. We also established a DIN ISO-certified environmental, occupational and safety management system, which we expanded in 2014 to cover the energy management system from the DIN ISO.


Henryk Badack

What other early actions did you take?

When I took over the department of environment, health, and safety at the company, I asked myself and the team what sustainability means holistically for us as a company – because I wanted to translate this message into easy and appropriate language for communication power. It wasn't 100 percent clear to me where we stood. When you join any department, it's a little like a navigation system in a car. First, you have to know your current position. Second, you have to know your destination. Third, you have to choose an efficient route. (Of course, when it comes to sustainability, no route is really bad because every bit of progress counts!)

We conducted an analysis to bring all our activities to the table to make them transparent and to understand our current position and progress. Over the years, we have invested in various infrastructure improvements and projects to reduce energy consumption, and have adopted energy efficient and environmentally friendly technologies. These actions were mainly focused on environmental aspects, but we felt it was important to develop a more holistic sustainability program with goals across the company.

Today, our sustainability program is based on four pillars. The first is the 17 sustainable development goals of the United Nations. These do not just cover environmental sustainability, but aspects such as no poverty, zero hunger, good health and wellbeing, quality education, gender equality, and so on. The second pillar is internal and external stakeholder dialogue, which includes our materiality metrics. The third is the DIN ISO 26000 guideline for social responsibility of organizations, and our fourth pillar is a collection of other guidelines, such as the EU's Corporate Sustainability Reporting Directive and Taxonomy, code of conduct, and more.

What facts and figures can you share to highlight Vetter's sustainability achievements?

I'm proud to say that we have generated many interesting figures! We have carried out more than 125 efficiency projects over the last decade. Since 2012, we have realized savings of more than 32 million kilowatt hours (equal to the consumption of 6,000 family homes per year) in electricity, natural gas, and biogas. We also began sourcing 100 percent renewable energy from hydropower starting in 2014. Since then, we have realized savings of more than 44,500 tonnes of carbon dioxide. We have invested approximately 9–10 million euros in special energy efficiency programs, and, since 2021, we have been carbon neutral at all sites. In 2022, we generated more than 7.3 million kilowatt hours of renewable energy with our own systems.

Some other important figures: our recycling rate is over 40 percent, which is very high for a pharmaceutical company, and we reduced our waste by 4.5 percent overall in 2022 – all despite growing the company. When I joined Vetter 20 years ago, we had around 1,400 employees, but today we have around 6,000 – and yet we are still able to reduce our waste and expand our sustainability efforts.

Our headquarters are based in a region with many villages, and we have calculated that our workforce commutes over 200,000 km every day to come to work, which is 5.5 circumnavigations of the Earth – daily! Therefore, over the years, we have developed comprehensive mobility concepts; for example, we have invested around 5 million euros to expand our mobility infrastructure at all sites, which includes bike rental stations on site and the implementation of charging stations for electric cars. We also encourage staff to use public transport for commuting by covering the cost of a public transport ticket. All this

helps to reduce our carbon footprint.

Other facts to note include:

- implementing more mobile working options after COVID-19
- using locally sourced products in our canteens
- joining the United Nations Global Compact in 2022
- winning various awards for climate protection and the impact on employees
- achieving platinum status in the EcoVadis rating platform in 2023 (we achieved gold in 2022).
- Though we can be proud of all these things, we must also recognize that we are not perfect. But we are very motivated, and I think we are on the right track.

How have customers reacted?

We find it very important to explain our sustainability programs to customers so that they can fully understand our impact on the environment and what we are doing to mitigate that impact. Our customers have also been impressed by our programs, and often use us as a role model for comparison with themselves or other suppliers. The topic of sustainability is now raised at almost every business review meeting or management meeting. Over the past 10 years, it has been incredible to see this topic receiving more focus. In some meetings with customers, sustainability is now at the very top of the agenda.

