Autumn 2025
#103

the Medicine Maker™

A Straightforward Process? Think Again

How much do you know about the complexities of the fill-finish step and the cost of mistakes?

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To be in the running, the technology must commercially launch (or be planned for launch) between November 1, 2024 and December 31, 2025.

Nominations will be open until **November 7, 2025.**

Access the nomination form at:
www.smartsurvey.co.uk/s/TCSP3N
or scan the QR code for more details.

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The Power List Personified: Getting to Know Kiran Mazumdar-Shaw

Learning more about the people behind the Power List 2025

Featuring Kiran Mazumdar-Shaw, Chairperson, Biocon Group

What inspired you to work in biopharma?

From the outset, I was driven with the purpose to harness the power of science to create meaningful benefits for society. I was inspired to work in drug development because I saw first-hand the stark inequities in global healthcare as life-saving medicines were often out of reach for those who needed them most. This was unacceptable to me.

Tell me about the most important or interesting project you've worked on...

I led the development of a groundbreaking bifunctional fusion protein antibody for solid tumors, currently in phase II/III clinical trials in the US. This first-in-class bispecific antibody targets both EGFR and TGF-β, overcoming limitations of existing therapies by directly inhibiting tumor growth and enhancing immune response. Initially incubated in India, this innovation is now advanced by Bicara Therapeutics, which Biocon founded in the US. This journey underscores the potential of Indian scientific innovation in global healthcare, demonstrating that with the right support, we can make a significant impact in oncology.

What's the most exciting trend or modality in the industry right now?

The convergence of biotech with AI-driven insights is transforming the way we develop and deliver medicines. AI and machine learning are accelerating target identification, predictive modeling, and clinical trial efficiency, helping us bring novel therapies to patients faster and at lower costs.

Another shift is the rise of precision medicine and advanced therapies, which are moving us from symptomatic treatment to curative solutions, especially in areas like rare genetic disorders, cancer immunotherapy, and regenerative medicine.

How can we attract more talented scientists to the field?

Through a fundamental shift in how we position this field. Instead of just being a career path, it should be projected as a mission-driven pursuit with the power to change lives. For young scientists, we need to showcase biopharma as a force for good. By integrating AI, machine learning, computational biology, and data science into biotech research, we can make the field more attractive to talent from computer sciences, engineering, and mathematics, who may not have otherwise considered a career in life sciences.

Make a prediction for the far-flung future of the industry that may seem like science fiction but could one day be a reality...

Imagine a world where precision medicine predicts an individual's disease risk at birth, allowing for customized health strategies. AI-powered biochips will monitor health markers in real-time, providing early alerts and triggering targeted therapies. We'll see the emergence of "living medicines" – self-evolving therapies that adapt to the body's needs, alongside bioengineered robots that repair cells and combat aging. Medicine will become fully personalized, tailored not just to DNA but to microbiomes and environmental factors. In this new era, healthcare will focus on engineering wellness rather than managing illness. The rapid convergence of biotechnology, AI, and quantum computing is accelerating this transformative journey, making what seems visionary today the foundation of tomorrow's healthcare revolution.

Check out the full 2025 Power List at www.themedicinemaker.com/power-list/2025/

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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.

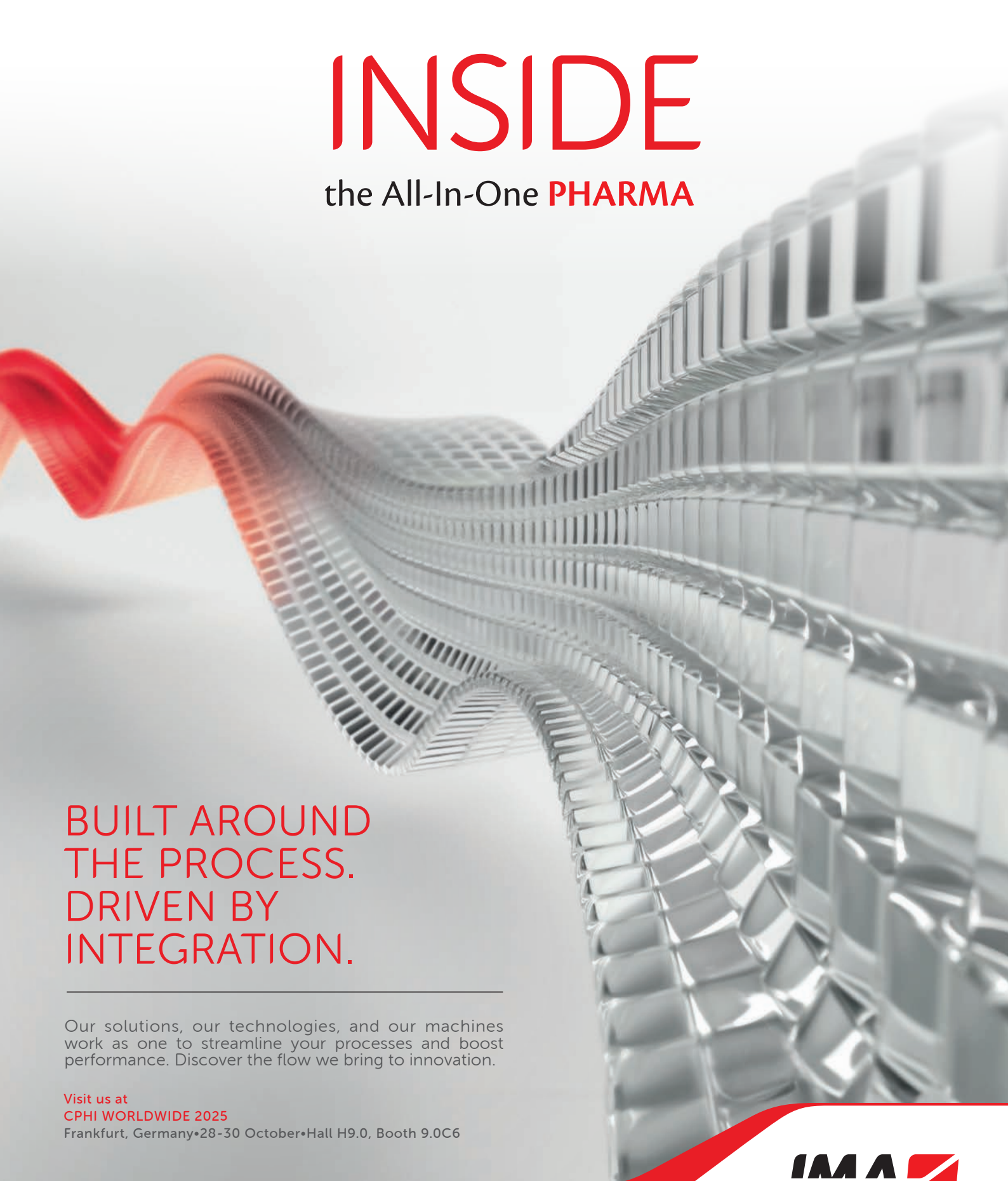
Finally, choosing a track-and-trace vendor that exhibits good practices and provides low-carbon footprint solutions is essential. The quality of the solution is vital for sustainability; otherwise, there is high wastage due to production line upgrades. Today, consumers and brands demand transparency, 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.

INSIDE

the All-In-One **PHARMA**



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Fill-Finish: *The Easy Step? Think Again.*

Mistakes in fill-finish can lead to lost batches, lost profits, and increased regulatory scrutiny. It's crucial that this important step gets the attention it deserves. Four experts discuss.

How much attention do you pay to the fill-finish process? And how much do you know about its importance?

The fill-finish step is the final and one of the most critical stages of the production process, where the drug product – often a sterile liquid – is transferred into its final container, such as a vial, syringe, or cartridge. For lyophilized drugs, the liquid is filled into the container and then freeze-dried in place. This step must be carried out under highly controlled and sterile conditions to ensure the product remains uncontaminated and safe for patient use. Once filled, the containers are sealed, labeled, and packaged, completing the product's journey from formulation to distribution.

Sounds simple, doesn't it? However, it's a very complicated process that can have serious consequences if anything goes wrong. Additionally, because fill-finish requires specialized facilities and equipment, it can become a bottleneck in production, especially during times of high demand or rapid product launches.

