SEPTEMBER 2021 # 79

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Seriously, Y'all. Stop It.

Pharma wants to empower patients to make informed healthcare decisions, but patients also need to be protected from misinformation

Earlier this year, I had a conversation with Mike Petroutsas – GSK's Senior Vice President of US Oncology – about patient centricity, patient engagement, access to treatment, and disease awareness and education. Mike also talked about the rife misinformation about medicines and vaccines for COVID-19, and how it is important for the pharma industry to "build back trust in the healthcare system and in our medicines" (1).

A recent case in the US emphasizes his point. In August 2021, unvaccinated Jeffrey Smith was placed on a ventilator after becoming ill with COVID-19. His wife, Julie Smith, requested that he be treated with ivermectin (2). Ivermectin has attracted a great deal of attention in the research community for COVID-19, but it remains unproven. A preprint paper recently reported that ivermectin could reduce the chance of death in COVID-19 patients by more than 90 percent; however, the paper was later withdrawn due to flaws in the data (3). The FDA has created a page on its website titled "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (4). In a tweet to promote the page (5), the FDA also said, "You are not a horse. You are not a cow. Seriously, y'all. Stop it."

When the hospital refused to dispense ivermectin as a treatment, Julie filed a lawsuit to force treatment. On August 23, 2021, a judge ordered the hospital to treat the patient with ivermectin. In early September, the court order was overturned, with the judge stating that the medical and scientific communities do not support the use of ivermectin as a treatment for COVID-19.

Smith's case is not the first lawsuit around ivermectin and likely won't be the last. Patients have rights and the pharma industry has often spoken of patient empowerment, but patients also need to be protected from clear misinformation and unproven medicines.

There is a known trust issue in the pharma industry that must be addressed. Patients need to feel that they can trust medicine manufacturers and regulators, rather than seeking out other avenues where there is a strong risk of misinformation. Pharma companies must continue to improve their reputation amongst the public, ensuring that they are engaging with patients and giving patients information about medicines and diseases so that patients can make informed decisions – in collaboration with reputable healthcare practitioners, of course.

Stephanie Sutton
Editor

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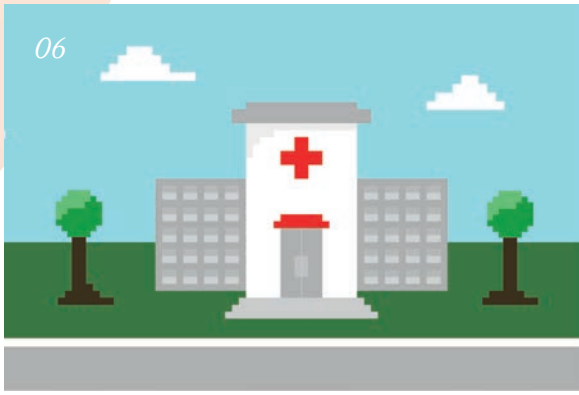

On The Cover

Will mRNA flourish in the future?

Upfront

In My View

the Medicine Maker

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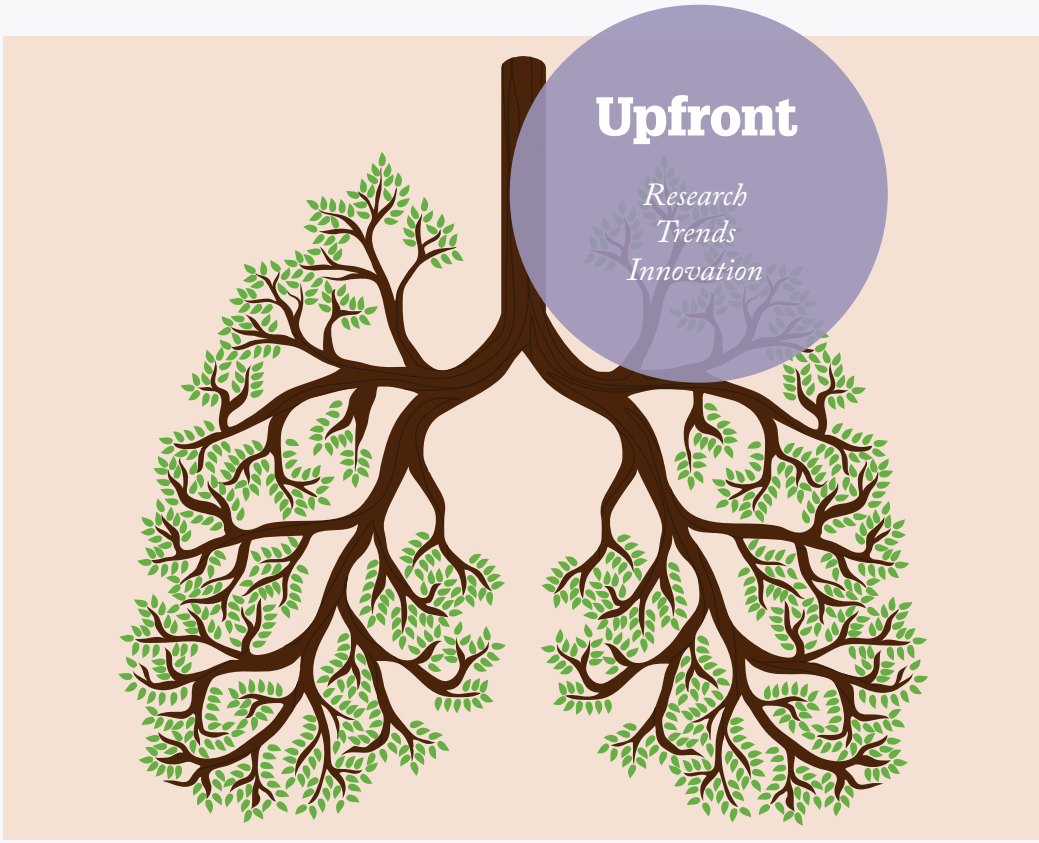

A Breath of Fresh Air

Inhalers have many issues; could computational modeling provide the solution?

Recent decades have seen inhalers revolutionize the treatment of pulmonary diseases. Today, scientists and medical practitioners are even administering some drugs through inhalers to provide relief to COVID-19 patients. However, the performance of these devices remains far from optimal; for example, drug dispersion from currently available devices and formulations can vary from 12 to 40 percent of the load dose and, worse, most drug particles are deposited on upper airways due to their large size (1).

At the University of Technology Sydney, a team of researchers are using computational fluid dynamics to model how drugs are delivered to the human respiratory tract – and they hope the findings will inspire a redesign of inhalers. Team leader Suvash Saha says, "Conducting in vivo experiments is extremely difficult. In vitro and in situ experiments are possible, but they can't properly explain local deposition. This leaves in silico (computer modeling) as the best option for visualizing local deposition and related phenomena."

Saha has worked in computational fluid dynamics for the better part of a decade and was inspired to move into inhaled drug delivery when his daughter was diagnosed with mild asthma. Though global air pollution – a major cause of pulmonary illness – is decreasing in certain parts of the world, it is a serious health concern in much of the developing world (2).

Using their new approach, the team found that more drug particles enter and are deposited in the right bronchi than the left due to the position of the heart. "Our findings suggest that drugs should contain smaller, finer particles to enable contact with the distal bronchi," says Saha. The team's next step is to perform more simulations for a variety of lung ages.

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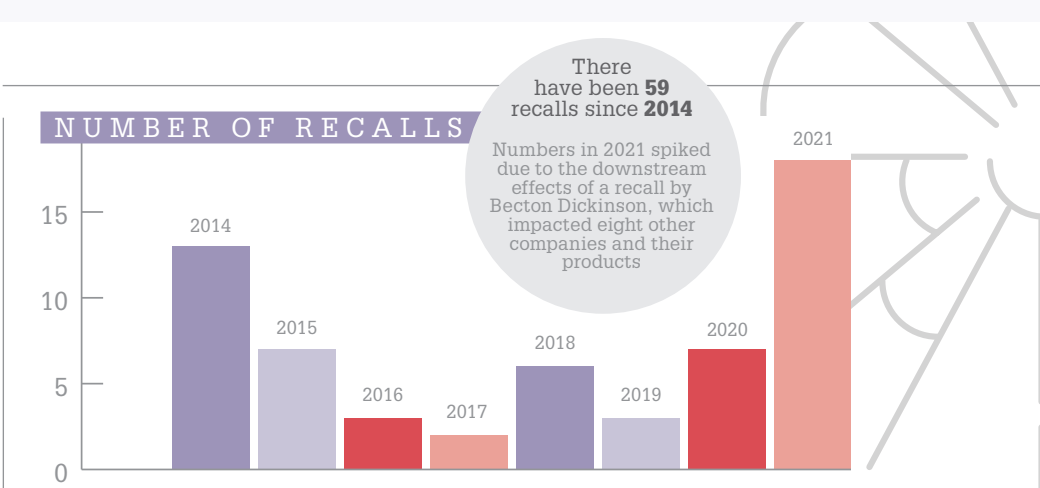
INFOGRAPHIC

Recall Rolecall

Examining drug recalls and the impact of glass packaging

Source: Sio2 Materials Science, "Glass-Related Recalls in Pharma: 2014 – July 2021" (2021). Available at: https://bit.ly/3DTBqc



BUSINESS IN BRIEF

The firm hand of the law, the fall of Purdue Pharma, and delicious, nutritious gummies… What's new in pharma this month?

- SK Bioscience and GSK's adjuvanted COVID-19 vaccine candidate, GBP510, has advanced to phase III trials. Around 4000 people worldwide will take part in a trial that compares the safety and immunogenicity of GBP510 against the Oxford/AstraZeneca vaccine. Results of the study are expected to arrive in the first half of 2022.
- Catalent has reached for something sweet in a proposed US$1 billion bid to acquire nutritional gummy, soft-chew, and lozenge manufacturer Bettera. If the deal goes ahead, it will bring Bettera's four US production facilities under Catalent's wing, along with a range of technologies, products, and packaging options. Catalent has said the move is part of an effort to "extend (its) leadership in a rapidly growing nutraceuticals market."
- Racho Jordanov and Rose Lin, co-founding top executives at Taiwan's JHL Biotech, have pleaded guilty to stealing trade secrets from Roche to help their 2012-founded business cut corners. The plea follows admissions from their co-conspirators and former colleagues at Roche's Genentech. Jordanov and Lin's sentences will be decided in December by a US District judge.
- Both Pfizer and Merck & Co have launched trials of experimental oral drugs for COVID-19. Merck is seeking to determine whether its molnupiravir can prevent the disease in adults living with symptomatic, COVID-19 positive patients. Pfizer's trial concerns symptomatic patients who have not been hospitalized and aren't at high risk of severe illness.
- Oxycontin producer Purdue Pharma has been dissolved in a bankruptcy settlement, which follows its plea of "guilty" to crimes that contributed to an opioid epidemic that crippled the lives of millions in deprived areas of the US. The Sackler family – who own the company – will be forced to hand over billions to help address the crisis, but will largely be absolved of liability and remain among America's richest families.

Archived Antivirals

Longstanding treatments for tapeworm could take on COVID-19

A decade ago, Kim Janda suffered from clostridioides – a bacterial infection whose multi-drug-resistant strains contribute to diarrheal disease outbreaks around the world. The experience prompted him to use his role as director of the Worm Institute at California's Scripps Research to develop new and better treatments using a library of modified salicylanilides – molecules already well-established as a counter against tapeworm infection (1).

Given the COVID-19 pandemic, Janda and his team have begun screening their library for antiviral properties against COVID-19 – and they've already uncovered some promising leads. One standout compound – mysteriously (or banally) named "No 11" – was readily absorbed into the bloodstream and was seen to interfere with endocytosis of SARS-CoV-2, hampering the production of new viral particles. Janda believes that "11" would have no trouble tackling COVID-19 variants, as it acts inside cells and not on viral spikes (2).

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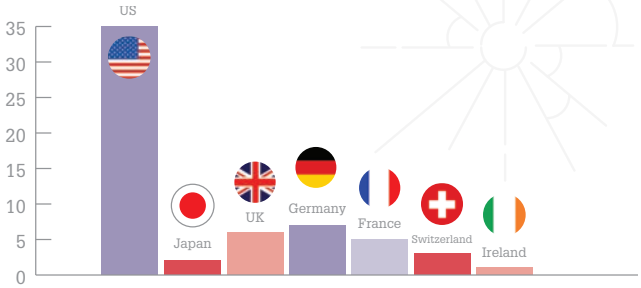
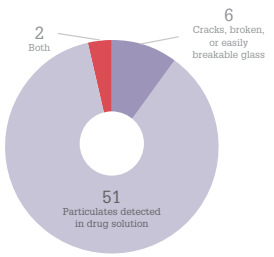
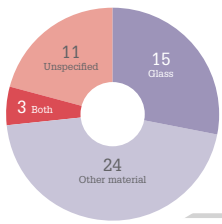
RECALLS BY REGION



REPORTED REASON FOR RECALL



TYPE OF PARTICLES IDENTIFIED IN DRUG SOLUTIONS



Of Medicine and Machine Learning

How should regulators approach the challenge of AI?

Following a "horizon scan" exercise, the International Coalition of Medicines Regulatory Authorities (ICMRA) has released a report to help regulators address the challenges that stem from the increasing use of artificial intelligence (1). In medicine, AI (including but not limited to statistical models, algorithms, and self-modifying systems) is expanding into numerous areas including preclinical development, clinical trial data analysis, pharmacovigilance, and even clinical use optimization. According to the report, "This range of [AI] applications brings with it regulatory challenges, including the transparency of the algorithms themselves and their meaning, as well as the risks of AI failures and the wider impact these would have on its uptake in pharmaceutical development and ultimately on patients' health."

The report uses hypothetical case studies to examine the challenges posed by different applications of AI, including in pharmacovigilance and the use of apps for monitoring patients, such as those in clinical trials.

Recommendations for medicines regulators in the report include:

- Developing regulatory guidelines in a number of areas including data provenance, reliability, transparency and understanding, and the use of AI for pharmacovigilance purposes and real-world performance and monitoring.
- International standardization of good machine learning practices in biomedicine.
- Adopting a risk-based approach to AI assessment and regulation, which could benefit with collaboration with ICMRA. According to the report, "The scientific or clinical validation of AI use would require a sufficient level of understandability and regulatory access to the employed algorithms and underlying datasets."
- Exploring the benefits of establishing a Qualified Person concept responsible for oversight compliance of AI.
- Engaging with ethics committees and AI expert groups to understand the ethical issues related to the use of AI in medicines development.

The report also examines AI activities at various medicines regulators; for example, Health Canada is developing its first industry guidance on "locked" AI/machine-learning enabled medical devices and has conducted surveys with marketing authorization holders on current and potential use of AI in pharmacovigilance systems. Meanwhile, Swissmedic has launched a digital initiative called Swissmedic 4.0 that looks at digital transformation, including the use of AI to detect safety signals.

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Lonza's Cantonese Dream

The Swiss firm continues investment in China with a manufacturing upgrade to its key Guangzhou site

Lonza has upgraded its "Nansha" site, equipping it with a new drug product fill and finish manufacturing line. The level-up is aimed at establishing capacity for clinical trial and commercial supply inside the People's Republic of China (1).

Hong Pan, Loza's General Manager for China, said, "[The upgrade] not only demonstrates our commitment to the Chinese market but also marks an important milestone in achieving our long-term ambition of increasing drug product capacity and addressing growing customer demand for an end-to-end drug product solution."

The investment marks the latest chapter in Lonza's longstanding interest in the Middle Kingdom, which centers around the Nansha site. Nansha opened in 2003 and is located on an island in the Pearl River delta in the southern reaches of Guangzhou.

Seven months prior and 1212 kilometres to the north, Lonza also boosted its presence in Shanghai, opening an office in the fashionable Xintiandi business hub (2).

