pharma's almanac

NICE INSIGHT'S RESEARCH & CONTENT COMMUNITY

VIRAL VECTORS
MONOCLONAL ANTIBODIES
DESIGNER BIOMOLECULES
COMPLEX CHALLENGES
COVID-19
PERSONALIZED MEDICINE
DIGITALIZATION
SPEED TO CLINIC
SPEED TO MARKET
CELL & GENE THERAPY
RECOMBINANT PROTEINS
BIOPHARMACEUTICALS
mRNA-BASED THERAPIES
INTERNATIONAL MARKETS

Frank Mathias
CEO, RENTSCHLER BIOPHARMA SE

CGMP MANUFACTURING
CLIENT-FOCUSED
DIGITAL SERVICE
AGILITY
BIOPROCESS DEVELOPMENT
STRATEGY 2025
INNOVATION
STRATEGIC ALLIANCES
HIGH-QUALITY
FLEXIBILITY
STRATEGIC PARTNERSHIPS
BEST-FIT SOLUTIONS

THE INNOVATION ISSUE

THE FUTURE OF HEALTHCARE

Q4 2020 VOLUME 6 NUMBER 4

Rentschler Biopharma

Rentschler Biopharma will continue building strategic capacity to fulfill the demand for emerging, life-saving therapies. We will drive supply and delivery to patients through collaboration with our clients and partners to develop mutually beneficial alliances. This will ensure reduced time-to-market, the highest-quality of biopharmaceuticals, and unrivaled efficiency — from mAbs to highly complex biomolecules.

ALEXANDER DETTMER
Chief Financial Officer

We have set ourselves ambitious, clearly defined goals for the future. Our secret to achieving them is focusing on sustainable value creation and not merely on short-term financial profit.

DR. THOMAS RÖSCH
Vice President
Capacity Expansion Engineering & Technology

Evolving to meet the needs of our clients and the changing biopharmaceutical landscape by optimizing our core: process engineering, technology applications, and highly flexible building setups across sites.

DR. JADRANKA KOEHN
Senior Director
Innovation Partnerships

I see innovation as the drive to reinvent ourselves and offer our clients cutting-edge technologies tailored to their needs — for both simple and complex therapeutics.

DR. CORA KAISER
Senior Director
Corporate Communication

Communication for me is raising awareness about our sector's contribution to simplifying the complexities of drug development — in the face of the pandemic and beyond.

FEDERICO POLLANO
Senior Vice President
Business Development

Ensuring that our clients receive the premium best-fit solutions for their molecules — through optimal, integrated, and customized solutions via our network of strong strategic partners is the essence of my work.

VIRTUAL LEADERSHIP MEETING

#UNITEDAGAINSTCORONA
#VIDEOCONFERENCE
#COVID19

SABINE LOTZ
Vice President
Human Relations

In a dynamic environment, changing demands on our employees drive the need for new skills and job profiles. I see it as our task to support and shape the company to ensure best results.

KAREN SAVAGE
Vice President
Milford Site

Extending our global footprint to the Boston area, a hotbed of biopharmaceutical activity, has enabled us to better offer our world-class services to meet our clients' needs internationally.

THILO GROB
Vice President
Process Science

Clients value and trust us for our expertise and experience — applying these in making the most complex projects reality inspires and drives me on a daily basis.

WOLFRAM SCHULZE
Vice President
Information Systems & Organization

Digital Transformation will continue to shape our industry in the years to come. Our secure data services turn data into insights and enable our clients to make smart decisions — saving time and money, while maintaining high quality.

DIANA WIEDMANN
Senior Vice President
Human Relations

Our employees are key to our success, and therefore we believe in empowering them through continuous development. We build our best teams by providing the right balance of challenge and support to grow.

DR. CHRISTIAN HUNZINGER
Senior Vice President
Client Program Management

We live our client-focused philosophy through our strategic client partnerships that offer customized solutions with maximum flexibility.

FRANK BAUERMEISTER
Vice President
Supply Chain Management

Our sustainable sourcing strategy strengthens our resilience and ensures business continuity, as well as the reliable delivery of world-class services to our clients.

SILKE STANG
Head of Academy

Growth within an agile, learning organization means nurturing leadership development across hierarchy to align with our strategic goals.

FACING THE CHALLENGES OF THE COVID-19 PANDEMIC

RENTSCHLER BIOPHARMA

In these unprecedented times, we are deeply committed to safeguarding the reliable delivery of essential therapeutics for our clients while also remaining dedicated to ensuring the safety of our employees and partners.

The continuous optimization of operational fitness has always been an integral part of our strategy. In alignment with local health authorities and with the help of an internal business continuity plan, we adopted comprehensive company-wide measures for the changing situation and successfully secured ongoing operations and supply continuity.

Across the industry, the COVID-19 pandemic has underlined the importance of the digital landscape and the need to stay connected and access critical information in real time. At Rentschler Biopharma, we saw an opportunity to enhance our digital infrastructure to move further toward digital meetings and paperless documentation and extended this approach to digitally integrate all departments using central storage and synchronization.

As a company that always strives to assess and reinvent ourselves, the pandemic drove us to evaluate operations through three lenses: resilience, reformation, and reimagination. We had launched an initiative to strengthen our resilience within the framework of Strategy 2025 before the COVID-19 outbreak. This held us in good stead in overcoming disruptions in global supply chains for raw materials – a major challenge during the pandemic – by establishing alternative sources and balancing global and local vendors. To address reformation, we assessed our core business processes to find ways to increase their sustainability and efficiency, importantly including our strategies to acquire and retain talent. Reimagination involved reflecting on the full picture of how we work internally and in collaboration with our clients to find ways to unleash the full potential of those interactions. This is notably done through the "Rentschler New Work" initiative, which is focused on interactive leadership training across our organization, addressing diverse topics, including the new economy, business model generation, and employer branding.

Focusing on our Clients' COVID-19 Programs

At Rentschler Biopharma, we are invested in our clients' success. Projects targeting COVID-19 have been given priority, enabling the rapid establishment and short-term provision of process development and manufacturing capacity for the production of drugs that can tackle the pandemic.

We recently announced an agreement to serve as CDMO partner for a COVID-19 mRNA vaccine program with BioNTech, a German biotech innovator focused on immunotherapies. Rentschler Biopharma is providing cGMP drug substance manufacturing of BNT162b2, an mRNA-based vaccine developed against SARS-CoV-2. The vaccine was developed jointly by BioNTech and Pfizer and has been submitted to the European Medicines Agency for a rolling review.

Unlike traditional vaccines, mRNA vaccines introduce mRNA encoding viral proteins, which function as a template to allow the patient's cells to produce the infectious protein to induce an immune response against the viral antigen with no risk of assembly of functional viral particles. Evidence suggests that mRNA vaccines may be more potent and straightforward to manufacture than traditional vaccines and may be easier to scale up to the level needed for true global vaccination efforts.

For a COVID-19 vaccine planned for administration on a global scale, it is critical to provide a highly purified drug substance to ensure its safety and tolerability in patients. The mRNA for the vaccine is produced by BioNTech in bioreactors using a cell-free process. Rentschler Biopharma will provide downstream processes to effectively remove process- and product-related impurities. Optimized downstream processes can also maximize the amount of mRNA that can be harvested by the upstream processes, increasing output and efficiency.

To best support the range and scale of services needed for the COVID-19 vaccine program on an accelerated timeline, we have established a dedicated mRNA production suite in the Laupheim facility to ensure that the needed capacity, equipment, and staff are available to work on the program without conflict.

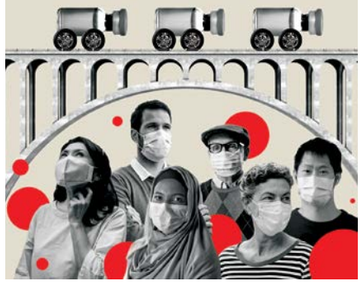
The partnership leverages a unique business model that creates maximal flexibility to address the scope of BioNTech's development and manufacturing requirements for a COVID-19 vaccine. Beyond the large-scale purification services for the mRNA vaccine BNT162b2, Rentschler Biopharma can also perform development and manufacturing for other BioNTech RNA programs for use in clinical trials, as needed.

For a COVID-19 vaccine planned for administration on a global scale, it is critical to provide a highly purified drug substance to ensure its safety and tolerability in patients.

Through this and other programs, we are navigating the pandemic by seizing the opportunity to innovate, finding novel ways to work and communicate more dynamically throughout our operations and in our partnerships. By finding new synergies and efficiencies, we create sustainable value for our client partners while helping to tackle the COVID-19 pandemic. P

THE INNOVATION ISSUE

THE FUTURE OF HEALTHCARE



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THE INNOVATION ISSUE FEATURE

The Future of Healthcare

By **David Alvaro, Ph.D., Emilie Branch**, and **Cynthia A. Challener, Ph.D.**, Nice Insight

Wearable Technology

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SPECIAL FEATURE

THE ROAD TO 2021

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On The Road to 2021

By Nigel Walker and Phill Neill, Nice Insight

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Nice Insight is the market research division of That's Nice LLC, A Science Agency, leading marketing in the life sciences.

The print version of *Pharma's Almanac* is delivered to a targeted group of 20,000 leaders from all sectors of the industry who are implementing new strategies and technologies creating collaboration models with drug developers to deliver on the global mission to provide the reliable supply of safe effective pharmaceuticals and therapeutic agents worldwide. The custom print distribution includes individuals across big pharma, the biotechs, midsized and specialty pharma, virtual pharma–biotechs, as well as regulatory and governmental agencies, academia, and consumer patient touchpoints.

→ **A NOTE FROM THE EDITORS**

INNOVATING FOR THE FUTURE DESPITE UNPRECEDENTED CHALLENGES

→ BY **CYNTHIA A. CHALLENER, Ph.D.,** SCIENTIFIC CONTENT DIRECTOR, THAT'S NICE LLC

The pharmaceutical industry, although quite conservative when it comes to implementing novel technologies, is still driven by innovation. The ability to maintain safety while advancing new treatments and manufacturing paradigms was on display in 2020, as novel vaccine and therapeutic technologies have advanced in the fight against COVID-19.

New therapeutic modalities, accelerated drug development strategies, supply chain reconfiguration, virtual clinical trials, and crisis management strategies will reverberate into 2021 and beyond. From drug discovery to distribution, established ways of working have come under the microscope and emerged in invigorated formats to further healthcare.

At *Pharma's Almanac*, we are privileged to learn directly from leading innovators in the pharmaceutical industry – and to share their experience and knowledge. In this Q4 Innovation Issue, we explore the myriad ways in which diverse members of the value chain have focused on moving forward, finding creative solutions to unexpected problems, often while managing challenges.

Directly related to the COVID-19 pandemic, we learn about fostering innovation through virtual trade shows and the importance of mobile research nursing. Insights are provided into how nationalism is affecting the pharmaceutical supply chain and the role that responsive, small molecule CDMOs have played in identifying practical routes for the manufacture of SARS-CoV-2 therapeutics. We also take a look at vaccine technology and manufacturing partnerships involved in the fight against COVID-19 and the challenges surrounding vaccine distribution.

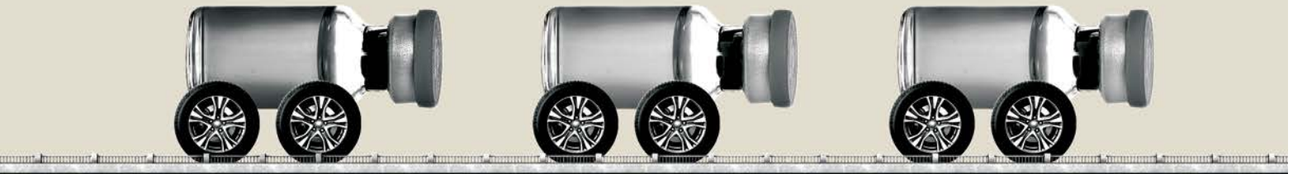
Of course, development of drugs and technologies unrelated to the novel coronavirus has also continued apace, and our contributors have been actively involved in the advancement of a broad spectrum of research and manufacturing solutions. Supercharged T cells are being designed to combat cancer, while undifferentiated allogeneic pluripotent stem cells are being developed to treat neurodegenerative diseases, and organoid technology is moving ever closer to fully functioning tissue building blocks. The development of viral vector manufacturing platforms will, meanwhile, help propel further advances in gene therapy.

To support all of these activities, access to data and manipulation tools are needed, a topic addressed from research, supply chain, and marketing perspectives. New ways to leverage single-use technologies and modular facility construction, as well as end-to-end support for antibody–drug conjugates and hot-melt extrusion solutions for poorly soluble APIs, are helping reduce time-to-market. Our feature focuses on advances in wearable technologies, the challenges to their use, and their potential to improve clinical outcomes.

On a final note, despite the COVID-19 pandemic, we were grateful during That's Nice's Silver Jubilee year to complete "The Road To 2021" campaign. We discovered insights regarding the future of healthcare on a 7,000+ mile journey around Europe, visiting 25 countries in just 25 days. This trip provided the opportunity to gain a better understanding of healthcare and the future needs of pharma service providers in Europe, as well as the general public. We are grateful to everyone who shared their thoughts, which we have relayed through our multimedia offerings, including in this issue of *Pharma's Almanac*. P

DELIVERING VACCINES DURING A PANDEMIC

By **Nigel Walker**, Nice Insight



Developing potential COVID-19 vaccines at an accelerated pace has been a tremendous challenge. Looking forward, the world faces another monumental task: administering those vaccines — once approved — to billions.

The Ultimate Supply Chain Challenge

As of October 7, 2020, more than 35.5 million confirmed cases of COVID-19, including more than 1 million deaths, were reported to the World Health Organization. There is a dire need for therapeutics and vaccines to fight this pandemic, and the biopharmaceutical industry has been working at a furious pace to develop effective products. Ten vaccines have entered phase III clinical trials around the globe (four in the United States), dozens more are in early clinical stages, and well over a hundred are in preclinical development.[1]

Once one, or more, candidate is proven to be safe and effective and granted marketing approval – most likely using emergency authorities of relevant regulatory agencies – those vaccines will need to be produced and distributed to a large percentage of the 7.8 billion people that comprise the global population. And this activity must take place without disrupting the production and distribution of existing medicines and vaccines, which will require additional manufacturing and logistics capacity.

Developing an effective vaccine is only the beginning of the challenge. The active ingredients need to be produced and then formulated into final products before being packaged for shipment. Delivery by air, which will be challenging given the shortage of air cargo capacity, can only occur through airports certified to receive pharmaceuticals, which can only handle so much product at a given time.[2] The vaccines will then be transported to distributors for allocation to hospitals, pharmacies, and vaccination centers, which will need to be established.

Issues remain concerning the availability of raw materials for the production of these vaccines, including adjuvants used in their formulation, as well as glass vials and stoppers to store them and syringes to administer them.[3] Enhanced security will be required to prevent theft of the valuable products, and many will also require specialized low-temperature packaging and shipping conditions.

Many companies are already tackling the production capacity issue, investing in expanded facilities and collaborating with contract manufacturers. The firms with the most advanced candidates have been proactive about securing needed raw materials and are even producing large numbers of doses before receiving approval so the vaccines can be immediately shipped once approved.

The level of distribution required is unprecedented. For instance, 174.5 million doses of flu vaccines were supplied to the U.S. market between September 2019 and February 2020.[4] The U.S. government's Operation Warp Speed hopes to distribute 300 million doses by January 2021.

Consideration of the challenges of distributing vast numbers of these new vaccines and the development of possible solutions are underway. A research project in India is seeking to engineer an efficient and sustainable delivery mechanism for the distribution of billions of doses of COVID-19 vaccines, including to low-income countries that lack robust cold chains.[5]

Assuring a sufficient portion of the population gets vaccinated is an enormous task. Even for efforts involving UN agencies and country networks, vaccination levels for polio and measles in some cases struggled to reach 70%.[4] The level of vaccination required to beat SARS-CoV-2 is unknown, but, due to its mutability, some have suggested a level greater than 90% might be necessary. Doing so will be incredibly difficult and even more challenging if two doses of vaccine are required.

Many Unknowns

Questions about the production and delivery of vaccines for the novel coronavirus abound. The timeline to approval of the first products is just one unknown, as are how many doses will be necessary, and who will get the first vaccines that become available. Will the newer companies developing vaccines, which have never before commercialized a product, be able to access robust supply chains? How will the cold chain be maintained across all countries to ensure maximum inoculation? How can raw material shortages be addressed? Can all of these additional doses be manufactured and delivered without impacting the production of existing medicines and vaccines? More broadly, with no less than a hundred vaccines in development and no indications yet which will be successful, how can the industry adequately prepare?

McKinsey estimates that 7-9, and possibly up to 20, new COVID-19 vaccines could be approved over the next few years.[6] As of early August 2020, vaccine manufacturers committed to producing 1 billion doses by the end of 2020 and 9 billion doses by the end of 2021. Some questions remain, however, regarding the data requirements of the FDA for granting emergency approval of any COVID-19 vaccines.

Once one, or more, candidate is proven to be safe and effective and granted marketing approval — most likely using emergency authorities of relevant regulatory agencies — those vaccines will need to be produced and distributed to a large percentage of the 7.8 billion people that comprise the global population.

In early September, the International Air Transport Association (IATA) warned that the WHO, UNICEF, and Gavi have already reported severe difficulties in maintaining their planned vaccine programs during the COVID-19 crisis due, in part, to limited air connectivity.

Even if billions of doses are produced in the next several months, the shortage of packaging raw materials remains a significant issue. There has been a short supply of medical glass since the beginning of the pandemic, although Corning is currently expanding capacity for the production of vials for coronavirus vaccines.[7] There is also a shortage of the sand required to make glass vials, and it has been estimated that it will take at least two years to produce enough vials for all of the needed doses.[7] Access to enough stoppers for vials may also be a problem, as each vaccine may require a different type of stopper to ensure no interaction with the formulation components.

Capacity for syringes is also insufficient for the administration of COVID-19 doses. The White House anticipates needing 850 million syringes, according to one source.[8] One potential solution is the use of multidose vials, which would reduce the number of vials required. The U.S. government is also relying on the use of plastic vials with a microscopic glass coating and plastic prefilled syringes produced using blow-fill-seal technology.[9] The latter would not require any glass or rubber stoppers.

In the United States, the situation is complicated by confusion regarding the roles that the federal government and individual states will play in vaccine distribution and those that the military and CDC will play.[8] Given the difficulties the federal government had with the distribution of remdesivir and implementation of testing programs, there is cause for concern. As early as August 2020, the National Governors Association was urging governors to prepare for all aspects of vaccine distribution within their states.

In the UK, one report estimated that roll-out of a COVID-19 vaccine could be delayed by as much as two years due to shortages of glass vials, refrigerated trucks, pallets, and PPE for medical personnel who will administer the doses.[10]

Transportation Uncertainties

Assuming that the raw material challenges can be overcome, COVID-19 vaccines produced, whether in glass vials or plastic prefilled syringes, will need to move from manufacturing plants to distributors. The need for rapid deployment and the temperature-sensitive nature of most vaccines will require shipment via air at a time when air cargo capacity is already limited due to the pandemic.

The challenge is massive. DHL, working with McKinsey & Company as their analytics partner, published a white paper on delivering stable logistics for vaccines and medical goods during COVID-19 and future health crises. One key conclusion: to provide global coverage of COVID-19 vaccines for two years, up to ~200,000 pallet shipments and ~15 million deliveries in cooling boxes – as well as ~15,000 flights – will be required across the various supply chains.[11] As a result of logistical faults and insufficient infrastructure, the study found that as many as 60% of the world's population may not receive a vaccine.[12]

Millions of passenger flights have been grounded around the world, significantly reducing international belly cargo capacity. Some of this capacity has been regained by converting passenger aircraft to handle cargo.[13] Even so, one industry expert estimates that vaccines for 1 billion people would fill 1,000 Boeing 777 freighters; Boeing has produced fewer than 200 of these aircraft since 2009.[14]

Not surprisingly, shipping prices have risen, not only because of capacity shortages, but also due to the uncertainty of the timing of vaccine approvals.[2] In addition, several smartphone and electronics product launches are scheduled for late in 2020 and could potentially coincide with the first vaccine distribution efforts.[14]

Furthermore, converted passenger planes cannot be used as-is for the transport of most COVID-19 vaccines, because they will require storage at 2–8 °C or even as low as -80 °C. Transporters will need to develop methods to ensure that such low temperatures can be maintained throughout the aircraft or rely on specialized low-temperature packaging. Of course, that means sufficient quantities of this type of packaging must be available.

