November / December 2024
#100

the Medicine Maker®

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A Year of Progress

What were the major talking points in 2024?

For me, one of the standout moments this year was approval of the first CRISPR gene-edited therapy: Vertex's Casgevy (developed in collaboration with CRISPR Therapeutics). Not only is this a hugely important milestone for patients suffering from sickle cell disease and beta-thalassemia – it's also a big step forward for the CRISPR field as a whole. More recently, there has been discussion about a CAR T-cell therapy for lupus, which has seen patients with the most serious form of the disease going into remission. Again, this is remarkable for patients.

Over the course of the past 12 months, there has been significant innovation across all areas of drug development. AI is one key topic, with its ability to enhance various processes, particularly in drug discovery. AI can predict protein structures and design molecules with high binding affinity, streamlining the drug development process and reducing time to market. Perhaps unsurprisingly, AI's growing role is emphasized by our Innovation Awards on page 9, in which numerous AI-based technologies make an appearance.

It will be fascinating to see how science and drug development continue to change as we hit the half way point of the 2020s. It feels like many areas are evolving quickly. If you'd like to share your thoughts on change and progress in the industry, please get in touch: rob.coker@conexiant.com.

And if you know of influential figures who are the harbingers of change in the industry, why not nominate them for our 2025 Power List? Find out more online: https://themedicinemaker.com/awards/power-list/2024

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Congratulations!

The 2024 CPHI Pharma Awards spanned fourteen categories, including Future Leader and Woman of the Year.

QUOTE *of the month*

"It is great to see a will to be competitive, but when I look at the EU pharmaceutical legislation that was tabled last year and voted upon by the parliament in April 2024, I am not quite sure that it makes the cut... Rather than increasing incentives such as the regulatory protection for new medicines in Europe, the legislation will actually decrease them."

Claus Zieler, Chief Commercial Officer at Astellas and a member of the board of EFPIA, on pharma legislation in Europe. Read more: tmm.txp.to/protecting-innovation-in-europe

Insulin Pens for $1?

Would such a move ever be possible? MSF calls for change

Credit: AdobeStock.com

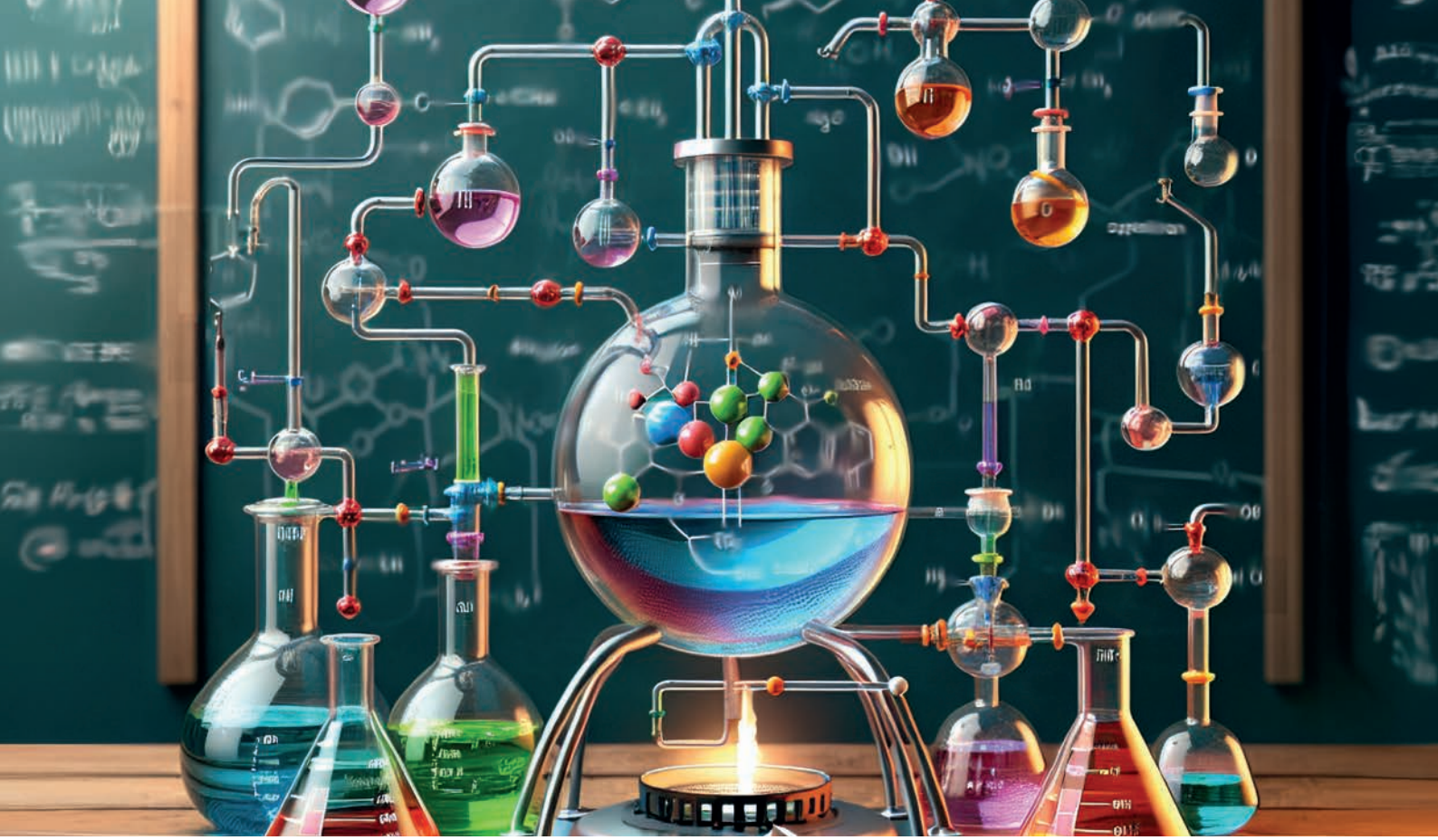
Médecins Sans Frontières/Doctors Without Borders (MSF) has called on pharma companies to make insulin pen injection devices available at $1 per pen – after publishing research showing that they could cost as little as $0.94 per pen, while still allowing companies to make a profit. Pens are usually patients' preferred delivery device for insulin injections, but are not commonplace in low- and middle-income countries.

In a statement, Helen Bygrave, non-communicable diseases advisor, MSF's Access Campaign, said: "Over 100 years ago, the scientists who discovered insulin wanted everyone with diabetes to have access to treatment, so they sold the patent for just $1, but since then, something's gone seriously wrong because now only about half of people around the world who need insulin can access it."

On average, insulin pens are sold at $1.99 in South Africa, $5.77 in India, $14.00 in the Philippines, and $90.69 in the US (1).

Reference

1. *MJ Barber at al., Diabetes and Endocrinology, 7(3) (2024). DOI: 10.1001/jamanetworkopen.2024.3474*



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The Intersection of Sustainability

How pharmaceutical companies are aligning their sustainability goals with the complexities of the modern supply chain

By Sreedhar Patnala, General Manager at Systech

We all understand the role of track and trace in ensuring the quality and safety of pharmaceutical products (and preventing counterfeits from entering supply chains), but have you ever thought about track and trace for environmental purposes?

Over the last few years, we have seen environmental, social, and governance (ESG) initiatives rise to the top of the strategic agenda for organizations worldwide. Consumers, stakeholders, and regulatory bodies increasingly scrutinize businesses' environmental impact, making sustainability imperative. According to PwC's 27th Annual Global CEO Survey, we have now reached a point where 40 percent of business leaders say they are willing to compromise profits in the short term to prioritize climate action.