Here, four experts walk you through why fill-finish is so important and offer their best practices for success.

What is the general perception of fill-finish activities? Is this step sometimes overlooked or underappreciated in its complexity?

Hanns-Christian Mahler: Sterile drug product manufacturing is absolutely underappreciated and overlooked. You can even see it in the term "fill-finish." Many assume that the process is just about filling a solution into a container – and how difficult can that be?! The answer is that it is a very important and challenging process. Many companies have experienced major crashes and issues during fill-finish, leading to project delays or even company failures.

Madhu Raghunathan: Drug substance manufacturing, which precedes the fill-finish step, is a complicated process, especially when it comes to biologics. In comparison, fill-finish can be seen as a simpler process with less complexity, but there are many technical aspects to consider to ensure quality, sterility and safety.

During fill-finish, the API is usually diluted with sterile water for injection followed by the addition of excipients and a final adjustment to the pH level. After the final steps of the formulation process and before final filling into sterile containers, sterile filtration takes place. Here, it is essential to maintain and monitor the integrity of the sterilizing filter. Contaminants are a threat along the entire process, so the use of appropriate infrastructure, equipment, manufacturing controls, inspection methodologies, and quality protocols are essential to ensure sterility of the drug product.

Meet the Experts

Hanns-Christian Mahler, CEO and board member at ten23 health

Kelly Christiansen, VP, Drug Product Operations at Grand River Aseptic Manufacturing

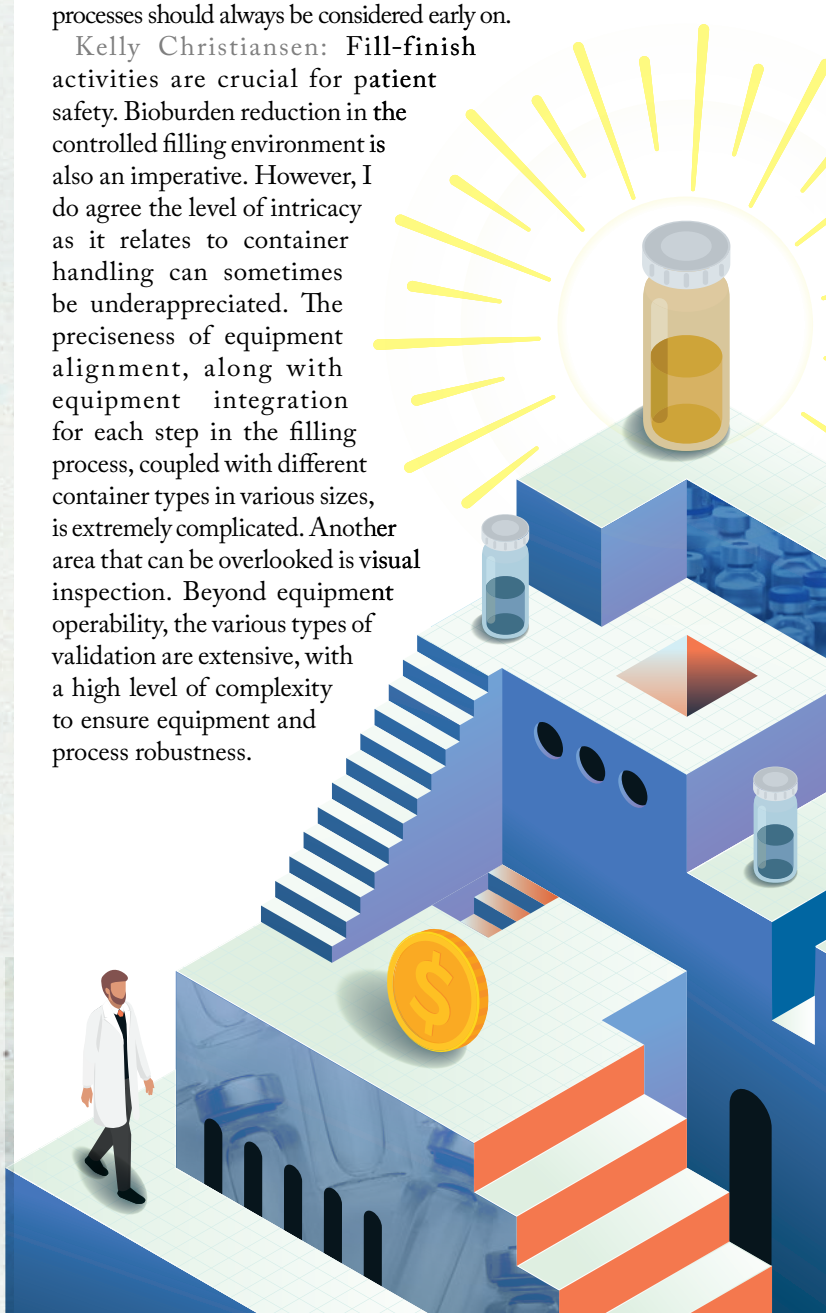
Josh Russell, VP, Technical Sales at AST Inc

Madhu Raghunathan, Senior Director of Business Development and Market Strategy at West Pharmaceutical Services

Any mistakes in fill-finish can lead to very costly outcomes, or even loss of an entire batch. It is very important to give fill-finish the appreciation and focus that it deserves.

Josh Russell: The broader pharma manufacturing industry takes fill-finish activities extremely seriously, as evidenced by the recent revisions of Annex 1 and the adaptations the industry has made to ensure compliance and improve overall quality outcomes. However, it is also true that fill-finish can be underappreciated by some companies, particularly during the early stages of clinical development or clinical trial manufacturing. The focus is often on the product and container, rather than the filling process itself, which can result in downstream manufacturing requirements becoming more difficult to automate at the commercial scale in an aseptic drug product environment. Commercial manufacturing and aseptic production processes should always be considered early on.

Kelly Christiansen: Fill-finish activities are crucial for patient safety. Bioburden reduction in the controlled filling environment is also an imperative. However, I do agree the level of intricacy as it relates to container handling can sometimes be underappreciated. The preciseness of equipment alignment, along with equipment integration for each step in the filling process, coupled with different container types in various sizes, is extremely complicated. Another area that can be overlooked is visual inspection. Beyond equipment operability, the various types of validation are extensive, with a high level of complexity to ensure equipment and process robustness.



What common issues can occur in fill-finish, particularly in less experienced companies?

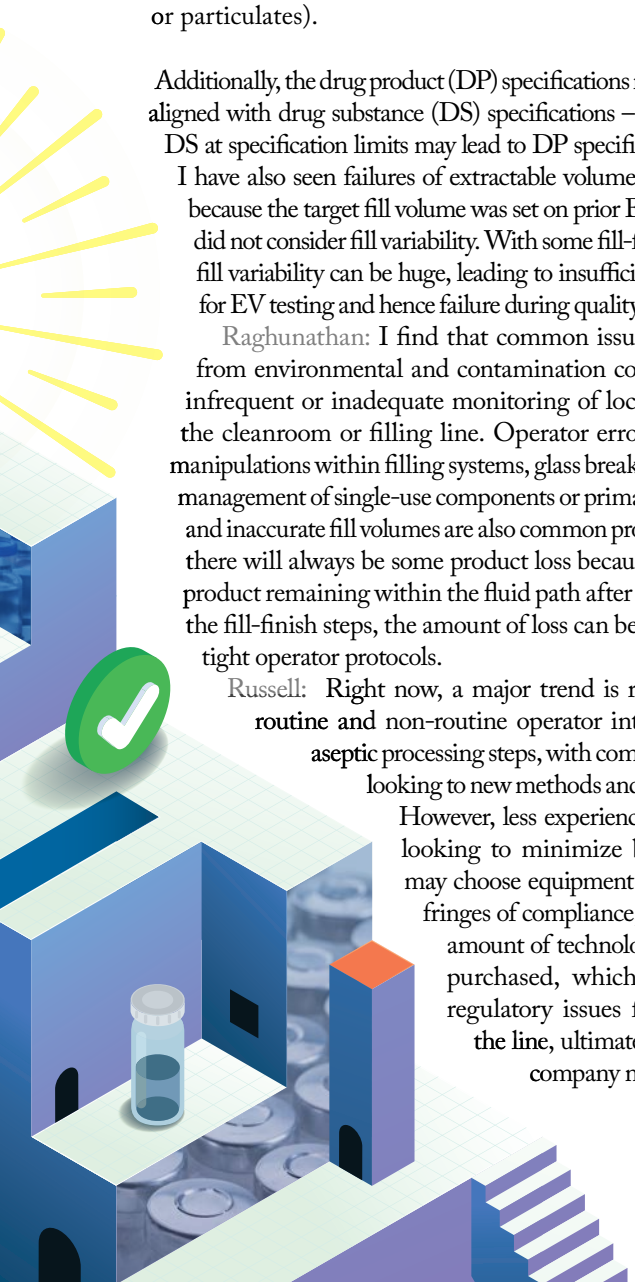
Mahler: Inadequate formulations or processes that were not properly assessed or developed can cause numerous issues. Common problems include:

- product instability (e.g., aggregation or precipitation of APIs during mixing or pumping/filling)
- material adsorption (from disposables or filters)
- evaporation of critical excipients (e.g., polysorbates, preservatives) leading to batch inhomogeneity
- product contamination because of processing materials used (e.g., disposables)
- environmental contaminations (e.g., microbiological or particulates).