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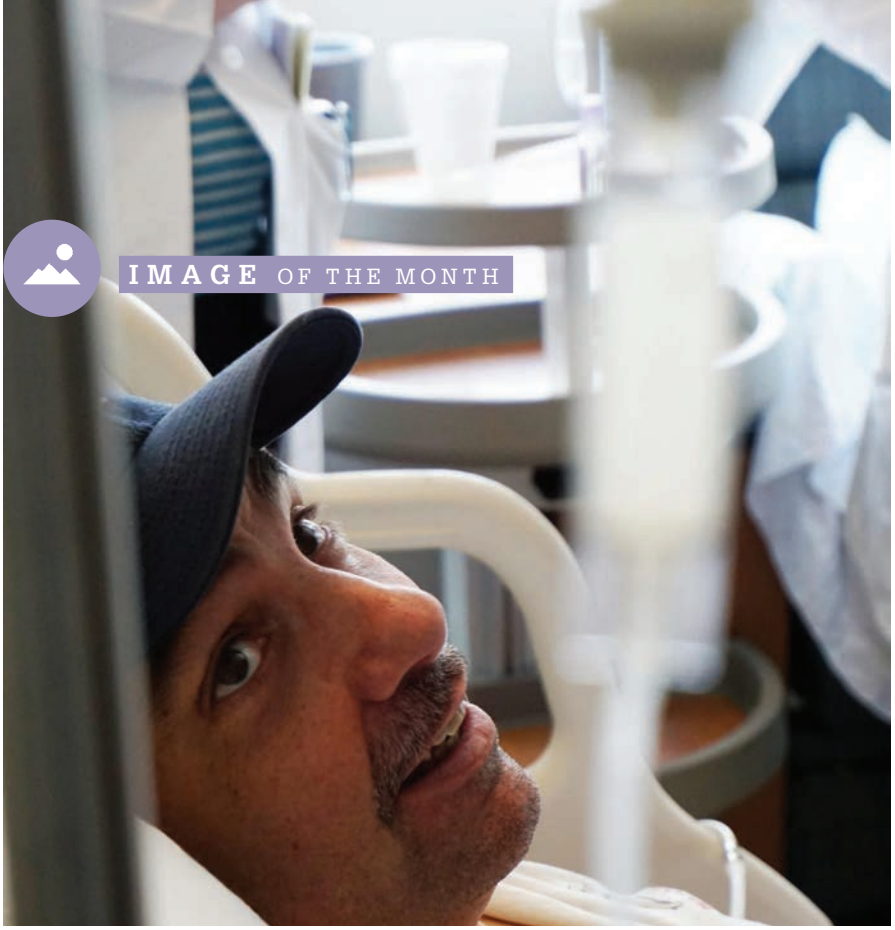

IMAGE OF THE MONTH

Life-Changing Therapy

Scott McIntyre watches his engineered T cells re-enter his blood stream via an intravenous drip. "This is scary, but exciting," he said at the time. The Center is the first site in Illinois to offer pioneering CAR T-cell therapy for cancer.
Credit: University of Chicago Medical Center

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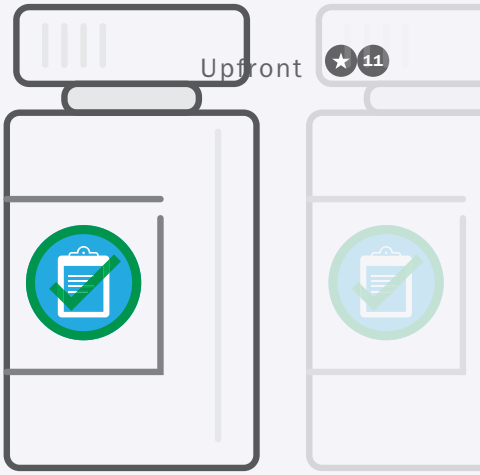
Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"There aren't a lot of things that almost every American could agree on, but I think it is safe to say that all of us, whatever our background or our age and where we live, could agree that prescription drug prices are outrageously expensive in America."

US President Biden, speaking on August 12 in the East Room of the White House, during opening remarks in a speech on lowering prescription drug prices as part of his administration's 'Build Back Better' agenda.



Comirnaty for the Community?

Pfizer-BioNTech's COVID-19 vaccine has received full FDA approval

The Pfizer-BioNTech COVID-19 vaccine (marketed as Comirnaty) was approved by the FDA for "emergency use" last year but has now received full approval for individuals aged 16 years and over. It remains under emergency use approval for children aged 12 to 15, and for a third dose in certain immunocompromised individuals.

According to Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, "hundreds of thousands" of pages of scientific data were reviewed as part of the evaluation, including data from around 20,000 vaccine and 20,000 placebo recipients. The FDA also evaluated post-authorization safety surveillance data; the prescribing information will include a warning about the risk of myocarditis and pericarditis in certain individuals.

In a statement (1), Marks said, "The public and medical community can be confident that although we approved this vaccine expeditiously, it was fully in keeping with our existing high standards for vaccines in the US."

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In My View

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

The Winding Road to the Frontline for Advanced Therapies

Four major considerations in easing the process of taking ATMPs to clinical trials

By Angi Robinson, Senior Vice President of Specialty Areas, Premier Research

According to the Alliance for Regenerative Medicine, there were 1,085 active advanced therapy medicinal product (ATMP) developers and more than 150 phase III trials underway at the end of 2020 (1). These numbers are not small, and they make it clear that ATMPs have much to offer in helping us overcome as-yet undefeated diseases.

ATMPs are different from biopharmaceuticals, and these differences influence the regulatory and clinical approaches that sponsors must consider when designing and conducting trials. In our view, there are four key considerations when it comes to trials. Let's take a look.

First, the need for early, proactive engagement with regulators is critical. This is an emerging field; regulations can change. Because ATMPs are complex biological products, the current regulations around them are also complex. We would advise all sponsors to initiate discussions with regulators early in their development planning. This is an opportunity to get clarification on topics such as data requirements, the need for biomarkers as outcome measures, the necessity of long-term follow-up (LTFU), and the possibility of accelerated approval. In the US, the "regenerative medicine advanced therapy" designation offers an expedited path to market for ATMPs that target serious or life-threatening conditions with unmet medical needs.

In Europe, the landscape is less uniform. The EMA subclassifies ATMPs as "gene therapy medicinal," "somatic cell therapy medicinal", "tissue-engineered medicinal", or "combination" products. There is also separate legislation for ATMPs and genetically modified organisms (GMOs). However, this distinction may not exist at the level of the EU's individual member states, and non-GMO advanced therapies may still be subject to GMO legislation, which may then require additional approvals. Engaging with regulators early on is necessary to ensure that you understand the requirements of your target region.

The second key consideration is understanding the needs and priorities of the full spectrum of stakeholders, from patients to payers. Competition is on the rise in this space, so again, early discussions are beneficial. Understanding what is important to patients and their families is paramount not only because patient experience data may be a regulatory requirement, but also because their preferences may influence the design and feasibility of clinical studies. Interactions with patients, families, and advocates can help foster a sense of collaboration, collect feedback on the protocol, and evaluate the meaningfulness of proposed outcome measures. These conversations are also opportunities to increase study awareness and inform recruitment plans.

You should also engage with key opinion leaders and healthcare providers to understand the standard of care in your countries of interest, as well as the protocols for validating study design and related assessments. This is especially important for rare diseases, where little is known about the condition's natural

history and progression. On the other hand, when sponsors know that ATMP development activity is robust, they can benefit from identifying relevant physician champions and collaborators early in their development programs.

Third, site selection is key to success. The ideal site will be familiar with the therapeutic indication and experienced in handling and administering the ATMP under investigation. When evaluating sites, sponsors should also consider the following:

- Past performance in similar studies
- Access to the target patient population
- If the ATMP is a GMO, the existence of GMO-specific standard operating procedures and best practices

Absolutely essential is site/staff experience with the mode of administration, especially for studies that require highly specialized procedures such as intracranial delivery. Depending on the ATMP, additional site certifications or approvals may also be required; for instance, accreditation from the Foundation for the Accreditation of Cellular Therapy or the Joint Accreditation Committee ISCT-Europe & EBMT. Human GMO products undergoing study in the US require approval from an institutional biosafety committee. In Europe, study start-up activities for gene therapy products vary depending on the product's regulatory pathway and the requirements of member-state-specific GMO regulations and related authorities.

The fourth and final key consideration is to remember that lifting barriers to family and patient participation in clinical trials aids both recruitment and retention. For rare diseases, it may be necessary to go to extraordinary lengths – such as relocating entire families for extended periods – to enable patients to participate in studies. For certain ATMPs, however, it may be possible to limit such disruptions by centralizing product administration and localizing follow-up. Whatever the approach to operationalizing an ATMP trial, it is crucial to budget for travel, lodging, off-site visits, and other study-related costs that maximize convenience and minimize out-of-pocket expenses for participants.

If LTFU periods are mandated, the challenge of retention grows exponentially. Patients may relocate or switch from being followed by a pediatrician to being seen by an adult physician. To meet their LTFU regulatory obligations, sponsors may need to create new sites with investigators unconnected to the initial study. Mobile health options and off-site nursing visits can be extremely helpful tools for minimizing patient burden and reducing cost during the follow-up period. Finding ways to sustain both site and participant engagement in the long-term requires creativity and diligence. In our experience, ongoing education and consistent communication are powerful tools.

ATMPs have the potential to provide life-changing benefits, or even curative options, for patients in need. The field is advancing rapidly, and the environment is increasingly competitive. Sponsors that keep pace with evolving regulations, engage with key stakeholders, and focus on study execution at the earliest stages of development planning are well-positioned to achieve both clinical and commercial success.

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A Nice Cup of RDT

Rapid-dissolve tablet technologies offer immense benefits, but the pharma industry has yet to fully realize their potential

By Aditya Kumar, Chief Marketing Officer, InstaPill, Bangalore, KA, India

Since orally disintegrating tablets (ODTs) first received regulatory approval in the mid-1990s, they have gained increasing attention as a preferred alternative to conventional forms of dosage. What sets them apart? Enhanced bioavailability, faster onset, and greater patient compliance and convenience. Most notably, ODTs are often developed to address dysphagia. This condition is most prevalent among pediatric and geriatric patients, who can find it difficult to swallow hard pills.

These are just some of the reasons

"Developing an oral formulation of insulin has become somewhat of a holy grail for drug developers."

the ODT market is predicted to exhibit a compound annual growth rate of 10 percent from 2019 to 2025 (1). In 2018, the market was valued at around US$2 billion.

There are interesting distinctions in the various regulatory definitions of ODTs. The US FDA states that an ODT "disintegrates rapidly usually within a matter of seconds when placed upon the tongue (2)," whereas the European Pharmacopoeia uses the term "orodispersible tablet" for tablets that disperse within three minutes in the mouth before swallowing. It is in the rapid-dissolve space (dispersion that takes place in mere seconds) that much of the current development focus lies.

In my view, a compelling application of RDTs is as a replacement for certain injectable medications. In particular, patients are keen for non-injectable versions of epinephrine and insulin. Developing an oral formulation of insulin has become something of a holy grail for drug developers, but what about epinephrine?

From a formulation perspective, the sublingual route is actually a promising alternative to injectable administration. This is mainly because the high vascularity of the sublingual mucosa, combined with the relatively low molecular weight of epinephrine, facilitates rapid absorption directly into venous circulation through the sublingual veins, as documented in the literature. Additionally, epinephrine is extensively metabolized after oral administration by the catechol-O-methyltransferase and by monoamine oxidase. When absorbed sublingually, epinephrine bypasses the inactivation in the GI tract and hepatic first-pass metabolism to reach systemic circulation while still remaining pharmacologically active.

Lyophilized RDTs are particularly appealing because the technique creates an amorphous, porous structure that can dissolve rapidly. This improves absorption and increases bioavailability.

The anaphylaxis market is relatively saturated with epinephrine auto-injectors. However, due to the widespread availability of existing treatments, it is highly competitive. Approximately 5 percent of the United States population will experience an anaphylactic condition – that's around 16 million people (3). There's certainly a market for an RDT formulation of epinephrine, although there are many scientific challenges to overcome to make it a reality. The same is true of insulin. The challenge is high, but there are ongoing clinical trials in the area and the rewards will be huge for any company that succeeds.

Across many different therapeutic areas, there is usually strong patient preference for oral administration routes over intravenous ones. One study for rheumatoid arthritis showed that 79 percent of patients would prefer a twice-daily oral tablet over an injection or IV infusion, provided the tablets met efficacy and safety expectations (4). Further studies have also evidenced a preference for ODTs over conventional tablets in the administration of olanzapine (61 versus 27 percent) (5).

Challenges that once presented a barrier for ODT formulations, such as palatability and taste, have also been addressed in recent years with the introduction of technologies such as alternate sweetener and binder/diluent systems and more robust taste assessments. For example, we were involved in the formulation of a sublingual tablet named Vomex. This tablet contains dimenhydrinate, an antihistamine used to manage nausea and vomiting. Consumers reported adverse experiences with the product on the market, citing unpleasant taste and texture as well as numbing of the mouth. We developed a series of formulations with different profiles; our aim was to reduce numbing and the number of particles upon dissolving, which created a gritty texture. We used our "Flavor Profile Method" (which involves the identification and measurement of several sensory attributes: sweet, sour, bitter, chalky, stinging, and numbing) to improve mouthfeel and palatability without changing the pharmacological profile. There is no doubt room for improvement in many marketed ODTs thanks to new advances in science. In my view, however, we should also be more seriously considering the use of innovative RDTs as new formulations in more challenging areas of drug development, such as insulin and epinephrine.

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Moving Beyond Clinical Manufacturing

There is a critical need to focus on the supply chain approach to help enable the cell and gene therapy field to achieve full bloom. We must ask ourselves: what and where are the pain points, how can we resolve them, and finally, how can we streamline the overall process?

By Joe Garrity, Head of Autologous Cell Therapy, Commercial Development at Lonza

As of 2021, around 20 cell and gene therapy (CGT) products have reached the US market (1) – and the field continues to expand rapidly, despite the COVID-19 pandemic. By 2025, 10–20 Biological Licence Application (BLA) approvals are expected by the FDA per year and nearly 10 times that number of Investigational New Drug (IND) applications are expected (2).

Though progressing to the BLA or Marketing Authorization Application (MAA) submission and approval stage is reason enough to celebrate, the challenges of providing the market with a regional or global product have only just begun.

Current methods for delivering CGT products to patients use variable entities and systems that require multiple levels, flow paths of information, and material at numerous process touch points. Cell therapy, specifically autologous cell therapy, arguably lays claim to the most complex and segregated product lifecycle, due to the requirement for the product-receiving patient to also serve as the donor of the product-starting material. This results in a concept referred to as "just-in-time" manufacturing.

This new concept poses many challenges. The patients are often undergoing treatment for an advanced stage of cancer or other critical illness, but to ensure success of the product, the patients must remain directly involved in the supply chain process. This means traveling to the clinical facility, undergoing the tissue collection process, and then subsequently receiving treatment while the tissue is transported to the target location for manufacturing and release. The entire process may take weeks or months before treatment is available for patient administration and for those patients with critical indications, that's time that may not be available.

Just-in-time manufacturing processes give rise to a variety of pain points throughout the chain of identity (CoI) and chain of custody (CoC) pathways and these supply chain issues can sometimes be underestimated as companies typically focus so heavily on successful manufacturing of the product. The issue is understandable, as the general system is set up for products to be developed in a staged approach, focusing on specific deliverables as the product moves through its lifecycle and associated clinical phases. Drug products that target common indications do not procedurally require automation for scalability until later phases, when the demand forces scale up to be initiated. While the initial focus is on safety, quickly followed by product efficacy, I believe there should be an increased focus on the commercial viability of the product at a much earlier stage. Yet again, this is an overlooked aspect of manufacturing. Developers should be asking three key questions: i) Is the manufacturing process a closed-system with reduced touch points? ii) Are the analytical methods validated to accommodate the target release criteria and period? iii) Is the process bill of materials (BoM) streamlined to limit external costs? The right answers to these questions will help establish low cost of goods (COGs) for the product but, no matter how robust the process is, if the supply chain process to achieve just-in-time manufacturing cannot bear the weight of the market, then your

"In our industry, nothing is more important than the recipients of the products, and focusing on supply chain today will absolutely benefit the patients of tomorrow."

product is going nowhere – figuratively and literally.

There are not many fully integrated service offerings in today's market that can assist in industrializing and streamlining supply chain logistics with full traceability throughout CoI/CoC processes, let alone at the scale demanded by common oncology indications. To attack the commercialization pain points and establish a robust, reproducible end-to-end process, one must understand both the market need for de-risking the processes from material collection to delivery of the therapy, and the available services that currently support the industry. As the CGT industry grows and matures, service providers are emerging to help with the challenges. Large-pharmaceutical companies such as Novartis and Gilead – as well as CDMOs such as Lonza – have supplemented their capabilities by using clinical management companies (for example, Be The Match Biotherapies) and logistics companies (for example, Cryoport) capable of linkage via an orchestration platform (for example, Vineti, TrakCel, Salesforce).