In early September, the International Air Transport Association (IATA) warned that the WHO, UNICEF, and Gavi have already reported severe difficulties in maintaining their planned vaccine programs during the COVID-19 crisis due, in part, to limited air connectivity. IATA's Director General and CEO Alexandre de Juniac indicated that, even if half of the COVID-19 vaccine doses are shipped by land, "the air cargo industry will still face its largest single transport challenge ever."[15]

Many countries have limited the movement of goods during the pandemic, which could also affect the ability of manufacturers to ship vaccines across borders. For drug products, some U.S. companies have been bringing products into Canada and then trucking them into the United States,[2] while others have chartered private planes. These approaches will be impractical for the transport of hundreds of millions of doses of COVID-19 vaccines.

The need for transportation may be reduced with the location of multiple manufacturing plants in different regions. Shipping vaccines in bulk could bypass some of the raw material shortage issues and reduced the number of shipments required. Shipment in less-than-container-loads (LCLs) for transport by ocean may be an option for vaccines that receive approvals down the road.[14] In August 2020, the International Air Cargo Association and Pharma. Aero announced plans to form a joint working group to provide air cargo guidance to the logistics industry for the transportation of COVID-19 vaccines.[16]

Temperature-Control Challenges

In many parts of the world, large quantities of vaccines that require cold storage are lost due to the inability to keep them at low temperatures. Maintaining the cold chain requires a reliable supply of electricity and access to refrigerators and, for some vaccines, advanced freezers that can reach extremely low temperatures. The latter is lacking in many parts of the world, and particularly in developing countries. The World Health Organization estimated in 2005 that up to 50% of vaccines are wasted globally each year due to an unbroken cold chain.[17] The value of these losses is estimated to be $35 billion.[3]

COVID-19 vaccines that require refrigeration will require a temperature-controlled management environment and must be shipped in certified shipping containers according to a number of international regulations, such as EU Good Distribution Practices, U.S. FDA and WHO regulations, and IATA's standards for temperature-controlled sensitive products published in the Temperature Control Regulations (TCR).[13] Truckers that provide refrigerated transportation for the pharma industry will need to meet the varying needs of different vaccines as well.

Companies that make temperature-controlled containers are working to boost production and precondition them in advance of the expected surge in demand. Shipping companies have also been preparing. FedEx has more than 90 cold chain facilities, including the FedEx Cold Chain Center in Memphis, boasting 20,000 ft² of temperature-controlled storage, including separate areas for healthcare produts.[18] UPS Healthcare recently brought online more than 1.5 million additional square feet of cGMP healthcare distribution space in key global markets and installed two freezer farms in Louisville, Kentucky, and Roermond-Venlo, Netherlands, for vaccine storage and distribution.[19]

Adequate refrigeration and freezer units, staffing, and supplies will also be required at hospitals, retail pharmacies, and pop-up vaccination sites. Even in the United States, the available cold storage capacity is estimated to be just 15%.[20] Other longer-term solutions may include new technologies for stabilizing vaccines so they can be stored and shipped at room temperature, such as that offered by UK-based Stablepharma[3] and researchers at the University of Bath.[21] Better visibility into the supply chain would help in the short term.

Given the staggering challenges that governments around the world face in developing an effective distribution system for COVID-19 vaccines once they are approved, it isn't surprising that politics is another piece of the puzzle that cannot be ignored.

Political Complications

Given the staggering challenges that governments around the world face in developing an effective distribution system for COVID-19 vaccines once they are approved, it isn't surprising that politics is another piece of the puzzle that cannot be ignored.

The initial question to address is who will be given the vaccine first, since it will take time to produce the total number of doses required to vaccinate the entire global population.[22] If some countries retain all of the doses prepared by domestic manufacturers, it will be even more difficult to achieve both efficient and fair distribution across the world.[2] The charity Oxfam has warned that wealthy countries representing 13% of the world population have laid claim to more than half of the promised COVID-19 doses.[23]

Who should manage vaccine distribution is another question. In the United States there is a debate over whether the Centers for Disease Control and Prevention (CDC), which operates existing vaccine distribution programs, or the Department of Defense (DoD) should lead the effort. Many are concerned that military involvement will undermine public confidence, which in some areas of the country is already low with respect to the safety of vaccines in general.

In mid-September, the Trump administration – through the U.S. Department of Health and Human Services (HHS) and the DoD – released two documents that "provide a strategic distribution overview along with an interim playbook for state, tribal, territorial, and local public health programs and their partners on how to plan and operationalize a vaccination response to COVID-19 within their respective jurisdictions."[24]

The approach relies on a combination of CDC Control health expertise, military logistics experience and resources, and a partnership with drug distributor McKesson Corporation[25] as a centralized distributor of future COVID-19 vaccines and ancillary supplies needed to administer vaccinations.

Any groups that want to administer COVID-19 vaccines (e.g., medical offices, clinics, hospitals, pharmacies) must enroll in the U.S. COVID-19 vaccination program and sign an agreement that they have the space, equipment, and trained staff to do so.[26] Doses will be requested through a state agency for each site, and the state will allocate the vaccine. The federal government is expected to send vaccine supplies first to sites that can reach the largest numbers of priority populations, and thus the CDC may override individual state allocations.

Vaccine orders will be shipped from McKesson distribution centers within 24 hours of approval, depending on supply, along with syringes and other ancillary materials required for administration.[26] It is also possible that national drug companies (e.g., CVS, Walgreens) could serve as administration sites working directly with the CDC. The DoD will handle all military allocations.

The Biden campaign is developing its own strategy for COVID-19 vaccine distribution leveraging experts from the Obama administration who oversaw pandemics and readiness.[27] They are speaking with contacts in U.S. health and safety agencies to monitor current activities and determine the needed solutions to overcome raw material and transport capacity shortages and manage distribution to millions of Americans.

Individual state and local public health departments will ultimately be responsible for administering vaccine doses. Having been underfunded for decades, these agencies are already overwhelmed by the challenges the pandemic itself has created, including finding sufficient treatment sites, medications, and PPE for medical care to tracking and tracing potentially exposed people as new cases continue to rise in many locations.[28]

Governors have been urged by the CDC to be prepared to begin administering the vaccine by November 1, which many doctors, nurses, and health officials say is not possible.[28] According to Dr. Kelly Moore, associate director of immunization education at the Immunization Action Coalition, a national vaccine education and

advocacy organization. “States will need more financial resources than they have now.”

Collaboration Is Essential

The pharmaceutical supply chain extends from basic raw material manufacturers through logistics suppliers to those involved in product administration. Overcoming all of the challenges the industry faces with respect to the development, production, and distribution of COVID-19 vaccines will require extensive collaboration and flexibility.

IATA urged governments to begin careful planning with industry stakeholders to ensure full preparedness when vaccines for COVID-19 are approved and available for distribution. “We urge governments to take the lead in facilitating cooperation across the logistics chain so that the facilities, security arrangements and border processes are ready for the mammoth and complex task ahead,” Juniac said.[15]

The COVAX initiative is one such global collaboration.[29] Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI), WHO, UNICEF, and PAHO Revolving Fund are working together to “guarantee rapid, fair and equitable access to COVID-19 vaccines for every country in the world, rich and poor.” UNICEF is the largest single vaccine buyer in the world (over two billion doses annually). The groups are working with manufacturers to plan vaccine handling and distribution and access to safe injection equipment.

Security concerns must also be addressed, and will require digital tracking of doses from the time they leave the factory until reaching the ultimate point of administration. Historically, vaccines have not been tracked by dose because of their low cost; that will likely have to change for COVID-19 vaccines.[30]

Sharing of manufacturing capacity for ultimately approved vaccines may be necessary. They must also be sufficiently flexible to meet varying levels of demand depending on the level of virus spread geographically and over time.[6] Transporters must be able to handle vaccines with different cold-chain requirements. Governments must implement their own distribution programs across the “last mile.”

Contingency plans will also be needed to ensure that companies can adapt when problems arise in both manufacturing and distribution.[31] In particular, companies need to be prepared to rescue vaccine shipments for which delivery is delayed or affected in some way so that temperature excursions do not occur.

Blockchain technology is attracting attention as a way for pharmaceutical companies to manage the supply chain for COVID-19 vaccines. This approach has the potential to engender confidence in the safety of vaccines beginning with raw materials and ending with doctors, nurses, and recipients.[32] P

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Mr. Walker is the founder and managing director of That’s Nice LLC, a research-driven marketing agency with 20 years dedicated to life sciences. Nigel harnesses the strategic capabilities of Nice Insight, the research arm of That’s Nice, to help companies communicate science-based visions to grow their businesses. Mr. Walker earned a Bachelor’s degree in marketing and philosophy with honors from London College of Communication, University of the Arts London, England.

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Stainless Steel to Single-Use: How to Adapt to the Changing Landscape in SUT

Avid Bioservices began transitioning to single-use technology (SUT) several years ago and has reaped considerable benefits, both to our operations and to the agile service we provide customers.

Saying Goodbye to Stainless Steel

Stainless steel facilities are on their way out. With the high titers obtained today, 2000-L single-use (SU) bioreactors are sufficient for most processes, and some vendors are developing systems up to 5000 L. When they are available, the range of SU bioreactor sizes can support the vast majority of biologic products on the market and in development, except perhaps global blockbusters.

Avid at the Forefront

Avid Bioservices was one of the first adopters of large-scale single-use technology. The decision to move to 1,000-L disposable bioreactors was made in 2007. However, at that time, the company had years of experience with SU biocontainers for buffer and intermediate product storage and single-use unit operations such as membrane chromatography.

Offsite Fabrication for a Reduced Construction Timeline

Avid’s Myford facility, designed to exclusively use SUT, was completed in 2016. The facility is truly a building within a building, with modular walls, ceilings, and many other components fabricated offsite and then installed within an existing building. There was no need for extensive external renovation, and this approach significantly expedited the construction process from groundbreaking to validation and facility start-up.

Access to Upstream Scale-Down Models

Unlike with stainless-steel reactors, scaled-down models of larger SU bioreactors are available from most vendors. These smaller systems (3L, 50L, 200L) are designed to mimic performance at larger scales, allowing process development to readily advance from the lab to the pilot plant and, ultimately, to production. While some gaps and issues remain, access to these scaled-down models confer a significant advantage on disposable technology.

Simplifying Investigations

Product quality investigations involving stainless-steel reactors are often incredibly complicated when all of the equipment and systems involved need to be examined or tested. SU bioreactors are inherently less complex and allow manufacturers to work with the SUT vendors to test the materials involved and help determine root cause. This simplification can enable faster investigation turnaround times, reduce investigatve costs, and prevent extended equipment tag-outs.

Constrained by Availability

As with any production system, SUTs have their own limitations. One of the biggest constraints is the low availability of different technologies. Only a few vendors offer bioreactors, tubing assemblies and other consumables have been limited until recently, and prepacked SU chromatography columns remain smaller than what would be ideal for commercial manufacturing. Additionally, only a few SU sensors are available, and considerable work remains to optimize their performance.

Users of disposable technology must also consider the consumables associated with SU equipment as critical raw materials. They are reliant on consumable vendors to ensure that production remains on schedule, which carries measurable risk. Vendors are impacted by natural disasters, including pandemics like COVID-19. Disrupted supplies, absent dual sourcing, or inadequate crisis plans can have a tremendous impact on the ability to continue manufacturing critical drug substances and drug products.

There are also concerns regarding the availability of testing data with respect to the integrity of biocontainer films, compatibility with various biologic and chemical compounds, and extractables and leachables (E&L). The largest vendors have been proactive in providing data packages to assess these issues, but all possible application scenarios cannot be evaluated in advance.

A Wish List for Vendors

Going forward, it will be critical for vendors to develop products that address the limitations of existing systems to boost flow rates and increase productivity, such as larger-diameter prepacked chromatography columns and larger and more efficient membrane filtration systems for harvesting and final product filtration. Standardization of the user interface for different systems would also greatly simplify things for operators.

Transforming Avid’s Offering

As a multiproduct manufacturer, there are clear advantages to SUT over stainless-steel technology, going well beyond eliminating the need for cleaning and cleaning validation, and reducing risks of cross-contamination. SUTs offer more flexibility and accelerated time to market with straightforward scale-up of upstream processes, simplified investigations, and much shorter setup and changeover times. With disposable systems, Avid produces products more quickly, expediting our ability to bring in processes, scale them up, and deliver products to customers and ultimately to patients. P

INDUSTRY LEADER INSIGHT

SHAPING THE FUTURE OF BIOPHARMA THROUGH NEXT-GENERATION CONTRACT DRUG MANUFACTURING

→ BY **FRANK MATHIAS, Ph.D.,** RENTSCHLER BIOPHARMA SE

As a leading CDMO focused on biopharmaceuticals in an increasingly complex global landscape, Rentschler Biopharma SE continues to strategically innovate through a unique go-to-market approach that is as flexible as it is nuanced. Sustainability and value creation are central focal points of the company's "Strategy 2025" initiative, a forward-looking vision that was created by gathering insights on how the world, societies, and the industry of tomorrow will function. Rather than building a strategy focused around maximizing ROI and exceeding benchmarks for financial key performance indicators (KPIs), the organization believes that building and executing the right approach is what is most important. Maintaining that focus will ultimately yield financial success.

With the biopharmaceutical industry undergoing significant transformation, it is essential that CDMOs evolve to meet the intricate, dynamic needs of their clients. As a family-owned business backed by strong partnerships – with an outlook toward the future and a commitment to continue to build sustainably – Rentschler Biopharma has gleaned external insights into trends and challenges in the biopharmaceutical industry that will guide how the organization operates over the long term. The company is focusing on expanding services and building up strategic alliances with technology leaders that provide complementary services to simplify the clients' complex challenges with best-fit solutions. Reducing time to market with the highest quality services is the top priority – not only in the core business of bioprocess development and manufacturing, but in project management, regulatory support, and consulting. In addition to these alliances with technology providers, the company is building long-term partnerships with clients in order to function as an extension of their operations, thus providing more strategic and holistic support.

STRATEGY 2025 — A UNIQUE APPROACH TO STRATEGIC PLANNING

Rentschler Biopharma's "Strategy 2025" adopts innovation, growth, and partnership to establish a formidable competitive advantage and create greater value for our clients in the future. The plan addresses all facets of our development and manufacturing activities – from the platform technologies we will need, to how our employees will work in the future, and how to continue to meet and exceed client expectations.

The inception of Strategy 2025 came in 2016, after I took on the role of CEO. It was important to develop a long-term vision for our organization to define what the company should look like in 2025, given the megatrends that will shape society, the industry, and the world. Over 18 months, we garnered insights and feedback from internal and external experts, including companies outside of the pharmaceutical industry, physicians from renowned hospitals, academia, patients, venture capitalists, recruiters, and – most importantly – our clients.

The heterogeneity of contributors created a vast data pool and a solid platform from which to determine the path the company should take moving forward. Our analysis has helped us make informed projections involving the treatment of patients with severe and rare diseases, the application of monoclonal antibodies (mAbs) as a therapy of choice, and the progression and importance of cell and gene therapies. Our findings highlighted the shift to personalized medicine, particularly in cell and gene therapies. Another impactful societal trend for the industry involves the aging global population, most of whom expect to stay active even after retirement. Younger people are also approaching healthcare differently and are focused on prevention; they expect to remain healthy well into the future.

CONTINUOUS IMPROVEMENT FUELED BY CLIENT NEEDS

Rentschler Biopharma recognizes the need to evolve to meet the changing demands of our clients, which is why we prioritize three pillars: improving conventional biopharmaceutical development and production processes, building on our existing capabilities for designer biomolecules, and meeting the needs for new therapeutic modalities. Our approach centers around improving processes to reduce time-to-clinic and time-to-market, including fit-for-purpose process solutions that not only improve efficiency and productivity but also enhance interactions with clients and partners to enable more participation in the development process. We develop standardized platform processes that are prevalidated and prequalified, offer a simpler, streamlined pathway, minimizing risk and reducing development timelines. Integrated design and development are combined with improved workflow strategies and approaches for reorganizing unit operations, including automation and process intensification.

We are committed to continuously developing methods that further enhance our proven capabilities to produce complex designer molecules. This includes the ability to produce customized expression hosts and supporting bioprocesses in optimized, integrated solutions for the efficient assembly and stabilization of biomolecules with complex architectures. Our smart bioprocessing approach enables the creation of optimized, robust, and replicable cGMP-ready bioprocesses from the start, reducing costs, time, and effort. Strategy 2025 also addresses innovative therapeutic technologies outside of mammalian cell culture, including viral vectors for the production of gene and cell therapies. We are broadening our already substantial knowledge of complex molecular entities into new biomolecules and modalities, as well as expanding into exciting new areas.

In addition to identifying ways to improve client interactions and innovate, planning for Strategy 2025 enabled us to identify opportunities for significant growth. When our North American clients expressed a desire for Rentschler Biopharma to establish a local site in the region, we took action. With about a third of our total revenue generated in the United States, we acquired a facility in Milford, Massachusetts, near the renowned Boston biotech hub. This expansion unlocked access to new technologies, a robust and diverse talent pool, and the opportunity to exchange ideas with leading industry and academic experts.

Strategy 2025 is also supported by our technology alliances with companies whose offerings integrate seamlessly into our business processes. These strategic alliances extend the exceptional level of services that we can offer while driving further innovation within the company. Our vision is to serve as a CDMO that can support our client–partners with services from gene to patient.

RENTSCHLER BIOPHARMA'S "STRATEGY 2025" ADOPTS INNOVATION, GROWTH, AND PARTNERSHIP **TO ESTABLISH A FORMIDABLE COMPETITIVE ADVANTAGE AND CREATE GREATER VALUE FOR OUR CLIENTS IN THE FUTURE.**

We will continue building strategic capacity to fulfill the demand for emerging, life-saving therapies and collaborating with our partners to develop mutually beneficial alliances that drive supply and delivery to patients with reduced time-to-market, the highest quality of biopharmaceuticals, and unrivaled efficiency – from mAbs to highly complex biomolecules and viral vectors. Strategy 2025 will ensure that our business models, services, and talent will continue to accelerate client projects from concept to market execution, cementing our reputation as a premium outsourcing partner translating fundamental research breakthroughs into effective treatments for patients.

OUR STRENGTHS AND EXPERTISE

We guarantee best-fit solutions for our clients' products by balancing timeline requirements with a comprehensive manufacturability assessment, with quality always paramount. This commitment is reflected in our outstanding regulatory track record, as well as our exceptional client-oriented project management and regulatory support.

Rentschler Biopharma's collaborative approach is strengthened by the foundational pillars of our core capabilities, including cell line development, process development, formulation development, analytical development, manufacturing, and project management.

Our expertise in cell line development includes the application of mammalian cell lines for the expression of recombinant proteins and the development of high-yield production cell lines. We also specialize in the development, optimization, and validation of cell culture and the purification of recombinant proteins, and we develop customized processes for active ingredients with efficient process transfer. Having expanded our formulation capabilities through our alliance with Leukocare AG, we offer improved stability of therapeutic proteins in dry and liquid formulations, including highly concentrated products. Our analytical methods ensure quality and purity according to all cGMP guidelines, and our testing services include identity, purity, and potency testing. Furthermore, our manufacturing capacities provide flexible multiproduct sites for upstream and downstream processes, with single-use (SU) bioreactors up to 2,000 L and stainless-steel bioreactors up to 3,000 L.

FINDING THE BEST-FIT SOLUTIONS TO REDUCE COMPLEXITIES FOR CLIENTS

To create new efficiencies for our clients by linking complementary services across the value chain under an integrated offering, Rentschler Biopharma seeks strategic alliances with best-in-class providers. Their offerings are integrated seamlessly into our business processes, ensuring that all parts of the project are aligned. These strategic alliances and collaborations extend the high level of service that our CDMO offers while driving further innovation within the organization.

One such alliance is with Leukocare, the exclusive formulation developer for Rentschler Biopharma, which provides a bioinformatic, algorithm- and database-driven approach to drug product stabilization. Unlike conventional approaches, Leukocare's technology explores a broader design space, which obviates the need for high-throughput screening while also increasing the probability of successful formulation. This alliance allows us to offer clients advanced formulation capabilities from concept to market and leverage Leukocare's formulation technology at every relevant step of the development and manufacturing process. The technology improves the stability and quality of antibodies and other biopharmaceuticals – including vaccines, live viral vectors and protein components of biologically functionalized medical devices – at all concentrations in liquid and dry formulations. This is accomplished by increasing the thermal stability of biotherapeutics, preventing molecular degradation and potentially improving storage at room temperature, and by enabling lyophilization of drug products, which can reduce manufacturing costs and increase the convenience of administration while maintaining efficacy and activity.