We cannot ignore that the pharma industry needs a lot of energy to produce its life saving products. For example, we have to run more than 20 cleanrooms in a 24/7 mode, and we need a high quality of resources, such as purified water and filtered air, to meet the high GMP requirements. Additionally, many filled products need to be refrigerated. We cannot avoid these needs; however, if we look at the entire value stream, there are opportunities in other areas for improvement – and that's what our customers are looking for.

"To inspire people, you have to talk to them. And that's why a good culture of communication and exchange of information is important."

What advice do you have for companies that want to be more sustainable?

You need to find a balance that works for your company in the long term. You cannot invest in or run a company that is super profitable but not sustainable, but you also cannot invest in or run a company that is super sustainable but not profitable. It is unsustainable and bad social responsibility if you have to close a company and fire thousands of employees because you left profitability out of sight.

You should identify sustainability measures to understand the impact of your business on the environment and on society. Once you understand this, you can set goals for where you want to be. I would advise establishing a structure and governance, with named responsibilities. Create communication spaces where you can talk about your successes and challenges. And use networks to expand your reach. Look at what other companies are doing; exchange ideas, goals, and benchmarking data; and don't forget to listen carefully to the ideas of your employees and what they are telling you about sustainability. It is important that you get all staff members engaged with your strategy – regardless of their level or role in the company.

How do you inspire your employees?

Our governance structure includes a sustainability team that meets on a weekly basis to discuss targets, challenges, new activities, and how we communicate those topics across the business. We have also established a sustainability circle with members from various departments; the goal is to bring people together every three months for cross-functional exchange of information, ideas, and challenges, and to discuss what we are hearing and seeing from customers.

We want to bring the issue of sustainability to everyone in the company. To inspire people, you have to talk to them. And that's why a good culture of communication and exchange of information is important. We have created a sustainability report, which has had excellent feedback from staff members, customers, and suppliers. The 85-page report covers all our efforts and activities. Every time I read it, I am impressed by our achievements, and I am proud of the company and our teams.

To engage with our employees, we also created an information microsite that takes a deeper dive into sustainability as a whole. There, we explain, for example, the influence of the food industry on the individual carbon footprint and encourage our employees to be more mindful with the small changes they can make. We don't just want employees to think about sustainability from a business perspective. All of us can play a role in making the world more sustainable, such as by thinking about what we consume and how much meat we eat, and so on.

If we are able to use the knowledge we have in our core team and circle, and combine it with the power of our supporters, management, the family owners, our employees, and their families, there are very few objectives we cannot achieve.

The Age of Upcycling Is Here

We are witnessing a new era in primary packaging for pharmaceuticals

By Michiel van den Berg, Global Head of Product Management, TekniPlex Healthcare

For packaging professionals who do business in Europe, there has been a key topic on our minds recently: EU officials are moving steadily towards a binding, continent-wide framework concerning packaging sustainability, including healthcare and pharma. Expected to be finalized as early as spring 2024, the Packaging and Packaging Waste Regulation (PPWR) is poised to turn guidelines into guardrails, mandating meaningful movement towards a more eco-friendly, circular packaging materials landscape.

The overarching goal of the PPWR is to ensure all packaging is reusable or recyclable in an economically feasible way. The PPWR requires boosting recycled content uptake, eliminating overpackaging, and reducing packaging waste. Understandably, given healthcare's unique role in keeping patients safe and protecting mission-critical medicines, the law is likely to grant a five-year extension to the sector, postponing recyclability mandates until 2035 rather than 2030, as for other industries.

Considering the materials science hurdles that must be overcome to meet

"Recyclability addresses the conclusion of a package's usage, but what steps are being taken to improve its inception?"

this delayed yet (in my opinion) still ambitious deadline, savvy pharma packaging suppliers are diligently working to create solutions that offer recyclability without sacrificing drug safety and efficacy. In fact, we're already seeing successes above and beyond the common-sense use of recyclable mono-material constructions for drugs without elevated barrier requirements. For example, a recyclable blister package has been developed that combines a barrier against moisture with transparency for ease of inline inspection.