Integrated solutions provide a de-risked approach for cell therapy products using full vein-to-vein traceability and allow for streamlined communication by linking all process points through one potential point of contact. The result is a resolution for the more common pain points (logistic delays, process variability, scheduling adherence, compliance issues, and scalability) by allowing the integrated partnership to focus on the pain points specific to their area of expertise. Thus the "jack of all trades, master of none" stigma is banished.

Right now, the CGT industry is locked into severe supply chain constraints. We must overcome these as an industry by evaluating the processes used and the partners available to help in creating a streamlined vein-to vein service offering. In our industry, nothing is more important than the recipients of the products, and focusing on supply chain today will absolutely benefit the patients of tomorrow.

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Tackling the High-Potency Trend

The increased emphasis on oncology drug development has led to rising demand for experienced service providers able to handle HPAPIs from development through to full scale commercialization. Here, Rebecca Coutts, General Manager of PCI Tredegar, discusses how to safely work with these highly potent – and often life-saving – drug substances.

What trends are you seeing in the oncology field – and how is this affecting demand for highly potent ingredients?

Right now, there is an increased focus on precision medicine, targeted therapy, and customized care. There has also been an explosion in growth for cell and gene therapies. Scientific advances allow drug developers to offer increasingly smart treatments to patients across all therapeutic indications, but oncology remains a key focus area for the industry as a whole. This is unsurprising given that the estimated number of new cases of cancer worldwide is expected to rise from 18.1 million in 2018 to 29.4 million in 2040, according to predictions from the World Health Organization.

Many oncology products use highly potent APIs (HPAPIs). And so, at our Tredegar site, we've seen an increase in the number of global development projects involving HPAPIs as pharma companies continue to develop innovative treatments at a rapid pace, as well as the need to offer the technical transfer of late clinical and commercial projects where the current incumbent is unable to offer the commercial scale manufacturing required. A number of potent drug products have also received breakthrough therapy designation from the FDA, requiring PCI to deliver expedited timescales and commercial launch services – highlighting the importance of these therapies.

What are the challenges of working with highly potency products?

Usually there is limited toxicity data available at the earlier stages of development. In the face of the unknown, it is crucial to focus on operator and environmental safety. The best practice is to use contained, state-of-the-art processing capabilities as opposed to more traditional personal protective equipment. Special requirements for the effective handling of highly potency products apply to both manufacturing and analytical testing – and safety must always come first!

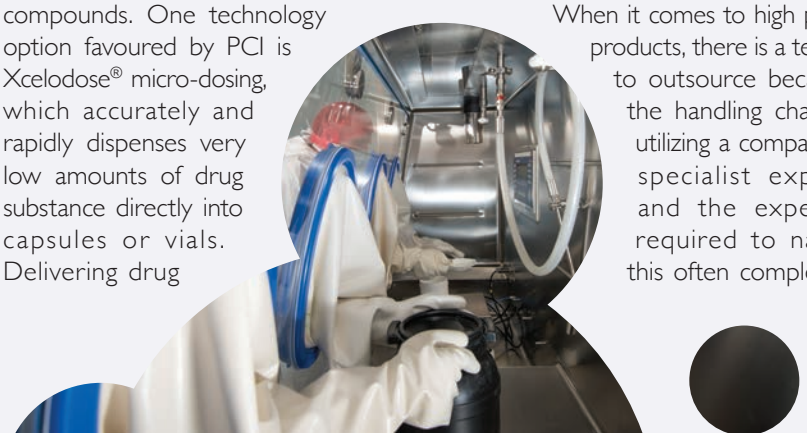
At PCI, our high levels of containment ensure an Occupational Exposure Limit as low as <0.01µg/m3 over an eight-hour time weighted average. This meets the intended regulations for Safebridge 3 and 4 applications. In my view, flexibility is also important. We optimize manufacturing processes based on specialist containment equipment, and we use the expertise within our development and operational teams to support clients with their potent (and non-potent) product development requirements.

As medicines increase in specificity, the value of the medicines themselves also increases, which drives the requirement for technologies that are accurate when it comes to handling highly potent compounds. One technology option favoured by PCI is Xcelodose® micro-dosing, which accurately and rapidly dispenses very low amounts of drug substance directly into capsules or vials. Delivering drug product directly into capsules or vials using contained micro-dosing, the technology removes the need for initial formulation development and associated stability, leading to faster first-in-human studies and cost efficiencies. We have found that the fully programmable system ensures exceptional levels of accuracy and precision, whilst minimizing wastage of these often expensive drug substances. We are proud to offer multiple options of micro-dosing technology that allows us to meet individual client volume requirements.

Xcelodose® technology also ensures the highest standards of safety by using full engineering containment for highly potent products. PCI has further invested in Xcelohood™ and Xceloprotect™ technology solutions to further enhance our contained solutions for the development and manufacture of highly potent drug products.

Why do most companies opt to work with a CDMO when it comes to highly potency products?

Outsourcing has numerous benefits – and this is why it is extensively used in all areas of drug development and manufacturing. When it comes to high potency products, there is a tendency to outsource because of the handling challenges; utilizing a company with specialist expertise and the experience required to navigate this often complex area



pci PHARMA SERVICES

is essential. As I mentioned earlier, high potency drug substances require specific containment strategies and state-of-the-art processing equipment and facilities; few drug developers have these available in-house and investment is expensive. PCI has expertise and capabilities in high potency product manufacturing and laboratory testing, and we offer access to innovative technology and digital platforms, such as PCI Bridge, which is designed around the customer experience to bring digital, smart solutions to every stage of the clinical supply chain. We also have expertise in toxicology and industrial hygiene processes required to assess safety requirements for working with potent molecules, as well as experience in navigating the highly regulated drug development framework around the world.

Some drug developers may choose to work with different suppliers at different stages of the development to launch cycle, but managing multiple suppliers and partnerships can be challenging. Most companies instead choose to work with an experienced single-source provider, like PCI able to manage products from the earliest stages of development through to commercial scale manufacturing and launch, for both ease and peace of mind.

What makes PCI stand out from the crowd?

We are the trusted partner for the biopharmaceutical industry, providing solutions with the shared goal of improving patients' lives. We put patients at the heart of everything we do, and we work collaboratively with our clients to deliver innovative, flexible, patient focused solutions.

Our comprehensive pharmaceutical development service offering includes new drug development, early stage formulation, and analytical development for both highly potent and non-potent drug products. Following early stage development, we continue with further development, scale-up, and process validation ahead of commercial launch for a variety of dosage forms, all supported by full in-house analytical development and a release laboratory.

We are also always keeping on top of technology trends. For example, roller compaction is a proven process providing a method of pharmaceutical granulation for materials that are known to be sensitive to heat and/or moisture. This process avoids the use of granulation liquids and high temperatures associated with other methods of manufacture, such as wet granulation with subsequent drying. We have added this technology to our already award-winning highly potent contained manufacturing facility in Tredegar to provide clients with a full range of granulation options.

We provide flexible and globally compliant commercial scale manufacturing and packaging of multiple dosage forms including tablets, capsules, creams, gels, ointments, and oral liquids. We also have a dedicated department of validation specialists to ensure a seamless transition from clinical phase to commercial launch, as well as supporting ongoing commercial supply through continuous process verification. Commercial manufacturing and packaging is supported by an experienced team of Qualified Persons, a full analytical release testing laboratory, and a GMP compliant temperature controlled warehouse with storage down to -20°C.

How is PCI preparing for the future?

In 2019, the Tredegar site began a US$20-million investment to expand its potent drug development and manufacturing capabilities as well as a new high potent commercial packaging suite. The investment involves an extension to the world-class, award-winning, contained high potent manufacturing facility that will double its large-scale commercial manufacturing capacity as well as adding extensive commercial packaging capacity to allow PCI to continue to meet the ever growing demand for our customers. The new facilities are expected to be operational early in 2022.

Meet Rebecca Coutts

Rebecca is General Manager of PCI's Tredegar, UK, site. She graduated from the University of Bath in pharmacy before completing a PhD in pharmaceutics at Cardiff University. She is also a registered member of the General Pharmaceutical Council in the UK.

"Over my 25-year career, I've shown a clear passion for development and manufacturing services. Before joining PCI, I held multiple roles including Head of Pharmaceutical Development for Vectura, and Group Leader, Manufacturing, Science and Technology Services at Abbott Laboratories," says Coutts. "I enjoy working with our clients to support their journey with PCI and collaboratively solving any technical challenges they may have. Being part of the process of developing new medicines for patients and seeing them through to full commercial launch is extremely rewarding."

PCI's Tredegar site offers early phase formulation, analytical development, and clinical and commercial manufacture, specializing in potent products, as well as clinical and commercial packaging. The site is well positioned to address global drug product development needs throughout the product life cycle, from phase I through to commercialization.

MRNA: REACHING *for the* SUN

The mRNA field is experiencing rapid growth in the wake of pandemic success, but what more needs to be done to ensure that it truly flourishes?

By Maryam Mahdi

Every success story starts the same way: with an idea. Whether those behind the idea enjoy early success or face setbacks along the way, innovators believe their work will ultimately help drive society forward. Take the likes of Apple or Tesla; without a certain degree of tenacity and determination, their impact on the global community may have not been as significant. The same is also true for mRNA vaccine developers. Though the field is still relatively young, the early efforts of the academics and companies driving progress have captured global attention.

mRNA-based vaccines and therapeutics were already gaining momentum prior to the pandemic, but COVID-19 vaccine success stories have injected additional excitement and hope – with new investment following close behind and research now blossoming throughout the industry. But what will happen next? COVID-19 provided companies with the right conditions to flourish; without the typical regulatory and legal restrictions in place (and with an unprecedented level of cross-industry collaboration), companies were able to accelerate drug development and get their product into the arms of patients quickly.

As the pandemic dust begins to settle and pharma (and the world) returns to some semblance of its former normality, mRNA developers will undoubtedly face a new level of scrutiny – and there will be those who question whether mRNA products will find long-lasting success in the industry. To move forward, companies will have to look back at the learnings they've gained to date.

THE COVID-19 EFFECT

The COVID-19 pandemic has shaped the way stakeholders both in industry and beyond view mRNA vaccines. Though some skepticism lingers within the general public, the uptake of mRNA vaccines as prophylactics against SARS-CoV-2 has been unprecedented. By mid-August 2021, more than 4.84 billion doses of COVID-19 vaccines (many of them based on mRNA) had been administered (1). But confidence in new vaccines was hard-won. Companies, government agencies, and regulators all had to ensure that people understood how the drug development process – a process well known to be notoriously long and riddled with challenges – was expedited to bring a new technology like mRNA to market in the space of a year.

Although mRNA seems new to the general public, those in industry circles are well aware that the R&D behind it has been years in the making. Amélie Boulais, Head of Market Entry Strategy at Sartorius says, "Researchers have been studying mRNA as a potential vaccine platform for indications such as infectious disease and cancer for almost 25 years. Before the pandemic, human trials were already underway for mRNA-based vaccines to prevent HIV, influenza, and Zika virus. This is because the antigen can be sequenced and manufactured very quickly, which makes it a practical solution from a commercial point of view."

Of course, the early mRNA pioneers couldn't have predicted that COVID-19 would emerge as a global healthcare crisis, but the scientific framework they developed allowed them to rapidly switch gears when the pandemic began. Prior to the pandemic, there was a lack of evidence to show the efficacy of mRNA in patients but this quickly changed as vaccine rollout programs began. Boulais says, "We were just waiting for the proof that mRNA could work in the real world. And we now have it. The success of the mRNA-based COVID-19 vaccinations created interest across the industry. There is a lot more funding available for companies seeking to enter the mRNA space, and now we are starting to see companies big and small developing mRNA-based vaccines. BioNTech and Moderna are pushing forward with mRNA-based vaccines for a variety of indications and creating a strong pipeline towards immunotherapy and even personalized therapies. Other major players in the field, such as Sanofi and GSK, are investing in mRNA too. Meanwhile, dozens of startups are popping up looking to discover novel uses for mRNA in vaccine development."

The growing interest sparked by COVID-19 will mean that mRNA-based products will have a greater influence on future drug pipelines. But what effect will this have on the use of more conventional products as the field continues to mature?

WEIGHING UP THE BENEFITS

Though traditional vaccines are some of the best and most widely available pharmaceutical interventions used today, it is not an easy road for pharma to travel. If vaccines survive the "valley of death" – the translational gap between bench and bedside – developers must still face multiple challenges related to their manufacture. Historically, vaccines have been associated with high costs and low returns – and therefore considered unattractive to drug developers.

"Most conventional (viral vector) vaccines against viral diseases are made from viruses grown in chicken eggs or mammalian cells. The process of collecting the virus and adapting it to grow in the lab is lengthy and can take months to produce by growing weakened forms of the virus," explains Stefan Randl, Vice President of Research, Development, and Innovation at Evonik. "In contrast, mRNA vaccines can be constructed quickly using only the pathogen's genetic code. It takes roughly a week to generate an experimental batch of mRNA vaccine. Producing and scaling up production is also relatively simple because the technology requires a standard production platform."

Simply put, mRNA allows the body to become its own drug factory. But to deliver mRNA into cells, we must rely on lipid nanoparticles (LNP). Once inside the cell, mRNA interacts with cellular machinery to "manufacture" the antigen and subsequently trigger an immune response. "They do this without integrating into the human genome making them particularly safe to use," adds Randl.

The mRNA technology available today also offers a potential solution to overcoming mutations in viruses, adds Dieter Schinzer, Director of the Institute of Chemistry at the University of Magdeburg. Referring to the latest COVID-19 vaccines he says, "When compared with classic vaccines, the flexibility of mRNA-based products shines. They can quickly adapt to mutations due to their mechanisms of action. They are more easy to produce and, for the most part, are cost-efficient."

But mRNA isn't without its limitations. Randl says, "Though players began to invest more heavily in the field at the start of the 2000s, the immunogenicity of these products has slowed progress and hampered commercial success. mRNA is not very stable and has to be delivered to cells. If not, the right proteins will not be produced. The fact that there were only a handful of companies working in the space in these early days meant that it took longer for solutions to be devised."

Knowledge of the structures formed by lipid–nucleic acid complexes in the form of LNPs as well as of the effect of particle size, lipid composition, and distribution on biological activity, are also essential for the design of products with improved transfection efficacy. Aurel Radulescu, senior scientist at the Jülich Centre for Neutron Science in Forschungszentrum Jülich – a German interdisciplinary research center – uses a small-angle neutron scattering diffractometer to analyze scatter data of various molecules, including mRNA. He says, "If the industry aims to expand the use of mRNA from vaccines into other therapeutic areas, new methods of delivery will have to be considered. Great progress has been made in achieving efficient and tolerable LNPs for the delivery of mRNA for intravenous and intramuscular administration, but challenges remain with subcutaneous self-administration. If this is improved it opens up the possibility of patient self-administration and, therefore, long-term treatment of chronic diseases."

Storage conditions add an additional layer of complexity to the use of mRNA-based therapeutics. Boulais even argues that it is the "greatest limitation." "In developed countries, where cold chain infrastructure is in place, storage is less of a problem, but this just isn't the case for low- and middle-income countries (LMIC), where these facilities are lacking. However, we are starting to see improvement in this space. For example, the Moderna COVID-19 vaccine has now improved stability and can be stored refrigerated between 2-8°C for up to 30 days prior to first use. Therefore by working both on the LNP and the formulation itself this challenge might be soon overcome," she says.

"The challenge of logistics and cold chain with mRNA is difficult to overcome quickly. Considerations will have to be given to the individual circumstances of countries' governments as well as the support available from the public and private sectors," says Randl. "If rectified, equitable access for patients could be achieved. But, for now, it is apparent that this will be a long-term goal for all parties involved. And patients in LMICs will have to continue to wait for fair and equal access to these innovative products."

Even if the right supply chain conditions were in place today, the limited number of high-tech facilities to produce mRNA-based products introduces another barrier for companies worldwide. "Only a few enterprises worldwide have the technology to provide the required lipids at very high purity for the formulation of these new vaccines. Existing facilities will have to ensure that they can supply the quantities of raw materials and vaccines needed to keep up with industry demand," Schinzer explains.

There's also a lack of equipment specifically made for mRNA. Boulais says, "Many processes today have been scaled up and developed very quickly, and due to the COVID-19 rush must be re-examined to identify areas for improvement," she says. "Due to the fast development, in the near future we expect to see further optimization in processes to increase efficiency and reduce the cost of goods solds (COGS). We also expect innovation coming into the space to be able to serve the different applications that mRNA might have in the future. The industry will learn from trial-and-error on a massive scale as different industry players test the limits and capabilities of mRNA in different areas of biopharmaceutical

design and production. The very nature of mRNA technology offers much potential to unlock a new pipeline of drugs for some of the world's most challenging diseases."