Another strategic collaboration enhances our services and offers complementary

TO CREATE NEW EFFICIENCIES FOR OUR CLIENTS BY LINKING COMPLEMENTARY SERVICES ACROSS THE VALUE CHAIN **UNDER AN INTEGRATED OFFERING, RENTSCHLER BIOPHARMA SEEKS STRATEGIC ALLIANCES WITH BEST-IN-CLASS PROVIDERS.**

U.S. Expansion into Massachusetts Biotech Hub

In January 2019, Rentschler Biopharma acquired its U.S. site in Milford, MA in the greater Boston area. This region boasts a rapidly growing, dynamic biotech community, including more than 1,200 biotech companies represented by the Massachusetts Biotechnology Council. Establishing a location here enables the co-development with world-class scientists and innovative companies in all stages of their growth.

The FDA-, EMA-, and Health Canada–licensed, 93,000-ft² facility is a multiproduct site that offers innovative client solutions. The first step in this expansion project was putting a 500-L SU bioreactor into operation. The smart, interconnected technologies being built into the Milford facility are integral to the Strategy 2025 vision. We are reshaping the existing labs with brand-new equipment and connecting them with digital solutions. This manufacturing approach is ideal for fit-for-purpose design solutions. Development timelines are shortened by removing traditional bottlenecks that delay time to the clinic. A building will feature large-scale SU manufacturing and lab capacities. With its innovative and highly flexible business model, we have already begun new projects at the Milford site, including complex and difficult-to-manufacture proteins. We are preparing to take on new work and are hiring additional personnel with the skills needed to transfer projects from clinical to commercial status.

WE VIEW OUR CLIENTS AS PARTNERS AND THE **BEST-IN-CLASS SERVICES THAT WE PROVIDE AS EXTENSIONS OF THEIR OPERATIONS.**

skills and experience along the biopharmaceutical value chain. On July 6, 2020, we announced a strategic collaboration with Vetter, another family-owned CDMO. This collaboration creates long-term value for our respective clients through the alignment of manufacturing approaches and holds great promise for further simplifying client solutions. By combining Vetter's expertise in aseptic fill and finish and secondary packaging with our expertise in drug substance manufacturing, including bioprocess development and active pharmaceutical ingredient (API) production, there are numerous opportunities for both companies to share knowledge and best practices and gain market foresight. We see long-term potential in this partnership between two industry leaders, both of whom have a presence in Europe and the United States, as well as important synergies between our business portfolios. We are confident that combining our expertise will allow us to deliver new pathways for biopharmaceutical development and to address challenges facing the industry with our collective insight.

CONTINUING EXTENSION OF EXISTING SERVICES BEYOND STRATEGIC ALLIANCES AND COLLABORATIONS

We have entered into a commercial licensing agreement with Horizon Discovery, a global leader in the application of gene editing and gene modulation for cell line engineering, whereby Horizon's CHOSOURCE™ platform would be used in combination with our novel in-house process for cell line development for difficult-to-express proteins. Horizon's gene-edited glutamine synthetase (GS) knockout Chinese hamster ovary (CHO) K1 cGMP-compliant cell line complements our existing service offering, providing a royalty-free, state-of-the-art alternative for the production of highly complex proteins.

Rentschler Biopharma's integrated platform process, together with Horizon's cell line, provides solutions that translate complex medical research into exceptional biopharmaceuticals, elevating the standard of protein expression and allowing clients access to a robust and flexible approach for designer protein therapeutics. Horizon's portfolio of tools and services helps scientists gain a greater understanding of gene function, identify genetic drivers behind human disease, and deliver biotherapeutics, as well as cellular and gene therapies for precision medicine. In addition, diagnostic workflows can be developed and validated to enable almost any gene to be altered or its function modulated in human and other mammalian cell lines. This alliance embodies the Strategy 2025 spirit of providing wholly integrated solutions across the entire value chain, significantly broadening our fit-for-purpose approach and empowering organizations of all sizes to drive efficiencies in biotherapeutic manufacturing.

The same drive to provide integrated solutions to our clients led to the recent licensing agreement that we formed with ATUM, an industry leader in synthetic biology solutions. This agreement offers full access to ATUM's proprietary Leap-In-Transposase® platform to enhance our ability to provide stable, high-titer manufacturing cell lines. The Leap-In-Transposase® platform combines proprietary algorithms and unique genetic vector elements to harness a mechanism based on transposons for efficient genomic insertion of genetic material – which is ideal for the development of recombinant antibodies, including complex, multi-chain proteins like bispecific monoclonal antibodies. In concert with the CHO GS KO platform licensed from Horizon, access to this technology will allow us to produce high-yielding cell lines under very rapid timelines, even for complex therapeutic proteins, creating a simple, integrated solution for these challenging programs.

STRATEGIC CLIENT PARTNERSHIPS TO SUPPORT NEEDS INTO THE FUTURE OF BIOPROCESSING

Rentschler Biopharma maintains a focus on client needs across our operations. Naturally, our clients are seeking high quality and optimum solutions for all their biopharmaceutical programs. To these ends, we are continually adding capabilities to our service offering. We view our clients as partners and the best-in-class services that we provide as extensions of their operations. We truly understand drug development and all aspects of the product through its entire life cycle, as well as the challenges our clients face to get their therapies into the clinic and into the market as quickly as possible. Our client-oriented philosophy touches upon every aspect of how we do business – from project management through the establishment of strategic alliances to our robust record of quality excellence – keeping our clients and our company ahead of the curve in the rapidly changing biopharma landscape.

The strategic partnerships that we forge with clients offer a next level of support. As always, we provide these clients with our expertise, experience, and quality guarantee, but such longer-term partnerships allow us to focus on the client's point of view. Under these partnerships, we commit to sustainable long-term growth along with our client partners, offering flexibility to adapt to changes in their development and manufacturing requirements, while still simplifying our own planning and allocation of resources. The approach ensures that capacity, staff, and equipment are ready when needed for our partners' programs without interrupt of other ongoing projects at our site, in a manner that is quickly and easily scalable to meet future demands. Such partnerships offer considerable benefits both to Rentschler Biopharma and our partner companies, as well as to the ultimate beneficiaries of all the work we do: the patients.

FAMILY-OWNED STRUCTURE ELICITS INNOVATION AND AGILITY

The company was founded in 1927 and has been developing bioprocesses and producing biopharmaceuticals since 1974. We received the first marketing approval for interferon in 1983 and in 1997 became an outsourcing pioneer and one of the first true CDMOs. We have been innovating to find new ways to support our clients ever since. For instance, we were among the first companies to install 1,000-L SU bioreactors and produce commercial batches in a 2,000-L SU bioreactor. We have nearly 50 years of proven expertise in biotechnology, having manufactured over 300 client molecules, with strengths in highly complex molecules, fusion proteins, and recombinant enzymes, as well as monoclonal and multi-specific antibodies, among other modalities. Over 10% of the molecules that we have worked on have already made it to the market, and many more are progressing through preclinical to phase III clinical development.

As a fifth-generation family-owned company, we can be rapidly decisive, implement innovative programs, and build long-term sustainability without the bureaucratic barriers that sometimes exist in larger, public corporations. Our organization is free to plan without focusing on short-term financial profit. The innovative spirit of our leadership has positioned us at the forefront of new developments in biopharma.

At Rentschler Biopharma, we know that our employees are the key to realizing the vision of the company and to our continuous, sustainable success. That is why we attach great importance to the personal and professional development of each employee – individually and over the long term. Staying true to our motto – "Many hands, many minds, one team!" – I am grateful and proud to have such a great team, and I thank them for their fantastic contribution. For three consecutive years, we have been recognized as one of "Germany's most attractive employers" by the F.A.Z. Institute, this year – for the first time – ranking first in the biopharma sector. I think this achievement speaks for itself! P

Partnering to Access the Japanese Market

Rentschler Biopharma has renewed the existing strategic partnership in Japan with Summit Pharmaceuticals International Corporation (SPI), a subsidiary of Sumitomo Corporation. Through strong collaboration with SPI, the CDMO has subsequently secured new contracts with additional Japanese pharmaceutical companies, outlining projects from the early clinical stages through commercial launch. Japanese companies are playing a significant and expanded role in the global healthcare market, as Japan is the world's third-largest pharmaceuticals market — with forecasts projecting the market to reach $89 to $93 billion by 2023.

There are over 100 domestic pharmaceutical companies in Japan, and many of the mid-sized and larger firms have recently been developing drug candidates with innovative and new modalities, such as biologics and gene and cell therapies, for markets worldwide. Japan has also seen an increase in biopharmaceutical start-ups, which is further driving the industry's growth – collaborating with these Asian companies fittingly aligns with Rentschler Biopharma's global vision for Strategy 2025

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In 1991, **Dr. Frank Mathias,** a freshly graduated French pharmacist of the Paris VI University, entered the German pharmaceutical industry, the largest at the time. Since then, he was able to experience different corporate and leadership cultures in multiple management positions: from then global giant Hoechst AG, via family-owned French Servier, followed by American top Biotech Amgen, to publicly listed German Medigene AG — leading him to Rentschler Biopharma SE as CEO in 2016. As Chairman of vfa bio, he is representing German biotech industry interests. Frank champions long-term strategic growth in the biopharmaceutical industry.

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MODERN STRATEGIES FOR DERMATOLOGY CLINICAL TRIALS

→ BY **ROSE BLACKBURNE M.D., JOHN MANNS, TIM RICH,** AND **MICHAEL NOSS, M.D.,** PPD

To be most successful, dermatology clinical trials should be accessible to a diverse array of qualified patients and designed to encourage patient participation. These trials should also reduce the patient and investigator site burdens, reduce start-up and enrollment timelines, and ensure consistent, high-quality assessments and data collection. With extensive experience in dermatology trials; an international network of sites with dermatology experience in key indications, such as psoriasis and atopic dermatitis; access to a large database of potential trial participants; and a commitment to tailored trial design and leveraging digital tools, PPD is ideally positioned to help sponsors rapidly and successfully complete dermatology studies, even in the face of challenges posed by the COVID-19 pandemic.

ACTIVE CLINICAL SPACE

While advances have been made in dermatological medicine, including the development of novel biologic drugs, unmet needs remain in most non-malignant dermatological conditions, including acne, atopic dermatitis, psoriasis, rosacea, alopecia, and skin rejuvenation (wrinkle revision with dermal fillers or botulinum toxin products).

Widely available over-the-counter (OTC) and prescription topical corticosteroids are generally first-line treatments for psoriasis and atopic dermatitis, but they are not long-term solutions owing to issues with side effects. Similarly, biologic products are expensive and not always included in health insurance formularies, and there are variable country-level guidelines and approvals of different products.

In addition to more traditional topical products and novel injectables, drug companies are also developing oral medications. There is also significant development activity in biosimilar products for the treatment of

psoriasis and atopic dermatitis and growing interest in plant-based/botanical type products, including those based on cannabidiol (CBD).

The dermatology development landscape can be further segmented into consumer health (OTC) and prescription markets, the latter of which includes topical preparations of various types, as well as oral and injectable products that include non-biologic anti-inflammatory agents, biologics, and biosimilars.

As we move into 2021, a significant percentage of clinical trials underway will be focused on atopic dermatitis across all phases. While many of these trials involve new chemical entities or new biologic compounds, many are focused on extending approvals of existing products intended to treat other disorders of an immuno-inflammatory etiology, such as rheumatoid arthritis and other autoimmune conditions, as well as dermatological indications, including psoriasis, atopic dermatitis, vitiligo, and rosacea. With a number of biologics coming off patent, there is also heightened development activity around biosimilar alternatives.

An increasing number of studies will also be evaluating new medications for previously less-studied indications, such as epidermolysis bullosa (EB), vitiligo, urticaria, hidradenitis suppurativa (HS), and pemphigus. Notably, several early-phase trials are focused on treatments for wounds (e.g., diabetic foot ulcers), burns, and scars, as well as for alopecia, which has traditionally involved hair clinics and cosmetic centers.

Another important trend in the dermatology clinical space is the increasing use of technology for televisits, remote electronic consent, and other applications, with the COVID--19 pandemic providing a real driver for uptake. As a result, teledermatology has gained more widespread use across the world for clinical consultation, patient assessment, and follow-up, with televisits of increasing interest in dermatology clinical trials as a way of reducing the study visit burden for both patients and trial sites.

PATIENT IDENTIFICATION AND ENROLLMENT CHALLENGES

With well over 500 dermatology clinical trials underway, there is intense competition for eligible patients, particularly in atopic dermatitis. Experienced dermatology clinical trial sites in Eastern Europe are rapidly approaching saturation in terms of identifying eligible subjects to meet trial enrollment targets. New and less experienced sites have to be identified and trained to meet clinical trial demands. Interest in trial participation also tends to wane in the summer and increase in the winter in response to a correlation between the severity of many dermatological conditions and the weather (symptoms are generally more severe in cold, dry seasons).

The nature of the drug and disease and the requirements of the trial can also impact patient motivation. Drugs that are easy to self-administer are preferential (topical, then oral). Injectable drugs that require self-administration or IV infusion in a clinic are less desirable. Similarly, studies that require intense pharmacokinetic/pharmacodynamic studies and frequent skin biopsies are more difficult to enroll.

There are also other study-related factors that increase the challenges to enrollment and study conduct. Study sponsors often want board-certified dermatologists to serve as investigators, though many patients consult their general practitioner first–a physician who may not have specific knowledge and experience in conducting dermatology clinical trials. Finding the right patients can also be an issue.

IMPORTANCE OF CONSISTENT ENDPOINTS

Because many endpoints in dermatology clinical trials are based on visual evaluation of the skin (e.g., plaques, flaking, redness, lesions, percentage of body surface area coverage) accurate, consistent, and objective assessments are crucial for these studies to succeed. The levels of detail and precision required for clinical trials are generally much higher with more rigorous patient evaluations than normally needed for general treatment.

Additionally, investigators and their teams at all participating sites must be trained according to the same procedures and protocols to eliminate the possibility of significant variance in assessments from site to site, and even physician to physician within the same site. Frequent retraining is also recommended. Where possible, patient visits should also be scheduled with the same investigator throughout the study to further ensure assessment continuity and consistency.

Evaluation of data for the placebo effect is equally important, particularly when patient-reported outcomes (PROs) are part of the study. The use of photography can introduce a measure of objectivity; however, these issues must be addressed during both site training and data analysis.

THROUGH PPD'S RELATIONSHIP WITH AES, OUR CUSTOMERS CAN RECEIVE 50–100% OF THEIR ENTIRE TRIAL ENROLLMENT FROM ONE ACCOUNTABLE SOLUTION, DELIVERED BY RESEARCH LOCATIONS THAT OPERATE UNIFORMLY ACROSS THE GLOBE.

ADVANTAGES OF DECENTRALIZED STUDIES

Traditional trials require patients to visit investigator sites for all physician interactions. Decentralized trials leverage a variety of digital tools and technologies to enable the completion of trial tasks that normally involve face-to-face interactions remotely without compromising efficiency. Moving to a decentralized model shows promise in mitigating some of the burden and cost of traditional methods while preserving the quality of oversight.

In the dermatology space, the large number of clinical trials in psoriasis has provided an opportunity to gain experience with digital solutions, including e-consent, televisits, and remote assessment using a variety of digital tools. Experience is also being developed in other indications where similar approaches can be used, including atopic dermatitis, alopecia, and vitiligo.

Indications where patients are healthy except for certain skin conditions, such as acne, are also well suited to decentralized trials. In indications such as burns and diabetic foot ulcers it is possible that, while some in-person interactions are required, certain assessments could be completed virtually.

Dermatology studies can include a number of PROs to assess the impact of the patient's disease on quality of life, where dermatological conditions can have a high burden on patients. The ability to report these via electronic PROs (ePROs) aids reporting of outcomes that patients may feel more comfortable reporting remotely rather than in person, such as more personal impacts of their diseases, including perceived quality of life, mood, and other outcomes. Furthermore, by combining all of the digital tools on one platform – ePROs, video conferencing, uploading of digital photographs, etc. – the burden on the patient, as well as on the site, can be reduced even more. The ability to provide patient reminders and check data in real-time also ensures higher levels of compliance and better-quality data.

Digital technologies also have the potential to improve the current high failure rate for screening potential trial participants. These could take the form of a prequalification questionnaire provided by text or email that covers key criteria that must be met. It could also include site staff of the investigator having a video chat with the patient using his/her personal desktop or mobile device.

Such an approach would provide clarification without requiring the patient to travel to the investigator site and help identify those with the best chance of qualifying. The end result would be a reduced screen failure rate and thus a reduced site burden and cost. Ineligible patients would avoid a trip to the clinic, saving time, cost, and inconvenience, while also avoiding potential exposure to the flu, COVID-19, and other illnesses.

A COMPLETE ECOSYSTEM OF CAPABILITIES

PPD is more than a contract research organization. Our Accelerated Enrollment Solutions (AES) business unit offers best-in-class site and enrollment solutions, providing greater speed, certainty, and control to clinical trial delivery through a global pay-for-performance patient-enrollment engine and standardized global site infrastructure that provides centralized and consistent operations and quality worldwide. Through PPD's relationship with AES, our customers can receive 50–100% of their entire trial enrollment from one accountable solution, delivered by research locations that operate uniformly across the globe.[1]

With a huge footprint of investigator sites – including both owned (AES sites) and partnered (PPD network) sites worldwide, PPD has established extensive expertise. Our project managers (PMs), clinical trial managers (CTMs), and clinical research associates (CRAs) are highly experienced and ready to tackle any obstacles your research might face. We also have a large pool of fully audited and approved vendors that are readily available to support studies without the need for vetting.

PPD continues to build out areas of expertise to ensure that we provide sponsors with the highest-quality, most efficient clinical study design, management, and operations. For instance, PPD continues to expand site networks to enable higher enrollment rates by focusing on high-performing site relationships and seeking ways to overcome the seasonality effect associated with dermatology trials, including leveraging sites in both the northern and southern hemispheres so that subjects can be enrolled continuously despite seasonal changes in individual countries.

With teledermatology on the rise, the PPD® Digital team is further developing various digital approaches that leverage our partnerships with industry-leading decentralized trial platforms.

Decentralized trials are not one-size-fits-all. With trusted consultants from PPD® Digital, a determination can be made on which technology or platform is the best fit based on the needs of sites, sponsors, and patients. We evaluate each trial carefully, considering the region, protocols, endpoints, regulatory constraints, and many other factors to determine what options are best for the sponsor. This thoughtful approach to strategic planning and study implementation based on a thorough analysis of all relevant data ensures that the most optimal solution is designed and deployed for each trial and customer.

GET STARTED WITH THE RIGHT TEAM

PPD has a unique position in the dermatology clinical trial space, having conducted more than 40 dermatology studies in the past five years that have involved nearly 700 investigators and greater than 10,000

Case Study: Rapid Rescue and Decentralization

The need for digital and operational tools that can rapidly support a transition from a traditional to a decentralized clinical trial has never been so acute as when sponsor companies came to grips with the impact of the COVID-19 pandemic. However, combining the resources of PPD's vast network, and our clinical operational, regulatory, and data privacy teams, we are able to develop custom solutions even under the tight timelines and increased pressure of the rescue of a dermatology clinical trial.

In one example, a dermatology clinical trial requiring the collection of several primary end points via in-person clinic visits was successfully underway in Italy when the pandemic hit. The Italian government mandated stringent controls to restrict the movement of people within the country, which would have prevented five patients from attending their final visits, and thus the collection of the primary end point data from these patients.

In order to save the clinical trial, it was necessary that a 21 CFR Part 11–compliant digital solution be implemented as fast as possible. In a matter of weeks, the PPD Digital team deployed a visual communication tool using the TeleVisit lite module — itself developed in response to COVID-19 — to facilitate investigator and patient interaction and consent issues, which allowed all patient assessments to be conducted as planned.