Additionally, the drug product (DP) specifications must be closely aligned with drug substance (DS) specifications – because using DS at specification limits may lead to DP specification failures. I have also seen failures of extractable volume (EV) for DP because the target fill volume was set on prior EV studies that did not consider fill variability. With some fill-finish facilities, fill variability can be huge, leading to insufficient fill volume for EV testing and hence failure during quality control (QC).

Raghunathan: I find that common issues often stem from environmental and contamination control, such as infrequent or inadequate monitoring of locations within the cleanroom or filling line. Operator errors from open manipulations within filling systems, glass breakage, improper management of single-use components or primary packaging, and inaccurate fill volumes are also common problems. While there will always be some product loss because of the drug product remaining within the fluid path after completion of the fill-finish steps, the amount of loss can be reduced with tight operator protocols.

Russell: Right now, a major trend is reducing both routine and non-routine operator interventions in aseptic processing steps, with companies instead looking to new methods and technologies. However, less experienced companies looking to minimize budget spend may choose equipment that is on the fringes of compliance, or reduce the amount of technology or systems purchased, which can lead to regulatory issues further down the line, ultimately costing the company more.



"There are three essential legs to the aseptic manufacturing stool: well-trained operators, clearly defined and robust procedures, and built-for-purpose facilities."

What are the most important best practices and considerations during fill-finish?

Raghunathan: Overarching best practices should include continuous and rigorous aseptic training for operators, a robust risk assessment, intervention protocols to identify and handle process risks and deviations, use of quality by design methodologies, and strong adherence to quality controls and procedures.

From an infrastructure and equipment perspective, I suggest the use of robotics and automation techniques to minimize operator intervention, use of ready-to-use packaging components, strong raw material assessment/management programs, implementation of continuous testing methodologies to ensure equipment and consumable adherence to pre-established thresholds, 100 percent in-process (non-destructive) weight checks, and fully automated visual inspection.

Russell: There are three essential legs to the aseptic manufacturing stool: well-trained operators, clearly defined and robust procedures, and built-for-purpose facilities. All three must come together to produce the highest quality drug products. Operator training, both in terms of aseptic techniques and operating today's sophisticated manufacturing systems, is essential. Equipment and control systems that emphasize best practices and minimize interventions or the chance of errors should be used to reinforce good operator training.

Christiansen: The three elements from my side are first, operational discipline, including following procedures, work instructions, and batch records, using good documentation practice principles with every step of the process. Second, attention to detail. Examples of this are listening to

equipment for potential unusual noises, verifying all 10 digits of an item number instead of the last three or four, and verifying the expiry date, including the year, for accuracy. Third is an operational excellence program that drives continuous improvement culture with the use of Lean Six Sigma principles.

Mahler: I would add that it's important to think about the drug product process holistically, from formulation to the manufacturing process, to testing, and QC. Prior knowledge and expertise can help to mitigate potential issues. This includes developing formulations appropriately; choosing process unit operations and related operating ranges wisely; and ensuring testing and QC specifications align with drug substance.

"Remote support and the ability to diagnose problems in real time, especially for products that have tight windows for filling, is a major advantage."

What separates good fill-finish equipment from average equipment (or bad equipment)?

Russell: Isolator technology is a key operational differentiator and is seeing rapid adoption within the fill-finish production space. Isolators provide an enhanced safeguard of the aseptic environment by fully enclosing the aseptic process, which also has the advantage of reducing the overall facility footprint. Additional considerations include technologies such as automated environmental monitoring and material handling, and real-time process feedback, such as advanced in-process weight checks.

Ease of maintenance and strong support from your equipment manufacturer are also critical to ensuring that a good fill-finish line stays running at its best. Remote support and the ability to diagnose problems in real time, especially for products that have tight windows for filling, is a major advantage.

Christiansen: The industry has turned to isolators or restricted access barrier systems (RABS) technology to reduce or eliminate human interaction with the aseptic filling environment. Additional advanced features include 100 percent fill-weight verification technology, missing and replacement stopper technology to reduce waste, and cap placement vision system technology to reduce defects at the point they are created by stopping the equipment. On the finishing side, automated inspection equipment promotes consistency and repeatability, and serialization to prevent counterfeiting.

Mahler: It is not about single pieces of equipment; sterile drug production should be a concept. A filling machine itself must obviously be designed to ensure appropriate airflows and to protect the product from any potential contaminations, while at the same time ensuring desired product parameters such as fill volume and precision. You need to take great care to consider the whole concept. Do you use isolator technology or the more outdated RABS technology? How do you design your facility? And what is your contamination control strategy? These are all very important questions to ensure everything runs smoothly.

Looking for more fill-finish insight? Check out part 2 of this discussion online

Understanding the Importance of Low Endotoxin Gelatin

Innovation in gelatin-based materials engineering is helping biopharma manufacturers reduce costs and increase compliance; here's how

By Martin Junginger, Global Category Manager Pharma & Bioscience at GELITA AG.

Gelatin has been used in hemostatic procedures for over 80 years, gaining popularity during WWII for frontline battlefield use. It has since become a staple in the medical device industry – an industry that tends to be conservative when it comes to radical changes. With over 20 years of experience in the field, I've seen how innovation often takes the form of incremental improvements.

Of course, other materials are available, but they tend not to be as versatile, easy to handle, or as effective as gelatin. Hence why gelatin remains a preferred choice for healthcare professionals. It's a tried-and-tested technology that continues to advance. We're seeing developments where gelatin is combined with other substances, such as chitosan, a hydrogel polymer, or fibrinogen, a key player in blood clotting. At Gelita, we've worked on plasma-activated surfaces using ionic gases, further enhancing the material's effectiveness. These are highly impactful changes.

When applied to a wound, a gelatin sponge initiates a biomechanical response by rapidly absorbing fluid and concentrating platelets to speed up clotting. Once wet, the sponge becomes pliable, conforming to the wound's shape while applying gentle pressure. This activates the body's natural clotting cascade, leading to fibrin formation – much like a cork sealing a bottle. As a protein derived from mammalian collagen, gelatin is extremely biocompatible, making it ideal for medical use. It's also biodegradable and can be safely left in the body after surgery. To ensure optimal safety and performance, Gelita maintains rigorous manufacturing standards and quality control protocols, especially when working with natural raw materials like bones, hides, and skins.

Gold-standard quality

With gelatin, it is important to control endotoxins, which, particularly from gram-negative bacteria, can cause fever and complications. Although we can't eliminate these bacteria completely from gelatin, because they exist naturally in animal raw materials, we can suppress their growth. Through the use of clean production environments, sustainable and traceable fresh raw materials, and carefully selected treatments that mitigate bacterial proliferation, we can ensure high-quality production processes, with quality checks implemented throughout the production cycle. Our MEDELLAPRO® line, for example, focuses on endotoxin-controlled excipients. A high purity, endotoxin controlled pharmaceutical grade gelatin that replaces human tissue grafts in blood clotting sponges, implants, wound dressings, bioprinted scaffolds, by nature and drug delivery, MEDELLAPRO® offers exceptional biocompatibility and minimal allergenic risks.