As the industry looks ahead, Randl believes that regulators – although very supportive thus far of mRNA-based vaccines for COVID-19 – may also have more questions for mRNA drug developers in the future. "The FastTrack designation given to COVID-19 vaccines was essential for lessening the impact of the pandemic, but I believe that companies will have to do more to understand the unknowns about mRNA. We have to anticipate certain questions from regulatory agencies. How toxic are they? How well are they degraded? We have to be willing and ready to answer them as we look to develop lifelong treatments for patients using them. But although there may be more scrutiny, many of these questions should become easier to answer as the field advances."

The Manufacturing Conundrum

With Amélie Boulais and Stefan Randl

How are mRNA-based vaccines manufactured?

Boulais: To produce mRNA, manufacturers begin with a DNA plasmid containing the sequence coding for a particular antigen. Plasmid DNA can be manufactured in-house or bought from a third party. Then, an enzymatic reaction takes place in a reactor where the plasmid, nucleotides, and enzyme are added. This in vitro transcription (IVT) reaction can vary depending on companies' manufacturing approach, but there is some uniformity as key enzymes for such reactions must be used; capping enzymes, which are critical for protecting mRNA from degradation, and T7 polymerases, which catalyze the formation from DNA to mRNA, are essential to the process.

IVT reactions last 3–4 hours. In my view, when compared to classic cell culture, the benefits become clear. A conventional cell culture relies on weeks of growth and bacterial fermentation that normally takes anywhere between 24 to 48 hours to complete.

Finally, the IVT process continues and several steps involving either precipitation or chromatography are used to purify the mRNA and encapsulate it in LNP.

What are the biggest manufacturing challenges?

Boulais: Despite the apparent simplicity of this process, there are still some limitations; for example, widespread adoption of this process could lead to shortages in raw materials such as plasmid DNAs and enzymes. Current enzyme production, particularly for capping enzymes, is limited to a handful of producers. During the pandemic, production capacity and yields had to be dramatically increased, which came with obvious challenges.

Additionally, the process development expertise needed to produce mRNA vaccines is not yet widespread and IVT protocols are far from optimal. The goal of the future development of the IVT reaction is to reduce the use of raw materials while increasing the yield. The average production value is in the order of 3-5 g/L but future trends might push this production to 10 g/L.

Randl: As Amelie says, scale-up is a crucial consideration and cannot be underestimated. Until 2020, Evonik hadn't manufactured lipids at the kilogram scale before. But all of a sudden, the demand massively increased. Developing a scalable, reliable process takes time and we also have to ensure that any process we do end up using can easily be validated.

Are you optimistic that these challenges can be overcome?

Boulais: This field is evolving extremely fast. All these challenges should resolve themselves as demand for mRNA-based vaccines increases. IVT protocols will evolve and the raw material supply chain will improve, which will help reduce costs.

Ultimately the scientific community will need to figure out where the sweet spot for mRNA technology is. It will take additional research and time to discover whether mRNA can truly realize its potential in different areas. The potential for mRNA vaccines against new – and even unmet – indications, as well as in cell and gene therapy, has so far been unexplored, especially in combination with the fast-growing area of gene editing and the use of CRISPR/Cas9 technology.

Randl: I believe that mRNA has the potential to revolutionize the pharma industry in a similar way as biologics have in the last two decades. Though no show-stopping interventions have yet been developed (if we exclude COVID-19 vaccines), we now have a wealth of data proving their safety and tolerability.

Though there are certain roadblocks in the manufacturing process, I'm confident that they will be addressed as new technologies are developed. We also have to remember that we can't foresee every future challenge that might occur, but we do have the level of insight to help us enhance manufacturing practices for the better.

MRNA: FROM BUILDING BLOCKS TO SKYSCRAPERS?

The field is currently experiencing a growth spurt so we can expect to see more mRNA-based products filling pipelines as innovation continues and funding continues to pour into the space. "Many in the sector are working to develop new delivery approaches for LNPs to cater to the growing spectrum of products being developed today," says Boulais. "The delivery of nanoparticles is still an important issue for us to solve. The first trials using these products only began in 2014 so there's plenty of room for growth."

For Schinzer, it will be important for companies to take a closer look at the nanoparticles themselves. "mRNA-based therapies are like building blocks. They can quickly be adjusted to meet new or emerging needs. At Corden Pharma International, plant-based cholesterol is used as an alternative to the animal-derived cholesterol currently used to produce LNPs," he says. "A product of non-animal origin, quite simply, avoids any potential animal source of contamination and has environmental benefits. Plant-based cholesterol uses a solid, renewable base of biomass as starting material and this will be important to overcome lipid shortages."

Another consideration for the industry is the specificity of LNPs. The current generation of products are not tissue-specific. According to Boulais, this is fine for today's needs, but it will need to change as the industry begins to explore its potential for advanced therapies. "If we are to use LNPs and mRNA-based products in the gene therapy sector, for example, a lot of basic science will be needed to modify current designs," she says. "I expect that in the near future we will begin to see progress here. Beyond these nanoparticle designs, manufacturers will also have to work to enhance facility design for mRNA-based vaccine production. From a manufacturing point of view, the lipids are usually dissolved in very high ethanol concentration, (typically around 98 percent). This makes the facility design challenging and lots of precautions need to be in place to ensure environmental and safety measures."

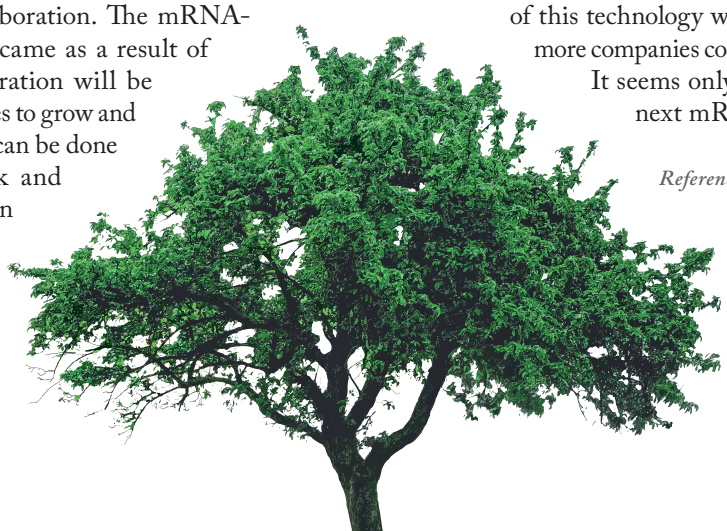
Though all these aspects of the future mRNA-based products are important, Randl and Radulescu make the case for continued collaboration. The mRNA-based COVID-19 vaccines came as a result of collaboration – and collaboration will be important as the field continues to grow and companies explore what else can be done with mRNA. Both Evonik and the Jülich Centre for Neutron Science have entered multi-year agreements with academic and industry partners to help push forward new projects.

"Evonik has entered a three-year deal with Stanford University in the US to develop a polymer-based drug delivery system to ensure the safe delivery of mRNA into cells, particularly as companies begin to further their applications for cancer immunotherapy and gene therapies," says Randl. "Though we have our own developments underway, we were keen to tech scout to find other promising work and support its growth," he says. The team came across the work of a research group at Stanford led by Robert Weymouth, Robert Eckles Swain Professor of Chemistry, who had developed a platform called "Charge Altering Releasable Transporters." The technology enables the delivery of mRNA into cells with a transfection efficiency rate greater than 99 percent.

"We initiated this collaboration as a strategic step to ensure mRNA technologies can be used fully and most effectively, and the platform developed by scientists at Stanford is promising because it is flexible and adaptable," says Randl. "The goal is to develop a technology for delivering mRNA to tissues and organs that goes beyond the current possibilities of LNPs."

Meanwhile, Radulescu and his colleagues at the Jülich Centre for Neutron Science have entered into a very different kind of agreement. As an academic group, their collaboration with AstraZeneca will see their research, which focuses on the use of neutron scattering studies, used to enhance mRNA-based products design for better subcutaneous drug delivery. "Our collaboration with AstraZeneca started in 2015 when scientists from AstraZeneca visited our center in Garching to carry out structural investigations on newly proposed LNPs as delivery systems for mRNA therapies," says Radulescu. "We provide beam-time for neutron scattering experiments and expertise for the analysis of the scattering data collected during such experiments. We're now aiming for structural characterizations of new formulations to increase the therapeutic application opportunities."

These efforts are seemingly steps in the right direction for mRNA drug developers. But are the teams optimistic about seeing their efforts realized? "Absolutely. Without a doubt, mRNA technology holds a promising future," says Boulais. "Years of research and development using this technology are what made the COVID-19 vaccine possible – and the future of this technology will only continue to evolve as more companies continue to explore its potential." It seems only a matter of time before the next mRNA breakthrough emerges.



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Expanding into Other Infectious Disease Areas

Evelina Angov, Chief, Laboratory of Molecular Parasitology, Walter Reed Army Institute of Research, believes mRNA vaccines could play an important role in the treatment of other infectious diseases – especially malaria, a disease that affects up to 200 million lives each year. Here, we ask Angov about her thoughts on mRNA-based therapies – and how the Institute is helping in the global goal of eradicating malaria by 2050.

What role can mRNA vaccines play in treating malaria?

A highly effective malaria vaccine would go a long way toward the goal of malaria eradication. mRNA vaccines' advantage over traditional approaches is the rapid transition from target discovery to manufacture. Similarly, this approach can be used to deliver more complex, multi-antigen vaccines by combining sequence variants and targets, which would broaden immunity.

What is the Walter Reed Army Institute of Research working on?

Recent successes of mRNA vaccine delivery for SARS-CoV-2 have propelled the long-neglected platform to the forefront of infectious disease research. In our recently published paper (https://go.nature.com/37Vex9x), we selected the immunodominant coat protein of the invasive stage of the malaria parasite, circumsporozoite protein (PfCSP), as the target to evaluate for the protective potential of mRNA malaria vaccines in mice. LNP encapsulation was used to protect and deliver the mRNA to the cell translation machinery and to supply adjuvant activity. We explored the effect of several factors, such as formulation, dose, number, and interval of immunizations, in two mouse strains, and showed the protective potential of a PfCSP mRNA-LNP against lethal, rodent-malaria transgenic parasites.

As people living in low- and middle-income countries are most vulnerable to malaria, what considerations will have to be made when developing suitable mRNA therapeutics?

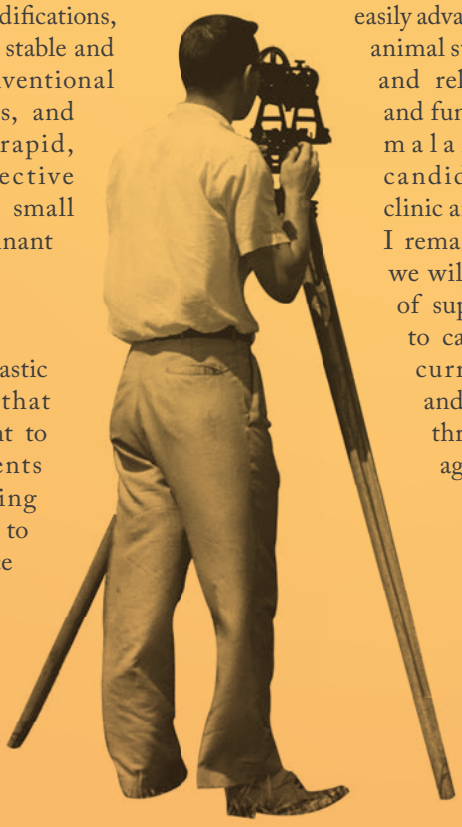
Firstly, safety is paramount for any target population. But the product profile of a successful mRNA vaccine in these areas will potentially need to address narrower cold chain and storage capabilities, as well as a price-point compatible with fiscal sustainability. The advantages of mRNA are that the transcript (coding) sequences can be optimized rapidly to adjust for variants, mutations, or other modifications, formulations are fairly stable and fieldable under conventional deployable conditions, and manufacturing is rapid, and more cost-effective by comparison with small molecules or recombinant protein technologies.

What's next?

Though we are enthusiastic with the findings that we reported, we want to explore improvements to the malaria coding sequence (transcript) to see if we can enhance immune responses, prior to moving into a more representative animal model, such as the non-human primate. Outside of the improvements to the PfCSP mRNA transcript sequence, we are also evaluating mRNA as a viable immunoprophylactic modality to limit infection and disease. This is an area of research and product development that can greatly benefit from overcoming the traditional challenges and development costs of recombinant antibody-based products.

What is your outlook on the future of vaccines?

I have been a scientist in this field for 26 years, and really feel that we are living in an exciting time for malaria vaccines and vaccines in general. Despite numerous challenges, there is great progress toward the development of protective vaccines against pre-erythrocytic malaria infection. There are new vaccine platforms and technologies that have never been so available or accessible. Though we can easily advance to preclinical animal studies, the stable and reliable resources and funding to advance malaria vaccine candidates into the clinic and beyond phase I remains elusive, and we will need this type of support if we are to capitalize on our current advantage and ultimately push through to a victory against malaria.



DON'T SHOOT THE MESSENGER

Today, mRNA vaccines are playing a key role in suppressing the COVID-19 pandemic. Could they tackle the flu tomorrow? We sat down to ask Russell Basser, Head of R&D at influenza vaccine manufacturer Seqirus, if we should buy the hype.

In both Seqirus and the wider industry, how much interest was there in mRNA-based vaccines prior to COVID-19?

Moderna was one of the largest companies involved in mRNA, but research was generally confined to a small handful of groups. As far as the industry was concerned prior to the pandemic, mRNA was untested water. At Seqirus, we were interested in mRNA and had a program in influenza, but, at the time, it wasn't a high priority. We developed a preclinical vaccine and obtained some pleasing data, but we weren't in a position to take advantage or to participate in developing a COVID-19 vaccine once the pandemic began.

The emergence of COVID-19 has probably accelerated the mRNA field by five to ten years.

Did people inside the industry expect mRNA COVID-19 vaccines to be so successful?

At the start of the pandemic, there was still quite a lot of skepticism about whether an mRNA vaccine could be developed successfully, as there were relatively few trials before COVID-19. We also didn't know enough about the SARS-CoV-2 virus at the start of the pandemic to say for certain if an mRNA-based approach would work. There were also practical considerations around the supply chain. But Pfizer, BioNTech, and Moderna have done a fabulous job – and the supply chain innovation has been remarkable, particularly early on when not a lot was known about the stability of the vaccines. The flexibility of RNA has helped greatly in generating a COVID-19 vaccine. The identity of the virus was identified and the ability to make mRNA vaccines soon followed, because all that is needed for an mRNA vaccine is a chemical reaction.

One thing that is perhaps not widely appreciated is that without SARS and MERS, the world would still be waiting for a COVID-19 vaccine because we wouldn't have known so early on what the target should be. People understood that the targets used in the SARS and MERS vaccines would probably apply to COVID-19, although it wasn't known how effective these targets would be at generating a response. The COVID-19 vaccines approved thus far have performed brilliantly. The data now coming out in the UK, Canada, and Israel show they are also protecting against the variants much better than we might have expected.

What's your view on COVID-19 booster vaccines? And how might efforts to tackle COVID-19 feed into seasonal influenza vaccines and strategies?

Thus far, there are no recommendations for COVID-19 booster vaccines from any countries, regulatory agencies, or vaccine immunization recommenders. However, that does not mean they will not come. There remains much debate over whether, if, and when a booster injection will be needed. Based on the available data, I suspect it won't be every year; rather, it will depend on how the variants evolve, and what sort of pressure they put on population health. The jury is still out.

In terms of pivoting to flu, mRNA holds much exciting potential. Moderna, for example, had a number of ongoing projects including influenza and infectious diseases before the pandemic. But I think we need to be careful about being distracted by the latest new "shiny thing." With flu, we already have a vaccine. There is room for improvement, but the current flu vaccines have decades of information behind them to show they are safe and effective. With the COVID-19 vaccines, we've seen there can be issues, such as myocarditis in younger people. The COVID-19 vaccines use one protein from a single strain of the virus, but with flu that will be four strains (and ideally more since that will help us to make a more effective flu vaccine), which could introduce challenges and side effects. People don't want to be regularly taking days off work every time they receive their annual flu jab!

I recently attended an Australian online scientific conference on mRNA and there was discussion on another RNA product that is indicated for rare diseases. The results showed positive outcomes for some young boys suffering from one particularly horrible disease. On the other hand, at the conference we also heard about a number of projects which had to be halted because of negative unintended consequences.