PPD CONTINUES TO BUILD OUT AREAS OF EXPERTISE TO ENSURE THAT **WE PROVIDE SPONSORS WITH THE HIGHEST-QUALITY, MOST EFFICIENT CLINICAL STUDY DESIGN, MANAGEMENT, AND OPERATIONS.**

patients. We have extensive experience with psoriasis, atopic dermatitis, pemphigus, and glabellar lines. Our dermatology experts regularly work with both large biopharma companies and small/emerging pharma and biotech firms.

PPD has invested heavily in the dermatology therapy area, and we understand the importance of selecting the right sites that can capture the right patients and use rater scales consistently. For our dermatology studies, PPD ensures that all investigators are experienced dermatologists with proven success in enrolling the right patient population and thus ensure quality data collection across the participating sites.

We also recognize that a standardized training plan must be developed and implemented at the study team and site levels. By having properly trained sites and staff, the quality and integrity of the data collected in studies will be preserved. PPD has developed a comprehensive training program leveraging our dermatology toolkit to educate our CRAs and site staff so that all studies produce the quality data required for regulatory compliance. We also leverage our partnerships with companies that offer technology-based rating-scale training in order to minimize assessor variance.

Furthermore, the AES network includes dedicated sites with dermatology experience in the United States and EMEA, and there are over 6 million pre-screened dermatology patients listed in the AES database. Our experience in dermatology, combined with access to this large network of sites, has enabled us to gain tremendous efficiencies. Sites are activated more quickly, allowing for faster than expected onset and completion of enrollment than expected, leading to time and cost savings.

A key differentiator for PPD is the investment we make in building a strong rapport between our sites and PPD's clinical teams, which helps to motivate sites to follow directives and complete requests during critical time periods, such as advanced, detailed planning of monthly data cleaning and review activities. Our collaborative approach creates a high level of cooperation across all PPD Functional groups and with sponsor counterparts as we all work towards the common goal of successfully implementing and completing high-quality trials that will enable needed medicines to reach the market.

As the clinical landscape continues to evolve, PPD has the resources to conduct trials in many ways, including traditional, hybrid, and decentralized trials, in the dermatology space. Our experience with eCOA, ePRO, telemedicine approaches, hybrid virtual trials, e-consents, electronic medical records, and remote source document verification (rSDV), among others, has enabled us to rapidly convert traditional trials to decentralized trials during the COVID-19 pandemic. Indeed, our experience, pooled knowledge, and access to the AES database of patients has allowed PPD to quickly pivot in response to unexpected and changing situations, providing the support and insight needed to address heightened risks and keep trials on track.

EXPANDING PATIENT ACCESS

Quality clinical trials cannot be achieved without the participation of qualified patients. Given the difficulties in finding these patients and the challenges patients themselves face in accessing dermatology clinical trials, PPD has taken several steps to help address these issues.

First, we expanded our country and site footprint – including both AES sites and others in the PPD network – with strong dermatology capabilities in the United States, Hungary, Poland, the Czech Republic, Serbia, Croatia, Italy, Belgium, Denmark, Israel, India, and South Africa. Efforts are also ongoing to train primary care providers so that they are equipped with the knowledge needed to recommend patients for clinical trials. Inclusion of non-specialist sites with solid trial experience provides greater access to potential patients who often first seek help from their primary doctors.

We have fully leveraged PPD's in-house medical expertise networking together our dermatologists and dermatology dedicated physicians across our functions from product development to pharmacovigilance through to AES site personnel.

To reach potential patients, our teams continue to create global awareness through a unique blend of various media platforms, webinars, and other forums. At the same time, we continue to innovate to accommodate evolving study needs, including the use of digital and/or remote patient and site activities.

We look at each trial individually to consider potential problems, such as seasonality and the placebo effect. We also seek to understand how the medication will be administered (topical, oral, injectable) and how that will impact interest from different patient groups. PPD teams also put themselves in the shoes of the patient. For instance, thinking as deeply as whether or not women will reject participating in a trial with a topical medication that must dry for two hours before they can apply makeup. Or, in other cases, groups may not participate if the drug is an injectable that must be administered in a clinic.

Because dermatology conditions like psoriasis, atopic dermatitis, and acne are not life-threatening, clinical studies must be designed so that minimal burden is placed on the patient throughout the course of treatment. On the other hand, given the significant impact that these diseases can have on quality of life – depression, low self-esteem, poor performance due to psychological effects, lack of sleep, etc. – patients can be highly motivated if a study is well designed. Therefore, it is essential to leverage new technologies as much as possible and work with sites that are specially equipped to work with this unique patient population, thereby generating excitement to participate in interesting and treatment-advancing clinical research.

LOOKING AHEAD AS ADOPTION INCREASES

The COVID-19 pandemic has accelerated the adoption of virtualized and decentralized trial protocols. Telemedicine and teledermatology are not new; dermatologists were using digital technologies to reach patients in areas where specialists are lacking long before the emergence of the SARS-CoV-2 virus. The pandemic has, however, pushed the development of new technologies and advanced versions of those that already existed specifically for use in clinical trials.

The goal of clinical studies for sponsors is to prove to regulators that their products are safe and effective to distribute to patients in need. It is hoped that wider use of the decentralized trial model during the COVID-19 pandemic will provide evidence that remote assessments and collection of dermatology endpoints can provide the same quality data as those obtained via on-site visits. In addition, accessibility and enrollment can be improved while the burdens on the patient and the investigator site are reduced.

Indeed, the current situation has presented a tremendous opportunity to compare results obtained using traditional on-site protocols with those collected remotely using a combination of digital tools. So far, at least one satisfaction survey has revealed that both patients and physicians feel that the quality of care and results obtained during televisits is equal to that of onsite visits. We also have the opportunity to produce early benchmarks for the accessibility of virtualized and decentralized trials and the impact that digital technology has on key components such as diversity and recruitment.

Going forward, we expect sponsors to start pushing for the use of hybrid solutions with a combination of site-based and remote activities as they seek to meet the evolving needs of patients around the world. P

Note: Additional insight provided by: Phil Pickford, Senior Director, Project Management, PPD; Norma Cantu, Senior Director, Project Management, PPD; Annika Dhondt, Executive Director, Project Management, PPD; and Cristina Nieto, Vice President, Project Management, PPD.

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In his current role, **John** provides vision and strategy on planning and executing decentralized clinical trials to solve operational challenges, particularly where there is a benefit to the patient. John brings more than 25 years of industry experience, including leadership positions in PPD's innovation and operational teams. John holds a Bachelor of Science degree in mathematics from the State University of New York at Cortland.

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Dr. Blackburne is a board-certified physician and experienced healthcare executive. As an industry leader, her career in healthcare spans over 25 years, including clinical practice, direct patient care, health management, and most recently as an executive in pharmaceutical, biotechnology, and medical device product development. Dr. Blackburne earned her medical degree from the Morehouse School of Medicine and an MBA from the University of Virginia Darden Graduate School of Business. Dr. Blackburne serves as Industry Representative Alternate (2016–2021) to the FDA Patient Engagement Advisory Committee (PEAC) to provide advice on issues relating to the regulation of medical devices and their use by patients and to develop agency guidance and policies.

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Dr. Noss has been a principal investigator on over 700 clinical trials in more than 70 therapeutic areas. Throughout his career, he has developed a large dermatology niche that includes serving as a principal investigator on 27 psoriasis, six atopic dermatitis, 14 acne, four actinic keratosis, two cellulite, one keratosis pilaris, 11 onychomycosis, one seborrheic dermatitis, one seborrheic keratosis, and nine tinea pedis studies. In addition, Dr. Noss has conducted 88 consumer-based clinical trials, including product use and tolerance, dermal patching studies, biopsy, and much more.

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IN CONVERSATION

SOLVING SOLUBILITY CHALLENGES WITH A POLYVINYL ALCOHOL EXCIPIENT AND HOT MELT EXTRUSION

→ WITH **DANIEL JOSEPH PRICE** AND **THOMAS KIPPING, Ph.D.,** MILLIPORESIGMA

Hot melt extrusion (HME) is an attractive method for the generation of amorphous solid dispersions of poorly soluble APIs. Polyvinyl alcohol has recently attracted attention for HME due to its unique behavior under higher shear forces and its high thermal stability. MilliporeSigma has developed a PVA excipient specifically designed for HME that provides prolonged supersaturation through drug–polymer interactions in solution.

Daniel Price and Thomas Kipping, Ph.D., discussed MilliporeSigma's contribution to overcoming solubility challenges with *Pharma's Almanac* Scientific Editor-in-Chief David Alvaro.

What is driving the trend toward more lipophilic and less water-soluble APIs?

Over the past few decades, many small molecules have become more lipophilic or more hydrophobic, which are not necessarily equivalent. More lipophilic molecules are molecules with a higher logP and thus higher lipophilicity. More hydrophobic molecules tend to be those with very strong crystal structures, but not necessarily higher lipophilicity. Their solubility is limited by the necessity to break these crystal structures into individual molecules.

There are a number of reasons why we see more lipophilic and hydrophobic molecules. First, therapies are aimed at more lipophilic biological targets, so by necessity lipophilic molecules need to be designed to interact with those targets to have a physiological effect.

Second, high-throughput synthetic chemistry techniques, such as combinatorial and click chemistry, which are now commonly used, tend to produce molecules with poorer physicochemical properties, with a skew toward very strong crystalline structures and high logP.

Third, several decades ago, when the pharmaceutical industry was still in the early development stages – even as recently as the 1970s – there was a still wealth of compounds exhibiting good physiological effects and physiological efficacy available for consideration as drug candidates. Over time, these types of sweet-spot molecules have become less and less common, this is known as the "low hanging fruit" hypothesis.

Looking into the future at what's next for orally delivered small molecules, we expect the chemical space to continue evolving toward yet greater complexity. Compounds such as peptides, oligopolymers, and PROTAC molecules, complex bifunctional molecules that trigger cell destruction, are key examples. These types of molecules are even bigger, even more lipophilic, and could well be even more poorly soluble than previous drug candidates, so the shift in this direction will increase in the future.

For orally administered medications, can you explain the different stages where solubility is a factor from the time a drug enters the body until its point of action?

Oral solid dosage forms are typically capsules or tablets. When a tablet is swallowed (ideally with the recommended 250 milliliters of water, but typically with a small sip), the water and the medication pass from the mouth through the esophagus and into the stomach. The stomach has a low pH of approximately 1.2. If the molecule is soluble at pH 1.2 (typical for basic compounds), it will begin to dissolve in the stomach.

Gastric clearance occurs next and takes place anywhere from 30 minutes to three hours after the tablet enters the stomach. Essentially, the entire contents of the stomach are released into the intestines, which are the main site of absorption for drug molecules.

In order for the drug to be absorbed in the intestines, it must be solubilized in the gastrointestinal fluids, which are more basic than the stomach, with a pH of approximately 6.5, and contain various bile salts and phospholipids. All of these components can contribute to enhanced solubilization.

However, if the drug substance is insoluble or has low solubility in the gastrointestinal fluids, it will not be absorbed through the intestinal membrane. The permeability of the drug substance in the intestines is also important – if the API has a low permeability, then it will also experience low absorption.

These two parameters – solubility and permeability – are the two key drivers for absorption from the intestine. They are also the two factors upon which the biopharmaceutical classification system (BCS) is based. This system groups drugs based on their solubility and permeability.

BCS class 1 drug substances are both soluble and permeable and thus do not present any bioavailability issues. They reach the intestine, dissolve into solution, and then pass through the intestinal membrane into the circulatory system.

BCS class 2, the most common class, comprises molecules that have poor solubility but good permeability. These drugs dissolve only to a limited degree, but the small amount of API that is dissolved has no problem passing through the membrane. Nevertheless, the low solubility limits the absorption.

TABLE 1 **Physicochemical and powder properties of Parteck® MXP excipient make it well-suited for use in HME.**

Product Properties	
Bulk density (g/mL)	0.53±0.02
Tapped density (g/mL)	0.74±0.02
Particle size (D50) [µm]	60–80
Loss on drying (%)	<3.0
Angle of repose (°)	35
Hydrolysis grade (%)	85–89
Solubility (%) (max. in water)	33
Mass average molar mass	approx. 32,000
pH value (4%/water)	5.0–6.5

T_g (by DSC)	T_m (by DSC)	T_d (by TGA)
40–45 °C	170 °C	>250 °C

Temperature	Melt Viscosity D=200 (s^{-1})	Melt Viscosity D=1,200 (s^{-1})
210 °C	702 Pa·s	283 Pa·s
230 °C	345 Pa·s	174 Pa·s

BCS class 3 drug substances have the opposite properties: good solubility but low permeability. These APIs readily go into solution but then have difficulty passing through the intestinal membranes, thus also resulting in limited absorption.

BCS class 4 compounds are molecules with both poor solubility and poor permeability. These APIs are the most challenging molecules to be absorbed by the body.

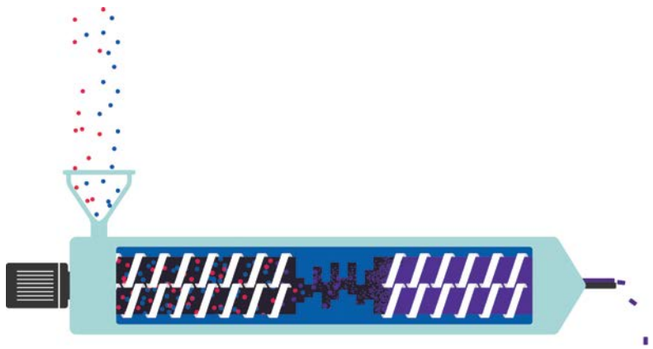
Among the formulation methods used to overcome poor solubility and lipophilicity, how does one determine which is the best approach for a given API?

There are two potential explanations for a drug exhibiting low solubility: dissolution limitations or solubility limitations. For solubility-limited compounds, the thermodynamic solubility of the molecule is inherently low. For dissolution-limited compounds, the thermodynamic solubility may be okay, but the rate at which the drug dissolves may be so slow that a low solubility is observed. Each of these two conditions requires a different approach.

For dissolution-limited solubility, this issue can be addressed relatively easily by reducing the particle size via micronization or, in extreme circumstances, nanosizing. Reducing the particle size increases the surface area of the drug exposed to the gastric fluids, resulting in faster dissolution rates, as described by the Noyes–Whitney equation. Poloxamer excipients and other surfactants can also be used to overcome dissolution-limited solubility, making the environment more favorable for dissolution and thus increasing the dissolution speed.

For solubility-limited compounds, the solutions are slightly more complex. The first possibility involves medicinal chemists exploring ways to modify the structure of the molecule, such as adding functional groups that slightly increase the polarity and slightly decrease the lipophilicity of the molecule or conversion into a prodrug with greater solubility that will be broken down in the body after absorption into the active API. Alternatively, the compound could be synthesized as a salt,

FIGURE 1 **In HME, the API is mixed with a matrix polymer in the extruder to enable homogeneous dispersion of the API within the polymer.**



dependent on the overall pKa of the molecule. More often than not, however, the medicinal chemists have already evaluated these options and found that any structural changes will negatively affect the efficacy of the drug product. Therefore, solubility-limited compounds are often addressed with formulation technologies.

For lipophilic compounds (compounds with high logP), it is often effective to use a lipid vehicle. The API is dissolved in a lipid, and that pre-dissolution allows for enhanced absorption once the drug substance reaches the gastrointestinal tract.

Complexation with cyclodextrin excipients is another option. The API is released from the complex into the solution at a higher rate than it would naturally dissolve, which can drive absorption. For many APIs, however, cyclodextrin complexes have rates of release that are too slow to provide any significant gain in absorption.

A third option is solid-state modification. Many compounds with low solubility have very strong crystal lattices. A crystal lattice is the structure of the intermolecular bonds that hold individual molecules together, and those bonds can be fairly week or very strong. In molecules with strong crystal lattices, molecules cannot go into solution very easily because of the tight bonds holding those molecules together in the crystal lattice, which require energy to be broken. A good example here is salt: at a certain point salt will not dissolve in a cold glass of water, but if the water is heated (i.e., more energy is supplied) then the bonds will be broken, and more salt will dissolve.

We cannot, however, heat up the contents of the gastrointestinal tract. Therefore, the crystal structure of the molecule can be a limiting factor for solubility in the body. What we can do, however, is remove the crystal structure altogether by formulating an alternative solid state. Of most interest for pharmaceutical applications is the amorphous solid state, in which no crystal bonds exist, and thus molecules are essentially loosely associated, making it easier for them to break away and dissolve. From a thermodynamic perspective, the solubility of an amorphous solid is substantially higher than the solubility of a crystalline solid.

The problem is that the amorphous solid state is not a normal thermodynamic equilibrium but a state of very high free energy, which typically results in recrystallization. To access the enhanced solubility offered by the amorphous form, we have to stabilize it.

Two main technologies are used to create amorphous solid dispersions (ASDs). The first involves the formation of a polymer-based matrix within which the drug substance molecules are homogenously dispersed and prevented from recrystallizing. The second method involves mesoporous silica carrier systems in which the highly porous mesoporous silica acts like a sponge, absorbing API molecules into nanoscale pores and again preventing them from bonding to one another in a crystalline form.

What are the practical considerations in formulating ASDs via hot-melt extrusion (HME)?

To form a solid dispersion using HME, the API is molecularly dispersed in a polymer matrix using elevated temperature and the mechanical force provided by extruder screws (Figure 1). In addition to enhanced API solubility and bioavailability, HME also increases the flexibility in drug release properties and is suitable for both immediate- and sustained-release formulations. In addition, HME facilitates various downstream operations, including direct shaping of the extrudate into tablets, direct tablet compression, pelletizing, and milling.

When developing HME processes, it is possible to test a model compound and screen different polymers to determine which might provide the most stable ASD. Various polymers traditionally used in HME processes include cellulose derivatives, polyacrylates and polymethacrylates, polyethylene glycols, and polyvinyl pyrrolidone (PVP).

All of these polymers are rather inert, with fairly simple structures to avoid radical formation during the HME process. The melt viscosities vary, and choosing a polymer with the right viscosity at the target process temperature is critical, because an appropriate viscosity is essential for achieving a homogenous and reliable process. The quality/grade of the polymer, such as the homogeneity of the particle size, is also important to ensure consistent feeding into the extruder.

> PVA-BASED PARTECK® MXP EXCIPIENT IS A PURE PVA WITH OPTIMIZED PARTICLE PROPERTIES THAT RESULT IN A CONSTANT PROCESS AND FLOW THROUGH THE EXTRUDER, LEADING TO HIGH REPRODUCIBILITY.

> IN ADDITION TO ENHANCED API SOLUBILITY AND BIOAVAILABILITY, HME ALSO INCREASES THE FLEXIBILITY IN DRUG RELEASE PROPERTIES AND IS SUITABLE FOR BOTH IMMEDIATE- AND SUSTAINED-RELEASE FORMULATIONS.

What can you tell me about using polyvinyl alcohol (PVA) in HME applications?

PVA is a relatively simple, stable, synthetic thermoplastic polymer particularly well-suited for HME. It has been used in approved drug products for decades and is generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA). With the introduction of lower-viscosity PVA grades, it has become useful for HME applications.

Notably, as the shear rate in the extruder increases, the viscosity of PVA drops slightly, which benefits the HME process because the higher the shear forces, the easier the extrusion – including higher throughput, improved downstream processing, optimized melt flow through the channels, and extended process ranges. PVA also provides a very high batch consistency.

How is MilliporeSigma's Parteck® MXP differentiated from other PVA products?

PVA-based Parteck® MXP excipient was specifically developed for use in HME. It is a pure PVA with optimized particle properties that result in a constant process and flow through the extruder, leading to high reproducibility. PVA is produced by the hydrolysis of polyvinyl acetate, and, for Parteck® MXP excipient, 88% of the ester groups are hydrolyzed, leaving 12% of the acetate groups.

Parteck® MXP exhibits amphiphilicity during the HME process that is not typically observed with other polymers. This is advantageous with respect to enhancing the flow of the generated ASDs and increasing and maintaining supersaturation during drug release for a longer time period. That is a clear advantage that you don't see in common polymers. Parteck® MXP also has a lower melt viscosity, which enables optimized melt flow behavior during the extrusion process.

How do the thermostability and molecular interactions of Parteck® MXP relate to its solubility-enhancement capabilities in HME applications?

ASDs release the API at a higher dissolution rate than would occur naturally, leading to concentrations that are substantially higher than the thermodynamic solubility, or supersaturation. Because more API is dissolved than would be possible under normal conditions, the supersaturated state is an unstable or meta-stable state. The system possesses a high amount of excess energy that it wants to be rid of, which is achieved by precipitating the API out of the solution.