A global Deloitte survey of biopharma supply chain executives in 2023 also revealed that companies were aiming to leverage their technological capabilities to improve sustainable reporting while better articulating their sustainability efforts to stakeholders. Twenty-four percent of surveyed executives noted that their organizations expect to be able to provide external stakeholders with a real-time view of how their sustainability initiatives are progressing in the next two years.

To create accurate and meaningful ESG goals, organizations must first ascertain how sustainable their manufacturing practices, product offerings, and services are. This approach should include measuring the true environmental impact of a product by charting the precise journey of how the product was made, including the suppliers and materials involved.

Tracking is a fundamental part of this approach. By following the origins of raw materials, organizations can select materials that are recyclable, biodegradable, or with a smaller carbon footprint. They can also choose suppliers with robust sustainability practices and identify ways to minimize waste along the product's journey.

Supplier quality checks represent another measure to ensure that ethical business practices are followed. Given that a significant portion of carbon footprint and associated risks lie within the supplier network, relying solely on internal control measures isn't sufficient – and that's why thorough supplier checks are imperative.

Good manufacturing processes and smart packaging, in tandem with automation via Industry 4.0 – can minimize waste and inefficiencies. Smart packaging, specifically, avoids additive technologies and uses digital fingerprinting to combat counterfeiting and diversion. Additional practices, such as tracking resources, performing quality checks, aligning finished goods with inventory, and overseeing low-carbon logistics within the supply chain are also key sustainability measures.

Choosing a track-and-trace vendor that exhibits good practices and provides low-carbon footprint solutions is essential. The quality of the solution is vital for sustainability; otherwise, there is high wastage due to production line upgrades. Today, consumers and brands demand transparency, so adopting technology that enables precise tracking and tracing is essential to building trust. Here, validating product authenticity via digital means – rather than additive ones – grants access to information about ingredients, raw material sourcing, and a product's journey. Whether or not the consumers choose to do so, the access makes them feel more comfortable about their purchase. Fast-growing digital passports record the entire product journey from raw materials to end-of-life disposal. They promote sustainability by providing transparency, enabling circular practices, and fostering conscious consumption.

Manufacturing pharmaceutical products demands vast amounts of energy and carbon. According to Deloitte, more than 70 percent of the emissions produced by life sciences and healthcare companies originate in their supply chains. These statistics reaffirm the importance of selecting the right vendors and solutions with better sustainability compliance to help contribute to waste management.

Sustainability has become a driving force for change, and pharmaceutical companies must explore new avenues that improve the visibility of their supply chains to make responsible choices, reduce waste, and enhance transparency. Given that the industry is heavily regulated, some sustainable practices that work well in other sectors cannot be applied to health-related products. For example, creating environmentally friendly packaging can be challenging because manufacturers must balance the safety aspects of recyclable or disposable materials. Nevertheless, sustainability best practices, technologies, and tight governance will all play a critical role in accomplishing these important goals, while differentiating companies and their products.

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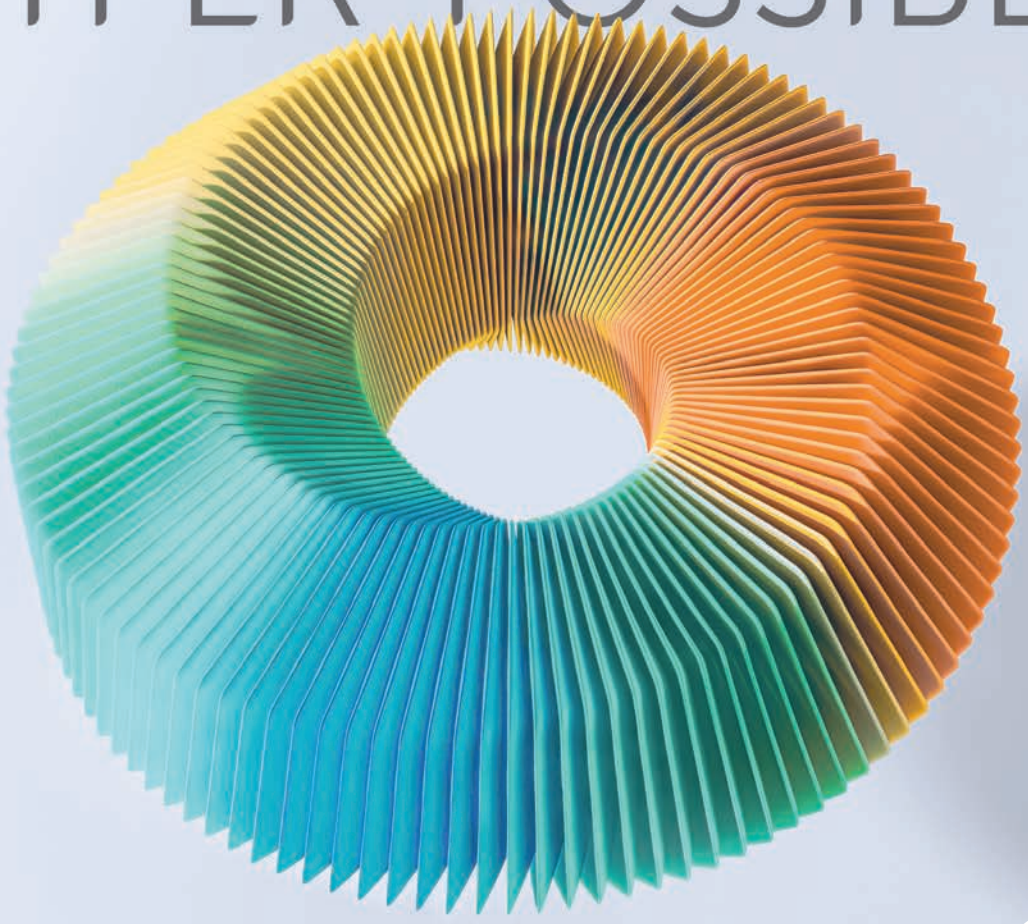

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INNOVATION *Awards*

Welcome to our annual celebration of the top development and manufacturing technologies released over the course of the year!

Another year of innovation in pharma draws to a close. As is customary at The Medicine Maker, we've taken the time to dig deep into drug development and manufacturing technologies released over the past 12 months.

This showcase has been compiled based on nominations received via The Medicine Maker website – but it's up to you to decide which technology should be crowned the overall winner. Summarized below you will find a shortlist of the standout innovations of 2024. Once you've read them all, head online and complete the voting form: tmm.txp.to/innovation/awards/online

Voting will close on January 28, 2025, with the winner having the opportunity to share the story behind their innovation in a future article. Last year, Lonza's Enprotect capsule technology took the grand prize. Who stands out this year? Check out the showcase below!

Atlas

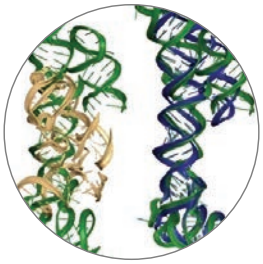
PAT platform for real-time process optimization and formulation confirmation

Nirrin Technologies

Atlas leverages tunable laser technology for chemical spectral analysis, utilizing advanced signal processing and analytical algorithms to characterize complex mixtures within one minute in applications ranging from bioreactors to final therapeutic formulations. In downstream bioprocessing applications, Atlas provides accurate and rapid at-line quantitation of excipients such as sugars, amino acids, and surfactants, and product titers such as antibodies, peptides, and vaccines, all from a single, 15 microliter drop. Taking advantage of the near-infrared spectrum for mathematical separation of biomolecular signals, combined with the exquisite signal-to-noise ratio of the tunable laser technology, the platform yields the specificity of Raman spectroscopy and accuracy of high-performance liquid chromatography in a single instrument.