The mRNA technology has worked brilliantly for COVID-19, but we need to ensure we use mRNA-based approaches appropriately. In fact, all the vaccine platforms have been highly successful with COVID-19, which suggests to me that SARS-

Russell Basser, Head of R&D at Seqirus

CoV-2 is – fortunately – a good target for the vaccine. However, it doesn't suggest that an mRNA platform is going to make existing vaccines better. There's still much to learn, but I think we can get a little excited about the great outcomes we could see.

In summary, mRNA won't immediately dominate the field, because there are risks attached to it. If we're to continue to protect the public, we must work ethically. If we suggest a way forward that is burdened by risk, then we're not doing our job properly. I believe we developers have a long way to go before we understand how mRNA for seasonal flu fits into that obligation.

How do you think regulations around mRNA might change?

This is the second pandemic where I've been involved in drug development; once events normalize, standard regulations will return. Many of the usual barriers were reduced for COVID-19 drug development because there was a global threat, but that won't last forever. The regulations may not swing back to exactly where they were before, but developers will have to prove safety, dosing, and long term efficacy. The regulators are not going to set the bar low and people who already make flu vaccines will want to be confident that any replacements they make are worth the cost. New platforms don't come cheap either.

How do we prepare for the next pandemic?

I believe that we still need to be ready for the possible event of a flu pandemic. When that day comes, we may have mRNA approaches at the right level for flu, or we may not. It is also worth considering that during a flu pandemic, the populations most at risk are not just older people, but often infants and pregnant women. Until mRNA vaccines have a strong track record, they won't be the solution we need.

For a variety of reasons, flu levels are down from last year. And that means that the world could be a little bit less protected from flu, which is causing some concern right now; if a pandemic did strike, we'd want to disseminate a proven vaccine among the entire population. We wouldn't have time to wait for a flu vaccine to be developed in mRNA, and proven across all age ranges. Put simply, our focus should remain on the strategies that are proven to be safe and effective.

RIDING THE NEW WAVE

What achievements will define the next chapter of the mRNA success story?

mRNA was an exciting field long before the pandemic accelerated its development. But now that the field has found a new level of success, how can it apply its learnings to improve treatment options for other diseases? Igor Splawski, Chief Scientific Officer of CureVac, shares his thoughts on what we can look forward to – if we keep the wheel turning.

How did you become interested in mRNA-based therapeutics?

It feels like I've always had an interest in discovering the genes behind diseases and disorders – certainly, it was the focus of my work starting with my PhD in 1992. I continued my gene identification research after the completion of my doctorate at the Howard Hughes Medical Institute, Children's Hospital Boston, and Harvard Medical School, where I became an assistant professor.

In 2005, I joined Novartis. While using the learnings from human genetics, I completely switched my focus to biologics. Most of my years there were spent working on ophthalmology and cardiovascular disease. Towards the end of 2011, I reignited my former interest – my "unfinished business" – by starting a group specializing in mRNA. The group began with one person but, at its peak, numbered around 50. Our primary goal was gene replacement with mRNA, where we showed several proof-of-concept studies in vivo and expression in non-human primates. Moreover, that's when I met some of my current colleagues from CureVac – the first ever mRNA technology company, founded in 2000 with the aim to successfully harness mRNA for medical purposes.

Last July, CureVac hired me as their Chief Scientific Officer. The work has proved extremely satisfying. To me, few things are more rewarding than working at the edge of knowledge in a whole new field of science, knowing and seeing that our work makes great contributions to health, medicine, and society.

Pre-pandemic, what were industry attitudes towards mRNA?

Prior to the onset of the pandemic, mRNA wasn't widely known. It appeared to be falling in line with gene therapy research. Certain scientific leaps helped change this. The discovery of small interfering RNA (siRNA) by Andrew Fire and Craig Mello was a key milestone – the Nobel Prize they won for it highlighted the importance of RNA to a wider audience. This was cemented in 2013 and 2018 with the approval of the first antisense oligonucleotide and siRNA drugs, respectively, compounds that directly affect mRNA.

While these achievements were incredibly significant, it is the COVID-19 pandemic that brought mRNA to the fore. Tens of millions of individuals around the world have now been vaccinated with the first two vaccines approved for emergency use. The Pfizer-BioNTech mRNA vaccine was recently fully approved for use by the FDA. But what was most stunning about this newfound success was the speed – in part driven by technological development, and in part by the worldwide need for safe, effective vaccines. The field is now exploding – in the last year, we have seen the launch of scores of mRNA biotechnology companies. Larger players have initiated efforts of their own, and in some cases are acquiring mRNA companies to jumpstart the process.

How do you think mRNA research will evolve post-pandemic?

Most mRNA trials before COVID-19 involved only a small number of individuals. Now, millions have been vaccinated with mRNA. The push to make this happen produced a great deal of research and learning. We have the opportunity to capitalize on the work, and explore all kinds of interesting applications based on the data we have acquired.

Though many companies will continue to explore infectious diseases, new data can and will be used to develop cancer vaccines and treatments for indications where there is a need to express intracellular proteins, inhibitors, or modulators.

"Disruption" is a hard buzzword to avoid; mRNA therapies have certainly changed the industry for good. The fact that more people are getting involved is exciting; outsiders are now joining the field, and industry veterans are learning from them. We can expect input from engineers and physicists, sociologists and ethicists, chemists and IT experts – all will have a say in the future direction of the field. These collaborations are so important because they connect us to forward-thinking minds outside the pharmaceutical industry. There is scientific talent in other industries that we can tap into and help grow (and vice-versa!).

And how is your work informing the future of the field?

COVID-19 remains a priority for us at CureVac. We are continuing to work on our current vaccines. We have already seen significant improvements in our second-generation product. We are also looking into the application of mRNA technology to

Igor Splawski, Chief Scientific Officer at CureVac

the treatment of cancer, as well as rare diseases. We have interest in the eye and lung, as well as other organs with applications that might differ depending on the indication that they're trying to address, and the medical need.

With our partners, such as GSK and the Bill and Melinda Gates Foundation, we are working on other infectious diseases. We are taking the learnings from the prophylactic vaccines into therapeutic vaccines, e.g. the use of mRNA vaccines for the treatment of cancer. There is only one approved cancer vaccine now – it's a very complicated indication. By the time cancer is diagnosed, in most cases it has already turned into many diseases that can hardly be treated with one approach. It is my hope that mRNA can make a great difference here, either alone or most likely in combination with alternative types of approved treatments, including antibodies, low molecular weight compounds, as well as cell therapies.

My colleagues and I are excited about mRNA's application to the treatment of rare diseases. Personally, this is where most of my interest lies – likely because of my 30 years of experience working on genetics and human disease.

How else will the field continue to grow?

I think the biopharmaceutical industry is courageous. And much of the courage comes from smaller companies that are usually founded on an idea and vision. It is those ideas that can take exciting new forms, or reach places not previously explored. It takes fortitude and hard work by pharmaceutical companies to bring out this species of innovative disruption. The pull from the medical field and the understanding of new technologies by society and regulators are quite important as well.

Here's another exciting thing that pharmaceutical companies need: new talent. Pharma and other tech industries need today's young people to return to sciences. In recent years, it seems there has been a drift away from science. But I want young people to know there will always be fulfilling jobs in all fields of science, combined with the thrill that discovery ignites. Of course, I'm biased, but I believe that nothing else compares to the excitement of science and medicine, and their contribution to society. Teachers, professors, and educators at every level are the other necessary and amazing contributors to society's development and advancement.

What scientific discoveries have thrilled you lately – and where do you foresee the next?

There are problems in physics that vexed people for over 100 years that were solved in the last one or two decades. The first siRNA drugs were approved just three years ago. Now, the first mRNA drugs are approved. Consider these are whole new classes of medicine! If people don't yet find this exciting, I hope they stumble across an article, teacher, or a friend that charms them with this knowledge and changes their minds.

Great discoveries come to those who work and think hard, and some things come as a bonus – and from places you'd never expect. Conversely, exciting discoveries don't happen on a daily basis. Sometimes there are times where one sees a period of negative results; notably, these should be viewed as something worthwhile and temporary, and we can share such learning experiences with younger scientists, so that they are not easily discouraged when the first signs of difficulty appear.

To me, discovery in life science comes in waves – there are peaks and troughs. People should enjoy riding the crest of the wave, and endure the ups and downs that come with waves. My own career has been enormously rewarding – and not because every success was easily won but because of the experience of discovering genes and drugs, because of the amazing people that I have learned from, worked with, and met along the way. I hope many more people choose science with the understanding that not everything can be discovered in one day, it is a long journey.

Of course, it's not an easy! However, the satisfaction that comes with discovery and pushing the boundaries of human knowledge make the journey so very invigorating, exhilarating, and deeply rewarding.

The Rise of mRNA: New Era, New Challenges

mRNA vaccines have provided one good answer to humankind's latest grand challenge, but the technology has yet to mature. If the success story of these nucleotide-based drugs is to continue, manufacturers must look to ease the headaches associated with their manufacture.

By Amelie Boulais, Nitin Chopra, and Jay Zhang

Within just a few decades, industry perspectives on mRNA-based therapeutics have drastically changed. In the early 1970s, only a handful of scientists were exploring the potential of mRNA and their work attracted little attention. Today, however, the power of mRNA vaccines is undeniable; they have dominated the industry's response to COVID-19 and questions are being asked about their influence on the broader therapeutic landscape. mRNA-related research is filling pipelines as manufacturers seek to be part of the industry's next success story; meanwhile, the achievements have piqued the interest of investors, who are keen to support the development of the next generation of successful mRNA-based products.

The relative newness of the market means there is still uncertainty surrounding the best approaches to process development and manufacturing – and there are many challenges to face.

Perfecting processes

To start any commercial journey off on the right foot, manufacturers must have a clear understanding of the processes that underpin their products. However, this is hard to do for very new products, such as mRNA-based therapeutics, which have not been commercially used before.

The processes for producing mRNA-based vaccines are very different compared to traditional vaccines. mRNA vaccines rely on an enzymatic reaction, which is, in essence, simpler than cell culture, but still in its infancy; innovations are still required to improve yield, stability, or translation efficiency. In addition, there is no reference or standard in vitro transcription (IVT) protocol available for all mRNA-based products. Therefore, manufacturers must develop and optimize their own IVT, leading to a considerable number of process variations in both upstream and downstream processes. As the field is still evolving, it is important that the toolbox of solutions is adjusted to meet market needs.

Once manufacturers are ready to put their process development plans into motion, Sartorius offers a toolbox of products ready to cover their end-to-end process needs. Our solutions include:

- The high throughput process development platform Ambr® to improve customers' understanding of IVT reactions and gather data
- A new generation of analytical column providing clear insight on IVT reactions by HPLC, to monitor target molecule production and reagent consumption
- A toolbox of monolithic columns for purification of mRNA, addressing most production scenarios with seamless scalability covering everything from product development to commercial needs

Controlling costs

An accelerated journey to market doesn't begin and end with access to the right equipment; we also help customers to map out their processes; for example, we highlight how process steps can be optimized, where cost-savings can be achieved, and how scalable development techniques can be used to tackle manufacturing woes.

Though all these services are of importance, we believe that cost awareness is a crucial factor in the product development process. The reason? mRNA-based products can be expensive to produce – in part due to the use of high-priced reagents. Around 80 percent of the cost of goods for mRNA-based products is tied up in raw materials, with roughly 60-65 percent of the cost attributed to the IVT reaction. An additional 15- 20 percent of the cost is tied to the formulation step, where mRNA is enclosed in lipid nanoparticles.

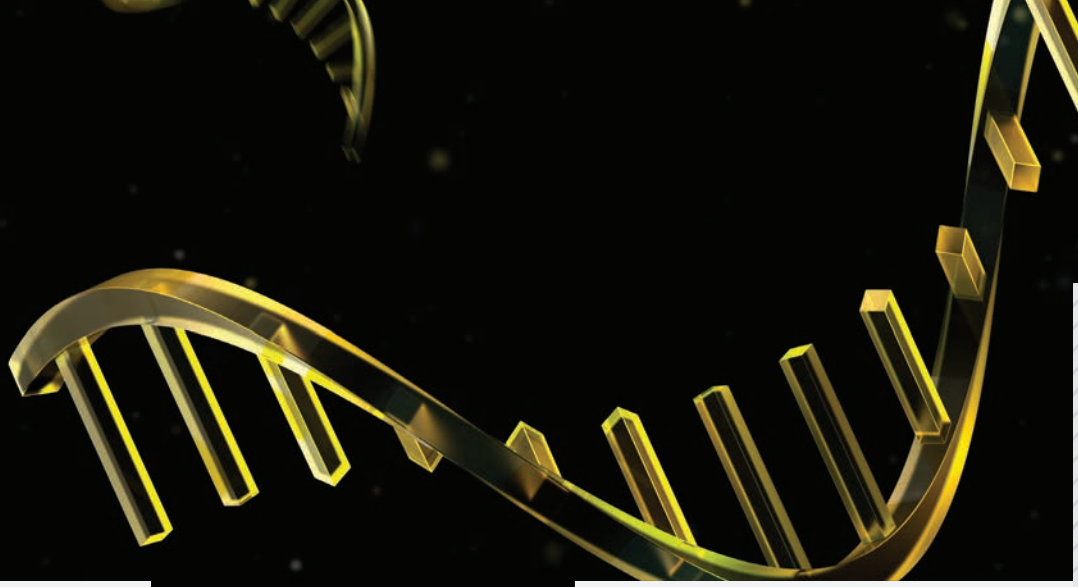
We support manufacturers in the optimization of costs with a small-scale high throughput platform for IVT, combined with our Design of Experiments software, helping developers to find the best protocol that results in the lowest utilization of costly reagents.

Facility design is another key aspect of our services. Our consultants ensure the best process solutions are selected, based on a product's properties and the customer's requirements. We work with developers to pick the right technology and equipment, estimate the yields and material requirements, and create timelines for efficient process scheduling. This approach allows us to work collaboratively with customers to make adjustments to either new or existing facilities to help them make the right decisions for their budget and in accordance with the latest regulation for biopharmaceutical production.

Managing tactical complexities

To add further complexity, mRNA products are inherently unstable molecules. Although significant progress is being made to maintain the integrity of the product over time (with new mRNA constructs and improved formulations), there are still two challenges that need to be addressed during manufacturing: RNase free processing and storage.

mRNA vaccines are unstable at room temperature and hence require cold



chain infrastructure to prevent spoiling and wastage. This is a significant hurdle for modern manufacturers, but they can draw inspiration from other product types as the field continues to mature. Take viral vectors for example; today, viral vectors can be stored at temperatures between 2-8 °C, but a few short years ago, temperatures as low as -20°C were necessary to maintain them. Over time the stability and storage facilities for mRNA will certainly improve. At Sartorius, we're constantly exploring how this can be achieved. We have 15 years of experience in designing freeze and thaw solutions from lab scale to large commercial scale. Our Celsius® portfolio offers an end-to-end, integrated approach that enables monitoring and controls to assure product quality and integrity at scale. This experience is invaluable when designing frozen storage and transportation solutions for these sensitive mRNA molecules – helping to tackle some of the issues manufacturers face today.

Another solution that is tailored for mRNA-based drugs is our tangential flow filtration technology. By providing an option for gamma sterilized ready-to-use format, we can help mitigate the risk of contamination by RNAse/DNAse – a challenge specific to mRNA production.

The road ahead

As we look ahead, we're optimistic about the possibilities that mRNA products could hold – and the pandemic has provided us with a practical example of how quickly mRNA products can be manufactured and distributed. Now, drug developers are eagerly looking at indications beyond COVID-19, including how mRNA-based products could influence the future of oncology and personalized medicine.

Industry suppliers and regulators will also have a role to play as the field continues to evolve. We are likely to see updated regulatory guidelines as regulators resume business as normal and analyze learnings from the mRNA COVID-19 vaccines. On the supplier side, there will be a need for innovative equipment specifically suited to mRNA manufacture. At Sartorius, for example, we are working collaboratively with industrial partners to develop the next generation of single-use products and solutions tailored to the needs of mRNA manufacturers.

The world can already see the promise; mRNA vaccines are already out there, protecting countless lives. As our customers continue to innovate, we will remain flexible to help support their success. An adaptable mindset and out-of-the-box thinking will help support the discoveries that will inform the future of the field. And as the field continues to evolve, we will remain reliable partners to the manufacturers aiming to bring life-saving medicines to patients in need.