With ASDs, therefore, the goal after achieving supersaturation in the gastrointestinal tract is to inhibit precipitation and maintain that supersaturation long enough to allow absorption. In HME formulations, Parteck® MXP does just that – it prevents APIs from precipitating out of solution. Altogether, this approach is referred to as the "spring and parachute" model of formulation. In this model, Parteck® MXP is able to act as both spring and parachute, by stabilizing and delivering the amorphous API and then preventing precipitation from the supersaturated state.

Good precipitation inhibition is achieved through certain interactions that occur between the drug and the PVA (or other) polymer in solution. A polymer cannot be too hydrophobic, or it will not interact with water molecules, and the API will precipitate. On the other hand, the polymer cannot be too hydrophilic, because then it won't interact with the drug molecule.

With Parteck® MXP, we have developed a grade of PVA with the right balance of hydrophilicity and hydrophobicity. It interacts with water and also rotates to form unique conformational structures that allow it to also interact with APIs, thus keeping them in solution. These interactions are illustrated in Figure 2.

Specifically, in addition to the hydroxyl groups of the PVA interacting with the water and the API, stabilization is also achieved through interactions between the lipophilic components of the API and the backbone of the PVA. In the example shown in Figure 2, the aromatic structures of the API interact with the PVA backbone.

In addition, PVA is stable up to 250 °C, which is much higher than other commonly used HME polymers, and extends

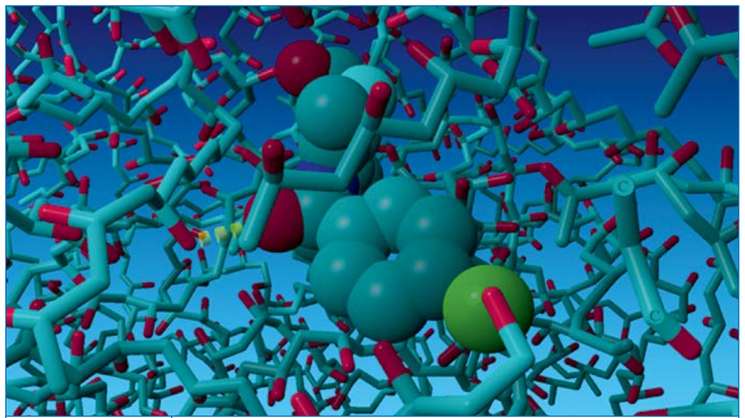


FIGURE 2 **Molecular interactions between indomethacin (ball-model) and a simplified PVA matrix (stick-model). PVA takes a dedicated conformation enabling an interaction between the PVA backbone and aromatic structures of the API.**

the normal operating range of hot melt extrusion.

HME is just one of the formulation approaches to solubility enhancement that MilliporeSigma supports. What can you tell me about the overall mission of your unit within the company and your commitment to helping customers overcome their formulation challenges?

As a business unit, we aim to tackle the biggest challenges in solid formulation.

The first challenge is solubility, which we continue to address. Low solubility remains a big challenge, and we particularly look forward to helping customers overcome issues presented by more complex novel modalities in the oral solid dosage form space.

The second challenge relates to enabling evolving manufacturing techniques. We already see the rise of continuous solid dosage form manufacturing and are actively developing products to facilitate that shift by our customers.

The third challenge is additive manufacturing. 3D printing is already an established pharmaceutical manufacturing technique, and we expect it to become even more prevalent in the future. In the near term, it will enhance the efficiency of early development through rapid prototyping and more streamlined clinical trial supply. Further into the future, it will become an essential enabler of precision and personalized medicine.

The final challenge involves digitization of formulation to enable more predictive capabilities. We are committed to this goal and are already working on solutions to achieve it.

What active support do you provide to customers beyond development of product solutions like Parteck® MXP?

As we develop new products, we gain a greater understanding of the challenges our customers face and more experience with process optimization. We are then able to share information about our new products as well as tips for how to implement processes more effectively.

We know that HME is a new and still emerging technology of interest to many companies. These companies want to move into HME but need support in the early stages to set up the equipment and establish the right parameters. MilliporeSigma is committed to providing advice and support to customers during this introductory phase and formulation development.

In what ways is MilliporeSigma differentiated from other companies working in this space?

From our perspective, the great advantage or differentiator of MilliporeSigma is our diversity. We are a company that has many experts in various technology fields relevant to the pharmaceutical industry, including those that are not always readily apparent. All of these experts from different fields working closely together really enhance our development capabilities because we can access input from many different sides and angles.

How close do you ultimately think that MilliporeSigma or the industry as a whole is at solving issues with solubility? Will APIs continue to become increasingly insoluble and require more novel technologies, or are you approaching the end of this challenge?

We see no reason to expect that drugs will stop being poorly soluble. On the contrary, we expect that, with new chemistry emerging in the solid space, such as protein interaction inhibitors and PROTAC molecules, the physical chemical landscape is going to become even more difficult. As a result, current solutions may not meet the demands of the future, which is why we are working on those solutions already today.

While it is hard to predict what will happen in the future, MilliporeSigma is continuously working on the formulation challenges that face our customers and the industry as a whole. P

WHILE IT IS HARD TO PREDICT WHAT WILL HAPPEN IN THE FUTURE, MILLIPORESIGMA IS CONTINUOUSLY WORKING ON THE FORMULATION CHALLENGES THAT FACE OUR CUSTOMERS AND THE INDUSTRY AS A WHOLE.

ABOUT THE PANELISTS

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→ COVID-19 VACCINE

HOW COVID-19 IS RESHAPING VACCINE DEVELOPMENT: INNOVATIONS IN VACCINE TECHNOLOGY AND PARTNERSHIPS

→ BY **GRAHAM BREARLEY, Ph.D.,** CATALENT BIOLOGICS, AND **JARED DAVIS, Ph.D.,** ARCTURUS THERAPEUTICS

The COVID-19 pandemic has stretched the limits of pharmaceutical development and manufacturing due to the pressing need for billions of doses to reach patients as soon as possible. It is clear that broad social change, science-driven development, and strong partnerships will be required to combat this public health crisis in the near term, but there will also be long-term benefits from this period of accelerated innovation. Here, we discuss the partnership between Arcturus Therapeutics and Catalent Biologics on a novel mRNA-based COVID-19 vaccine program and how we are collaborating to enable and expedite scale-up to large-scale manufacturing, including how that applies to the pandemic and future vaccine development.

AN UNPRECEDENTED CHALLENGE

The challenge of developing a vaccine against the SARS-CoV-2 coronavirus for widespread distribution in a fraction of the time typically required is completely unprecedented and logistically daunting. To compete in this high-pressure environment, pharmaceutical companies are stepping up their game – weeding out inefficiencies, doubling laboratory shifts, and reshuffling development stages or even running some processes in parallel. Around the world, upward of 200 companies are attempting to create a vaccine, antiviral, or other therapeutic agent for potential use in the fight against COVID-19. At Arcturus and Catalent, through our current collaboration, we are excited to be among them – for the challenge of bringing a novel mRNA-based vaccine into existence, the contribution we make in helping turn the corner on this pandemic, and the chance to play a role in the industry-wide innovation that is helping to bring a vaccine to market.

TIME TO THINK DIFFERENTLY

The scale of the challenge and absence of a roadmap have sponsor companies questioning conventional timelines and looking for ways to transform their operations and practices on multiple levels. Some are seeking to access new expertise, production capacities, and geographies. Many are taking on business risks that they would not consider under other circumstances, such as scaling-up production and assuming some significant financial risk before a product is approved. Others are adopting new, more scalable technologies. Regulatory agencies are removing barriers to the timely arrival of an effective vaccine through a variety of approaches, including providing funding for development and scale-up, helping sponsors find manufacturing capacity, and ensuring timely review of materials. Arcturus Therapeutics and Catalent Biologics are leveraging these strategies and more in our effort to meet the challenge to scale production as quickly as possible.

STRONG PARTNERSHIP

The Arcturus/Catalent partnership is a case study in how cutting-edge technology and collaboration can help address the situation at hand.[1] Arcturus, a leading clinical-stage messenger RNA (mRNA) medicines and vaccine developer, was founded around a biodegradable lipid nanoparticle (LNP) platform with the goal of delivering medicines more safely to the liver. That technology evolved to become LUNAR®, a proprietary four-lipid component system that binds with cell membranes and endosomes to deliver its contents to cells.

The inclusion of proprietary ionizable lipids in the LUNAR® vehicle distinguishes Arcturus' technology from other mRNA platforms. LUNAR® works by binding to cell surfaces and entering cells via fusion with the cell's endosome. As the endosome ages and degrades, pH-sensitive ionizable lipids in LUNAR® change their shape, disrupt the endosome, and liberate its mRNA contents into the cytoplasm. Antigen expression can then occur, and an immune response is elicited.

Arcturus has since expanded from a platform company into a therapeutics company, with a focus on mRNA-based therapeutics. The company's most advanced program is LUNAR-OTC, an intravenous mRNA therapy in phase 1 for the treatment of the life-threatening genetic disease ornithine transcarbamylase (OTC) deficiency.[2] Other programs in Arcturus' pipeline include an inhaled agent that addresses the root cause of cystic fibrosis (developed in partnership with The Cystic Fibrosis Foundation), and, in the vaccine space, Arcturus has partnered with pharmaceutical companies in animal health.

THE SCALE OF THE CHALLENGE AND ABSENCE OF A ROADMAP HAVE SPONSOR COMPANIES QUESTIONING CONVENTIONAL TIMELINES **AND LOOKING FOR WAYS TO TRANSFORM THEIR OPERATIONS AND PRACTICES ON MULTIPLE LEVELS.**

The decision to partner with Catalent to manufacture a novel COVID-19 vaccine was straightforward – Catalent has hands-on experience in mRNA vaccine production, something quite rare in the industry, and suitable manufacturing facilities were available. Their Madison, Wisconsin facility – originally designed for traditional mammalian cell culture using single-use bioreactors – houses three manufacturing clean rooms or "flex suites" where mRNA therapeutics can be made in large volume. An Arcturus/Catalent partnership was already in place for a separate non-COVID program, which was yielding exciting preclinical results, when COVID hit in early 2020. With the technology, the expertise, and the partnership all there, Arcturus felt uniquely poised to develop a vaccine against COVID-19 and felt an obligation to try.

When approached by Arcturus about manufacturing their mRNA vaccine against COVID-19, Catalent had to consider whether they were willing to procure materials and begin manufacturing before a formal contract was in place for the program. Ordinarily, the answer would be no; it just doesn't make business sense to take on that risk to order

WE ARE CURRENTLY WORKING ON AN INTERMEDIATE-SCALE PROCESS AND **PLANNING A LARGE-SCALE PROCESS THAT WILL ULTIMATELY PRODUCE HUNDREDS OF MILLIONS OF DOSES.**

long lead time materials and initiate preparatory activities at the site before an agreement is signed. But these are not ordinary times, the team thoroughly analyzed this case, taking into consideration that every day of delay is a day without a potentially life-saving vaccine available to patients. Catalent concluded that the best course of action was to accept the risk and do what would be best for patients.

LUNAR-COV19

mRNA vaccine technology avoids some of the potential concerns surrounding conventional vaccines, as live viral particles and adjuvants are not needed. Arcturus' coronavirus vaccine candidate LUNAR-COV19 leverages the proprietary DNA self-transcribing and replicating mRNA (STARR™) technology. Delivered via Arcturus' non-viral LUNAR® platform, STARR™ mRNA encodes not just the vaccine target protein (in this case, the SARS-CoV-2 spike protein), but also the self-replicating bioproteins that sustain production of the antigen. As a result, STARR™ mRNA does not disappear within hours like native mRNA; it self-perpetuates for about 40 days, allowing for sustained antigenicity and an amplified signal to the immune system. The hope is that a clinically meaningful immune response may be mounted from a minuscule mRNA vaccine dose.

A very low-dose mRNA vaccine – micrograms rather than milligrams needed with a traditional vaccine – has advantages. First, mRNA sequences are fast to make via this process, enabling us to produce a vaccine quickly and respond to wild-type viral mutations should they occur.[3] Second, we could make many more doses – perhaps thousands more per batch – from a single manufacturing run. This is critical during a pandemic when the goal is to vaccinate billions of individuals quickly. Third, the vaccine can be formulated for a single injection (most others are looking at a two-shot series), which would likely translate into a more fully immunized population, while lowering the burden on the healthcare system and patients.

FULL TILT

Within seven weeks of agreeing to collaborate, the first GMP batch was manufactured. That usually takes 10–12 months. Three months after that, phase I clinical trials began. Arcturus plans to enter phase III quickly, in months rather than years and hopes to have a vaccine in 2021. In terms of production, we are currently working on an intermediate-scale process and planning a large-scale process that will ultimately produce hundreds of millions of doses.

At Arcturus, we are taking a multi-pronged approach to accelerating our timeline. We are using a highly efficient method for making mRNA; so, in our initial stages, we were able to define a construct, manufacture it, and get it into the clinic in rapid succession. The rate-limiting step is making the DNA template. But each microgram of DNA can make 50 micrograms of RNA, enabling RNA production to be scaled up quite easily. We are designing clinical trials with accelerated timelines and working more closely with agencies to get rapid feedback. We have taken a number of steps at risk, such as scaling up to commercial level manufacturing even before we have the readouts from the combined phase I/II clinical trial.

Improving efficiency from a manufacturing perspective is key. Many vendors for raw materials and consumable supplies have increased the lead time from order to receipt during the pandemic. We are learning to be more proactive about procuring supplies – preordering materials and building inventory – and resolving delays expeditiously when they happen. We are learning to think 9, 12, and even 18 months ahead instead of 3 or 6 months ahead and moving towards a dedicated staffing model for programs run in the flex suites.

In terms of the process itself, some steps cannot be accelerated, and certain sequences need to be followed. What we have not done is compromise product quality or deviate from GMP. But we have been able to shorten downtime between shifts, for example, by performing them back-to-back rather than waiting overnight. That requires adding second shifts and expanding shift coverage. We are also looking at producing consecutive batches or "campaigning" (rather than producing an individual batch) and accelerating real-time testing for both in-process samples and product release.

The U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Biomedical Advance Research Development Authority (BARDA), and other regulatory agencies are prioritizing COVID-related programs via funding, accelerated submissions, and other measures. It may be that sponsor companies will be allowed to submit a "rolling" Biologics License Application (BLA), submitting sections for review as they are completed rather than waiting until the end. In the meantime, once efficacy is demonstrated, it is possible that vaccines can be made available through emergency access or compassionate use protocols. These modified pathways are fluid at the moment, and the guidance can change quickly. Agency guidance around mRNA vaccine development is even less clear but also evolving, which is perhaps appropriate given the novelty of the modality.

CURRENT STATUS AND ONGOING CHALLENGES

In preclinical studies, the sponsor is seeing impressive neutralizing antibody titers and cell-mediated immune response (a balanced T_H1-T_H2 ratio and a strong antigen-specific $CD8^+$) to the vaccine. The phase I/II randomized, double-blinded, placebo-controlled, ascending-dose study in collaboration with Duke University and the National University of Singapore is actively enrolling adult subjects.[4] In phase I, four single-injection dosages will be evaluated sequentially in younger adults (21–55 years). Two dosages will be selected for evaluation in phase II in both younger and older (56–80 years) adult cohorts. The primary outcome is safety and tolerability; secondary outcomes are seroconversion rates and neutralizing antibody titers.

An mRNA-specific challenge is the need for ultracold storage. In general, most mRNA products require long-term storage at –80 °C, with allowance for brief periods at –20 or –4 °C during shipping. We are addressing this by optimizing our means for gathering temperature-excursion data and looking into product lyophilization. We are confident that the LUNAR® vehicle and mRNA components can scale up quickly; however, another challenge is the potential for a bottleneck at the fill-finish step. Of course, this will be a challenge for all COVID-19 vaccine manufacturers, regardless of modality, due to the sheer volume of the demand.

AN EYE TOWARD THE FUTURE

The availability of effective vaccines will be cause for great celebration. There will be market space for multiple vaccines, given the number of people that will need to be vaccinated. Companies that understand their strengths and excel at collaboration stand the best chance to provide solutions.

What follows breakthrough vaccine development is anybody's guess. We don't know, for example, how long natural immunity and/or vaccine-induced immunity will last. We don't know if the virus will mutate, and, if so, how often a new vaccine will be needed. It is doubtful that this will be a one-and-done endeavor. COVID-19 may resurface in waves around the world for many years. The industry has to be prepared for ongoing challenges that will require us to think on our feet.

Our new normal in pharmaceutical research and development is going to be very different than our previous experience. From remote work to speed-to-contract, and new ways of communicating between developers and manufacturers, many practices that have evolved rapidly because of COVID-19 will likely survive long after. In the past, for example, clients looking at different contract development manufacturing organizations (CDMOs) would conduct on-site visits and quality audits; but the virtual tours and audits we have been doing during the pandemic have been quite successful. The pandemic is also already causing the industry to rethink how it plans. There will likely be a continued emphasis on secondary sourcing and domestic sourcing for critical materials.

While this is a formidable challenge, it has also been very positive and very heartening. People are working around the clock, all over the world to help. Hopefully, this will get us to an effective vaccine – or a handful of effective vaccines – as soon as it is practically possible. We're cautiously optimistic that LUNAR-COV19 will be one of them.

The most impressive aspect of this experience has been the pace. From initiating, contracting, and going through the regulatory approval process – the speed is completely unprecedented. Once COVID-19 becomes less pressing, pharmaceutical production timelines will probably land somewhere in between where we were before and where we are now. We won't be going back to business as usual anytime soon. P

A VERY LOW-DOSE mRNA VACCINE — MICROGRAMS RATHER THAN MILLIGRAMS **NEEDED WITH A TRADITIONAL VACCINE — HAS ADVANTAGES.**

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SEAMLESSLY SHARING SUPPLY CHAIN INFORMATION TO DELIVER MEASURABLE EFFICIENCIES FOR CLIENTS

→ BY **MORGAN BRANDT,** PCI PHARMA SERVICES

There is tremendous opportunity to elevate customer experiences and enhance internal operations through digital transformation. At PCI Pharma Services, we embarked on a digital transformation two years ago and most recently, we launched our pci | bridge platform, which is helping customers manage their clinical and commercial programs more efficiently by providing real-time data access to comprehensive supply chain information, combined with digitalized workflows, experienced project management capabilities, and customizable reports.

A DIGITAL TRANSFORMATION JOURNEY

PCI began its digitalization journey approximately two years ago with the goal of improving our processes and increasing both efficiency and transparency, effectively transforming our organization from a successful packaging and labeling company to an integrated pharmaceutical supply chain company.

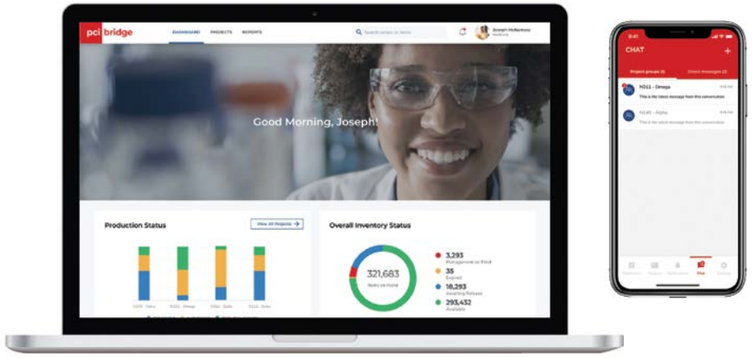
We began with the implementation of foundational technologies for both front and back-office operations and have become a much more collaborative organization through the use of Microsoft Teams. All of our managers and their employees are capable of working remotely, which has been crucial during this challenging year.

Data analysis and modeling tools are enabling us to drive new insights that inform decision-making processes throughout the company, from procurement to production scheduling and many other supply chain/value chain decisions, including pricing. Digitalization of our core business processes and integration of these new digital tools without back-office and sales force systems is enabling our employees to focus more on value-added activities for our customers. One example is the implementation of an electronic quality management system – and more are on the way. We have a roadmap covering a range of business processes to be digitalized, including invoicing, sales order processing, and material requisitioning.

The PCI approach is focused on looking toward the future and seeing the potential that digitization and technology hold for the pharma supply chain. We have found that replacing manual tasks with data-led digital decision-making technologies can provide a 10–20% gain in efficiency, while data-driven supply chain management for improved inventory control can afford 2–8% cost savings.