For other uses, such as vaccine stabilization, we produce shorter protein molecule chains under the VACCIPRO® brand. These collagen peptides are often used for vaccine stabilization – trusted by leading manufacturers, VACCIPRO® has been key in multiple vaccine developments. With ultra high purity, precise molecular weight control, low allergenic potential, and exceptional biocompatibility, VACCIPRO® complies with FDA standards. It is the gold standard scaffold for safe, stable liquid, and lyophilized vaccines.

For both, MEDELLAPRO and VACCIPRO, Gelita also ensures traceability according to the related ISO standard. For our products produced in US, we maintain a Drug Master File with the FDA, which our customers can link to their own documentation during regulatory submissions. This kind of support is a distinctive aspect of our approach.

The future of gelatin science

Gelatin's gelling strength can be fine-tuned, much like you can adjust the firmness of jello or gummy bears. We can therefore produce gelatin that can be used to coat surfaces, or as a nutrient medium in labs for cell culturing. We provide gelatin powder suitable for any use. Our customers can dilute and process the material to suit their own requirements and, from previous experience in manufacturing sponges, I know how the porosity and absorbency properties significantly impact performance. Achieving consistency in pore size, softness, and pliability is a form of art.

As a chemical engineer with patents in wound healing systems, and having observed the deep gratitude of patients for the use of well designed products, that's the kind of expertise that motivates me – and it aligns perfectly with Gelita's mission to improve quality of life for those that need our products.

It's true that the core gelatin technology has not seen many radical changes over the years. Incremental changes, however, are happening. The industry is looking for alternatives to animal-derived materials, for example. Gelita is addressing this trend by biotechnologically developing a recombinant collagen protein using modified yeast, which also qualifies as a non-GMO product. Small batches will soon become available for trials. In this way, Gelita is at the forefront, engineering the future of hemostatic materials, tissue engineering, artificial organs, and vaccine stabilization.

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The Front Lines of *Tuberculosis Vaccine Research*

There has been no new TB vaccine for over 100 years, but a candidate at the Gates Medical Research Institute in phase III recently enrolled the target of 20,000 participants


Alemnew Dagnew

"For me personally, this project is very close to my heart. I spent about a decade at Novartis and GSK, and I've brought that experience to Gates MRI to focus on diseases that disproportionately affect underserved populations and present significant challenges to global health. It's an exciting time. This project means a lot to me, not only because of its scientific importance, but because of its potential to make a difference in the lives of millions."

Alemnew Dagnew grew up in Ethiopia and saw firsthand the impact of tuberculosis (TB) on the community. Today, he works at the Gates Medical Research Institute (Gates MRI) and is leading the clinical development of a new TB vaccine candidate, which is in phase III and earlier this year finished enrolling the target of 20,000 participants across 54 sites in five countries.

TB is the world's deadliest infectious disease, with around 1.25 million people dying from TB in 2023, according to statistics from the World Health Organization. TB has been affecting humans for thousands of years, but there is only one vaccine available: the BCG (Bacillus Calmette-Guérin) vaccine, which was developed in the early 1900s.

We spoke with Dagnew about why TB research is so scientifically challenging, and the progress being made with the new vaccine.

What is your background and how did you get involved with vaccine research?

I'm originally from Ethiopia, which is one of the high-burden countries for TB. During my time as a medical student, and later while practicing medicine, I saw firsthand the devastating impact TB has on communities.

TB disproportionately affects people from lower socioeconomic backgrounds. As a young physician in Ethiopia, TB was one of the most common conditions we encountered. The burden was – and still is – immense.

I eventually transitioned into the pharmaceutical industry. I spent about a decade at companies such as Novartis and GSK, working on various vaccines. In 2020, I had the opportunity to join the Gates MRI. For me, this was more than just a job; it felt like a way to give back to the communities I came from. Working on a TB vaccine here gives me a chance to contribute to something with the potential for real global impact. It keeps me motivated every day.

Why is TB such a challenging disease to develop new vaccines?

The current vaccine – BCG – has been in use for over 100 years. The challenge with BCG is that while it can provide protection against severe forms of TB in young children, such as TB meningitis, it offers little to no protection against pulmonary TB in adults. This is a key issue because it's adolescents and adults with pulmonary TB who are primarily responsible for transmitting the disease.

The vaccine candidate that we are working on at Gates MRI is focused specifically on preventing pulmonary TB in adolescents and adults. If it works, the impact could be enormous, both in terms of saving lives and reducing transmission.

As for why TB has been such a stubborn disease to tackle with vaccines; there are several reasons. First, Mycobacterium tuberculosis (Mtb), the bacterium that causes TB, has been co-evolving with humans for thousands of years. It's been around since ancient times. Evidence of TB has even been found in Egyptian mummies. Because of this long co-evolution, the TB bacterium has developed very sophisticated ways of evading the human immune system.

Even today, our understanding of the immunology of TB remains incomplete. Significant gaps persist in our knowledge of how the immune system responds to Mycobacterium tuberculosis, particularly in distinguishing protective from non-protective immune responses. This complexity makes it challenging to design a vaccine that offers robust and lasting protection.

Gates MRI is working on a vaccine candidate for TB. What work has been done so far?

The vaccine candidate is a recombinant fusion protein called M72, derived from Mtb antigens called Mtb32A and Mtb39A, combined with GSK's proprietary adjuvant AS01E. GSK worked on this vaccine for many years. Over the years, they've conducted multiple phase I and II studies to assess safety and immunogenicity across various populations.

The most recent of these was the phase IIb proof-of-efficacy study – the final study GSK ran before transferring the vaccine candidate to us. That study showed really encouraging results. The vaccine demonstrated an efficacy of 50 percent in preventing pulmonary TB in adults. The Gates MRI licensed the vaccine in 2020 to continue its development and registration in low- and middle-income countries should the phase III results be supportive.

Since the Gates MRI started work on the vaccine, one of the studies we've conducted focused on evaluating the vaccine in people living with HIV. The MESA-TB study was carried out at six sites across South Africa to assess both safety and immunogenicity in this population – given the high overlap between HIV and TB in many regions.

That study was recently completed, and the results helped

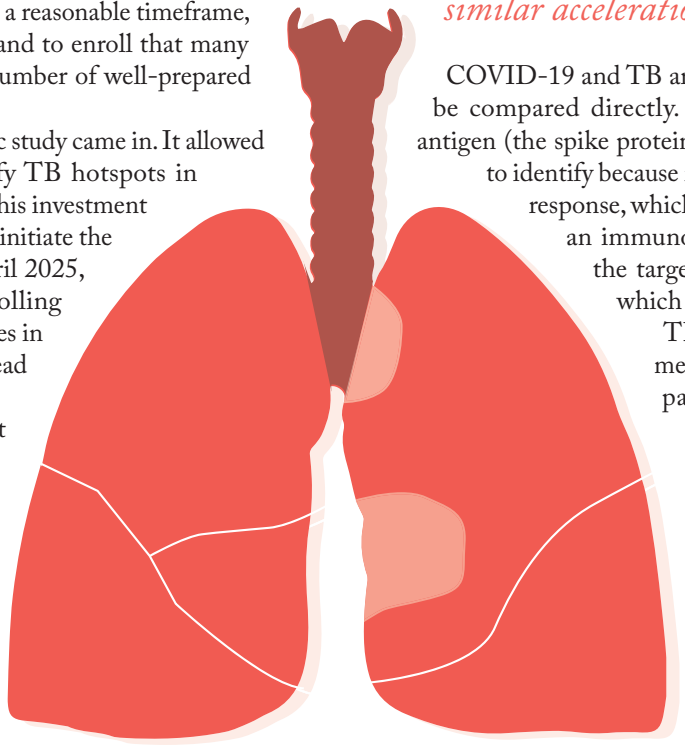
us make an informed decision about including more people living with HIV in our current phase III trial. The results of the MESA-TB study were recently accepted for publication in *The Lancet HIV*.

How have you prepared for phase III?

We conducted a large epidemiologic study across 14 countries and 45 sites as part of our preparation for the phase III trial.