Still, this promising progress leaves an elephant in the room: what about the other end of the packaging life cycle when the user discards the packaging? Recyclability addresses the conclusion of a package's usage, but what steps are being taken to improve its inception?

Unfortunately, the short-term answer is "not much." This inaction is partly due to the pending PPWR law, which exempts healthcare packaging from any benchmarks for post-consumer recycled (PCR) content. Logically then, pharma packaging providers are prioritizing PPWR's purview over packaging's back end – namely, recyclability – while disregarding front end sustainability. Recycling stream viability has taken center stage, relegating issues such as PCR content to the regulatory sidelines.

Buttressing PPWR's hands-off approach toward recycled content in pharma packaging is a blend of sound reasoning and long-standing precedent, including pharmacopeia language prohibiting the use of scrap material and insisting that any recycled materials incorporated into packaging solutions be properly validated. All of this has severely discouraged PCR content's utilization for primary pharmaceutical and medical packaging. The rationale is clear and justifiably uncompromising: for patient safety's sake, there can be no risk of contamination entering the supply chain, and current mechanical recycling processes cannot guarantee this.

This precedent exemplifies the historic


Michiel van den Berg

cautiousness of the pharma industry, where being a sustainability pioneer could backfire. Notably, detrimental consequences of incorporating PCR content into primary packaging wouldn't even require in-field failure; the mere perception of a package providing less product protection could significantly impact its acceptance and, through it, a company's bottom line. Simply put, pharma players are hesitant to stick their necks out for fear of exposing their heads.

Increasingly, though, technology is changing pharma's entrenched risk-reward assessment of PCR. Flying fast into these headwinds is the advancement and proliferation of next-level forms of chemical plastics recycling that significantly reduce the risk of materials contamination versus mechanical recycling processes, and ultimately produce virgin-quality resins that meet pharma's unparalleled purity standards. In my view, we are at the dawn of a new era in pharma packaging sustainability – one where recycled plastics and patient safety are companions rather than competitors.

Upcycling

Like any nascent enterprise, incorporating PCR plastics into primary pharma packaging means developing concise, coherent best practices. One crucial issue concerns

"It is this combination of cost and effectiveness that is dictating the current PCR landscape, not just in pharma but in all packaging-relevant sectors."

the fact that, from a recyclability standpoint, not all plastic resins are created equal – and these discrepancies require differing recycling methods. Let's look at three common substrates used in pharma packaging: polyethylene terephthalate (PET), polyethylene (PE), and polypropylene (PP).

As mentioned, conventional mechanical recycling cannot produce pharma-grade plastics – at least not yet. However, PET has proven highly conducive to what could be considered the next level of recycling complexity: chemical recycling. Sometimes referred to as advanced recycling, chemical recycling breaks plastics down into their original building blocks in a process known as depolymerization. The result is a recycled resin essentially identical in its chemical makeup to virgin, fossil fuel-derived resins.

PE and PP are more complex. Both require a more rigorous decomposition process, resulting in a substance called feedstock – a general term given to raw materials used for processing or manufacturing another product. On the downside, this extent of recycling granularity is more laborious and expensive than depolymerization recycling (which, in turn, is more labor-intensive and costly than traditional mechanical recycling). The upside is feedstock recycling allows polyolefin polymers (PP and PE) to be recycled in a way that makes them viable for pharma-grade applications in a way mechanical recycling methods could not.

It is this combination of cost and effectiveness that is dictating the current PCR landscape, not just in pharma but in all packaging-relevant sectors. For example, though producing a fully chemically recycled PET package may be prohibitively pricey, a controlled blending of virgin plastics and chemically recycled PET could produce a package that is, say, 30 percent PCR – a figure that aligns with the PPWR's near-term goals for recycled content in non-pharma applications.

A similar process, called mass balance, can be conducted to incorporate percentages of PE and PP into plastic packaging that originate from recycled feedstock. With the mass balance approach, the recycled feedstock is intermittently dispersed in the entire output, but the resin can be purchased via 100 percent recycled content certificates. Again, this mixing of virgin and feedstock recycling is largely a function of cost; the higher the PCR content, the costlier the production process (for now).