Amélie Boulais is Head of Market Entry Strategy, Viral based Therapeutics, Nitin Chopra is a Platform Technical Consultant, and Jay Zhang is a Process Technology Manager (Gene Therapy, all at Sartorius

Domain Expertise

The newness of mRNA products means that the talent pool (the technical aptitude and skills required to respond to the challenges) is limited. In fact, most of the industry's expertise with mRNA sits with a few key players, such as BioNTech, Moderna, and Curevac, but many other manufacturers are now receiving investment and entering the mRNA space.

Even before the mRNA vaccines were considered for the COVID-19 pandemic, BIA Separations (a company recently acquired by Sartorius) had been working on this budding technology. With labs dedicated to analyzing and conducting extensive research on the purification of mRNA. Why? Because mRNA was attracting increased attention in the industry and held the potential for developing new therapeutics. In the past few years, Sartorius has invested in infrastructure, technologies, and experience that have helped our customers build their mRNA expertise and processes without compromising their current development pipelines. Put simply, our Cornerstone® process development services enable rapid product development by offering effective tools and expertise so that customers can feel supported as they pursue new therapeutic avenues

NextGen

R&D pipeline
New technology
Future trends

Malaysia in the Middle: Tackling Hep C in an Unfair World

How the Drugs for Neglected Diseases Initiative worked successfully with local and global partners to improve left-behind lives in Southeast Asia

By Angus Stewart

When it comes to beating infectious disease, middle-income nations face a two-pronged problem: they're too poor to pay for patented medicines upfront, and too wealthy to qualify for voluntary licenses – the charitable exceptions to patent paywalls which (in theory) improve drug access in the world's poorest countries.

Malaysia is not one of the world's poorest countries. In the UN's human development index, it places at 62 out of 189 countries (1). World Bank figures from 2020 place Malaysia at 58 out of 199 in GDP per capita (2). Though Malaysia's economy is on track to transition from "middle income" to "high income" by 2024, growth has been lopsided and the outlook is less than certain. The poorest 40 percent of the population are financially vulnerable, and more than one in 20 households lives in absolute poverty (3). Much of the population is susceptible to ailments that citizens of the world's wealthiest countries are by-and-large shielded from – hepatitis C being a prime example. At present, around 400,000 people among Malaysia's population of 32 million are infected.

A real burden

When asked which groups in Malaysia suffer most from hep C, Radzi Hassan, a practicing consultant physician and gastroenterologist, and recent appointee as the Head of Service for Internal Medicine under Malaysia's Ministry of Health, says, "Based on my observation, people who inject drugs constitute the vast majority of hepatitis C patients in Malaysia. The other key populations of hepatitis C include people living with HIV, people living in prisons and rehabilitation centres, men who have sex with men, and sex workers. Generally, hepatitis C patients in the country are made up of vulnerable groups, characterized by a relatively low socioeconomic status."

Hassan also lays out the economic angle: "Malaysia is pursuing the global goal set by the WHO to eliminate hepatitis C as a public health threat by the year 2030; ensuring accessibility of effective direct-acting antivirals (DAAs) is exceptionally important. However, the use of DAAs in Malaysia was once restricted by their exorbitant prices. Many patients were, therefore, not treated timely and died from the chronic complications of hepatitis C, including cirrhosis and hepatocellular carcinoma. Having more treatment options can create a more competitive market for DAAs, and indirectly make them more affordable."

In 2016, the Malaysian government introduced a three point strategy to help achieve the 2030 goal: i) seek out hep C infected patients in the country; ii) lower the price of DAAs; and iii) decentralize hep C treatment to make it easier for patients to access.

The government began working on plans to identify patients and decentralize treatment, but to achieve the pricing objective the government had to negotiate with Gilead Sciences with regards to the hep C blockbuster drug Sovaldi (sofosbuvir). The drug came with a cost of around $1000 per pill at the time - working out at around $84,000 per treatment course. The negotiations ultimately failed, but in response Malaysia issued a "government use" compulsory license, granting access to generic sofosbuvir (priced at $300). In counter-response, Gilead granted voluntary licenses to not only Malaysia but also Thailand, and Ukraine, where clinical trials of a new DAA called ravidasvir were planned.

Enter the DNDi

The Drugs for Neglected Diseases Initiative (DNDi) was well aware of the price controversies surrounding sofosbuvir. The initiative was founded in 2003 after Médecins Sans Frontières (MSF) dedicated a portion of their 1999 Nobel Peace Prize to exploring a new, alternative, not-for-profit model for developing drugs for neglected patients. According to François Bompart, Chair of the Access Committee and Former Director of HIV & Hepatitis C Initiative at the DNDi, hep C treatment before sofosbuvir was complex, badly tolerated by patients, and ineffective. "Sofosbuvir brought about a total revolution: this was the first drug that could, after 3–6 months of a well-tolerated oral treatment, actually cure patients entirely and prevent people from transmitting the virus to others. This huge innovation was hailed as a 'miracle drug.' The problem is that this innovation was priced at a level that was unheard of at the time. Even for high-income countries, such a price level represented a major challenge. Some were able to negotiate more reasonable prices for sofosbuvir and its successors, but the drug remained out of reach for many countries."

More from Radzi Hassan on taking the fight to hep C

"Hepatitis C is one of the first viral diseases with a cure. When the disease is curable and treatable, and the drugs are made available, treatment becomes something like a human right. Everybody should be offered the treatment," says Hassan.

As a practising doctor for almost 30 years, he explains, "Historically, treatments for hep C were somewhat horrible, and perhaps toxic, because you are dealing with treatments like interferon and ribavirin whose side effects are awful." This unfortunate truth about past treatments is compounded by the fact that they had a cure rate of only around 50 percent.

The discovery of direct acting antivirals (DAAs) transformed the treatment landscape, because these drugs inflicted fewer side effects and exhibited a higher cure rate. However, the cost of these treatments remained prohibitive for patients in the low and middle income countries most afflicted by this disease.

Hassan, who is based at the Sultanah Bahiyah Hospital in Alor Setar, Kedah says, "I can't really explain how ecstatic we felt when we were selected to run the DNDi clinical trial using ravidasvir and sofosbuvir. The main reason is simply because there was no other treatment at that point – there were no DAAs. We were so happy for the patients. They had all been waiting for so long, just like us.

"Now we can tell the patients, 'I have the treatment for you', and it has been proven that the treatment is efficacious. A majority – almost 100 percent – of those patients who have been treated through the clinical trials have been cured of the virus. This is amazing, and this is something new to us."

Shing Chang, DNDi R&D director at the time, set about looking for alternative DAA candidates. "A few years earlier, MSF had been a leading force in the global movement that fought against the high price of antiretroviral medicines (ARV) for the treatment of HIV/AIDS in Africa," says Bompart. "DNDi and MSF therefore decided to join forces to develop a new DAA combination. The purpose of that development was to demonstrate that another way of developing new drugs was possible, led by the objective of optimizing the new drug's public health impact, not its financial benefits, and relying on partners from the most affected countries; in other words, middle-income countries."

In 2016, DNDi identified ravidasvir – a DAA candidate developed by the US company Presidio Pharmaceuticals that had reached phase II clinical trials – as the best possible candidate to use with sofosbuvir as a companion drug. "The treatment of HCV infection is based on a combination of drugs that act on different viral targets," says Bompart. "It is necessary to combine drugs from different families that act on different parts of the virus' metabolism. This increases the likelihood of an effective treatment and prevents the development of resistance. Non-structural proteins 5A and 5B (NS5A and NS5B) play a key role in hepatitis C virus RNA replication. Ravidasvir is an NS5A inhibitor and sofosbuvir in an NS5B inhibitor."

MSF decided to fund DNDi's development program through its Transformational Investment Capacity (TIC) initiative. One key industry partner in the project was Egypt-based company Pharco Pharmaceuticals, which had previously taken part in Egypt's national strategy to fight hep C and shown in early clinical trials that the ravidasvir/sofosbuvir combination was highly effective in genotype 4-infected patients, the most frequent genotype found in Egypt. "Pharco's CEO, Sherine Helmy, had expressed very early on his personal commitment to help fight HCV around the world, not as a business-based strategy, but as a public health priority. The $300–500 target price of ravidasvir at launch, set right from the beginning of the drug's development, was a clear sign of this commitment," says Bompart.

The DNDi has had an office in Malaysia since 2004. DNDi and the Malaysian state's collaboration on a new hep C treatment was aided in particular by Noor Hisyam Abdullah, Director-General of Malaysia's Ministry of Health, who holds a seat on the board of DNDi thanks to the Malaysian MoH's historical role as one of the founding members of DNDi.

In 2016, DNDi initiated a phase II/III study in Malaysia and Thailand that aimed to assess efficacy, safety, tolerability, pharmacokinetics, and acceptability of 12- and 24-week regimens of the ravidasvir and sofosbuvir combination. The study, named STORM-C-1, was a huge success. Results published in The Lancet in April 2021 (4) showed cure rates of 97 percent, and high tolerance across a diverse adult population. The drug combination was able to cure people infected with genotype 3 of the virus, a particularly hard-to-treat variant. The study was a key cornerstone of the registration dossier that led to ravidasvir's conditional registration by Malaysia's National Pharmaceutical Regulatory Agency in June 2021.

If I may be provocative...

Both Hassan and Bompart agree that development has had its ups and downs. Patient enrolment was a particular concern early on because many hep C patients were reluctant to come forward. Hassan says, "We noticed that many more patients were – and still are – hiding themselves in the community, partly due to the stigmatization of the disease." To help find participants, the government enlisted the support of the Malaysian AIDS Council, the Third World Network, and several local civic organizations, but Hassan expects that finding the "missing millions" will remain a major challenge.

Bompart adds that it's important to remember that ravidasvir is still a very young drug. "Quite a lot of work is still needed to properly assess its key efficacy and safety features, in particular against HCV genotypes that were not tested in Malaysia and Thailand, and to find its space in the global DAA armamentarium."

So far, however, the results of the project have been a huge success. "Malaysia is deeply honored to present a wonderful gift to the world, a new pan-genotypic and yet highly affordable DAA combination," says Hassan. "This marks a historic moment for Malaysia as a middle-high-income country to make significant contributions in drug development for a global endemic."

Beyond the Southeast Asian nation's borders, Bompart hopes that the project has sent a message. "We are pursuing registration opportunities in middle-income countries where generic sofosbuvir is available or stands a high chance of becoming available. The registration file approved by Malaysia's NPRA is our key asset. Even though this project concerned ravidasvir, we are actually advocating for access to all affordable, safe and effective DAAs that countries may choose. We are now rolling out plans to help a handful of countries improve access to all DAAs through policy, financing, and intellectual property. This is being prepared in partnership with MSF, FIND (the global alliance for diagnostics) and the Treatment Action Group."

This recently announced partnership has been titled The Hepatitis C Partnership for Control and Treatment, or Hepatitis C PACT for short. In its mission to tackle ongoing disparities in access to diagnostics and treatment for Hep C, the "pact" will look to low and middle income countries, where three in four of all people suffering from the disease live today.

This is not simply a story of aspirations and improvements; there is a huge political dimension to the story about ensuring that all countries – regardless of economic

conditions – have access to affordable therapeutics. Bompart spells it out:

"If I may be provocative: ravidasvir was developed at a time when few DAAs were available, and one can always hope to bring new benefits with a new drug. However, our agenda was largely political from the beginning, with the objective of opening the eyes of decision makers to two sets of issues: first, the realities of HCV; second, the ability that political decision-makers have to act when the abusive use of intellectual property leads to unaffordable prices that prevent access to life-saving drugs. Everywhere in the world, in rich and poor countries alike, affordable DAA prices only exist where governments fight for them."

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Rice farmer and recovering drug user Sharol on life before and after treatment

Sharol, a self-employed rice farmer from Kedah, received his diagnosis of hepatitis C over 10 years ago, but chose not to seek treatment due to fear.

Sharol discovered that he had hep C while he was seeking rehabilitation treatment for using methadone. "I had a bad habit – drug abuse by injections, and I shared needles with others. Before I started the methadone treatment, the doctor did a blood test and that is when I found out. I was disappointed in my heart, because I was trying to get rid of a bad habit and become better, but found out that I had another dangerous disease."

Sharol went on to successfully complete his drug rehabilitation on methadone but was hesitant to seek treatment for the hepatitis C he was living with. "I used to be scared from my friends who took the previous hepatitis C medicine via injection. They experienced side effects of all sorts. One friend had the chills, fever, and his whole day was condemned. He could not do any work at all because of the effect of the medicine, the old hepatitis C injection." Sharol waited for a few years before he had the courage to seek the treatment.

Luckily by then, there was a new option for treatment. The DNDi and the Malaysian Ministry of Health's clinical trial for the combination of ravidasvir and sofosbuvir in the form of pills had begun. Following a recommendation from his doctor, Sharol registered himself for treatment. To his surprise, within 3 months, Sharol was cured of hepatitis C with minimal side effects – a stark contrast to his fears, which had been based on his friends' past treatment experiences.

"I feel really surprised, because this medicine had no side effects on me at all. I did not feel any pain, and everything was comfortable. I'm well now, and I'm relieved. I'm so happy that the treatment didn't disrupt my daily routine at all. In the end, everything was okay."

Bringing Certainty to CAR T-Cell Discovery

How do we get closer to perfection? It starts with looking at the complete picture.

By Jim Ross, CTO and co-founder of Axion Biosystems, Atlanta, USA

CAR T-cells shifted the cancer treatment paradigm as soon as the first therapy was approved in the US in 2017 (1). In the decades before CAR T-cell therapy, whether through surgery, radiation, or systemic treatments, such as hormonal therapy and chemotherapy, physicians tried to do what the immune system wasn't doing on its own: obliterate cancerous tissue through intense intervention. These treatments, however, are risky and exhibit widely variable success rates, leaving the door open to much-needed advancements in cancer therapy.

CAR T-cell therapy brings personalization into cancer treatment to help increase the chance of therapeutic success. For those unfamiliar with CAR T, physicians first remove T-cells from the patient, then scientists genetically engineer those cells to express the CAR protein on their surface – the CAR protein enables them to recognize cancer-specific antigens. Finally, the CAR T-cells are infused back into the same patient, where they stimulate the immune system to attack cancer cells. In effect, CAR T-cells augment the immune system, prompting it to identify tumor cells as foreign objects that must be killed. In a phase II clinical trial, Yescarta proved 92 percent effective in patients with relapsed or refractory indolent non-Hodgkin lymphoma (2).

According to one forecast, the CAR T-cell market is expected to grow to $6.1 billion by 2030 (3). However, developing these potentially life-saving therapies is not a straightforward process. To continue their growth in the long term, CAR T-cell manufacturers must implement rigorous monitoring tools to guarantee their safety and efficacy.

Complex product, complex production

As CAR T-cells therapies become increasingly commonplace, scientists are learning more about the unique challenges involved in their development and manufacture at scale (4). Cell immunotherapy development involves working with living cells that operate via molecular mechanisms that researchers are still working to fully understand. As a result, cell immunotherapy development is inherently more complex than its small molecule or even traditional biologic development cousins. Developers must not only identify the appropriate molecular targets, but also understand the pathways that determine their function. Optimizing the manufacturing process is also essential to produce these therapies as quickly and efficientl as possible.

Given the variability of immune cell activity, scientists must consider several factors as they design cell immunotherapies for patients. One crucial step in creating safe and effective

Figure 1: Interdigitated electrodes embedded in the cell culture substrate at the bottom of each well in a microtiter plate

cell immunotherapies is identifying sufficiently specific target molecules. Aimed at the right antigen, a CAR T-cell will attack tumor cells without harming healthy cells, but finding targets that confer both efficacy and specificity to CAR T-cells can be a serious challenge. For example, the most commonly targeted CAR T-cell antigen (CD19) is not present on all cancer cells. Conversely, solid tumors often express multiple antigens that may be present in low levels on the surfaces of healthy cells (5). Beyond identifying cancer antigens, CAR T-cell manufacturers must also establish optimal conditions for the efficient transduction of the CAR gene, for cell expansion, and for cryopreservation. Finally, they must continually assess how all of these factors affect the potency of the therapy.

Cell therapy companies have many molecular targets, cell sources, and bioprocesses to test, making it difficult to identify a standard protocol that will yield a maximally effective CAR T-cell therapy. Therefore, scientists must not only develop in vitro cancer models that accurately reflect the biology of a patients' tumor cells, but also adopt a cytotoxicity assay that offers a comprehensive picture of how CAR T-cells function in this environment. In vitro potency assays can produce data that indicate how variations in CAR T-cell development protocols impact the cells' function and can help CAR T-cell developers optimize their workflows during early-stage clinical trials. Furthermore, these assays can enable companies to rank candidate therapies born from different protocols and screen out suboptimal batches, helping to maximize the production of therapies more likely to succeed in treating patients.