TB primarily affects people living in low- and middle-income countries, so naturally, you have to conduct your phase III study in the regions where the disease burden is highest. But running large efficacy trials in those settings isn't easy. To complete a study of this magnitude within a reasonable timeframe, you need a large sample size – and to enroll that many participants, you need a large number of well-prepared clinical sites.

That's where the epidemiologic study came in. It allowed us to prepare sites and identify TB hotspots in advance of the phase III study. This investment paid off because we were able to initiate the trial in March 2024 and in April 2025, we reached our target of enrolling 20,000 participants across 54 sites in five countries eleven months ahead of schedule.



It's been a tremendous amount of work since we licensed the vaccine from GSK, and GSK has also been deeply engaged in preparing for vaccine manufacturing and scale-up. Our colleagues in Chemistry, Manufacturing, and Controls (CMC) have done an incredible job – not only to support phase III but to help prepare for eventual commercial supply, if the vaccine proves successful.

What have been those key moments where you and others started to get really excited about the prospect of success for this vaccine?

A trial with 20,000 participants is a major undertaking. Originally, we had planned to complete enrollment over two years, but we finished a year ahead of schedule, which was a huge and very exciting milestone.

This is an event-driven trial, which means we'll conduct the analysis once we've accrued 110 lab-confirmed cases of pulmonary TB. Reaching that event threshold is going to be a pivotal and emotional moment, regardless of the result.

Of course, I'm hopeful about the potential results. I'd love to see the vaccine replicate – or even surpass – the efficacy from the phase IIb study. At the same time, I recognize that the outcome is not something I can control. What we can control, however, is the quality of the trial conduct. We must ensure rigorous execution and a robust analysis that can support regulatory decision-making.

During the pandemic, a lot of COVID-19 vaccines were developed on vastly accelerated timelines. What is needed to allow vaccines for other important diseases to benefit from similar acceleration?

COVID-19 and TB are quite different, so they cannot be compared directly. With COVID-19, the target antigen (the spike protein) was relatively straightforward to identify because it elicited a neutralizing antibody response, which was linked to protection. From an immunological standpoint, identifying the target antigen was relatively simple, which allowed for rapid development.

TB is much more complex. As I mentioned earlier, it's a challenging pathogen.

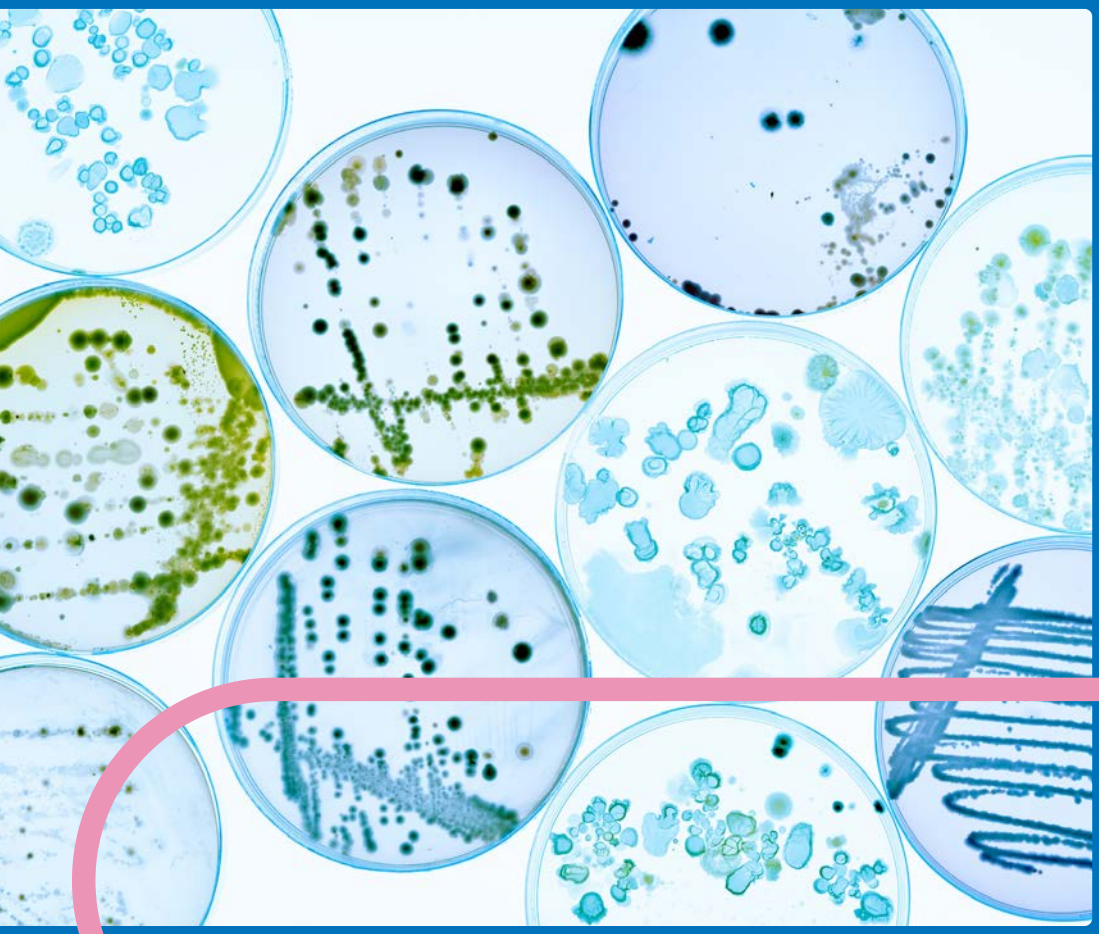
The phase III trial would not have been possible without the funding and support from the Gates Foundation and Wellcome. Their commitment made this large-scale effort feasible.

GSK also invested many years in the development of this vaccine. Even after we took the project over, we continue to work closely with GSK on technology transfer, manufacturing, and other aspects of development.

While TB remains a difficult pathogen, the experience has shown that collaboration across organizations, combined with sustained funding, can make accelerated development possible, even for tough diseases like TB.

Have you thought about the cold chain and other logistical challenges in delivering the vaccine?

The vaccine is a two-vial presentation. One vial contains the lyophilized antigen, and the other contains the adjuvant in liquid form. Before administration, the two need to be mixed. In terms



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of storage, the vaccine needs to be kept between two and eight degrees Celsius, which is standard for many vaccines. From a cold chain perspective, it's manageable and similar to existing vaccine products that are already being distributed globally.

There's a lot of work behind the scenes taking place in terms of preparing for vaccine access, implementation, and broader delivery planning. It's a major effort, involving many partners.

How do you hope that this work and the collaborative efforts involved can influence other projects?

Infectious diseases and health threats do not respect borders; they move with people, and the rise of antimicrobial resistance only compounds the challenge. TB might currently affect people primarily in low- and middle-income countries, but it's still a global issue. We've already seen recent examples of TB cases emerging in countries like the US.

Pharmaceutical companies can play a leading role in addressing global health challenges. Big pharma has a wealth of expertise, infrastructure, and talent. This vaccine is a strong example of what can be achieved through collaboration, and there's a real opportunity for companies to do more, whether it's through product development, sharing technologies, or supporting access initiatives. The partnership between GSK, Gates MRI, the Gates Foundation, and Wellcome is a model that others can follow.

Ultimately, the message is simple: collaboration works. If more organizations come together with a shared purpose, we can make a real difference in tackling diseases that continue to cause so much harm around the world.

Final comments?

This study is a massive undertaking, and it would not be possible without the dedication and collaboration of many. I'd like to express my sincere thanks to my colleagues at Gates MRI; the trial participants and their families; the Principal Investigators and site staff; our contract research organizations and vendors; the Independent Data and Safety Monitoring Board; the Community Advisory Boards; the Scientific Advisory Boards; Ethics Committees; Health Authorities; and our funders. I am especially grateful to the Gates Foundation and Wellcome for their critical funding support.

And of course, I want to acknowledge GSK, not just for developing this vaccine over many years, but for continuing to collaborate with us closely throughout this next phase.

For me personally, this project is very close to my heart. I spent about a decade at Novartis and GSK, and I've brought that experience to Gates MRI to focus on diseases that disproportionately affect underserved populations and present significant challenges to global health. It's an exciting time. This project means a lot to me, not only because of its scientific importance, but because of its potential to make a difference in the lives of millions.