CREATING A COHESIVE DIGITAL ENVIRONMENT

For the digitalization of our customer-facing activities, we turned to our customers, asking them: "What if you could unlock your productivity with digital workflows, manage plant inventories with real-time supply chain information, and enable faster decision-making with data visualization?" Once we identified their needs, we focused on developing a technology platform that would address them in one cohesive environment, rather than providing individual plug-and-play tools and multiple digital add-ons.



"It's unique in the way that PCI reached out and involved its clients. It was a well-thought-out process that was truly collaborative, with a brainstorm and follow-up conversations, not just PCI asking us questions. **I appreciated the team's approach to how it was being analyzed and how they involved the voice of the client. Overall, we were very happy with it."**

Kevin Gregorczyk,
Director, Development Operations at eFFECTOR Therapeutics

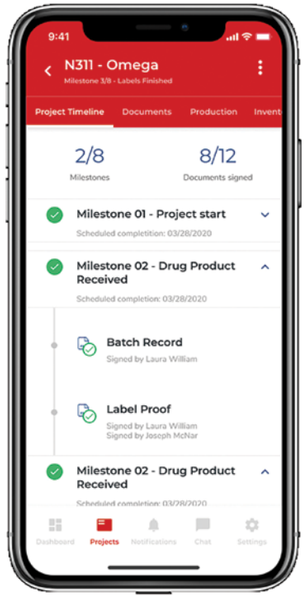
THE PCI | BRIDGE PLATFORM

The culmination of our collaborative work with clinical and commercial clients is our new customer platform – pci | bridge. Developed to complement our client services and project management capabilities, pci | bridge creates simple and efficient ways of working together.

At the highest level, the platform helps customers make informed and timely decisions on inventory, production, distribution, and more, using real-time supply chain data. The platform does this in a highly secure environment, protecting customers and their data from vulnerabilities.

In addition to real-time supply chain insights – and we truly mean real-time, with minimal lag time – pci | bridge includes three other key components: digital collaboration tools, organized data dashboards, and the ability to generate customizable reports. The digital collaboration tools include Smartsheets, DocuSign, and other third-party plug-ins, as well as some internally developed tools for more efficient interactions.

The data dashboards established throughout the platform provide an easy way to access and digest commonly sought-after supply chain information very quickly and in a consistent format. A project timeline is also available in pci | bridge, clearly indicating current progress



"Having this platform is going to streamline processes and really help with cutting down emails and waiting for documents to come through. Now that we are virtual, being able to see, review, and sign documents online as part of the platform is going to be so helpful. The benefits I see of using pci | bridge is that it eliminates the need for clients to constantly reach out to the project teams for updates. **Now, we will have that information at our fingertips and can instead focus on the bigger picture with PCI, such as what's coming next."**

Kevin Gregorczyk,
Director, Development Operations at eFFECTOR Therapeutics

and set milestones. Chat functionality in the platform enables customers to speak directly with the project team from the outset of a project, helping to facilitate up-to-the-minute information sharing. We have also included a document-sharing capability with version tracking to make exchanging files easier.

In addition to being able to see and access all of their data, customers can create customizable reports to meet different business requirements and run them as frequently as they like. Users can also access pci | bridge from their desktop, laptop, tablet, or mobile phone. The mobile app has all of the same functionality, except for some reporting capabilities that currently push past the limits of resolution on a screen of that size.

With all of the features incorporated into pci | bridge, PCI Pharma Services customers can make informed decisions based on real-time insights, collaborate more effectively, speed validations, create customized reports for greater efficiency, and do so knowing that their sensitive project information and data is protected in a cyber-secured platform.

STREAMLINING INTERNAL OPERATIONS

The pci | bridge platform provides real benefits to PCI Pharma Services project teams. In many instances, because clients are now able to directly access their own project information, they no longer need to contact their PCI project team as frequently, which has dramatically reduced the email burden and increased the convenience on the client side. At the same time, new digital tools (e.g., chat, document sharing) within pci | bridge make it possible for the project team to interact with clients in new ways that did not previously exist and in a more organized and coherent fashion. The result is that managing the day-to-day aspects of their jobs is much easier, freeing up time to focus on value-added activities.

ROLLING OUT TO CUSTOMERS

The launch of pci | bridge began in late September 2020 and will continue throughout the remainder of the year. The first customers to receive the system were those who collaborated on building, designing, and developing the platform, but eventually, all customers will be introduced to it. The feedback has been very positive, with many clients indicating that the system goes above and beyond anything that they have worked with before. They are also excited about the future possibilities for pci | bridge and have been suggesting additional features and functionalities that would be beneficial to include in our next version.

Most users are accessing the system on their desktops, which is not surprising, given that pci | bridge is a business application heavy in data. Approximately one quarter have been using the apps designed for mobile phones and tablets, both instead of, and in addition to, desktop access.

INDIVIDUALIZED SECURITY

Security within the pci | bridge platform has been carefully established, taking into consideration the needs of different types of users on both the clinical and commercial sides of our business, and both internally and at our clients' organizations. We implemented a multistage approval process in terms of who can access the platform, what data they can access, and when they can access it. Each client employee has an individual user account, complete with specific roles and permissions, which are managed through the multistage approval process. We also have a detailed system for managing blinded and unblinded data for clinical trials.

THE COVID-19 TEST

The emergence of the COVID-19 pandemic was an early, real-life test for the pci | bridge platform, occurring while it was still under development. Fortunately, PCI was already on our digital transformation journey and ready to implement solutions required to keep our operations and our clients' projects on track. Building the platform while experiencing the challenges created by COVID-19 also created greater insight into customer needs for daily information and enhanced project management capabilities.

BRIDGING THE SUPPLY CHAIN

The pci | bridge platform is a bridge to our customers' full supply chains that enables them to access and understand all of their data and information – and it also serves as a bridge in many other aspects. For instance, PCI is focused on serving as a bridge between life-changing therapies and patients by helping our customers' products effectively reach consumers.

In addition, pci | bridge is a powerful tool for increasing the comfort level of clients moving from clinical trials toward commercialization. All of their information is organized in the same format on the same platform. Combined with the extensive project management capabilities included in the system, the transition is seamless and offers customers real peace of mind. Furthermore, the platform is suitable for clients of any size with one or many projects at different development stages and involving small to large volumes. The pci | bridge system has been designed to be effective for very small clinical trial projects as well as very large-scale commercial products.

IN TODAY'S ENVIRONMENT, THE NEED TO SHARE REAL-TIME DATA IS ONLY GROWING. WITH EVERYTHING TRANSITIONING INTO A DIGITAL ENVIRONMENT, THERE IS A NEED TO NOT ONLY HAVE DATA AVAILABLE, **BUT TO PROVIDE IT AS NEAR TO REAL TIME AS POSSIBLE TO FACILITATE TRULY INFORMED DECISIONS.**

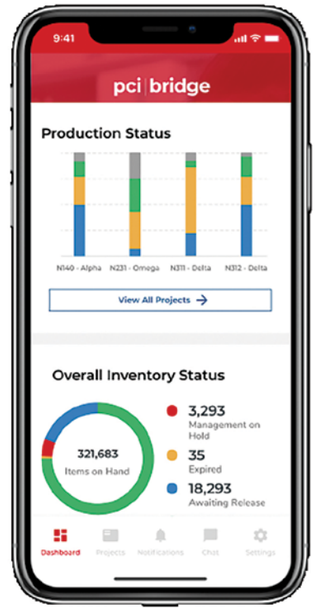
Finally, pci | bridge connects our customers to a broad array of PCI Pharma Services' capabilities. Customers that use the platform are able to see everything from inventory through production and distribution, and thus gain a macro perspective of PCI operations from project management all the way across the supply chain. The platform functions as a mirror image of what it's like to work with PCI. In that way, the platform is an important reflection of PCI's commitment to providing positive customer experiences and a bridge for ensuring true customer satisfaction by continuing to improve.

EMBRACING THE FUTURE

Built to deliver key benefits for our clients, pci | bridge is one way we are anticipating and embracing the future through digitalization and technology. Although we have only recently launched the platform, we are already building for the future with different functionalities and capabilities. One example is requesting shipments, but there are many more – the update will include added customization and enhancements.

In today's environment, the need to share real-time data is only growing. With everything transitioning into a digital environment, there is a need to not only have data available, but to provide it as near to real time as possible to facilitate truly informed decisions. As consumers increasingly expect almost real-time service, the ability to translate that personal experience into a business mindset and business experience is becoming essential.

Our focus is to make life easier not only for our clients, but also the patients they are serving. That goal is always on our minds as we make digital connections possible and will continue to be important as we build out the pci | bridge platform. We know our customers are working tirelessly to make a better future for patients everywhere a reality. P



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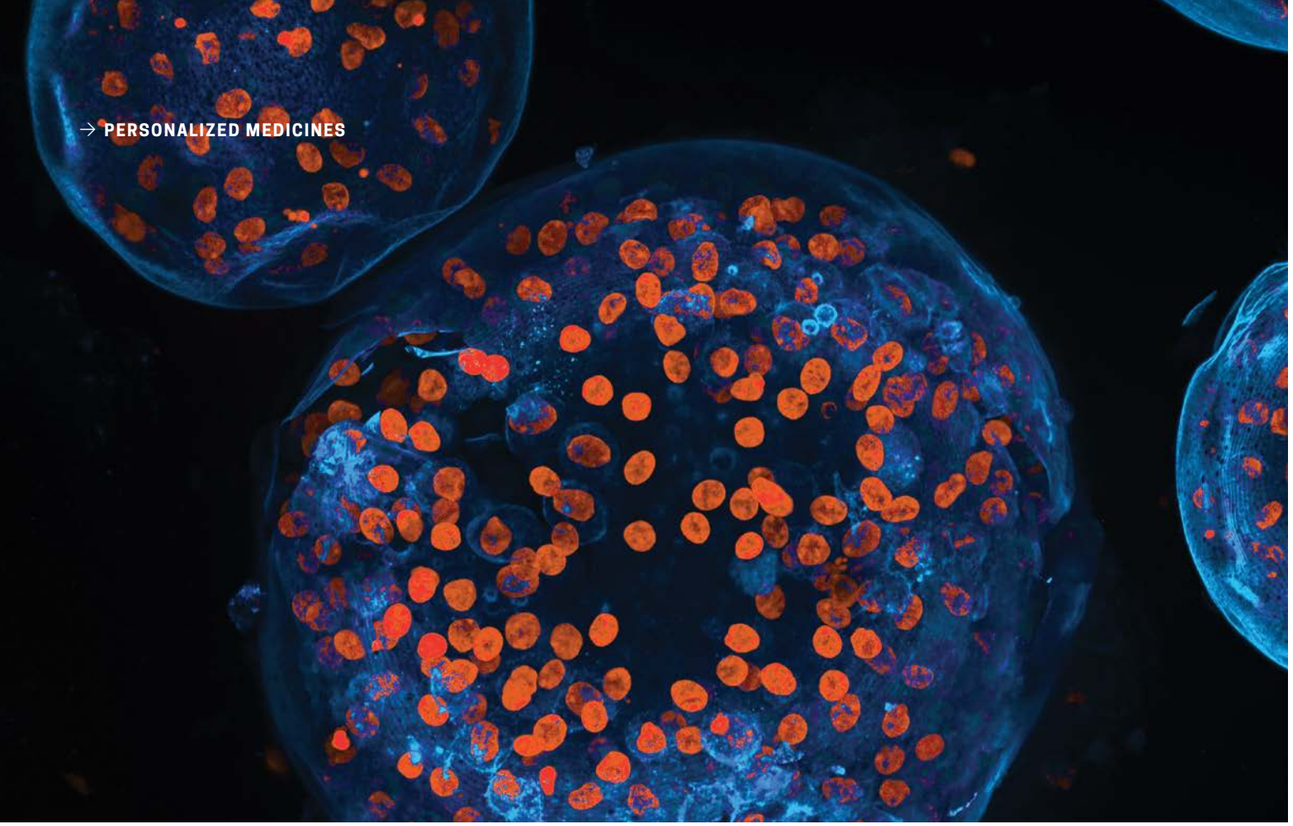

DISRUPTIVE TECHNOLOGIES IN LIFE SCIENCES: PERSONALIZED MEDICINES

→ BY **ALEJANDRO MONTOYA, SHABANA ISLAM, Ph.D., ELIZABETH ABRAHAM, HILARY SHERMAN,** AND **BEN JOSEY, Ph.D.,**
CORNING LIFE SCIENCES

Personalized treatments are poised to have a tremendous positive impact for patients across disease indications. However, a number of challenges to the discovery, development, manufacture, and administration of these novel therapies remain unresolved. Corning Life Sciences — through its many optimized products for organoid growth and creative tools and technologies for simplifying workflows, such as cell separation and engineering, among other activities — is committed to enabling the accelerated development and commercialization of precision medicines.

PIVOTAL TIME POINT FOR PERSONALIZED MEDICINES

The trajectory of personalized medicine is at a pivotal moment, owing to our expanding understanding of human biology and disease behavior and access to dynamic tools that continually increase our knowledge. More than ever before, we are able to visualize and analyze human physiological processes, gathering data *in vivo, ex vivo,* and *in vitro* using advanced imaging technologies and discovering previously unrealized patterns and connections using artificial intelligence and other computational tools.

In addition, technologies such as the expanding clustered regularly interspaced short palindromic repeats (CRISPR) toolbox and new mRNA approaches afford the ability to engineer genetic information. New models that mimic complex human anatomy in a dish or on a chip via tissue engineering are disrupting conventional drug discovery models. In particular, chimeric antigen receptor (CAR) – patient T cells genetically engineered to express antigens targeting cancer cells – and organoid technologies (tiny, self-organized three-dimensional tissue cultures derived from stem cells) will continue to disrupt the cell and gene therapy and regenerative medicine fields, translating early successes with liquid cancers to solid tumors and beyond.

Overall, these technologies will continue to drive the further development of personalized medicine, with all of them ultimately working together to match the right patient with the right treatment at the right time. One challenge to overcome, though, will be the higher cost of these novel solutions. Once their effectiveness is definitively realized, the focus will shift to making them more efficient and accessible. In addition, once it has been demonstrated that these technologies have broad usability, they will serve as a foundation that can help reduce risks – both to patients and in terms of costs and timelines – of future clinical trials.

ORGANOIDS AND PRECISION MEDICINE

Organoids present enormous potential in both drug development and precision medicine. When effectively leveraged, they can reduce the cost and risks associated with novel therapies by enabling precisely targeted treatments for individual patients. With their ability to serve as valuable model systems for studying the tumor microenvironment, organoids are accelerating discovery efforts in cancer biology and enabling rapid screening of potential new therapeutics.

Organoids are generated using tissue-specific stem cells, which are typically undifferentiated epithelial cells. It is also possible to generate organoids from patient cells to investigate the genetic alterations within an individual's cancer cells. Of particular interest is the ability to culture precancerous cells that are not fully transformed, which have not previously been accessible to the research community.

For instance, tumor organoids in a dish can be generated from cells collected during a biopsy by mixing them with a semi-solid matrix and then exposing the mixture to media containing growth factors. The resultant organoid can be used for drug screening rather than administering different medications to the patient to see which might provide a positive response. These types of organoids can also be inserted into mice (xenografts) that can be challenged with different therapeutics.

In some cases, organoids provide a means for evaluating potential therapies where no practical solution currently exists. At present, postmortem human retinal explants are the only human models available that achieve a reasonable level of complexity for the evaluation of ophthalmology treatments. Results from small animal models are often not translatable to humans, as they do not fully represent the human retinal system. Organoids thus offer the potential to transform the paradigm for drug discovery and development for eye diseases.

As part of the effort to develop a treatment for COVID-19 infections, organoids are being used to determine the mechanistic pathways by which the novel SARS-CoV-2 virus affects different organs in the body, such as the lungs, liver, and kidneys.

MOVING BEYOND THE BASICS

While organoid technology has been continuously evolving, challenges remain, particularly with respect to the creation of vascularized, multilineage organoids containing the blood vessels needed to provide oxygen and nutrients, remove metabolic waste, and facilitate communication between different cell types. All of these capabilities are essential for them to mature into fully functional tissue building blocks. Technology improvement is needed that can overcome this limitation and allow for the integration of organoids into clinical practice. Recently evolved microfluidic technology, which includes a variety of 3D fabrication techniques, presents one opportunity for achieving this goal.

WITH THEIR ABILITY TO SERVE AS VALUABLE MODEL SYSTEMS FOR STUDYING THE TUMOR MICROENVIRONMENT, **ORGANOIDS ARE ACCELERATING DISCOVERY EFFORTS IN CANCER BIOLOGY AND ENABLING RAPID SCREENING OF POTENTIAL NEW THERAPEUTICS.**

More progress will also be needed on the scale-up of organoids to facilitate their use in the development of new drugs and personalized treatments and to increase their potential to reduce the number of clinical trials required. Effective validation of organoids to ensure that they accurately recreate the tissue of interest must also be consistently achieved. In addition, because purity is crucial, solutions are needed to ensure that contaminants and undesired cell types are removed from organoids derived from tissues.

Finally, while organoids have been developed that represent organs such as the heart, liver, and kidneys, scientists are looking to expand into new models that possess more functionality. One primary example is pulmonary organoids that can replicate the air–liquid interface, which would be valuable for both fundamental research and drug testing.

FROM ORGANOIDS TO ENGINEERED TISSUES

Creating engineered tissues with more complex functionality is the next goal in

the organoid field. Recent developments in cell culture technology have opened up new opportunities for improved physiological cell-based assays for disease models and regenerative medicine. By combining fabrication and 3D printing technology with cellular biology, for example, it is possible to create 3D printed organoids that better mimic *in vivo* conditions.

However, the challenge remains to ensure that the engineered tissue has vasculature, the correct composition of different cell types (i.e., neuronal cells/fibers, cardiomyocytes, skeletal myocytes, smooth muscle cells, etc.), and the appropriate ratio of different types of innervation (sympathetic, parasympathetic, sensory, and enteric phenotypes).

True engineering of organs-in-a-dish, therefore, will require extensive collaboration between different functional areas, such as developmental biology, stem cell biology, biomaterials, 3D biofabrication, and regenerative medicine.

Some progress has been made with organoids and organ-on-a-chip systems. In one case, liver, heart, and lung organoids were bioprinted to develop a multiorgan-on-a-chip platform for the investigation of the interactions between organs and their individual and collective responses towards drugs and toxins.[1]

ONTO BIOFABRICATION FOR TRANSPLANTATION

Given the significant shortage of donated organs, the ultimate goal for many organoid developers is the biofabrication of full organs suitable for transplant into humans. Here again, creating vasculature is the big hurdle.

The development of vasculature does not involve endothelial cells alone. Other cell types, such as pericytes, smooth muscle cells, and immune cells, play roles in providing structural and functional support, as well as signaling guidance. The development of technologies that enable the incorporation of these multiple cell types will be required to build more comprehensive *in vitro* models.

As a start, 3D microfabrication technologies are helping organoid developers overcome the lack of vascularization in organoid model systems. Indeed, a variety of bioengineering approaches, such as organ-on-chip and 3D printing technology, can establish 3D microenvironments for organoids that mimic the physiological environment. In addition, microvascular patterning and microfluidic technology will allow the incorporation of the right cells at the right locations. Furthermore, human stem cells – with their high potency and ability to proliferate and differentiate into multiple cell types – are well suited for organ fabrication.

To date, some organoids have been transplanted in animal models for investigation of their behavior. In one study, a method was developed for successful transplantation of human brain organoids into the adult mouse brain.[2] The organoid grafts were observed to progressively differentiate and mature, resulting in functional neuronal networks interconnected synaptically with host neuronal circuits and extensive infiltration of the host vasculature within a few days after transplantation.

In another example, kidney organoids transplanted into a mouse model of unilateral urethral obstruction (UUO) were observed to become vascularized and found to survive in the transplanted graft for at least two weeks after UUO and transplantation.[3] Organoids are also being explored for the treatment of liver diseases. Bioengineering approaches for liver cell therapy using liver spheroids/organoids as transplantable units may provide suitable alternatives to further improve liver regeneration and therapy.

FACILITATING THE ORGANOID FIELD

Work at Corning Life Sciences is helping the organoid field to expand and achieve its full potential. Our goal is to provide the research community with better tools and resources for organoid applications and to further the science of organoid models by listening to their needs and translating them into products that add value.