ATOM-1

Large language model for predicting RNA structure and characteristics



Atomic AI

RNA structure prediction has been historically hindered by limited data and inadequate computational models. Atomic AI researchers have created a platform that leverages large-scale, chemical mapping data (including millions of RNA sequences with over a billion nucleotide-level measurements) collected using custom wet-lab assays. The technology can predict structural and functional aspects of RNA, including key characteristics of RNA modalities, such as RNA-targeted small molecules, mRNA vaccines, siRNAs, and circular RNA. Atomic AI is using these unique insights to overcome key challenges in the development of RNA-targeted medicines.

Figure 5: Structure predictions for a probe of ATOM-1 compared to the baseline without foundation model embeddings. The baseline model is identical to our probe architecture but does not use ATOM-1. Predictions are overlaid on experimental structures for different test set RNAs: (A) a Pre-Q1 riboswitch (PDB ID: 8FB3 [46]), (B) a G-quadruplex (PDB ID: 7SXP [47]), (C) a synthetic tRNA (PDB ID: 7URI [48]), and (d) a cloverleaf RNA fused with a tRNA (PDB ID: 8S95 [49]).

Constellation with cryoFIL

Automated vial filling with full robotic automation of CGT processes

Cellular Origins and 3P innovation

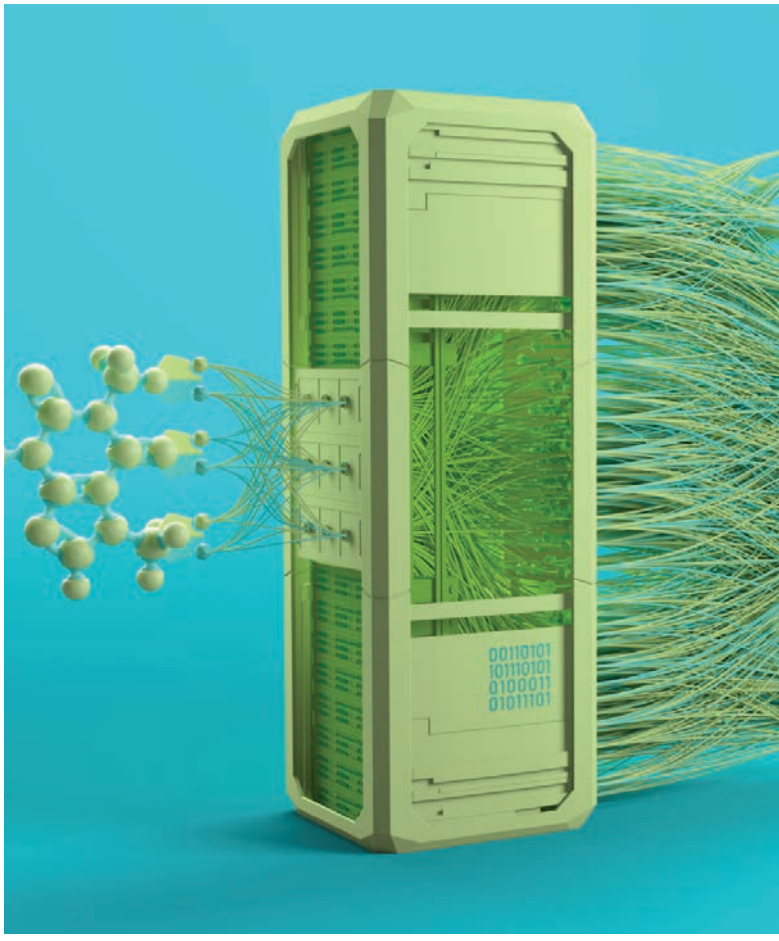
3P innovation's cryoFIL platform is designed to automate and streamline filling processes in cell and gene therapy workflows, delivering closed-loop filling with 100 percent weight verification, and reducing waste and contamination risks. It is combined with Cellular Origins' Constellation – a modular, robotic platform designed to automate existing end-to-end cell therapy processes at an industrial scale. Constellation's physical and digital Industry 4.0 framework incorporates proven cell therapy technologies, including cryoFIL, to eliminate manual steps, reduce labour, maintain sterility, and enhance quality monitoring and control. Both companies believe that full automation is essential for reducing the costs of cell and gene therapies and to reach the scale that the success of these therapies now urgently requires.

FDmiX

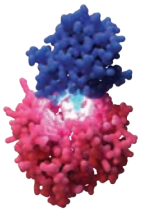
Mixing device suitable for nucleic acid encapsulation

Lonza, FDX Fluid Dynamix, and Fraunhofer IPK

For mRNA-based products, the active ingredient is encapsulated in a protective coating generated by mixing the active ingredient with a lipid or polymer solution. Efficient mixing of these solutions across various scales, especially for commercialization, is challenging. FDmiX was developed in a collaboration of different companies to optimize the encapsulation process by using an oscillating flow to achieve faster, more homogenous mixing, resulting in higher yields, higher quality, and fewer filtration losses. The technology is now GMP-ready and can encapsulate mRNA, RNA, and DNA, with the potential to expand to peptides or small-molecule APIs.



GlueSEEKER



Drug discovery platform for novel molecular glue degraders

PhoreMost

A drug discovery platform for the development of novel molecular glue degraders, GlueSEEKER exploits a cell's proteostasis mechanisms by inducing close proximity between a target protein and an effector protein, such as an E3 ligase, and gluing them together. The technology uses computationally designed insertional libraries to create surface-edited E3 ligase variants, and introduces researchers to knowing – rather than estimating – relevant disease mechanisms, improving target hypotheses. The combination of computational approaches and molecular biology enables identification of induced degradation events for almost any nominated neosubstrate and ligase pair.

mPredict Co-Crystal Prediction Service

Service to enhance API solubility by identifying best drug and co-former combination

Merck KGaA, Darmstadt

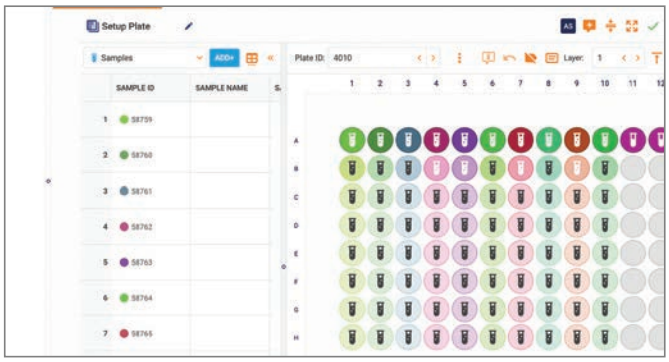
Many drugs in the development pipeline are poorly soluble but co-crystallization is one way to address the challenge. A combination of a promising API and a co-former results in co-crystals with properties that improve drug solubility and stability. Choosing the right co-former, however, is difficult – especially when the selection is API-specific and needs to be comprehensive. mPredict is an AI-based tool that predicts optimal co-formers for an API. According to Merck, the process is 96 percent faster than traditional experimental screening and uses fewer resources.

Particle Formulation Technology

A solution to create high-concentration suspensions for injection

Nanoform

Subcutaneous formulations are a challenge to develop. Conventional strategies use hyaluronidase enzyme, which is co-administered with the active ingredient to degrade the cellular structure, creating a cavity. However, this approach is limited by the requirement for on-body auto-injectors and time spent in hospital. Nanoform's technology removes these limitations through particle formulations that enable high drug suspensions in non-aqueous vehicles at levels greater than 400 mg/ml. It also opens up the opportunity for IV to subcutaneous switches, and reduction of the number of injections required to deliver the daily dose. Being spherical, the particles are morphologically unique versus other approaches, meaning high concentration formulations have low injection forces and can be used in low volume formulations that can be administered subcutaneously without hyaluronidase and on-body auto-injectors.