Technologies tend to become more efficient and less expensive as they evolve, and recycling processes aren't likely to break this rule of thumb. The most important factor here is that these technologies work – so well, in fact, that it's impossible to tell the difference between chemically recycled resins and their virgin counterparts.

For proof, we need only turn to regulation. It's become so hard to distinguish chemically recycled from virgin plastics that companies incorporating the former must certify their resins as such. This is undertaken via the International Sustainability & Carbon Certification, also called ISCC Plus, which has essentially become a monitored marketplace for recycled resins and, simultaneously, a means of dissuading dishonest players from labeling virgin plastics as recycled.

Whether or not it is eventually regulated and mandated, chemically upcycled content in primary pharma packaging is a hurdle that will be gradually eroded and ultimately erased. As sustainability transitions from megatrend to mainstay, an increasing set of enterprising pharma companies will stick their necks out and their hands up. And they will be counted among the pioneers that made recycled content in primary pharma packaging the forward-thinking rule rather than the extraordinary exception.

Making Miracles

Sitting Down With…
Fiona Killard-Lynch, Director of Research and Innovation at NIBRT

What kicked off your career in bioprocessing?

Even as a child, I was always interested in health, diseases, and drug development. Interests like this become a passion in childhood, setting you on a particular path. Then, life unfolds in front of you and the pathway becomes serendipitous. The spark was always there, it just needed to be developed.

At the same time, I also knew that I wanted to be involved in something meaningful and impactful – I wanted to be engaged. As I progressed in my career, I developed a real passion for research and how important it is to open debates. Emerging research in bioprocessing has a real world impact on people's lives. Seeing therapies developed for diseases, such as multiple myeloma, and seeing people help babies with neurodegenerative disorders were considerable drivers for my trajectory into the sector.

My current role at NIBRT is a great environment for research because the Irish government has invested significantly in biopharma R&D.

What's your greatest achievement in research?

During the pandemic, there was a real risk of research being shut down. Along with my team at Trinity College, Dublin, we were able to secure almost 10 million euros from the Irish government, and we worked very hard to disseminate it as quickly as possible so that as much research as possible could continue. Researchers were given assurance that they could continue and their career wouldn't be impacted by COVID-19.

The funding went across Trinity and was given to researchers from countries where COVID-19 had been particularly devastating. In some cases, researchers had family members who had died from COVID-19. The funding allowed them to continue their careers. I'd say it had an immeasurable impact.

What factors are detrimental to research?

Knowledge security is one. There needs to be a balance between what you're doing and what the industry wants – improvements in manufacturing processes, for example, and building on knowledge that comes from other research groups. There is also a lack of clarity around research careers. Some researchers remain on precarious contracts – it's not a stable landscape for them, so there's a risk of a brain drain from academia into industry.

Academic research is sometimes viewed by the outside world as a very comfortable lifestyle, but from the inside I can attest to the fact that they are struggling. In Ireland, the third level sector is very underfunded; second level students are funded at a greater level, but PhD candidates are not on a living wage. When you look at the biopharma sector and how strong it is in Ireland, it should be much more tempting to stay in academia rather than move into manufacturing where there are so many opportunities and so many great companies.

What challenges have you faced in your career?

As a woman in science, meetings tend to be dominated by males, and whoever is speaking will speak with the guys in the room. You could see it during the pandemic, in particular, where I was, maybe naively, a little surprised by how many childcare responsibilities still fell on women. The impact affected grant applications and scholarly outputs from female academics. However, if you start to dwell on that topic too much, you can start to drown in it. I've been extremely fortunate in the Irish system because most of the presidents or provosts of Irish universities are inspirational female leaders. The former Dean of Research is now the provost at Trinity. I worked with her for years and she's just an incredible person. She taught me to just keep moving forward.