"Immune cell–mediated killing of cancer cells is a highly dynamic, variable process."

Immune cell-mediated killing of cancer cells is a highly dynamic, variable process; the timing of immune cell activity can differ between donors and between batches. Yet, the most commonly used cytotoxicity assays today do not provide the kind of temporal data that cell immunotherapy manufacturers need to assess their products' behavior in an in vitro cancer model. Common techniques, such as chromium release assays and other colorimetric assays, only capture data at predefined time points, which can lead a developer to miss critical information. The only way to guarantee capture of all the data needed to characterize immune cells is to monitor their killing behavior in real time.

Getting the complete picture

One tool that can provide this real-time measurement of immune cell activity is a bioelectronic assay that employs biosensing electrodes to detect tumor cell viability. This kind of assay measures electrical impedance caused by the cells' obstruction of current flow between electrodes. Electrodes can be embedded into each well of a microtiter plate, enabling researchers to capture data from multiple cultures non-invasively and in real-time. As living cells attach themselves to the well, impedance rises; as cells die and detach, impedance decreases. The experiment can be replicated in multiple wells, enabling developers to test how variations in dosing and other factors impact CAR T-cell function.

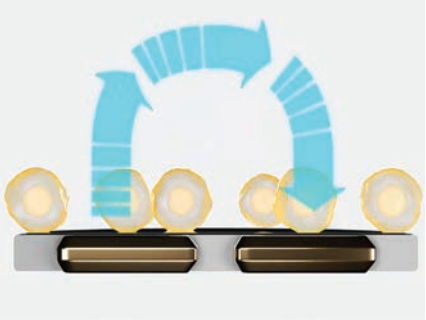

Figure 2: The electrodes detect small changes in the impedance of current flow caused by the cells' presence, attachment, and behavior

Recently, researchers used a bioelectronic assay to identify a novel CAR T-cell target for glioblastoma therapy by monitoring CAR T-cell-mediated killing over the course of

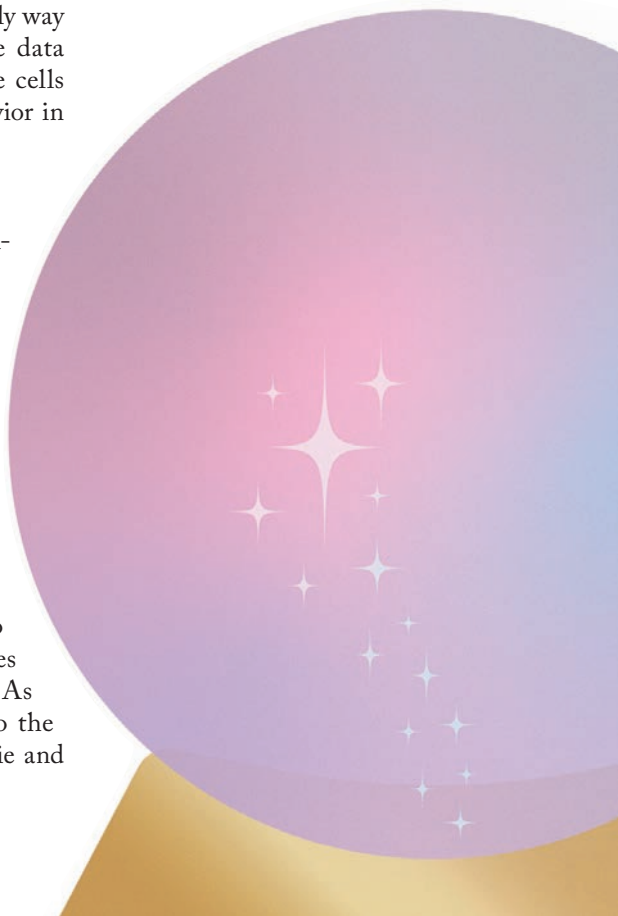

Figure 3: In an immunotherapy potency assay, the user adds the target cancer cells to the well first. After they attach, they grow and divide over the next 22 hours. Then, they add effector cells, such as engineered or native T cells, and any additional therapeutic agent such as a checkpoint inhibitor. As these cells and other agents kill the cancer cells, the platform calculates percent cytolysis automatically by comparing each well to the untreated (no effector) and fully lysed wells. In a live-cell assay, the user has access to every timepoint among the continuous data. The speed at which effector cells kill target cells, how many are killed, and how long the effect lasts are used to quantify the potency.

several days (6). Lohitash Karumbaiah and his team first cultured human glioma cells in a 96-well plate containing bioelectrodes. Two days later, they added CAR T-cells targeting GD2 – a common tumor-associated antigen present on glioblastoma cells – to multiple wells at different effector-to-target ratios. They used the bioelectrodes to monitor CAR T-cell-mediated killing of the glioma cells over the course of seven days.

Even at the lowest concentration of 0.1:1, the bioelectronic assay revealed that GD2-targeted CAR T-cells killed at least 50 percent of their target cells, suggesting that GD2 could serve as a potential target in glioblastoma therapy. The researchers also observed reduced efficacy over time in the assay and, using flow cytometry, confirmed the presence of early markers of exhaustion.

The inherent complexity of CAR-T development creates a need for a new level of analytical testing to ensure safety and efficacy of cells. Unlike endpoint assays, bioelectronic assays can capture the dynamics of CAR T-cell activity and provide developers with the flexibility to identify the cells, targets, and protocols that will yield CAR T-cells that are more likely to succeed in patients.

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(Precious) Metal Will Never Die

Precious metals-bearing catalysts are essential in some pharma processes – but, once they're spent, they still hold value. Here, Brad Cook, Vice President of Sales and Marketing at Sabin Metal, reminds us that not all catalysts – and not all recyclers – are the same.

Please introduce us to Sabin Metal...

Sabin began as one man pushing a scrap cart around post-WWII Brooklyn! Today, we are the largest domestically owned precious metal refiner in North America. Most of your readers will know that pharma uses precious metal-bearing catalysts for the processing and production of pharmaceutical products – at Sabin, we don't produce the catalysts; rather, we recover platinum group metals (PGMs) from those catalysts. PGMs are probably the most recycled material on earth – and with good reason; did you know that all the platinum ever mined in human history would fit in a four-bedroom house?!

What's the recycling process, in a nutshell?

When the catalyst is worn out, clients ship it to Sabin where we extract and analyse a representative sample. This serves as the basis for the agreed precious metals content and the money (or pure metal ounces) can then change hands. In this way, the pharma company can recoup costs, or more commonly, recycle those precious metals back to their catalyst manufacturer for use in the next round of fresh catalyst.

What are the key trends in the PGM market?

Over 95 percent of all platinum and palladium comes from Russia and South Africa, and this – alongside many other factors – can render prices volatile. Every once in a while, there will be a 20–30 percent price swing. In spring 2021, for example, floods disrupted work at two of the giant mines in Russia where roughly one quarter of all the platinum and palladium in the world is drawn. As you can imagine, that caused an upward swing.

Most customers try to avoid pricing volatility by using bridge leases. Essentially, they lease the precious metal for their catalysts and then close the lease once the metal has been recycled.

How can our readers get more informed about the intricacies of PGM recycling?

You can explore our "Knowledge Center" on our newly revamped website. There, we pull back the curtain on sampling, contracts, and the key points of procurement and purchasing that companies really need to pay close attention to when they're comparing different precious metal refiners. Never assume that all refiners are the same – nor that all fresh catalysts are the same. Engineers can trial a new catalyst on the bench, but it's not possible to do that when you've asked someone to recover your precious metals. Due diligence is the key: I'd strongly advise pharma companies to investigate the ethics and financial soundness of any and all potential business partners.

Best Practice

Technology
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Crafting a Magic Bullet

The field of antibody drug conjugates has seen many ups and downs, but, with new science shedding light on how to better design and engineer these therapies, it's certainly never boring. Colin McKee, Head of Technical Services at Sterling Pharma Solutions, gets us up to speed on advances shaping this dynamic space.

By Stephanie Sutton

Why has the concept of "magic bullets" caused so much excitement in the pharma industry over the years?

The concept of developing drugs that specifically target disease, whilst leaving healthy tissues and organs unharmed, is a key goal for the industry. The term "magic bullet" – coined by Paul Erlich in 1900 – really captures this. Antibody-drug conjugates (ADCs) are an embodiment of this concept because they are both highly effective and highly targeted. There have been several setbacks over the years, but over the last decade there have also been success stories. As one example, consider Roche's Kadcyla, the ADC of the breast cancer antibody Herceptin by Genentech. The ADC concept was used to improve Herceptin and offer better outcomes for patients (1).

ADCs have also shown remarkable benefits against cancers previously considered hard to treat – or where traditional chemotherapies cannot achieve durable results following treatment. As an example, consider Adcetris; in patients with classical Hodgkin lymphoma after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens, and in patients who are not auto-HSCT candidates, all of whom show progressive disease, Adcetris has been shown to achieved long and durable disease control (2).

Because of these successes, and the knowledge gained in developing these molecules, the scientific community is starting to "blue sky brainstorm" and is coming up with many different ways in which these ADCs can be exploited.

What have been the highs of ADCs?

The recent approval of Zynlonta for ADC Therapeutics was an especially high point for us. Sterling (formerly ADC Bio) developed the conjugation process and performed process characterization to support the Biologics License Application (BLA). This work was carried out between 2014 and 2020, and demonstrated how quickly ADC molecules can progress from research and development to commercialization.

There is now an increasing number of ADCs gaining approval and entering the clinic each year. The value of recent deals for ADCs is also staggering; AstraZeneca and Daiichi signed a $1-billion deal in 2020 – and AstraZeneca has also committed $6 billion to Daiichi's ADC Enhertu. Also in 2020, Merck Sharp & Dohme acquired VelosBio in a deal worth $2.8 billion (VelosBio's lead investigational candidate is an ADC).

And what about the lows? What setbacks has the field encountered?

There are still ADCs that enter the clinic and fail to achieve the results needed to progress, which results in projects being terminated. There is still a relatively low success rate for advancing a molecule through the clinical phase to commercialization. In 2018/2019 there were some high-profile withdrawals, and a high percentage of clinical trials were terminated. But, according to one review from The Beacon database, only a handful have been terminated since then (3).

What are the biggest scientific challenges associated with designing and developing ADCs?

ADCs have many moving parts and "designing" the right combination to work against each unique disease (type of cancer) remains the biggest challenge. Finding and validating good targets is the first challenge. There are a number of well-agreed rules on which properties constitute a good target; for example, being present only on diseased cells rather than on healthy cells; internalizing the ADC; and not shedding into circulation. Many "low hanging fruit" targets have also already been addressed. For example, numerous companies have

ADCs in development against HER2. Identifying new targets brings us back to the fundamentals of biology – and, as with all biopharmaceutical drugs, these are hard yards.

Once there is a validated target and an ADC format has been decided upon, the "fun" really begins. Making the antibody and selecting a conjugation chemistry and drug combination was once (relatively) simple, but now an ADC developer has many choices for all three main components of an ADC. Should it use a simple human mAb, or an engineered format designed for a specific conjugation chemistry? Should it focus on improving targeting to a specific cell; such as a bispecific mAb for example. Or should the ADC be engineered to stay in the cell once internalized to improve the amount of drug delivered?

Then, there are many new ways in which the conjugation can be performed, and choices to make with regards to the drug to add. It is easy to design and make ADCs that can kill target cells in test tubes and "cure" mice, but it is still a struggle to translate this science to safe and effective molecules that work in humans. An ADC team must be truly multi-disciplined: combining experts from chemistry, protein sciences, toxicology, biology, safety, manufacturing sciences, and many other fields.

Bigger pharma companies are able to build large teams of people and dedicate a great deal of resources to developing ADCs. Many different molecules can be made, tested, and optimized through iterations before being progressed and (potentially) terminated before a good one gets to market. Smaller biotechs however, may take a different approach and rely on precedent from approved ADCs, looking to quickly combine the best available knowledge and design into their specific ADC. Velos Bio, for example, moved very quickly based on a good target, ROR1, and an already available mAb, UC961, and simply followed the pathway from the development of Adcetris, using the same conjugation chemistry and toxin linker. Leveraging the vast safety data set that exists now for Adcetris allowed its ADC to get into the clinic quickly, and generate the data that really mattered – the efficacy profile in real patients. And its subsequent acquisition by Merck validates the approach!

What are the challenges associated with manufacturing?

Making either a small molecule or a protein therapeutic is already a complex process. However, when both approaches are combined into one molecule and the issues associated with the very potent nature of these molecules are taken into account, the degree of complexity further increases. The small molecule and antibody will be managed by scientists who may be used to making these as stand-alone molecules, but now they need to consider their products as raw materials for the conjugation, and understand what changes can be made without impacting subsequent steps. In addition, the regulatory and analytical requirements are a hybrid of the two very

different small molecule and biomolecule disciplines. Analytics in particular are very complex, as many ADCs are a mixture of many subtly different forms of the drug, each of which needs to be understood.

The next step is to make the necessary components and combine them. This can either be done by building out that capability in-house or by outsourcing; however, there are very few experienced ADC CDMOs, and choosing one that can align with the capacity and lead times needed for a program can be challenging. Typically, it is the chemistry CMOs that work with highly potent molecules and are experts in the containment required for ADCs, but their knowledge is usually very limited in terms of biologics manufacturing. Conversely, biologics CMOs typically understand proteins and cleanrooms, but know less about the containment and the chemistries involved in making an ADC.

Why are things starting to change? What new science and approaches are emerging that could boost the ADC field?

Knowledge and understanding of ADCs is the key driver. The more we know, the better our designs will be, and the more likely we are to design out issues that have stopped other ADCs from progressing!

What activity are you seeing now in the ADC space?

ADC clients range from single academics all the way through to large pharma companies and this demonstrates the volume of work and interest in this drug format. I would say that the percentage of non-traditional ADCs we are asked to work on has been a significant change; the number of these types of projects is increasing compared with "traditional" ADCs (considered to be an antibody combined with a highly toxic small molecule drug, which directly kills the cell for use in oncology).

We are now seeing different carriers used in place of the antibody, such as peptides, nanoparticles, antibody fragments, and antibody-like proteins. The drugs are not all direct cell killing, with some now stimulating the immune system, and others amplifying the body's natural killing mechanisms against cancer. These new ADCs have shown the ability to not only kill off a cancer, but also to provide a patient's immune system with some memory that prevents re-growth of new cancers (4). We are also seeing the "magic bullet" concept being turned against other diseases such as infection, inflammation, and autoimmune disorders.

Now that the pyrrolobenzodiazepine (PBD) dimer payload has been truly clinically validated following the Zynlonta approval, this opens up more opportunities in that space. The termination of Abbvie's Rova-T ADC in 2019 caused many to think that this payload class was just too toxic. However, the ADC Therapeutics success shows that the payload is manageable – as with all other highly potent ADC payloads – when combined with the correct antibody, directed to the right target, and administered in an optimized way.

What do you know about the current pipeline of ADC therapeutics?

Since the approval of Zynlonta – an ADC that we were involved with – there has been another approval. AIDEXI was approved in China in April 2021. However, we're also working on a number of other ADC products.

It is estimated that 14 new INDs will be filed for ADCs this year, and over 100 clinical trials initiated (3). It is hard to keep apace with this field, but thankfully there are several good resources including the Beacon Database, ADC specific conferences, webinars and review publications that help by providing regular update summaries. Those in the know anticipate approvals from Seagen and Immunogen with their own and partnered ADCs. ADC Therapeutics' next molecule, ADCT-301, is also at phase II.

Most of the ADCs close to approval use toxins that are already approved, such as auristatins, maytansines, and PBDs, but one interesting molecule is Byondis' duocarmycin-containing ADC. Duocarmycins were used in some early ADCs by BMS/Medarex without much success, so seeing a promising one in the clinic is good for that payload class.

Despite the setbacks, why do you remain excited by the future of ADCs?

I make ADCs and I like the challenges that this work brings. It is clear that these molecules are at the very least transformative, and maybe one day we will use the descriptor "curative" for them. Helping ADC developers get new molecules into the clinic and to the patients who need them excites me. In doing so, I learn something new every day – be it a new analytical technique to answer a question we could not answer previously or a new conjugation method that overcomes challenges. There is a lot of innovation in this field – and it is never boring.