Sapio ELaiN

AI-powered virtual lab assistant

Sapio Sciences

Sapio ELaiN (Electronic Laboratory Artificially Intelligent Notebook) is an AI-powered lab assistant, integrated into Sapio's Lab Informatics Platform. ELaiN understands context-specific scientific queries, and helps researchers automate repetitive tasks, streamline workflows, and reduce the time spent navigating software. Researchers can ask the Sapio electronic lab notebook (ELN), LIMS or scientific data cloud to conduct various tasks, such as create experiments, analyze data, or manage inventory. The interface is driven by simple voice or text commands, minimizing the need for specialized training and eliminating coding requirements. The goal of ELaiN is to make researchers more productive and sophisticated lab informatics more accessible.

The SCIEX 7500+ system

A triple quadrupole mass spectrometer for ultrasensitive quantitation

SCIEX

SCIEX reports that this system is the fastest mass spectrometer in its nominal mass portfolio. The system can be used for ultrasensitive levels of quantitation across drug development, emerging contaminants, and life science research. It is capable of monitoring up to 800 multiple reaction monitoring transitions per second and includes Mass Guard technology to reduce the risk and frequency of instrument contamination by novel ion filtering, maintaining a high sensitivity for up to two times longer in complex matrices. With sustainability in mind, this system was designed by SCIEX to use up to 24 percent less energy, relative to oil-sealed pumps.

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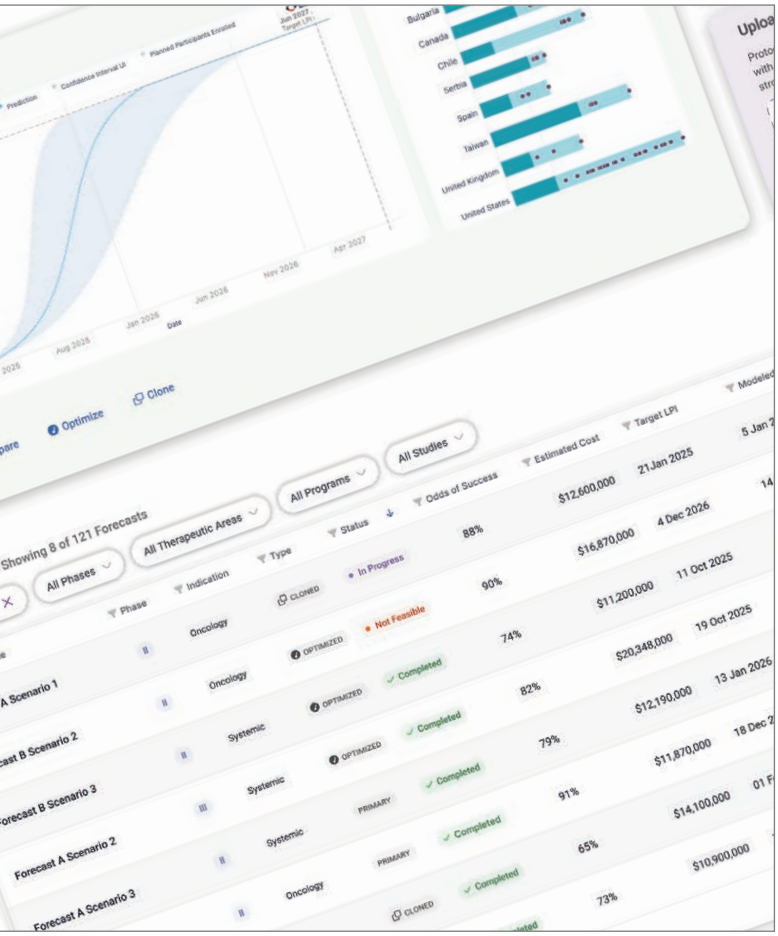


Spectrum

Software for optimizing clinical trials, and controlling timelines and costs

Lokavant

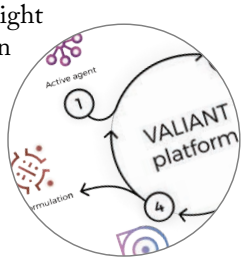
Spectrum is an AI-based clinical trial feasibility software solution that can predict, optimize, and control trial timelines and costs in real-time, enabling iterative feasibility analysis and mid-study course correction. Key features include high-throughput scenario planning, rapid enrollment projections and related probability of success, site startup sequencing, and a "causal AI" algorithm that recommends country and site configurations based on user-defined constraints. The platform is powered by proprietary historical data from over 2,000 studies, encompassing more than 14,000 investigators, 12,000 healthcare institutions, 3rd-party site performance data sources, and more than 500,000 third-party trials.

VALIANT

AI and robotics-driven platform for drug formulation design and optimization

Intrepid Labs

VALIANT uses AI and a data-driven approach to explore formulation design space and can refine multiple parameters simultaneously. The technology can be used to support the development of various formulations, including injectables, solid dosage forms, and nanoparticles for parenteral drug administration. The process begins with an API and target product profile. Using semi-autonomous or autonomous workflows, the platform selects, prepares and characterizes a starting formulation. With oversight from experts, the formulation is then refined and optimized. Intrepid Labs claims that the platform can help address failure from efficacy or toxicity issues by identifying optimized formulations earlier on.



Vericheck ddPCR Empty-Full Capsid Kit

High-precision assessment tool for capsid characterization in AAV production

Bio-Rad Laboratories

Empty/full capsid analysis is critical in gene therapy because the ratio of empty (non-therapeutic) to full (therapeutic) AAV capsids directly impacts the safety, efficacy, and dosage of the treatment. Vericheck ddPCR Empty-Full Capsid Kit is a high-precision solution to quantify empty and full AAV capsids with minimal amounts of either crude lysate or purified samples for reliable quality assessment. The kit provides simultaneous viral titer and capsid content measurements throughout the AAV production process, with multi-sample type compatibility, low-sample input, fast turnaround time, and easy data analysis.

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CELL AND GENE

The Journey of CRISPR-Cas9

The past, present, and future of gene editing

By Jon Chesnut, Senior Director of R&D, Cell Biology at Thermo Fisher Scientific

In the summer of 2012, the Doudna Lab at the University of California, Berkeley published an article announcing, "Programmable DNA Scissors Found for Bacterial Immune System." The discovery – sandwiched between a much-anticipated Facebook IPO and a landmark Supreme Court ruling on healthcare coverage – entered the world largely under the public's radar. But it wouldn't stay there for long. Just a few years later, this new technology for genome editing was named "Breakthrough of the Year" by Science Magazine, gracing the mainstream media covers of both Time and National Geographic in 2015, and earning co-authors Jennifer Doudna and Emmanuelle Charpentier the Nobel Prize for Chemistry in 2020.

Today, therapies leveraging CRISPR-Cas9 technology have been approved by the European Medicines Agency and the FDA, making clinical gene editing a reality. The first example of such a therapy came with the recent FDA approval of Casgevy, developed by Vertex Pharmaceuticals and CRISPR Therapeutics. The indications of this treatment are sickle cell disease (SCD) and beta thalassemia.

In the years to come, it will be exciting to watch where CRISPR technology goes next, what other indications see breakthroughs, and how further emerging technologies play a key role. Nearly 700 cell and gene therapies are in development across the US with approximately 30 products already approved by the FDA. Success in leveraging CRISPR in this area will encourage greater investment in gene editing and greater investment in the creation of these advanced therapies.