The extracellular matrix (ECM) is an important component in generating 3D models, because it provides biochemical properties and structural support that helps mediate signaling for cell migration, cell behavior, and polarization in organoid structures.

Corning provides the gold standard ECM – Matrigel® matrix – for organoid research and disease modeling. We recently launched a new version of the Matrigel matrix for organoid culture. This formulation has been optimized to support growth and differentiation of organoids from both healthy and diseased cell origins. Each lot of Matrigel matrix for organoid culture has been measured for matrix stiffness (elastic modulus) to best support organoid workflow. Each lot is also pre-qualified to form stable "3D dome" structures commonly used in organoid culture. As a result, the reproducibility and consistency that is essential for organoid research is achieved while reducing the need for time-consuming screening.

OUR GOAL IS TO PROVIDE THE RESEARCH COMMUNITY WITH BETTER TOOLS AND RESOURCES FOR ORGANOID APPLICATIONS **AND TO FURTHER THE SCIENCE OF ORGANOID MODELS BY LISTENING TO THEIR NEEDS AND TRANSLATING THEM INTO PRODUCTS THAT ADD VALUE**

The throughput for screening with 3D models has also been increased by Corning with the launch of high-throughput plate formats that provide ready-to-use options for drug screening with organoids. The Corning Matrigel matrix-3D 96- and 384-well microplates come predispensed with Matrigel matrix and provide the reproducibility and consistency required for drug discovery research resulting in saving time. Work can be further accelerated by leveraging the range of Application Notes prepared by Corning scientists on the use of our products for organoid development.

Corning also provides media, growth factors and plastic consumables unique to the market and optimized for organoid culture environments, including spheroid microplates that enable 3D growth based on many different cell types. Via collaborations with the Hubrecht Organoid Technology (HUB), a pioneer institute that amplifies the work of Professor Hans Clevers and his methods for growing stem cell–derived human "mini-organs" (HUB Organoids), Corning has demonstrated applications supporting the culture of various organoids using Corning Matrigel matrix and our other consumables.

IMPROVING WORKFLOWS FOR OTHER PERSONALIZED MEDICINES

Corning Life Sciences is not only interested in facilitating the development and application of organoids for precision medicine. Cell and gene therapy and immunotherapy are other major areas of focus. Immunotherapy refers to any therapies that work by activating or suppressing a patient's immune system. While the field includes more conventional immunomodulator therapies, including interleukins, cytokines (such as interferon), and immunomodulatory imide drugs, the focus in immunotherapy for cancers (immuno-oncology) has been on CAR-T therapies. In these modalities, T cells are harvested from a patient (autologous therapies) or a healthy donor (allogeneic therapies) and genetically engineered to express a particular CAR selected to target an antigen present on the surface of tumors. Once these CAR-T cells encounter a tumor antigen, they activate, proliferate, and become cytotoxic, leading to destruction of the tumor cells. Following FDA approval of Novartis' Kymriah and Kite Pharma's Yescarta, we have seen an explosion of clinical trials exploring CAR-T therapies for blood cancers and solid tumors. However, safety concerns surrounding long-term effects – particularly concerning cytokine release syndrome and neurological toxicity – remain. CAR design has already undergone a number of generations of design, adding co-stimulatory domains and cytokines and synthetic control mechanisms to increase efficacy. Despite growing efficacy data, challenges remain to manufacturing these therapies, including the complexity of their manufacturing and the needed supply chain infrastructure, a logistically challenging, high-touch commercial model, and the high costs and ensuing reimbursement challenges.

We understand that developing and manufacturing high-quality clinical-grade cell therapies for large-scale patient use remains a challenge. To bring groundbreaking treatments to patients as quickly as possible, researchers and manufacturers need to improve on manual, time-consuming processes.

Corning has many roles to play in facilitating cell therapy workflows, from the time blood samples are collected through separation of blood components, viral vector manufacture, cell engineering, expansion, and formulation.

Recently, we launched the X-SERIES cell-separation platform to help streamline and automate many of the steps involved in cell processing. This flexible, multisystem platform provides a streamlined solution and performance gains in purifying mononuclear cells, washing contaminants from cell fractions, selecting specific cell populations, and concentrating cellular suspensions. All are crucial steps in the development of life-changing cell therapies.

Beyond enabling these activities, we are also supporting researchers in their creation of organoid models that closely resemble patient tumors, both across patient populations and on the individual level, that aid in the development of treatments with higher efficacy with reduced risk.

While immunotherapy and cell and gene therapy are in their infancy, they are growing rapidly, and advances are bringing the possibility of developing effective treatments for solid tumors. Facilitating the development of such life-changing therapies and making them accessible and affordable for all patients is a great honor that also brings great responsibility.

We take that responsibility seriously and are committed to creating and collaborating on new tools that enable further technological advances and developing solutions that simplify and optimize workflows for researchers to develop personalized medicines. P

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LIFE IMITATING SCIENCE: ARRANTA BIO'S COMMITMENT TO CORPORATE SOCIAL RESPONSIBILITY AND DIVERSITY

→ BY **MELANIE CERULLO** AND **SUSAN SURABIAN**, ARRANTA BIO

As a pioneering CDMO innovating solutions in supplying live biotherapeutics, Arranta Bio is at the forefront of some of the most exciting advances in the microbiome space. Since the inception of the human microbiome project in 2007, the number of academic publications and active patent families around the microbiome has grown exponentially.[1]

Problems within the human microbiome have been shown to contribute to the development of a myriad of health problems that are not exclusively associated with gastrointestinal disorders and food allergies, but also affect organs and systems throughout the human body, including cardiovascular, metabolic, autoimmune, and neurological disorders, as well as diabetes and cancer.[2]

Estimates of the microbial population in the human body is between 10 and 100 trillion, and the genes within these microbes outnumber the genes in humans by a factor of 150, sometimes being referred to as the "second genome."[3] Established at birth, the microbiome develops as humans grow and is affected by diet, the use of antibiotics, genetics, and various environmental factors, with around 80% of the species being beneficial. However, when the microbiome enters a state of imbalance or dysbiosis, systems may begin to stop functioning properly, and researchers around the world are studying ways to harness gut microbiota to treat a variety of conditions.

ALIVE Biotherapeutic Products® (aLBP) is Arranta's trademark for the world-class LBPs we develop, leveraging over ten years of process development expertise in manufacturing aerobic, anaerobic, and spore-forming organisms. ALIVE is an acronym for Accelerated development, Long-lasting stability, Immediate release and recovery, Viable, high-activity, and Efficient, scalable process. Headed by a management team and technical experts with a proven track record in both process development and contract manufacturing – from fermentation to lyophilization and encapsulation of live biopharmaceuticals – Arranta Bio offers the knowledge and resources necessary to help clients develop and manufacture promising new microbiome therapies to meet patient needs. We continue to invest heavily in both process development and cGMP manufacturing capabilities for the supply of clinical trial material in the microbiome space, as well as investing in commercial-ready facilities primed with the capacity and specialized expertise to bring novel medicines to patients.

Perhaps equally important to Arranta Bio's commitment to bringing efficacious microbiome therapeutics to market is our commitment to making a difference through corporate social responsibility (CSR) initiatives. What we do is as important as how we do it. These principles not only aim to make Arranta Bio a heterogenous team of employees from all walks of life, but to extend that heterogeneity to industry and science, technology, engineering, and mathematics (STEM) programs holistically.

MORE THAN JUST MARKETING

We believe that, in order for life sciences to continue to thrive, a commitment to equity, diversity, and inclusion cannot be "just another initiative." It must be the cornerstone of company policy, entrenched in every fiber of our DNA from the top down, and to manifest itself not only in recruitment, but also in professional development, retention, and promotion strategies. We also select vendors who have – and practice – the same diversity principles. Currently, we have prioritized extending our reach and message into our communities. In addition to being the right thing to do, numerous studies have demonstrated that, the more diverse a business is, the more successful it is – and even more importantly, in such a competitive environment, companies cannot thrive without drawing from the best talent on earth, regardless of their gender, race, ethnicity, ability, religion, socioeconomic standing, or other differences.

This approach has a metaphorical resonance with the therapeutics we manufacture; the human body thrives on a healthy, diversely balanced microbiome to function properly, and our company culture and demographic makeup is no different. There are correlations between overpopulated and underpopulated microorganisms in the microbiome that contribute to disease, and optimal diversity is required for systems and organs to function properly. On a biological level, a diverse microbiome contributes to our overall health – juxtaposing this scientific knowledge with our approach to CSR is not a difficult bridge to build; we believe having diverse backgrounds and opinions makes our business stronger and more competitive and leads to greater innovation.

ARRANTA BIO CARES

Arranta's CSR program is built on three primary pillars. The first pillar is centered around diversity and inclusion, driven by

ARRANTA BIO IS A MODEL CORPORATE CITIZEN THROUGH A WELCOMING, DIVERSE CULTURE THAT PROMOTES RACIAL, SOCIAL, AND GENDER EQUALITY. **WE BELIEVE IN MAKING OUR COMMUNITY STRONGER THROUGH EMPLOYEE VOLUNTEERING AND GIVING BACK.**

making our recruiting pipeline as diverse as possible by educating ourselves with and engaging in our communities to encourage minorities and under-privileged individuals to pursue careers in life sciences. The second pillar involves our community outreach efforts, including the causes and charities Arranta supports through donations and volunteering. The third pillar aims to ensure that our vendors align with our priorities and show a commitment to diversity and sustainability within their respective organizations, so that we are procuring materials and services from vendors who share our vision and values as well as implement internal sustainable practices.

In addition to choosing vendors that align with our mission and vision, Arranta Bio also works internally to partner with organizations that allow us to impact those around us and provide employment opportunities across socioeconomic boundaries. We celebrate being an equal opportunity employer, bringing together different cultures and ethnicities to support our mission of becoming the best-in-class CDMO. Arranta Bio's CEO Mark R. Bamforth has made diversity a defining feature at the company. "We can be paralyzed by the challenges and divisions in our society. We can feel overwhelmed until we recognize that there are many actions we can take to make a difference. It's our duty to open doors and support those of color and from

ALIVE™
Biotherapeutic Products

About ALIVE

Echoing the ALIVE brand for our LBP products, we use ALIVE to describe our values as a company:

A - Accelerated development
L - Long-lasting stability
I - Immediate release & recovery
V - Viable, high activity
E - Efficient, scalable process

ARRANTABIO CARES

diverse backgrounds to pursue a fulfilling career in life sciences," he noted. The Arranta Bio CSR vision statement reads, "Arranta Bio is a model corporate citizen through a welcoming, diverse culture that promotes racial, social, and gender equality. We believe in making our community stronger through employee volunteering and giving back."

From our two locations in Watertown, Massachusetts and Gainesville, Florida, we have made connections with local organizations that are aligned with our CSR goals. Arranta Bio is a member of MassBio and a supporter of MassBioEd, an educational branch of MassBio and a leader in diversity and inclusion in the life sciences. MassBioEd works to build more diverse workforces through collaboration with various life science organizations who work in the state of Massachusetts to provide grants and opportunities to underserved and underrepresented groups. We also work with BioFlorida, which represents 6,700 establishments and research organizations in BioPharma, MedTech, HealthIT, and BioAg that collectively employ nearly 94,000 Floridians.

We also partner with Year Up, an organization that seeks to close the opportunity gap by connecting young people from diverse backgrounds to training and internships and proven paths to successful careers. We are partnered with American Corporate Partners (ACP), a nonprofit organization engaged in corporate career counseling for veterans that helps connect them to career opportunities. We are establishing programs with local colleges, high schools, and middle schools, to provide classroom presentations about microbiome and biotechnology in order to raise awareness of the various careers in life sciences. Through uniting the human and financial resources of Life Science companies and industry leaders, we support service organizations that do the best work in fighting poverty in our communities, such as Life Science Cares, an organization that coordinates the efforts of the Life Science industry to eliminate the impact of poverty on our neighbors in the greater Boston area.

Arranta Bio believes that in order to build a more diverse workforce, we need to start educating young people about the opportunities in life sciences and providing resources to train the younger generations for these roles. We need to debunk misconceptions about a Ph.D. or even a bachelor's degree being the prerequisite for a fulfilling career in life sciences. The life sciences industry would be well-served to focus on identifying and training individuals on job-specific competencies rather than focusing on college degrees for many positions. In addition to partnering with school-based organizations, we also empower our employees to volunteer in the community. Each employee can take paid time off to volunteer for causes that are important to them, above and beyond their paid vacation.

RECRUITING OUTSIDE OF THE BIOTECH BUBBLE

Like other biopharmaceutical companies, Arranta Bio has certain roles that require undergraduate or graduate degrees or previous experience. We also recognize that there are many roles within the company where we can recruit and train individuals from different backgrounds based on the core competencies required for the role. While some professions, locales, and courses of study have some level of diversity inherently built into them, it can be difficult to ensure a fully diverse workforce in the life sciences. For example, there is a robust talent pool of Caucasian and Asian candidates in these fields due to the demographic makeup at colleges and universities. However, African American and Latino individuals are underrepresented in our industry. This may be attributed to multiple factors, including the current requirement to have a degree in science for entry into the life sciences workforce, lack of resources for STEM programs during elementary and secondary education, and a general lack of awareness and exposure to career paths in life sciences. We understand the challenges to building a diverse workforce extend further back than the candidate pool from which we are recruiting, and, as such, our approach at Arranta is to influence diversity in STEM as early and as often as we can. By educating high school and middle school minority students on careers in STEM and encouraging students to pursue such careers, Arranta strives to help create training programs that can produce high-quality candidates outside of the traditional college programs. Thus, Arranta is working to cultivate tomorrow's talent pool, which we hope will set a new bar for life science diversity.

WE UNDERSTAND THE CHALLENGES TO BUILDING A DIVERSE WORKFORCE EXTEND FURTHER BACK THAN THE CANDIDATE POOL FROM WHICH **WE ARE RECRUITING, AND, AS SUCH, OUR APPROACH AT ARRANTA IS TO INFLUENCE DIVERSITY IN STEM AS EARLY AND AS OFTEN AS WE CAN.**

Recruiting for Arranta Bio's Gainesville, FL facility comes with a unique set of challenges, particularly given that the local pool of candidates with extensive biotech industry experience is limited, by contrast to the candidate pool in Massachusetts. This illustrates the importance of a corporate philosophy that emphasizes competency-based hiring. When we have an open position, we evaluate the baseline skills needed to do the job, and fully invest in training our employees to carry out the specific tasks required to be proficient. This is a massive shift from the traditional hiring practices in life sciences, which are generally focused on the need for prerequisite experience and degrees. If we can find critical thinkers with the ability to execute the physical techniques required for a role and the aptitude to operate in a GMP environment, we can train them on our platform-specific tasks and deliverables, allowing us to widen the candidate pool exponentially and staff our facilities with a foundational mindset of diversity and inclusion.

FOSTERING PROFESSIONAL DEVELOPMENT OPPORTUNITIES ACROSS LOCATIONS

Arranta Bio's training and development work streams include leadership training across all levels, with fundamental skills training initiatives to develop current and future managers. Additionally, we launched career development plans for every employee at Arranta Bio to help each employee align their career development interests and goals. The focus of these plans is on creating a roadmap for developing skill sets now for a position that the individual wants to grow into in his or her next role. We also launched a mentorship program so that members of the leadership team can mentor our more junior employees and help steer them on a path to achieve their future goals at Arranta Bio.

We work to ensure that these efforts are available across departments and locations. Many companies face challenges pertaining to cross-location cultural continuity, but the foundation of our cohesive efforts is a transparent, two-way communication and feedback loop. COVID-19 presented a unique opportunity in the midst of uncertainty to make employees at Arranta Bio feel safe, connected, and heard. In compliance with expert guidance, we quickly pivoted to ensure we provided a safe work environment for our employees. These endeavors included a shift to remote work for many of our employees, which also presented opportunities to connect staff at our Watertown facility to our Gainesville facility through weekly virtual town hall meetings and twice-weekly "lunch & learn" sessions where information and feedback and ideas were freely exchanged.

We launched an intranet site aimed at ensuring that employees have all the necessary resources at their fingertips as a part of our CSR initiatives. We have consciously and intently developed communication processes to ensure consistency and collaboration across both our facilities in Massachusetts and Florida so that we can achieve our goals related to diversity and inclusion in recruiting, professional development, and career advancement and are synergistic across sites.

Arranta Bio is dedicated to celebrating diversity within our company. We hold ourselves to the highest standards, and our internal and external processes follow our diversity mission. We expect to hire 200 employees over the next two years and are committed to addressing barriers that exist for people of color and welcome employees from diverse backgrounds who share our core values to be a part of our team. P

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Susan Surabian joined Arranta Bio in 2019 as one of its first employees. She serves as Arranta Bio's Corporate Social Responsibility Leader and the Executive Assistant/Office Manager for the Arranta Bio Leadership Team. In both her personal life and business life, Susan is a lifelong champion of equality and inclusion and has dedicated the last 15 years to help serve the disadvantaged populations and children with special needs through volunteering, community outreach, advisory boards and mentoring. Susan is an advocate for making radical changes to protect the environment through sustainability practices. She believes diligence is the key to improving the future of the life sciences industry and beyond – in both the workplace and in employees' everyday lives.

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AIDING MATERIAL QUALIFICATION AND RISK ASSESSMENT FOR SINGLE-USE BIOMANUFACTURING

→ BY **JESSICA SHEA,** MILLIPORESIGMA

Single-use technologies provide many benefits; however, they require additional preparative work before being implemented. This includes regulatory approval and assurances that extractables and leachables (resulting from the use of disposable equipment) remain at or below acceptable levels. Vendors can facilitate extractable and leachable studies by providing robust, reliable, and accessible information, thus reducing the time and resources needed to prepare documents for drug approval submissions.

INCREASING ADOPTION OF SINGLE-USE TECHNOLOGY

Access to the right information is crucial across the pharmaceutical industry. When stainless-steel equipment was predominant, the focus was on obtaining information about the raw materials used to produce drug products. The increasing adoption of single-use (SU) technologies (SUT) has created the need for additional information about the components of disposable systems.

Drug manufacturers require both access and clarity to information, which is driving greater collaboration and more innovative means of sharing. MilliporeSigma has one of the broadest product portfolios in the pharma sector, covering basic chemicals, complex SU devices, and the biocontainers, pumps, tubing, filters, and components comprising them.

To improve the ease of use of SU systems for our customers, we have committed to understanding what information they need. We are providing the documentation required in an easy-to-access solution that comes with additional support services and the ability to customize data for tailored analyses and assessments.

THE EMPROVE® PROGRAM

The Emprove® Program began with the provision of chemical data for pharma raw and starting materials. This data is easily accessible and designed to facilitate regulatory compliance. Our original focus was on offering higher-quality products with full supply chain transparency and the information necessary for performing quality assessments.

The program expanded into filters and single-use products approximately five years ago and more recently into cell culture media and chromatography products. SU technology offers many benefits, including faster setup and the reduction or elimination of cleaning and cleaning validation. It creates reliance on SU vendors for manufacturing equipment at a level on par with raw materials. In addition to assurance of supply, extractables and leachables (E&L) must be addressed.

The Emprove® Program for SUT provides comprehensive data sets for customers and gives them a higher level of support around regulatory acceptance and approval as they work through their validation processes. It entails organized, detailed product information and assistance to help customers with material qualification and risk assessment of biomanufacturing devices, as well as process optimization. By avoiding the need to develop test methods, search quality-related documents, or evaluate scientific data, customers can reduce the effort required to prepare documents for drug approval submissions.

At the base level, MilliporeSigma has developed specific information for the materials for our SU products. Customers may need this information to support audits or other quality-based functions. Material Qualification Dossiers (MQDs) report on a material's fundamental properties and also feature manufacturing

THE EMPROVE® PROGRAM FOR SUT PROVIDES COMPREHENSIVE DATA SETS FOR CUSTOMERS **AND GIVES THEM A HIGHER LEVEL OF SUPPORT AROUND REGULATORY ACCEPTANCE AND APPROVAL AS THEY WORK THROUGH THEIR VALIDATION PROCESSES.**

THE OED INCLUDES PRODUCT-SPECIFIC DATA REQUIRED TO SUPPORT THE USE OF DISPOSABLE SYSTEMS IN DRUG MANUFACTURING. THEY INCLUDE PRODUCT QUALITY REPORTS WITH ELEMENTAL IMPURITIES INFORMATION AND EXTRACTABLE PROFILES **AND SPECIFY THE ANALYTICAL PROCEDURES USED TO OBTAIN THIS DATA. THE GOAL IS TO PROVIDE HIGH-QUALITY TEST DATA TO SUPPORT OUR CUSTOMERS.**

flowcharts, product characterization, regulatory statements, and more.