If you want to maintain a forward momentum, you can't get bogged down by convention. People have many different challenges, so it's important to persevere (even when it frustrates you).

Where I get a lot of satisfaction is in people saying, "It was hard!" Research is hard, but when you break through to the other side you commit to making it easier for the people coming behind you. Empower and enable them – especially other females – to have as positive an experience as possible. Converting all that stress and frustration into energy used for developing somebody else's life and career is what I try to do. Yes, there may be glass ceilings, but let's just keep breaking through them.

What do you see in biopharma's future?

We're on the cusp of something incredible. I'm not one for hyperbole, but some of the new therapies emerging are nothing short of miracles. We all remember a time when cancer was (and still is) a frightening thing. There is now a war against cancer and a real future for cancer patients is within touching distance. There has been a huge surge in developments in cell and gene therapy, too. We are going to see a world where people live longer and better lives. NIBRT's CONCEPT, a core facility for early-stage biotherapy, could be a key enabler of these developments where researchers and industry can generate optimized cell lines and biological material for advanced therapeutics and biologics experiments.

Now, the onus is on the nations of the world to work together to realize these miracles. And it begins by recognizing and supporting the incredible work of researchers – the young people dedicating their lives to enabling these changes.

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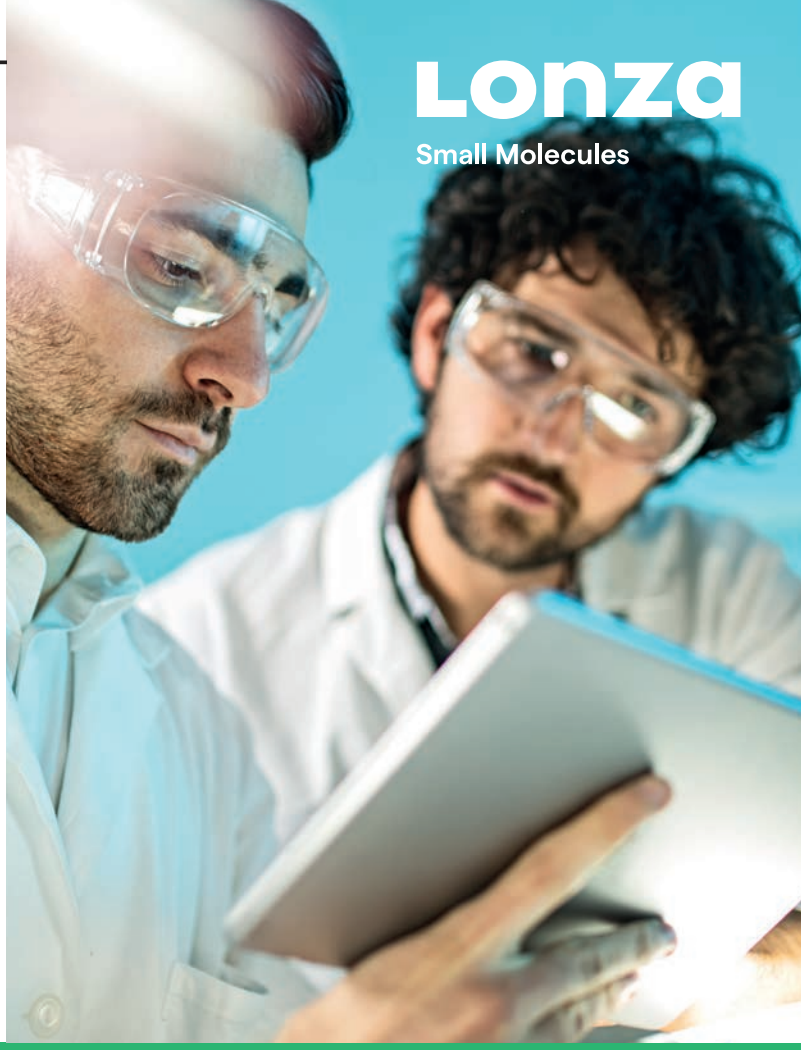

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