Conditions like SCD, where only one genetic mutation must be corrected, will continue to be strong candidates for CRISPR-based treatments. For other indications, the initial success of CRISPR in SCD and beta thalassemia will serve as a proof point, encouraging other developers to invest in new treatments for rare conditions in small patient populations, for example. Indeed, the rise of CRISPR has been rapid – there are currently more than 100 clinical trials underway using this technology, among other gene editing tools.

"The important thing to remember is that each step takes us closer to solving today's most critical challenges."

Advances in CRISPR clinical applications could also pave the way for treatments (or even cures) for more common diseases, such as multiple myeloma and type 1 diabetes. And the playbook can only be strengthened with new gene editing solutions; for example, most gene editing treatments in development are based on double strand DNA cutting, but new technologies – such as base and prime editing – are looking to modify the genome without double strand breaks, thereby reducing the chance of unwanted DNA damage.

Though the approval of Casgevy brings hope to millions of people, true success will come when patients worldwide can access and benefit from these treatments. One way to accomplish this is by exploring different development and manufacturing processes that can help reduce costs and bring discoveries from bench to bedside more quickly. For instance, shifting to an allogeneic process, where "off the shelf" therapies are derived from a common donor to treat multiple patients, could help reduce the high expense and long timelines associated with autologous processes. Further down the road, we may even see the industry working to find a balance between the two processes to help reduce costs, decrease timelines, and simplify manufacturing where possible.

When it comes to the future of CRISPR, the road to progress will always have its twists and turns. The important thing to remember is that each step takes us closer to solving today's most critical challenges.

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BIOPROCESSING

Boosting Vaccine Stability with Gelatin

Maintaining the stability of vaccines over time and during temperature excursions is a crucial aspect of production, transport, and delivery. Here's why gelatin can help

By Martin Junginger, Product Manager Pharma at Gelita AG

There are many factors driving the development of more thermostable vaccines, including the need for cost-effective production, a reduced reliance on cold chains, tighter regulations on animal-based materials, and ensuring return on research investment. A less discussed but equally important aspect is excipients used as stabilizers in vaccine formulations. The type of stabilizers used in viral vaccines largely depends on the vaccine type – particularly the characteristics of the active ingredient or antigen. A mounting body of evidence, however, suggests that gelatin and collagen possess the qualities needed to ensure that vaccines remain potent and effective from production to administration (1, 2).

Immunization is one of the biggest success stories and a milestone in global health. Today, vaccines are available to prevent more than 20 life-threatening diseases, allowing people of all ages to live longer, healthier lives. More than just an administration exercise, vaccination is a cornerstone of primary healthcare, a basic human right, and one of the best investments in health. They're essential to prevent and control outbreaks, they are key to global health security, and a powerful weapon against antimicrobial resistance.

Vaccines typically contain an agent that resembles a disease-causing micro-organism, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and "remember" it, so that the immune system can more easily recognize and destroy any of these micro-organisms that it later encounters. They also contain other ingredients to keep the vaccine safe and effective.

This article will focus on stabilizers, and how gelatin and its hydrolysate collagen are perfectly suited to this role. The effectiveness of vaccinations relies heavily on their stability. Depending on the type of vaccine, the inclusion of stabilizing agents can be crucial in terms of protecting the functionality of the API and ensuring the efficacy of the delivered dose. Stabilizers prevent degradation reactions from occurring within the vaccine, and prevent the individual components from adhering to and interacting with the walls of the vial. Among others, they comprise sugars (lactose, sucrose), amino acids (glycine), proteins (recombinant human albumin, derived from yeast), lipid nanoparticles (LNPs) (3) and, of course, gelatin.

Stability by ingredient: the benefits of collagen/gelatin

Many of the stabilizers used in live and/or attenuated vaccines are enriched with protein excipients, such as gelatin and human albumin. Gelatin is classified as GRAS (generally recognized as safe) and is known to have an extremely rare incidence of anaphylaxis (one per 2 million cases). As a key component of the lyophilization process, it helps to safeguard vaccines from temperature-related effects.

Indeed, gelatin has a pedigree of application in pharmaceutical applications, as noted in the 2014 paper "Drug Delivery System of a Radio-protective Inclusion Complex" (4). Working with a novel radio-protective drug, 9-phenyl symm octahydroselenoxanthene (POSX), the authors aimed to improve both solubility and defence against radiation during brachy therapy using complexation and encapsulation. POSX is known to be insoluble in water and unstable in atmospheric oxygen.

Complexation with 2-hydroxypropyl beta-cyclodextrin (HPCD) was shown to improve the water solubility – and thus the bioavailability – of the drug, whereas radio-protection of the resulting inclusion complex was achieved by spray drying with both poly D,L-lactic-co-glycolic acid (PLGA) and gelatin. Following a series of in vitro irradiation tests, it was shown that "the final ointment formulation inhibits neoplasm development and provides efficient protection effect against radiation." Furthermore, during in vivo tests, it was found that the application of 5 mg/kg (calculated as POSX) doses in mice and rats 7 days before irradiation inhibited the development of any tumorous cells and significantly reduced its inflammation effects on healthy tissue. What's more, the POSX-HPCD complex encapsulated in gelatin showed a faster release rate compared with formulations developed with other capsule matrices. The authors conclude that this novel drug delivery

FUTURE PERSPECTIVE: ANIMAL-FREE COLLAGEN STABILIZER THROUGH FERMENTATION

To meet the ongoing needs of food, health, nutrition, cosmetic, pharmaceutical and medical innovators, there is increasing demand for non-animal alternatives to existing products. Animal-free fermentation-derived gelatin offers several game-changing benefits in a wide range of applications, hence in vaccine stabilization (1). For example, if the yeast Komagataella phaffii (also known as Pichia pastoris) is used during the fermentation process, then the resulting product is endotoxin and animal free by design. In fact, a final value of 0 EU/g, which is used as endotoxin unit (6) is theoretically possible depending on downstream processing. All the other positive properties of gelatin/collagen peptides are retained if the product is hydroxylated in a similar way to nature (7). This provides future users with a variety of unique advantages compared with other commercially available solutions.

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system is highly recommended for brachy therapy when healthy tissue needs to be protected from radiation injuries.

In another paper, "Formulation and Stabilization of Francisella tularensis Live Vaccine Formulation (LVS)," the authors set out to stabilize a "promising vaccine candidate to protect against F. tularensis exposure (5). Despite the drug being "a particularly thermolabile vaccine and difficult to stabilize sufficiently for storage under refrigerated conditions," progress in the past had been made using a modified freeze-drying method – with sugar-based formulations – called foam drying to create a solid dosage form.

Biopolymers such as gelatin were incorporated to a solution containing F. tularensis to evaluate their ability to stabilize the drug product. The authors note that the inclusion of 5 percent (w/v) gelatin to the base formulation – 30 percent (w/v) trehalose and 25 mM potassium phosphate at pH 8.0 – significantly improved the stability of foam dried F. tularensis stored at 37 °C; the rate constant of degradation was reported to decrease from −3.5 log10/week0.5 to −0.9 log10/week0.5. Furthermore, the inclusion of gelatin decreased the residual water content from 5.2 to 2.5 percent and increased the Tg from 57.6 °C to 99 °C.