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Now You See It

What are the challenges and best practices in quality control for difficult-to-inspect products?

By Andrea Sardella, Pharma Inspection Product Development Manager, Stevanato Group

The manufacture of biologics is well established, but new challenges are emerging as protein products become more complex. In addition, the industry is now also pursuing personalized medicines, which present new challenges. Manufacturing hurdles are being widely discussed in industry, but a far less common – yet still important – topic is that of visual inspection. We have observed a sharp increase in the number of new therapeutics that are difficult to inspect, including suspensions, emulsions, lyophilized, and highly viscous products.

Each dose of a drug embarks on a long and complex journey between the point of manufacture and the point of administration. Every care is taken to ensure that integrity is not compromised, providing the necessary guarantee that the treatment patients receive is both safe and effective. A vital process during the journey is quality control, which encompasses the visual inspection of products. Irrespective of the type of primary container used or the nature of the drug held within, visual inspection provides assurances that the packaging and contents have been subject to rigorous review, facilitating detection of particles and cosmetic defects, and testing for leakage. This process is essential in identifying whether any potential issues during manufacturing or any adverse interactions between drug and container-closure system have adversely affected the purity of the contents. Though data on the risk of human exposure to infused particles is relatively limited, there is some evidence to demonstrate clinical implications for patients, from inflammation and infection to venous and arterial emboli (1).

Visual inspection can be characterized as a process with a simple and straightforward objective: safeguarding product quality. In typical applications, the process itself is relatively straightforward, particularly where the clarity of a drug product makes it an ideal candidate for inspection using inspection equipment, such as high-performance cameras, appropriate illumination levels, and container rotation mechanisms.

There is a growing emphasis, however, on products that are defined as difficult-to-inspect, which include concentrated suspensions and emulsions, lyophilized cakes and powders, and opaque and deeply coloured solutions. With biopharmaceuticals, the drive to address unmet needs in chronic diseases and rare cancers can often result in the formulation of complex and fragile proteins that require specialized manufacturing techniques. These proteins can be challenging from a visual inspection perspective for a variety of reasons. For example, with nanoparticle suspensions that present in opalescent and milky forms, the visual clarity required for imaging purposes becomes compromised; for high-viscosity products, inspection via pre-spinning becomes unsuitable because particle movement is severely restricted; and in the case of high-concentration vaccines, proteins can be prone to agglomeration, creating visual anomalies that can be falsely identified as external bodies.

The trend towards personalized medicine can also be a headache when it comes to visual inspection because of challenges relating to the highly tailored nature of the production process. Typically, batch sizes are small, levels of product variability are high, and products are often presented within soft bags, complicating handling and greatly limiting particle movements. And that means visual inspection equipment must be configured for each individual process, in contrast to commercial production environments designed for consistent, high-volume manufacture of transparent therapies packaged in clear primary containers.

Overcoming inspection challenges

For therapies that present as thick suspensions or emulsions, and where there is separation between liquid and sediments, the visual inspection process is even more difficult. Insulin is a common example of a therapy that presents in this way, requiring rehomogenization via spinning to ensure products undergo an accurate visual inspection. The precise level of inspection accuracy will, however, ultimately depend on the type of image processing technique employed in the camera-based inspection system – a point that is particularly relevant to high-speed inspection lines, where the rapid motion of cylindrical containers can be challenging for image capture and analysis.

Evidence has shown that line-by-line processing methods, based on continuous analysis, generate higher quality images with a finer level of detail when compared with frame-by-frame image processing. Even for very thick emulsions that are difficult to inspect manually, a visual inspection set-up involving line-scan cameras and appropriate lighting enables the detection of even white fibres, including hair fragments at 0.5mm and rubber fragments at 0.3mm. This is achieved because the line-scan camera avoids any time lapse between frames, and so can suppress the residual optical background "noise." At a line rate of 30kHz, the defect detectability (DR) rate is 99.9 percent and the false reject rate (FRR) is less than 0.8 percent (2). In contrast, a matrix camera operating at 200 frames per second has been found to register a DR of 68.4 percent (2), while the FRR for frame-by-frame visual inspection techniques stands at around 10 percent. Of course, the lower the DR and the higher the FRR, the greater the risk of particles going undetected, and the greater the associated costs of

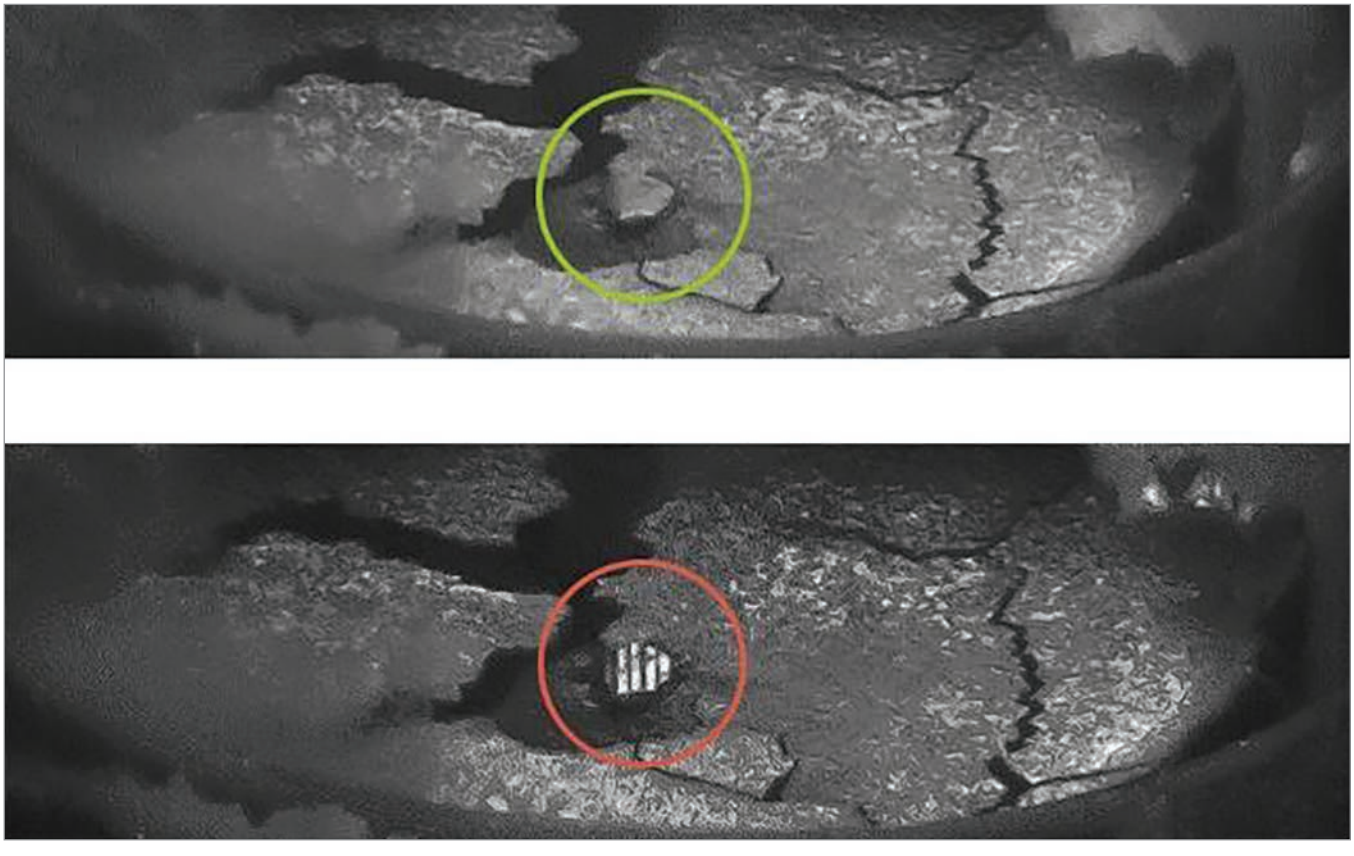

Figure 1: Lyo top inspection, glass fragments, and black particles

Figure 2: The glass wall of the vial acting as a light guide

Figure 3: The apparent rotation speed of the potential contaminants is used to determine if they are inside or outside of the liquid

business interruption.

The relationship between DR and FRR is particularly complex in the case of lyophilized products. Here, there are intrinsic physical variations in visual appearance that can occur between batches and within a batch – not all of which necessarily warrant rejection. These variations may be present in the form of differences in colour, structure (from dense to porous), topography (presence of skin, bumps, cracks and peaks), and the presentation of shrinkage, both uniform and non-uniform. The task for visual inspection is to maintain the highest level of DR accuracy while managing the higher risk of recording a false reject.

Let there be light

Evaluating container integrity for lyophilized products is also complicated, owing to the presence of dust, cracked cake, and product splash on the sidewall of the container. These elements can interfere with the analysis and increase the FRR.

Addressing this particular challenge requires the implementation of a specialized chip and crack (C&C) detection station, which uses the container glass as a light guide. Lights enters at a point far from the field of view, propagates within the container, and then exits with higher intensity at points of discontinuity, highlighting flaws while ignoring the presence of any benign elements. Particulate detection on the top and bottom of the cake also relies on the use of light and is achieved by exposing disparities between the optical characteristics of the various potential contaminants, the container, and the product itself. Glass fractions, for example, will not display the same diffusive properties as the cake and instead demonstrate a mirroring effect, which presents in an anisotropic angular dispersion. Notably, black particles display isotropic diffusion characteristics.

The inspection of lyophilized products from the side angle presents less of a challenge but must accommodate the inspection of cylindrical surfaces. Using linear cameras, the full lateral surface of the cake can be imaged at very high resolution, providing a multi-dimensional view of the product and enabling defects to be identified even in awkward locations, such as under the stopper and crimping.

Just as lyophilized products require a specialized approach to visual inspection to sustain a high DR for contaminants, the same is true for highly viscous products. These therapies are increasing in popularity, driven by the benefits long acting injectables (LAIs) deliver in terms of patient convenience and compliance, and the reduced burden on healthcare

professionals. Because of their higher levels of viscosity, however, these products are not necessarily suited to the typical automated inspection route based on spinning the liquid and measuring the subsequent particle movement when the container is stopped. At a dynamic viscosity above 4-5 centipoise (cP), this method of particle detection becomes ineffective.

Instead, high-viscosity liquids maintain constant rotation during inspection, with all potential contaminants tracked through 360 degrees. Where contaminants are located on the outside of the container, they will register at a higher speed, as well as a broader trajectory path and can, therefore, be disregarded. Analyzing the image against a dark background also accentuates the identification of contaminants such as white fibres, which can be distinguished from scratches through their speed of trajectory.

High viscosity as a by-product of protein concentration is one of the many attributes that make the growing field of biologics more challenging for the automated inspection process. These delicate products can be difficult to inspect as a result of attributes such as their high density and turbidity, while the fragile nature of their long-chain protein structure means they also have a higher sensitivity to shear force, UV light, and mechanical shock.

To cope with these challenges, new innovations in equipment are being seen. P-handling mechanisms, for example, smooth transitions up to 660 ppm, with a view to minimizing mechanical shock and limiting the cavitation effect induced in the liquid. Exposure to shear force is also reduced by accelerating liquids slowly and carrying out inspection while the container is in rotation at a steady speed.

Defining the future

Where next for visual inspection? The introduction of artificial intelligence brings great potential to visual inspection, raising the possibility of a system that can detect, measure, and quantify every particle within a container. AI-based machine-learning and deep-learning techniques are trained on data. Images of the particle in different positions can be automatically extracted, labeled accordingly, and fed into a central repository. Over time, this could become a self-managed intelligence centre that continually grows as it expands its "knowledge" of defects and its capability for recognizing defects.

Figure 4: Low acceleration pre-spinning

Figure 5: Detection while spinning dirty cancelled by correlation

The application of this deep learning approach has huge potential for the future of production. Here, flexibility and agility will be key attributes to accommodate the rapid and cost-effective production of smaller production batches in line with the trend for more personalized medicines. Bringing the learned intelligence of AI to modular robotic inspection stations could quickly deliver batch-level defect-detection capability, while introducing the potential for continuous improvement via sustained retraining and the ability to scale by increasing the number of units. Such a model would differ significantly from existing visual inspection systems, but would be driven by the consistent objective of maintaining the highest levels of productivity and product quality. Ultimately, patients must be the priority for innovation in drug therapies, and if those therapies present as difficult-to-inspect, then organizations have a duty of care to respond in an equally imaginative, innovative, and personalized way.

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The Watcher

Sitting Down With… Peter Marks,
Director of the Center for Biologics Evaluation and Research (CBER) at the FDA, USA

How did you start your career?

I went into college thinking I was probably going to become a PhD biochemist. At the time, cell and molecular biology were becoming more popular and they caught my interest. After I got a part-time job at a hospital taking blood, I started to think about going to medical school and working in medical research. Ultimately, I chose to become a physician-scientist but, over the years I've occupied several different roles in academia and industry.

How did you get involved with the FDA?

My first industry role was with Genzyme, involving interacting with the Center for Biologics. The Center had both applied scientific research and regulatory components, as well as a nifty set of products. It was so interesting to me that, in 2011, I applied for a job there. At the time, gene and cell therapies were becoming exciting – and, as a hematologist-oncologist, blood products interested me. The opportunity to have an impact on the development and availability of important medical products was attractive. It meant I could make use of different skills in one job. What I do now combines science, medicine, administration, and even a little teaching.

What skills are important for a regulator?

You need to understand science and medicine really well to do a good job as a regulator. This includes the fundamental science, product manufacturing, and the technologies involved. Without that knowledge, you can't make necessary decisions about cutting-edge products. You also have to know how to manage people. The Center for Biologics has around 1,300 full-time equivalents. They are mostly knowledge workers… and managing knowledge workers can be challenging. You need to know when to zoom in to the data, and when to zoom out and let others deal with the weeds while you make the high-level decisions. That, to me, is an important balance to have.

What is the biggest challenge you face?

The biggest challenge is uncertainty. For example, on one hand, a gene therapy may help to cure or treat a disease long-term. On the other hand, there may be side effects. Not knowing exactly what will happen ahead of time is what makes the job challenging. Sometimes, it takes a long time to know whether a decision was a good idea or a bad one. The challenge is to negotiate the uncertainty as skilfully as possible.

What work are you doing in terms of harmonizing gene therapies?

This is one of my favorite topics and an area we are actively working on. We're developing a white paper on global harmonization of cell and gene therapy regulatory approaches. If we have different regulatory frameworks in different countries, then patients in different countries likely will be deprived of these therapies simply because of the cost of market entry. If studies are performed in one location and are then required in a different location, that will present a barrier. We're going to need a lot of work to move toward harmonization and we'll need to start small. Right now, if someone in the US develops a therapy for mucopolysaccharidosis type I and someone in the EU develops a therapy for mucopolysaccharidosis type III, the regulatory requirements may be different and the therapies may never cross the Atlantic. This means patients would have to travel to get access. Harmonization could help therapies enter other countries.

How far are we from being able to manufacture gene therapies at scale?

We're not that far away, but there are challenges. With mAbs, people came together to help develop technologies that could produce and purify large protein quantities. With gene therapies, there is still a lot of proprietary work that can limit information-sharing. One of my goals is to help the field share information and grow. I think we can make better cell lines and purification methods and develop continuous methodologies for producing these gene therapies. But that will require a type of collaboration and cooperation that we haven't yet fully achieved.

What advances in gene therapy do you think could be transformative?

In vivo genome editing has tremendous potential because it can help overcome some of the problems we have with current gene therapy vectors, including longevity of expression. You need expression of an editing construct for a period of time – ideally in the dividing cells – but after your correction occurs, you're done. Too much persistence is undesirable because it can lead to off-target effects. Genome editing could treat many diseases, but there is a whole regulatory paradigm that we have yet to fully create for genome editing. It's very exciting – and it's advances like this that keep me coming to work every day.

What advice do you have for developers of therapies?

Engage with the FDA – or whatever regulatory authority you are applying to – frequently. Do not be afraid to ask the hard questions. And do not be afraid to question the regulator's responses if they don't make sense. Such dialogue between developer and regulator is really important. I recommend closing the loop: you ask a question, the regulator responds, and then you respond back with, "From your response, we think we need to do X." Often, regulator comments can be open to interpretation but, if you close the loop and give feedback to the regulator on what you have heard, it becomes unambiguous. For example: "We hear you. We need to have a potency assay before we proceed to phase III. Is that what you mean?" The regulator can then confirm, and you'll know you're on the right track.

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