I'm hopeful that the vaccine will prove effective, that it will be licensed, and that it will be used across the globe.

Bringing Velocity to Fill-Finish Lines

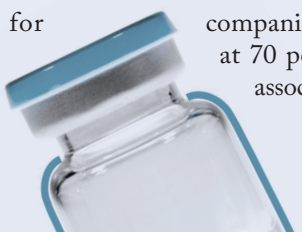
Find out how Corning® Velocity® vials can minimize flow disruptions, and improve efficiency and speed on fill-finish lines by reducing surface friction

There are many factors to consider when assessing the compatibility of a container for a drug product, but fill-finish is often where critical challenges arise.

When vials are prepared for use, heat used during depyrogenation can change the surface properties of the glass, making it what Matt Hall, Technical Affairs Director at Corning Pharmaceutical Technologies, refers to as "sticky." He explains, "This stickiness becomes problematic when vials meet each other, such as on the fill-finish line. They can jam or become scratched and damaged. This can lead to particulate being released (a leading cause of recalls) – and in some cases, cracking or breakage. When this happens, the entire flow of vials through the line can be disrupted."

Interruptions in the process typically require human intervention to fix, which then presents a risk to the sterility of the drug product. Beyond product risk, there's also the matter of cost and efficiency. This equipment is expensive to operate, so keeping it running smoothly and consistently is a top priority.

Corning® Velocity® vials have an exterior coating that improves how the vial behaves during processing by reducing friction, preventing damage, and enhancing handling. The coating is a polyimide-based material – renowned for excellent thermal and mechanical durability.



Corning Valor® and Viridian® vials are also equipped with Corning's low-friction external coating technology.

"The coating acts like a lubricant," says Rohit Kataria, Business Director at Corning Pharmaceutical Technologies. "The smoother movement helps reduce particulate generation and keeps the fill-finish line running with fewer interruptions. It's a small change with a big impact on consistency and safety. A company making the switch to Velocity can report the change in their annual report."

With some coating technologies, there is a risk of migration to the inside of the vial, where it can potentially integrate with the drug product. The Velocity coating is bonded to the vial's exterior surface using a special process. "Velocity is a robust and durable layer that stays exactly where it's applied," says Hall. "We've also implemented control systems during manufacturing to ensure that the coating is only on the outer surface; never on the sealing surface of the vial flange, and definitely not inside the vial."

Pandemic data

Velocity was first introduced to the market as a container for a COVID-19 vaccine during the pandemic. A contract manufacturer using Velocity closely tracked the performance of their filling line, including glass-related downtime, such as vials breaking, tipping, or jamming on the line.

The manufacturer was running both conventional, uncoated vials, and Velocity vials – and the results were striking.

"There was a 35 percent increase in line efficiency when using Velocity compared to uncoated vials," says Hall. "A 30-times reduction in glass-related cosmetic defects was also observed."

Fill-finish equipment manufacturers are constantly improving their machines to increase production speeds and throughput. Until now, however, vial innovation has not kept pace, with companies often needing to run lines at 70 percent capacity to avoid issues associated with uncoated vials.

Kataria says, "With Velocity, we've seen improvements of 20 to 30 percent in overall throughput, just from switching the coating. Velocity vials enable manufacturers to use the full potential of their upgraded assets. One of the best pieces of feedback we've gotten from a customer is this: 'Velocity has brought velocity to our lines.' That really says it all."

An open ecosystem

Velocity is available directly from Corning, but the technology has also been licensed to Gerresheimer, Nipro, and SGD Pharma. Why do this? Hall says: "When we first introduced Velocity, one of the most common questions from customers was: 'can we get this from more than one supplier?' Supply chain resilience is a top priority."

"We've made sure that companies can adopt Velocity without having to navigate a completely new approval process," says Kataria. "However, many pharma companies are hesitant to change their established supplier relationships, which inspired us to create an open ecosystem to make this valuable technology accessible through trustworthy companies. We're continuously reinventing not only the technology itself, but also how we bring it to customers. Ultimately, we want as many patients as possible to benefit from this safer, smarter solution."

Learn more about Velocity at:
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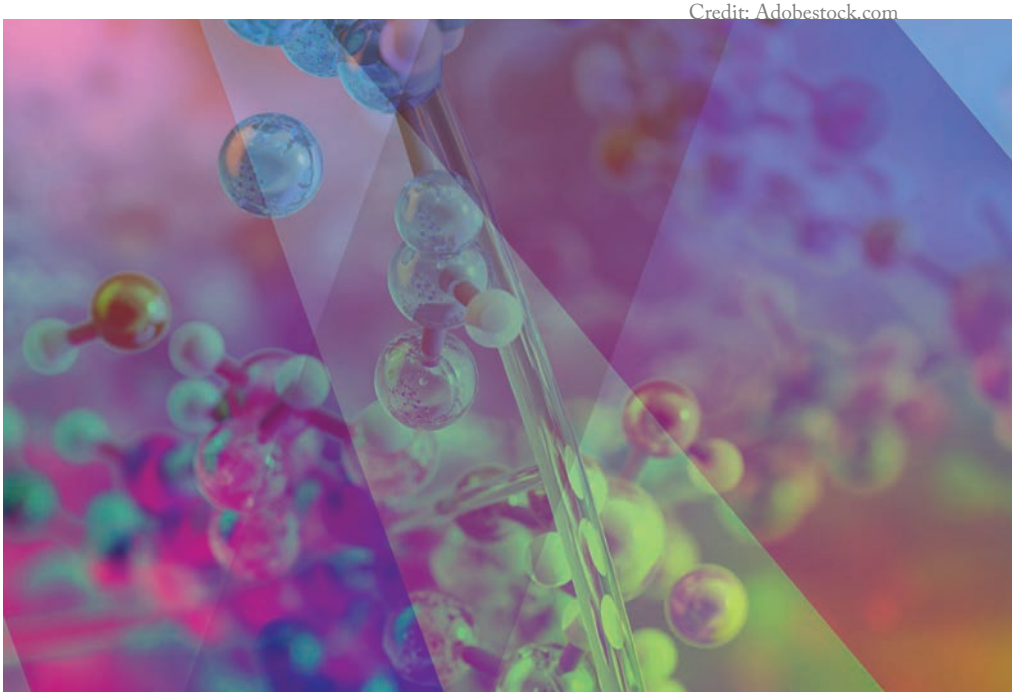

NEXTGEN

How Oligonucleotides Work Their Magic

The industry is investing big in oligonucleotides, but what is it that makes this class of drugs so special?

By Hilary Brooks, VP and Modality lead for Oligonucleotide Therapeutics at Evotec

Genetic medicine is completely transforming the way we think about disease. Thanks to whole genome sequencing, we no longer have to group diseases purely by symptoms. We can identify the specific gene that might be responsible, which changes everything in terms of diagnosis, and begin to think about therapies that target the culprit gene directly.

This is where oligonucleotides come in. Oligonucleotides are designed based on specific genetic sequences and offer an incredible level of precision. A short strand of nucleotides can bind uniquely to a single target RNA allowing an incredible level of precision.

This precision is also one of the key strengths of antibodies or 'biologics'. They offer a level of precision that small molecule drug development has lacked, but antibodies can only access what's on the cell surface or circulating in the bloodstream. Oligonucleotides, however, can get inside the cell and shut down a toxic protein at its source.

In the early days of oligonucleotides, development focused on monogenic rare diseases, where the genetic cause was well understood and where lengthy target validation wasn't necessary. For example, in Huntington's disease, the causal mutation is an expanded repeat in a known gene, so the idea of using an oligonucleotide to 'silence' the faulty gene for patient benefit was no big step to take.

Nowadays we are more courageous and are thinking outside monogenic disease and small patient populations to larger, more impactful targets. In many diseases, we already know what needs to be targeted but have failed using other modalities. Some of these traditional drug targets, such as phosphatases or ATPases, have been incredibly difficult to address because the binding sites are often shared with many other proteins. This makes it nearly impossible to get the required specificity (and therefore safety) from a traditional small molecule drug.

Although there are some limitations, oligonucleotides ultimately help solve two huge problems in drug development: reaching the target and hitting it with accuracy. They provide exquisite specificity and are not constrained by the location of the protein.