The relative effectiveness of the gelatin-containing formulations became clearer upon comparing their storage stability at lower temperatures. In summary, the optimized F. tularensis formulation, which contained trehalose, gelatin and Pluronic F68, remained stable for approximately 1.5 weeks at 37 °C (time required for the vaccine to decrease in potency by 1 log10 colony forming unit) and for 12 weeks at 25 °C. At refrigerator storage conditions (4 °C), stabilized F. tularensis LVS vaccine exhibited no activity loss for at least 12 weeks. This stabilization method uses conventional freeze dryers and pharmaceutically approved stabilizers; as such, it can be implemented at many manufacturing sites for large-scale production of stabilized vaccines. Plus, the improved heat stability of the LVS could mitigate any risk of vaccine potency loss during long-term storage, shipping and distribution.

Effective excipient

As evidenced by the published research, gelatin and its collagen hydrolysate are presented as ideal vaccine stabilizers because of their unique properties that help to maintain the integrity and effectiveness of vaccines. Critical criteria include the following:

- **Thermostability.** Gelatin and collagen are highly effective at protecting vaccines from temperature changes, which is key when it comes to keeping vaccines stable during storage and transport, especially in areas with limited access to refrigeration.
- **Protein structure protection.** These stabilizers help to preserve the structure of the viral antigens or biological active ingredients in vaccines, preventing them from degradation with time. Gelatin forms a protective "gel-like barrier" that shields the vaccine's active components from environmental stresses such as heat or freeze-thaw cycles.
- **Biocompatibility.** Gelatin and collagen, being the most abundant protein in animals is therefore biocompatible by nature, meaning they are safe for use in the human body and well tolerated. Their low allergenic potential makes them suitable for use in human and animal vaccine formulations.
- **Versatility.** They work well with a wide variety of vaccine types and can be tailored to different formulation needs. Whether in liquid form or freeze-dried vaccines, they help maintain a vaccine's potency throughout its shelf-life.
- **Stabilizing effects during freeze-drying.** Gelatin is particularly effective at stabilizing vaccines during lyophilization, which is used to prolong vaccine shelf-life and reduce the need for cold chain storage.
- **Moisture control.** Acting as a hygroscopic agent, gelatin absorbs excess moisture from the vaccine and prevents crystal formation. This efficient moisture control helps to preserve vaccine stability during extended storage periods.

Further benefits include the fact that gelatin is both sustainable and biodegradable: its biodegradable nature aligns with sustainability and safety principles. Plus, it undergoes enzymatic degradation to create harmless by-products within the body, thus ensuring safe use. Finally, when sourced appropriately, gelatin with high levels of purity and a consistent molecular weight ensures reliable antigen stabilization.

Overcoming the threat of endotoxins

In pharmaceutical, medical device, and healthcare environments, endotoxin control of ingredients and production environments is crucial to ensure product safety and patient well-being. If left unchecked, for example, endotoxins – lipopolysaccharides found in the cell wall of Gram-negative bacteria – can trigger severe immune responses and cause tissue inflammation or even septic shock. This is why regulatory bodies enforce strict thresholds for ingredients such as vaccine stabilizers and end products. Of note, it is the responsibility of the legal manufacturer to ensure that end-product limits are met and approved.

Collagen peptides have shown to be safe and effective stabilization excipients in both human and animal vaccines. Already recognized by global vaccine producers, these ingredients are ideal for liquid and lyophilized formulations, serving as an excellent scaffold to stabilize vaccine antigens and other protein-based components.

Collagen peptides and gelatin are considered to be stable ingredients being biocompatible by nature used in a wide range of biomedical applications. With some suppliers now offering versions that comply with US and European pharmacopeial monograph requirements, further research is currently under way to produce completely endotoxin-free products in the future.

See references online at:
tmm.txp.to/boosting/vaccine/stability

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SMALL MOLECULE

Small Molecules Are Still Here – and Still the Most Affordable

We asked over 100 industry professionals for their views on the future of the pharma and biopharma industries: Looking ahead to the next 5–10 years, what will be the key disruptors and/or what can be improved upon in the pharma industry? Here's how Jordi Robinson, Chief Commercial Officer at Navin Molecular, answered the question. His view? Small molecules will remain dominant

One of the biggest changes that the industry has witnessed in the past 10 years has been the rise of biological-based drugs and the emergence of new modalities as therapies. With the promise of targeted delivery and improved safety profiles, the rise of biologics was seen to have the potential to replace traditional small molecule drugs and deliver better outcomes for patients. This drive has been exacerbated by legislative changes in the US, which favors the development of biologics over more conventional therapies, leading to a record year for biologics' approvals in 2023 – and a record number of large-molecule therapies in drug companies' pipelines.

However, with hindsight, it could be questioned whether it is realistic to suggest that biologics are, in reality, "replacing" small molecules, which have been the mainstay of the pharmaceutical industry for more than a hundred years. Despite the obvious benefits that biologic drugs can bring, the economics of biological manufacturing simply do not add up when compared to small molecules – not just in relation to their manufacturing costs, which are often an order of magnitude greater without a similar elevation in efficacy – but also in relation to the size of the (potential) patient populations and – more importantly – the number of healthcare systems that can actually afford to approve biologics for use.

Similarly, the protocols of almost all global healthcare systems are predicated on the use of cheaper small molecules as first-line therapies. Unless a disease is exceptionally rare and/or no other therapies exist, it is highly unlikely that biologics would be used initially. Other issues with large molecules, such as the challenges of reproducible manufacturing and the lack of capacity for manufacturing certain classes of biologics, are easier to solve, but changing the majority of the world's healthcare providers' protocols for their prescription would appear to be a greater challenge for drug companies.

Perhaps the biggest "threats" to the rise of biologics are not the size of patient populations or their manufacturing cost, but from the continued development of new small molecule therapies. The increased use of AI in drug discovery is leading to an explosion of new candidates being developed, and advances in manufacturing techniques mean that targets that were once considered either inaccessible – or at least uneconomical to produce at scale – are becoming viable. Similarly, the safety profiles of new small molecule drugs are significantly improved from those developed 20-30 years ago because of a much deeper understanding of the pharmacokinetics and better manufacturing processes, allowing the synthesis of exceptionally pure materials with a very high degree of reproducibility and control.

Although biologics have the potential to bring significant benefits to patients, the likelihood is that these will be unevenly distributed. Ultimately, despite many opinion pieces over the years claiming the opposite, small molecule therapies will be with us for the foreseeable future, and will almost certainly continue to be used as first-line therapies for the next 10 years. In the vast majority of global medicine, small molecule therapies are likely to be the sole therapy used in a patient's treatment, with biologics being more a medicine of last resort – and depending upon the nature of healthcare systems and payors.

So, although I have no doubts that pharmaceutical companies will continue to invest heavily in large molecule research and development over the next 10 years, I would prefer that, rather than eulogizing over the benefits of these therapies, perhaps the focus should be more about developing safe, effective medicines that can be accessed by the widest range of patients and, in the short to medium term, these will likely to be traditional small molecules.

Want to read more views on the future of pharma? Check out: themedicinemaker.com/the-multifaceted-future-of-pharma

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The Status Quo of Oligonucleotides Is Not the Future

The science of oligonucleotides is advancing, and advanced manufacturing techniques are needed to optimize their impact

Historically, oligonucleotide therapies have targeted small patient populations with rare conditions, but with excitement growing in tandem with the potential of the treatments themselves, innovators are looking to target indications with larger numbers of patients.

When one particular company was looking to optimize a manufacturing space for oligonucleotide manufacturing, Asahi Kasei Bioprocess (AKB) and CRB were invited to offer expertise in terms of the floor design and process equipment. The focus of the project: improving quality, purity, and output, while minimizing environmental impact. Here, AKB Vice President of Operations Brian Crawford and CRB Process Engineer Doug Chritton tell us more.

What are the big trends in oligonucleotide manufacture?

Doug Chritton: CMOs are building out capacity to support these drugs and capacities are also being boosted on the clinical side with an eye to even larger throughput in the future. There's also interest in advancing production techniques. The traditional way of building a molecule – one nucleotide at a time on solid phase supports – is no longer the best approach; it uses a lot of solvents, isn't sustainable, and isn't designed to produce quantities to suit the demands of a large patient population. We're now seeing a push for enzymatic synthesis to link molecules and reduce the number of harmful chemicals and flammable liquids, while also increasing yield.

For example, if a 20 nucleotide long oligo product (20-mer) is 98 percent effective at every linkage, you have around a 67 percent yield, which isn't great but is acceptable for drugs targeting small patient populations. As we look at longer chains and larger populations, however, that yield becomes less feasible. A 100-mer, for an application such as a guide RNA for CRISPR therapies, may only have around a 13 percent yield. These longer chain molecules aren't necessarily targeting large patient populations, but would still benefit from enzymatic production methods and improved yields. There is also room to improve other manufacturing steps. Advanced drying techniques, such as spray drying, are seeing increased attention, as are enhanced purification methods.

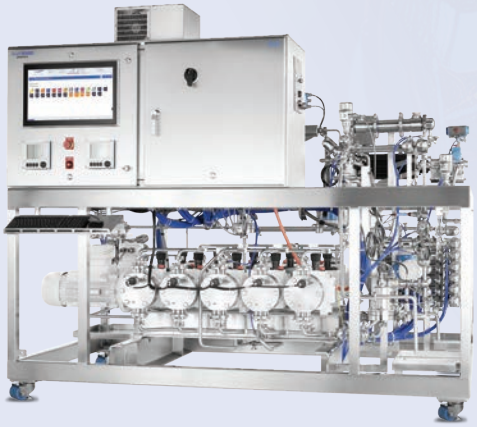
The industry is recognizing that the status quo is not a sustainable production approach if we need large quantities of oligonucleotide therapies in the future.

What are the main challenges in optimizing a manufacturing space for oligonucleotides?

Brian Crawford: The oligonucleotides field is booming, but there is a dearth of experienced personnel for this emerging modality. And it is always a challenge to outfit a facility for current state-of-the-art manufacturing methods, while also considering and building flexibility for future manufacturing advances. It is important to keep advanced methods in mind. Whether enzymatic processes, liquid phase synthesis, building the sequences with nucleotide triphosphates rather than phosphoramidites, there are all kinds of advanced manufacturing techniques that could be employed to solve the current challenges being seen in oligo manufacturing.

You are also best finding a partner who is familiar with the challenges. There are many aspects to consider – and many timelines must converge – to get a new manufacturing space qualified and ready to go. You must consider local government permits, inspections timing, associated utility supply and piping, HVAC, qualification, construction of warehouse space and storage, supporting labs for product testing and clearance, and more. Simply ensuring that essential equipment can fit into elevators, through halls and corridors, and into the appropriate room is often overlooked!

Collaborating with an experienced partner brings familiarity and expertise in navigating all challenges. Scale up is not always about making everything bigger. The emphasis should be on increasing throughput, yield, and purity, which can increase the amount of product manufactured without requiring infinitely scalable machines.



How does the complementary expertise of both companies come together in the project in question?

DC: CRB was initially asked to perform a small gap analysis for a client involving an oligonucleotide project, including a review of the facility and potential improvements, and then was hired to design support systems, such as solvent supply, reagent supply, buffer preparation, and waste handling systems. AKB was tasked with providing a large portion of the process equipment. Both companies worked closely together to ensure the equipment fit the facility and supported the needs of the client.

Even before this project, we already had a collaborative relationship where we would often share trends and help each other understand what clients need and want.

BC: AKB and CRB are aligned in solving shared customers' manufacturing challenges in a way that drives the industry forward. On this project, we were selected as the equipment supplier for three of the manufacturing lines. Our history with CRB was advantageous because they already had experience with our equipment, understanding how we can tie it into the plant-wide controls and ancillaries that feed manufacturing processes.

What were some of the big discussion points in the project?

BC: There were discussions around how the customer wanted to approach the plant-wide controls for data management, including considerations for the future, such as further automation, industry 4.0 initiatives, and space planning. Indeed, a great deal of space planning went into the design of our oligosynthesizer, our UF/DF systems, and chromatography purification systems to make sure that they fit into the vision for the customer.

DC: In oligo facilities, handling corrosive halogenated waste is a huge discussion point. If you put the deblock or detritylation reagent undiluted into a stainless-steel piping system, then you'll have issues with corrosion. It's a very hazardous safety and environmental issue. Halogenated waste is a small portion in comparison, so evaluating the trade off is something that needs to be weighed carefully.

What will define the success of this project?

BC: Thus far, the project has been a success in that we've been able to handle shifting priorities and keep everything on-track or ahead of schedule. The real success will be defined by the customer when their first batches of clinical and process-scale oligonucleotides are complete. From an equipment standpoint, we know we're on track as two full pilot scale trains are installed and qualified. The process scale train is currently in validation testing and everyone is very happy so far! We do recognize, however, that this is just the start. We're now shifting focus to operator training and setting them up for success prior to production. The aim is to contribute as much as we can by ensuring the equipment is set up optimally and ready to run.

What are your top tips for optimizing an oligonucleotide manufacturing space?

DC: For contract manufacturers, flexibility is key. Don't design your facility by honing in on existing processes; 5–10 years down the road, you will need to either add, change, or modify your equipment and facility. Think about how you can accommodate that by planning, planning, and planning some more! Consider not just the process, but the entire operation.

BC: I agree. Knowing what the ideal use case is and planning for change over time is important. Keeping operations in sequence, thinking about critical interfaces between the building, the operator, and the ancillary support systems are also key focal points. At AKB, we focus on developing systems for these challenges that also save down-time, floor space, and drive up the production capacity for customers.

What are your thoughts on the future of oligo drug development?

BC: I'm excited because of what these treatments represent. Rather than palliative or symptomatic treatments, oligos can be curative – whether through gene silencing or RNA interference. There are many developments targeting rare diseases that have no treatment, but it's also exciting to think about using oligos in diseases with potentially hundreds of millions of patients.

We're also seeing more breakthroughs in effective delivery to tissues and we will see more approvals in the future. The status quo will be pushed to one side; the state-of-the-art will be pushed further. It's exciting, on a professional level, to be able to contribute and help drive the field forward.

When it comes to manufacturing, I don't think there will be a single, golden manufacturing approach. It will likely be hybrid – or possibly something new that hasn't been considered yet. But whatever the approach, it seems clear that there will be an emphasis on larger scales, greater efficiency, and improved sustainability.

DC: Oligonucleotides with conjugates is really exciting. New targeting ligands are starting to unlock parts that have been difficult to treat; access to these targets will create new treatment options. By conjugating to an oligonucleotide, we can harness a long duration of action or potential curative action to treat diseases with unmet needs. As we find more conjugates, the oligo targets will diversify to other organs too, resulting in even faster growth of the market segment.

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"After completing medical school and my first doctoral degree, I started my medical training in general medicine and nephrology."

Let's Make a Real Difference in Cancer

Sitting Down With… Lars Erwig, Director of the Centre of Drug Development at Cancer Research UK

What first inspired your interest in drug development?
It all started with my mother being diagnosed with cancer, undergoing several years of treatment and ultimately dying of cancer when I was 11 years old. It led me to pursue a career as a medical doctor with the ambition to develop new medicines. I studied medicine in my hometown of Hanover in Germany and began my research career with a fellowship in the US, studying oxygen transport, while I was a medical student.