When it comes to safety profile, oligonucleotides behave much like a class of drugs, so we've learned where the general red flags are. Yes, there have been mistakes and initially the regulatory pathway wasn't set up for oligonucleotide drugs, which has slowed progress, but the industry is figuring it out. Unlike small molecules, where every new chemical entity comes with unknown toxicity risks,

"Although there are some limitations, oligonucleotides ultimately help solve two huge problems in drug development: reaching the target and hitting it with accuracy."

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oligonucleotides are more predictable. With small molecules, you often don't discover safety issues until it's far too late – sometimes not until the patient stage. But with oligos, we know what to look for and how to test for it early on.

This also makes oligonucleotides relatively straightforward to design. The challenge lies more in the biology: understanding your target and what happens when you modulate it. Take Huntington's as our example again. It turns out that we can very successfully remove the toxic mutant protein with our oligonucleotide approach, but the benefit hasn't been the revolution we hoped for in patients and this is because a functional, normal version of the protein is still missing and is apparently essential. Toxicity in patients isn't just about removing the mutant form – it's also about losing the good version. That's biology for you, and we face these issues with any modality.

Today, we have an even greater understanding of the potential benefits of oligonucleotides. They allow us to shut off the production of a toxic protein before it's even made, or reshape it via altering RNA splicing into something that's no longer toxic. These mechanisms of action are fundamentally different from traditional therapies and open the door to a new world of therapeutic options.

Boom, bust, and formulation challenges

Right from the early days of oligonucleotides, everyone could see the potential. There was a huge wave of enthusiasm. Biotech companies sprang up, but many collapsed just as quickly. Big pharma also got involved, Millions were invested and lost.

Early on, one major issue was the cost of goods. Oligonucleotides are made synthetically, and the manufacturing process is more complex than that of small molecules. Over time, however, processes across industry have been standardized. Costs remain high but are slowly coming down as more oligo drugs reach the market.

Today, there is a huge focus on delivery. Oligonucleotides are not orally bioavailable and have no gastrointestinal absorption. This is a big shift for pharma, which is so used to the classic Lipinski Rule of Five and designing drugs that fit neatly into a target product profile. Patients want pills. Pharma wants pills. But oligos don't play by those rules!

There are also delivery and stability issues. A naked, unmodified oligonucleotide, if injected, typically has a half-life of less than six minutes. Our bodies have evolved defense mechanisms specifically to eliminate foreign RNA (think viruses!) – which is a good thing for biology, but a challenge for therapeutic delivery.

Over time, the industry has developed chemical modifications that protect oligos from nucleases and enhance protein binding. Now, even though systemic circulation is still not fantastic (less than 24 hours), it's good enough to push an oligo into tissue. Once in the tissue, it stays there – so the drug will remain active long after a single dose. The result for the patient is that although it is still an injection, it is very stable, which significantly reduces the burden of injection to once every few months.

Some groups are trying to develop oral oligos. Maybe one day we'll get there, but the industry isn't close. That said, the incredible uptake of GLP-1 analogs for weight loss shows that patients are open to injectables – even when the disease being treated isn't life-threatening. That shift in patient behavior is a big deal – and oligos could benefit.

Another challenge is the restricted biodistribution pattern. Double stranded oligos, such as siRNA, do not cross the cell membrane by themselves and need either a lipid or a conjugate that will be actively transported into the cell. Single stranded antisense oligonucleotides (ASOs) will cross the cell membrane without delivery aids, but the large part of the drug will accumulate in the liver and kidneys. Diseases in these organs are good targets for oligonucleotides. Oligos are also successful in settings that allow for local administration, such as the eye. The skin is another area of interest.

But how do we deliver oligos to treat indications such as cancer? That's still an ongoing challenge, but we have learned that conjugating oligos to other molecules, such as antibodies, peptides, and carbohydrates, can dramatically change where they go in the body. GalNAc conjugation, for example, has opened new doors. It has been clinically validated and shown 30- to 50-fold increases in liver uptake. The transferrin receptor is also showing similar promise for heart, muscle, and even the brain.

We're not yet at the point where we can pull a delivery solution off the shelf and plug it into any oligo, but we know how to approach it. Through collaboration between industry, academia, and regulatory bodies, we'll get there.

Next-generation oligos

Today, marketed oligo drugs are generally evenly split between ASOs and siRNAs, but within the ASO category – especially the single-stranded DNA oligos – about half don't work by degrading their target RNA. In other words, they don't cause "knockdown," which refers to reducing gene expression by destroying the messenger RNA so that the protein isn't produced. Instead of degrading RNA, they act by steric hindrance, which means they can physically block certain interactions. The target might be an RNA-binding protein, or perhaps it interferes with the secondary structure and the structural stability of the RNA itself.

There are many things you can do with these steric blockers. What makes them unique is that they're fully modified, which means they don't recruit RNase H or the RNA-induced silencing complex to degrade the target. Instead, they sit on the

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RNA and block whatever was supposed to happen next.

So far, the most prominent application of this has been splice switching. Consider a patient with a mutation that confuses the cell's machinery when it's trying to splice introns and exons. By masking that mutation, we can help the cell "skip over" the faulty signal – allowing it to correctly recognize and splice the necessary exons. It's not 100 percent perfect, but there is clinical proof of concept that this approach can improve disease states.

We can also flip this approach on its head. Sometimes, we want to induce a splicing error. If we know that a particular exon contains an expanded repeat that will produce a toxic protein, we might deliberately exclude that exon. The result is a shorter protein that's less toxic but still functional. Thus, oligonucleotides can be used to tell the cell: "Make a mistake – but make this specific mistake." In doing so, the disease burden can be reduced.

The industry is also starting to look at RNA editing. If there is a mutation, you can trick the cell into correcting the RNA transcript after it's been made, without changing the underlying DNA. It's not gene therapy in the classic sense because it doesn't permanently edit the genome, but the effect is still therapeutic – and can be sustained with repeated dosing.

Of course, delivery remains a challenge. These newer constructs are often larger, so getting them into the cell is more difficult. But the good news is that all the knowledge we've accumulated through aptamers, siRNAs, and earlier oligos applies. New generation oligos will benefit from the foundational work. It's a rising tide that lifts all boats.

In science, new mechanisms are often discovered entirely by accident. We're still just beginning to understand the full potential of oligonucleotides. We're only seeing the tip of the iceberg. The basics are in place – we know how to make oligos, we know how to manufacture them and check for safety, and we know, broadly, where they go in the body. This has allowed the industry to focus on the low-hanging fruit.

"But how do we deliver oligos to treat indications such as cancer? That's still an ongoing challenge, but we have learned that conjugating oligos to other molecules, such as antibodies, peptides, and carbohydrates, can dramatically change where they go in the body."

It didn't take much to ignite the field again. Just a few molecules for rare diseases, and then a big shift with Leqvio, which was the first time a major patient population received an oligonucleotide-based therapy. It was proof that the approach worked – and it brought investment back. Now the mindset is: "Let's start again. Let's revisit what we know about these molecules – and figure out how to maximize their potential."

Don't forget safety

It's incredibly exciting to think about what we could achieve. For me, I still haven't gotten over the first wave of excitement – the fact that you can inject an oligonucleotide and show consistent function in known tissues is an incredible advance. We know oligos get to the liver. We know they get to the kidneys. And they can also be used in the central nervous system. There are already so many disease indications that could benefit from what we have today, and I look forward to seeing what happens when we put these molecules to work on the right targets to solve human disease states.

I'm delighted to be able to make a small contribution to this exciting field. I see a lot of early-stage programs – many are very promising, with great data and potency. But although they may have nailed efficacy and proof of concept, safety for chronic human use is often neglected at the early stages. This is where my colleagues and I step in. We look at the program and ask: "What data do you have and what is missing? What do we not know? What are the red flags from a safety standpoint?" Then, we map out what needs to be done.

Safety is still too often overlooked. You need to take the right steps early on. Benchmark against known clinical failures. Use assays that are appropriate for oligonucleotide modalities. Look for the red flags – which should now be well understood across the industry. Don't wait until you are in the clinic to ask, "should we check for off-target effects?" Do it early. Build it into your program from day one, the power of big data 'omics is at your fingertips – harness it!