After completing medical school and my first doctoral degree, I started my medical training in general medicine and nephrology. My research focused on the innate immune system and the role of macrophages in inflammation. My clinical focus was on multisystem immune diseases such as lupus and vasculitides.

And what led you to the role at Cancer Research UK's Centre for Drug Development?
I started to conduct clinical trials in addition to my basic science laboratory work – and I was increasingly exposed to the pharmaceutical industry. After contributing as a consultant to the development of a novel treatment for lupus, I gave up my academic career and joined GSK. Next, I became the CMO of a joint venture between GSK and Google, developing implantable devices to treat autoimmune diseases. For the last four years, I worked for Johnson & Johnson, trying to find new promising therapies in academia and biotech, with the aim to accelerate pharmaceutical development.

I joined Cancer Research UK as director of our Centre for Drug Development in February 2024. I want to use my experiences in academia and industry to develop more effective, tailored therapies that are better tolerated by patients. I want to help turn the great ideas from Cancer Research UK and our partners into clinical programs that are executed to the highest standard and make sure that they are partnered appropriately to set them on a path to benefit patients expeditiously. I also hope that we can turn our attention to some of the rarer, harder to treat types of cancer.

How much of the clinical trial burden in rare indications falls to non-profit? Is there a lack of interest from pharma companies?
There is a much lower financial incentive to develop treatments for rare indications; the challenge of recruiting from smaller patient populations pushes up the development costs, and the limited market size makes it even harder to recoup that cost. Orphan drug designation and other regulatory measures encourage more investment in rare diseases, but there is still a gap in available treatments. Non-profit organizations are crucial to filling that gap. If we do not fund these trials, no one else will.

How are non-profits partnering with one another to ease the pressure?
Cancer Research UK is one of the only cancer charities in the world that has established an in-house drug development facility capable of executing early-stage clinical trials with standards fit for regulatory approval downstream. It is essential that high-quality research funded by non-profits can be translated into benefit for patients. We need to expand the capabilities of the Centre for Drug Development to make sure that, through collaboration with other non-profit funders, patients across Europe can access our most transformational trials.

We initiated partnerships with KWF Dutch Cancer Society in November 2023 and the Norwegian Cancer Society in March 2024. These are two leading cancer research charities that share Cancer Research UK's patient-first vision of developing treatments. The partnerships allow us to pool patients, resources and expertise, taking the most promising breakthroughs in our respective research networks through to the clinic where together we'll have access to more trial sites and patients.

The groundwork for these partnerships began long before I joined the Centre for Drug Development, but I can already see the power of this collaboration model and am committed to expanding our partnerships further.

What other success stories can you tell us about?
The first trial under the partnership with KWF focuses on improving radioligand therapy outcomes for children with neuroblastoma, a rare cancer that accounts for around 6 percent of total childhood cancer diagnoses. This is a follow-on trial to a previous Cancer Research UK-sponsored study (NCT02043899) that, despite promising results, couldn't progress because of a loss in manufacturing capabilities within the UK.

With the wealth of nuclear medicine expertise in the Netherlands and extra funding from KWF to support a clinical trial, we can continue working towards this unmet need. The trial will be led by University College London in the UK and the Princess Máxima Center in the Netherlands. It would not have been possible without our partnership with KWF.

What call to action would you make of pharma?
Promising compounds in pharma companies are frequently discontinued for limited commercial value, particularly in rare and pediatric cancers. We may be able to take these molecules forward because we define value differently in a non-profit organization. If we can partner with big pharma to advance these compounds and de-risk them in the process, they may reach a threshold that enables regulatory approval and direct patient benefit. We are not always aware of these compounds sitting on companies' shelves and I would urge pharma companies to reach out.

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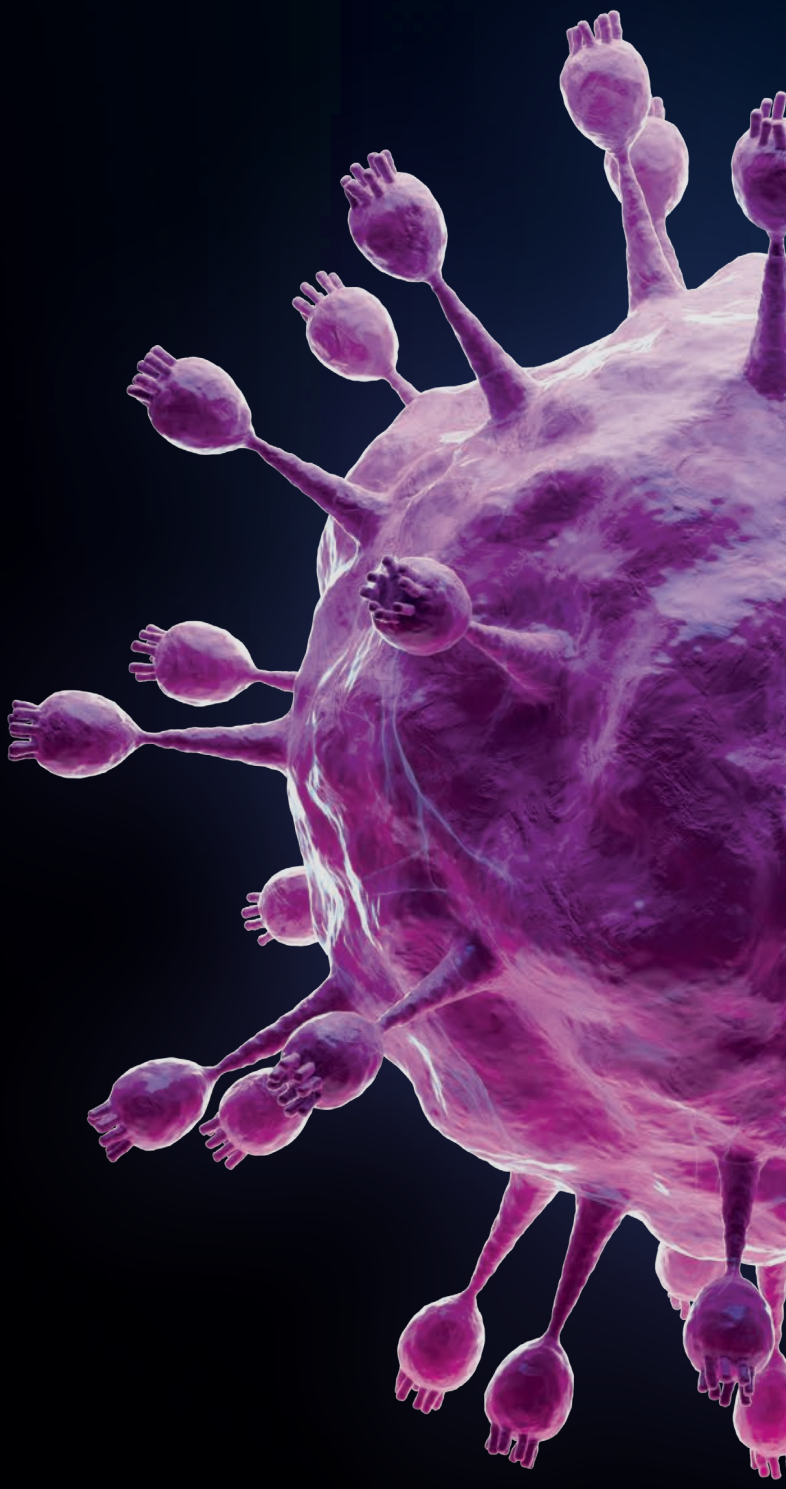

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