There are over 20 oligonucleotide drugs on the market and hundreds more in clinical trials. We've learned a lot. And the best part? The most potent and safest versions of these molecules – the latest generation of chemistries – are still in development. We're already seeing great results. And there's more to come.

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"The industry needs to be asking, are we listening and understanding patient needs, and serving them in a way that is best for them?"

Kite, CAR Ts, and Access for Patients

Sitting Down With…Cindy Perettie, Executive Vice President and Global Head of Kite, a Gilead Company

Why did you join the pharma industry?
I did basic research in academia at Johns Hopkins for several years, and while I loved it, I realized something important: basic research is foundational and is where everything starts, but if you really want to see its impact on patients, then you need to take it further.

I watched others move into the pharma industry, and I saw how they were able to translate that foundational research into something tangible for patients. That's when it clicked for me. I wanted to have that broader impact too.

You've worked in several companies over the years. What are the most memorable milestones or rewarding moments?
One of the earliest milestones in my career was when I was doing basic research on VEGF (vascular endothelial growth factor); at the time, I was focused on it from a research perspective, but about five or six years later, I joined a pharma company and had the opportunity to develop anti-VEGF approaches into an actual therapy. Seeing it go from a scientific concept to something that was helping patients was incredible. That therapy ended up being approved in 19 different indications. It was amazing to witness that journey from research to real-world impact.

I've also been able to work on potentially curative therapies at Genentech and now at Kite. It's incredibly fulfilling to be part of something that can profoundly change cancer treatment, especially for patients who might not have had options before.

How did you join Kite?
I hadn't worked directly with cell therapy before, but I had worked with therapies in the blood cancer space. Before joining Kite, I reached out to some physicians to get their perspectives on cell therapy and the different companies in the space – without mentioning Kite specifically. What really stood out to me was that all of them, independently, said the same thing: "If you're going to go into cell therapy, you need to join Kite." They told me that Kite is the global leader in cell therapy and praised their reliable manufacturing capabilities.

When I finally spoke with Gilead and Kite leadership, it became clear that it was the right place for me. Why you join a company comes down to three things: the people, the culture, and the science. Without question, Kite had all three.

What is Kite working on at the moment?
Depending on the country, only about two in 10 eligible patients, on average, receive CAR T-cell therapy. These are potentially curative therapies, so a major focus area for us is realizing the full potential of CAR T and ensuring more patients have access. This means meeting patients where they are. For instance, how do we treat someone in their town, rather than have them travel all the way to a treatment center in a far-away city?

Beyond that, Kite has an incredible pipeline. We have approved therapies for lymphoma and leukemia, and we recently completed studies for an investigational multiple myeloma therapy. We're also expanding into solid tumors. We are looking at glioblastoma and neuroblastoma, and we have research underway in hepatocellular cancers. At the end of last year, we filed an IND for our first program in autoimmune disease. We are also working on several therapies that are next generation, including dual targets and armoring.

At the same time, we continue to improve our manufacturing process. We're in nearly 30 countries already and we're working hard to reduce turnaround times for patients. In the early days of cell therapy, it would take several weeks to get therapies to patients. In the US, we've brought that down to just 14 days. Outside the US, we're at 17 days. This is a massive improvement, and it's all thanks to automation, advancements in manufacturing processes, and enhancements in quality testing.

What are the most pressing challenges in the industry and where do you think the priorities need to lie in the next one to two years?
Receiving a CAR T – and knowing that more than 50 percent of patients who had a complete response are still alive at five years and in remission – is life-changing. But right now, it pains me to think about how most patients cannot access these therapies. We need education and awareness around CAR Ts. Right now, there are patients out there who will never hear about CAR T from their doctor. In many cases, CAR T is not even presented as an option. This has to change.

And for those who can receive a CAR T, we need to make sure the burden isn't on the patient. The healthcare system should be set up so that treatment is accessible and so that patients don't have to travel far. This means moving into more regional or community settings. The industry needs to be asking, are we listening and understanding patient needs, and serving them in a way that is best for them? To this end, there are a lot of innovations happening in manufacturing, such as truly rapid manufacturing and manufacturing in a box that could be placed near all major hospitals and airports.

At Kite, we're looking at everything, including expanding authorized treatment centers, improving education efforts, and driving innovation that makes cell therapy more accessible. Over the next two years, our focus is clear: getting these transformative therapies to more patients. And that means looking at every part of the ecosystem. My hope is that in two years, when we speak again, we'll be talking about four or five out of 10 patients receiving CAR T therapy – not just two.

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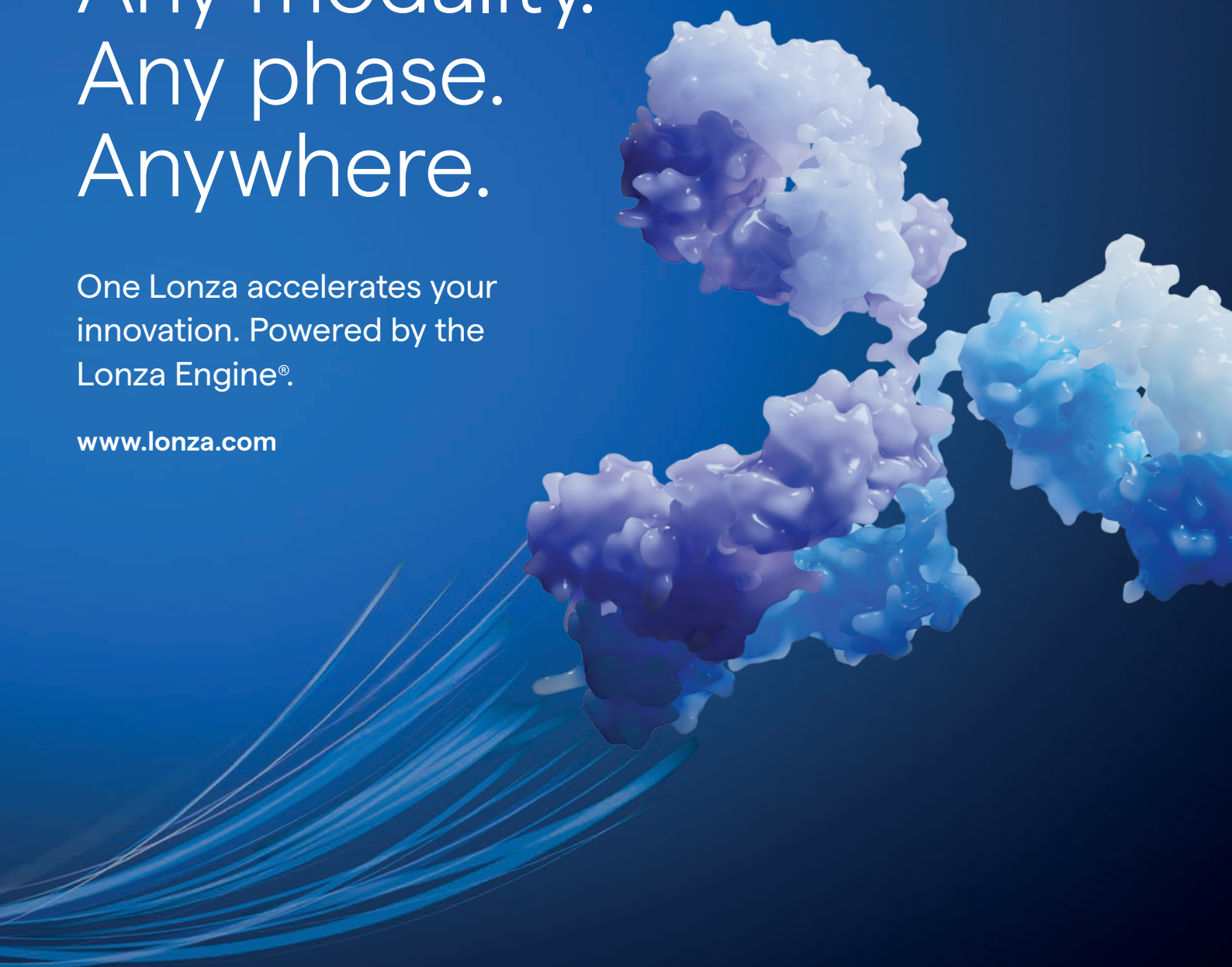

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