Quality Management Dossiers (QMDs) include a self-assessment of quality while documenting detailed supply information for the material, including its complete chain of custody from manufacture to final release. These dossiers present additional useful information, such as shelf-life data, sterilization, validation, and packaging requirements.

The most comprehensive and valuable piece of the Emprove® Dossier offering for our SU products is the Operational Excellence Dossier (OED). The OED includes product-specific data required to support the use of disposable systems in drug manufacturing. They include product quality reports with elemental impurities information and extractable profiles and specify the analytical procedures used to obtain this data. The goal is to provide high-quality test data to support our customers.

MQDs are accessible directly on the MilliporeSigma website. Access to the higher-level QMDs and OEDs are offered via a subscription service. While these aspects of the Emprove® Program can theoretically be purchased individually, we encourage customers to become members of the Emprove® Suite so that they can source all of the documentation reports for our SU products, as well as filter devices, chemicals, cell culture media, and chromatography resins.

While there are still some chemicals available that are not included in the program, we have found that customers really appreciate the advanced documentation offered by the Emprove® Program, because it can be used for their approval processes. The program has added significant value to our product lines and exemplifies our commitment and willingness to support and collaborate with customers.

Since bringing the filter and SU products into the program, we have received valuable feedback from customers as they have worked through their final drug product approval processes. The OEDs, in particular, provide comprehensive data sets that aid their ability to conduct risk evaluations. Our Emprove® Suite subscribers appreciate how all of the information is provided in a consistent format that they can readily use for their own assessments.

BALANCE BETWEEN FUNCTIONALITY AND EASE-OF-USE

The flexibility and mobility of SU systems in combination with the elimination of cleaning processes provide a tremendous advantage over stainless-steel systems. Cost, time, and the risk of cross-contamination are all reduced. These benefits and functionality are achieved because of the use of plastics, which can contain certain additives to ensure stability and function. There is a reasonable expectation that the levels of these additives in a drug product will be low.

SU technologies are designed with this consideration in mind. They are extensively tested to ensure that E&L profiles are minimal. If drug manufacturers use SU systems as recommended, such as flushing filters before use, the E&L risk to patients is significantly reduced. The key is making sure the right functionality is achieved with the right materials during process optimization and drug product formulation combined with risk mitigation.

FOCUS ON EXTRACTABLES & LEACHABLES

When the plastics used to make disposable manufacturing equipment are exposed to media, cells, buffer, drug products, and other materials used throughout biologics production processes, there is a potential for chemicals in the plastic SU components to be extracted into the bioprocess fluid.

Extractables represent the comprehensive range of chemicals that could potentially be extracted into a drug product formulation. They are identified by exposing the plastic materials under a range of highly aggressive conditions intended to represent worst-case scenarios in the manufacturing environment. Model solvent streams are used, such as 50% ethanol, as well as highly acidic and highly basic solutions. Leachables are the process-specific compounds with the potential to be extracted into the drug product formulation under actual processing conditions.

The ultimate goal of E&L testing is to ensure patient safety. As such, once potential E&L compounds are identified, the next step is to determine whether they will pose a risk to the patient if present in the final drug product. Relevant risks could include anything from a rash to cancer, as well as any potential reactions between E&L compounds and other ingredients in the drug product formulation that cause a problem, either acute or long term.

In general, drug manufacturers must evaluate the SU components that are in contact with the product under the given process conditions, such as duration, temperature, solvents, or material characteristics. Any risk-mitigating steps occurring later in the process can be taken into consideration. At this stage, an extractables profile, if available, would facilitate product, process, and dosage-specific assessments. If thus far, the patient safety evaluation indicates no risk, the findings may simply be reported and monitored for future changes.

On the other hand, if there is a risk to the patient, a leachables study may be conducted under normal product application or storage conditions. Risk may also be mitigated through a process-step modification, such as including an additional flush. A final option could be to change the material of the component.

MULTIPLE ANALYTICAL METHODS

Determining risk and interpreting extractables data to construct a reasonable validation strategy is a complex process. If only one chemical could potentially be extracted from SU systems, E&L strategies would be fairly simple. However, there are often multiple chemicals that must be detected and quantified, and there is no single method that can be used. Multiple analytical methods must be employed to gain a broad understanding of the different potential compounds. The challenge is to design an effective E&L strategy that provides consistent and meaningful data.

Whether a pharma manufacturer conducts E&L testing in-house or relies on a contract testing lab, the process is expensive and time consuming. The Emprove® Program helps alleviate this burden. With the Emprove® Dossier, results of multiple analytical methods are used to evaluate a wide range of compounds, including volatile, semivolatile, and nonvolatile organic compounds. These methods include gas chromatography mass spectrometry, both headspace and direct injection, and liquid chromatography mass spectrometry with multiple detection modes, along with other methods. In addition, inductively coupled plasma mass spectrometry is used for evaluation of elemental impurities. Subscribers to the Emprove® suite have immediate access to this large data set, eliminating months if not years of work.

REGULATORY CLARITY

There are no specific regulatory guidelines pertaining to E&L used in the manufacturing of drug products, other than that pharmaceutical manufacturers must demonstrate that the materials used are not reactive, additive, or absorptive. There is also a regulatory expectation that researchers will test for E&L. Agencies such as the U.S. FDA's Center for Biologics Evaluation and Research (CBER) recommend a risk-based approach to evaluation.[1] In such an approach, indication, safety, product characteristics, dosage, formulation, and stability are all factors. If there appears to be a lower risk with the materials in question, the sponsor can submit supplier data, a detailed justification for applying this data, and an explanation of why no more testing is required.

If there is relevant risk, the sponsor may have to determine toxicity based on maximum dosage of potential leachables derived from extractables data. If the risk of maximum dosage of potential leachables remains, leachables evaluation and testing may be necessary. Furthermore, if product quality could be affected by potential leachables, studies may need to assess the effect on product quality, including efficacy. These evaluations are possible when the supplier provides extractables data, which can supplement final product quality assessments.

Beyond the regulatory sphere, a range of industry organizations have created best-practice strategies for implementing extractables studies. The Parenteral Drug Association's PDA Tech Report 66 is a good consensus document within the industry, not just on E&L, but regarding single-use technologies in general.[2] It has been quite useful for customers that are just beginning to adopt disposable manufacturing solutions.

The BioPhorum Group, a global consortium of large biopharmaceutical manufacturers, has also been active in the E&L space. In the absence of official E&L-specific guidance, many manufacturers are fulfilling regulatory expectations by following the BioPhorum[3] and/or U.S. Pharmacopeia (USP) <665>[4] draft recommendations.

While these protocols are not identical, the general approach is similar, and at least one or the other can apply to most drug products and substances. Testing is performed at various time points and temperatures. Resulting extraction solutions are subjected to robust and extensive analyses to determine what levels of volatile, semivolatile, and nonvolatile organic compounds and metals have been extracted. Either approach will produce an array of data that must then be evaluated in the context of the proposed process.

USP is expected to finalize USP <665>[4] and <1665>[5] in the near future. These documents are a starting point for global guidance. However, they still lack information on how to conduct extractables studies. Which model solvent stream should be used is indicated, but not what testing should be conducted. More comprehensive guidance is still needed.

There is currently a workstream through the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) to standardize the risk assessment approach for E&L. The final concept paper "ICH Q3E: Guideline for Extractables and Leachables (E&L)" was published on June 30, 2020, outlining the issues to be addressed in the proposed guideline that the working group will develop.[5]

THE BENEFITS OF EMPROVE® DOSSIERS

It can be complicated to understand how the extractables that might come out of a filter or other SU system relate to the product in a vial, but that is ultimately what a pharma manufacturer must determine. MilliporeSigma's Emprove® OED provides the comprehensive data set needed to start making that determination. Having access to that consistent data set for all of our products can really streamline the process because we have standardized our data based on the BioPhorum and USP recommendations.

Using the broad data set on extractables, customers can identify the potential leachables for each specific product/

IF THERE IS RELEVANT RISK, THE SPONSOR MAY HAVE TO DETERMINE TOXICITY BASED ON MAXIMUM DOSAGE OF POTENTIAL LEACHABLES DERIVED FROM EXTRACTABLES DATA. **IF THE RISK OF MAXIMUM DOSAGE OF POTENTIAL LEACHABLES REMAINS, LEACHABLES EVALUATION AND TESTING MAY BE NECESSARY.**

process. Since the data we provide is generated under worst-case conditions, it may be beneficial for the customer to conduct leachables testing if their actual process conditions are much milder. MilliporeSigma can support these efforts as well, not as part of the Emprove® Program, but through other services offered by the company.

VALIDATION SERVICES

The Emprove® program for many customers is in fact a starting point. While many big pharma customers have in-house toxicologists and E&L assessment capabilities, many small and medium-sized firms do not have these resources. MilliporeSigma's BioReliance® Validation Services can provide the support they need to conduct full risk assessments, starting with choosing the model solvent streams and conditions based on the process information provided, all the way through to performing the safety evaluation.

If the worst-case scenario data suggests the need for further leachables testing under actual process conditions, the validation services group can also conduct that additional product-specific testing. For instance, leachables testing is often required for large-volume parenteral drug products that are administered frequently and in large doses to patients, such as fluids given to dialysis patients multiple times per week.

INFORMATION EXPANSION

As single-use technologies evolve and new classes of drug candidates enter the pharma pipeline, data needs continually change. In addition, as regulators become more comfortable with SU technologies, their information requirements are evolving too. As a result, the content of the MQDs, QMDs, and OEDs within the Emprove® Program will always be in flux.

The expansion of information included in our Emprove® Dossiers is the result of collaborations between MilliporeSigma and our customers, who bring us requests for new types of information on a regular basis. Most recently, discussions centered on packaging validation and additional supplier information could be added to support customers in this area. These are just two possible examples; we fully expect the Emprove® Program to constantly evolve with the industry.

Despite these constant improvements, MilliporeSigma is committed to maintaining the integrity of the data we provide through the Emprove® Program; we recognize the value of the peace of mind afforded by robust and reliable data. As importantly, through strategic development in conjunction with our customers, we continue to strive to simplify and streamline the data acquisition process.

RELYING ON EXPERT GUIDANCE

SU technologies provide numerous benefits for pharmaceutical manufacturers. However, there is additional preparative work required, much of which relies on access to reliable and robust data. Despite the current absence of guidance, regulatory expectation does require evaluation of patient safety with supporting data for manufacturing components that directly come into contact with drug manufacturing process streams. Readily available extractables data can help manufacturers using SU technology to accelerate product qualifications, risk assessments, and process optimization.

E&L risk analysis is a complex process, and expert guidance is critical to ensure compliance and drug safety. While the task of analytical E&L test data interpretation and submission can be daunting, the right SU system supplier can save time by providing SU system E&L data in well-organized, easy-to-use formats. The right information must be available for conducting risk assessments depending on the specific processes and products involved.

Having confidence that vendors of disposable systems are using safe and appropriate materials and providing correct information is essential to facilitating the use of SU technologies and enabling manufacturers to fully realize the advantages they provide. Relationships grounded in trust are a must for success. That is why MilliporeSigma has taken the steps to establish the Emprove® Program, not only for pharma raw materials and intermediates, but for filters and other SU technologies. We pride ourselves on providing this high-quality service built through close collaborations with our customers and continue to work hard to earn and deserve their business. P

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Jessica is a Marketing Manager, managing extractables projects and supporting implementation of the Emprove® Program with specific focus on our filtration and single-use portfolio of products. Previously with the company, she was a global senior validation consultant and laboratory manager for BioReliance® Validation Services. She has more than 13 years of extractables and leachables (E&L) and single-use validation experience, including designing E&L services and interpreting industry and regulatory guidance.

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IN CONVERSATION

MEETING THE CHALLENGES OF THE PANDEMIC THROUGH VIRTUAL TRADE SHOWS

→ BY **JUSTIN KADIS,** FEDERAL EQUIPMENT COMPANY

Federal Equipment Company, a long-time leader in the provision of used manufacturing equipment to the pharmaceutical, chemical, plastics, packaging, and food and beverage industries, has responded to the COVID-19 pandemic by becoming a pioneer in organizing virtual trade shows to fill the gaps left by the necessary cancellation of traditional trade shows.

Pharma's Almanac **Editor-in-Chief David Alvaro, Ph.D. had a (virtual) conversation with Federal Equipment Company's Justin Kadis about how the company is using virtual means to support their business and that of allied companies.**

Justin, what can you tell me about how Federal Equipment Company got involved in the Virtual Pharma Expos and what that experience has been like so far?

Our team recognized early in the coronavirus outbreak that most trade shows would be canceled this year, which would have a detrimental impact on our business and other businesses around the country and the world. Our response to it was to take ownership and get ahead of the situation. One of Federal Equipment Company's most important resources is our strong relationships with original equipment manufacturers. We were able to leverage our relationships with OEMs to launch the Virtual Pharma Expo – our first event took place in May and featured 13 speakers from 12 different companies.

The first expo turned out better than we originally anticipated. We had around 1,100 unique registrations from the event; the feedback from exhibitors was overwhelmingly positive. One of the reoccurring comments we received was both the surprise over price and the corresponding reach – the exhibitors were able to reach a large audience at once, and at a fraction of the cost of exhibiting at INTERPHEX, CPhI, or similar events.

To make the virtual event a success, we partnered with Pharmaceutical Online, who helped coordinate behind the scenes, including managing the video webinar platform, and Techceuticals, our partner here in Cleveland that operates out of our pharmaceutical warehouse. Techceuticals' Mike Tousey was the moderator for the event, and his personal relationships with all of the exhibitors helped assure everything ran smoothly.

Because of how well things went in May and, owing to requests we had from exhibitors interested in more virtual events, we decided to hold a second Virtual Pharma Expo this September with 24 speakers representing a more diverse group beyond the solid dose machine companies at the first event.

With these successes, are you planning on holding more expos?

The next event will likely be held February 24–25, with 10 speakers focusing on aseptic/sterile processing and packaging on the first day and another 10 speakers discussing pharmaceutical packaging on the second. If there are equipment manufacturers out there that would like to participate, they should contact me. We will likely move back to oral solid dose manufacturing for the fourth event, which will most likely be held in early May 2021.

I would imagine that it's easy to transfer talks into a virtual format. But are you looking to find ways to replicate the booth exhibits experience as well?

That's a great question. For the first two events, we focused on the presentations but used a platform that incorporated polling questions and other ways to interact with the audience. As we speak to exhibitors regarding future events, we want to stress to them that this is essentially taking the place of trade shows. So, if you can stand with a machine behind you and maybe talk about what it is and how it works, this is your opportunity to do so, because you're not necessarily going to be able to do it at a physical show. But for our next expo, we are exploring some additional technology platforms that can enable breakout and networking sessions and other possibilities.

For some companies at trade shows, the booth presence is minimal, so there probably isn't much disruption. But for Federal Equipment, showcasing physical machines is more critical. Does that create greater challenges for you?

We considered this when planning our presentation for the first Virtual Pharma Expo and decided to step outside of the box. When our President Adam Covitt gave his presentation, we had five different machines behind him, and he was able to discuss those machines and how they were a representative sample of the type of equipment that we sell. We received feedback that it was the best presentation of the event.

When you originally were pitching the expo to potential exhibitors, was it a tough sell or was there immediate interest?

The interest was strong from the start. Between Adam's and Mike Tousey's relationships with these OEMs, they were able to reach out right away and say: "Listen, trade shows aren't happening but here's a great opportunity to get involved, get in front of a lot of people; really get some leads that you wouldn't necessarily be getting this year, because there's nothing else going on." Again, the response was tremendous.

An important differentiating factor with the Virtual Pharma Expo is that you're getting exposure to a new audience. When you're using your LinkedIn and your email list to try and promote to your typical audience, that's one thing, but with all of these different companies – along with us, Techceuticals, and Pharmaceutical Online –promoting it to their audiences, it reaches a larger group that may be different than who you're already touching.

Were there any things that didn't go as planned or lessons learned that will influence how you do things going forward?

Absolutely. One of the biggest hurdles that we've run into is bandwidth issues for some of the presenters. We're doing our best to put together a toolkit of better equipment that can be purchased, most of which are inexpensive but go a long way in making everything more professional, and learning from our experience with the first two shows to home in on what's worked and what hasn't. For example, Klöckner Pentaplast had two experts interviewing one another in their presentation, and that conversation was very effective. So, that would be a tip for some folks to look into next time around.

At this point, are you seeing these expos as only a solution for the duration of the pandemic, or do you think that you would continue with virtual expos when things return to normal?

I think that there may still be an opportunity to continue Virtual Pharma Expo even once things got back to normal, although it's unclear at this point how strong the appetite will be for that. We're getting a lot of value out of it, both from a revenue-generating perspective and a contact- and lead-generating perspective. We'd love to keep doing this.

It will be interesting to see what happens, because people's ability to adapt to technology today is on such a steep curve compared with where we were nine months ago, and it's not totally clear what the event business is going to look like in the future. Are people really going to need a 20 x 20 ft. or a 50 x 50 ft. booth at INTERPHEX or CPhI to be able to accomplish what they want to accomplish? If that's the case, does that just mean that people are going to scale back their presence? Will people focus on virtual shows moving forward? I don't necessarily know what the future will hold, but it's clear that it will look different than what it looked like before COVID-19.

We recently updated the website from a Virtual Pharma Expo website to a broader Virtual Expo Series website, imagining that at some point we will expand to other industries. Pharmaceutical is really our bread and butter, but there may be an opportunity to organize a chemical show in the future.

Is the audience you are attracting to these expos representative of what you would get at a conventional trade show or somewhat different?

We have a lot of the traditional contract manufacturers and big pharma companies participating, but we are also seeing some original equipment manufacturers tuning in to see what their competitors or partners are talking about as well. I think that in a live environment, a competitor avoids direct interaction, but the digital perspective offers a unique opportunity to learn from the competition.

What can you tell me about some of the other virtual solutions you've developed other than aspects of your business: tours, audits, or auctions?

Before the pandemic, auctions had already mostly transitioned to virtual models. On top of that existing framework, the world has learned very quickly that there are so many things that can be done remotely and virtually. At Federal Equipment Company, we are communicating internally better than ever before and expanding our capabilities to perform virtual inspections better than what we previously had in place.

Sometimes customers will have to travel here because they need to see the ins and outs of a machine before deciding on a purchase. If we can save them a plane ticket through a FaceTime inspection that allows them to buy the machine and get it into service a lot quicker, that's a great solution for all parties, now and even after the pandemic is resolved.

One of the major things we're working on for 2021 is a solid strategy for improving and extending our web presence. Beyond search engine optimization and enhancing the search functionality to make it easier for companies to evaluate equipment virtually, we are looking to launch a comprehensive parts business. We participate in many liquidations where we acquire machines as well as related parts. I would imagine we have several thousand different units of parts in our pharmaceutical warehouse, and we are in the process of cataloging those parts and putting them on a separate e-commerce website, which will become **PharmParts.** This will be a single, discrete location where customers can find the parts that they need for their machines, whether they are tablet presses, capsule fillers, mills, or other machines.

Most of these initiatives were projects that we were discussing in the past, but the pandemic provided an opportunity to step back and readjust our sights a little. We have been able to look internally to determine whether we have the right people on the right processes, and focus on whether there are projects that can help us grow our business in the future – this intensified our motive to complete them much faster.

How important is Federal Equipment Company's long history and credibility to making customers comfortable acquiring equipment that they may only have inspected virtually?

Federal Equipment Company has been in the business for a long time, and our name carries a guarantee. The trust that we have built with customers over the years is critical to our success. While we do sell one-off items to companies to meet discrete needs, we always aim to convert that transaction into a long-term relationship.

During the pandemic, customers' options for in-person inspection of equipment are limited, but that established trust gives customers peace of mind that we will ensure the quality and operability of all equipment we sell, which often means bringing in a technician from the OEM to get a machine into the shape the customer is expecting before it is shipped.

Is there anything else you can share about Federal's strategy to face other challenges in the coming years?

We'd like to focus on developing more investment recovery programs, as we have already done for a couple of our long-term clients. There's tremendous value for companies to understand their assets and their worth, and whether they might want to redeploy them to other sites – if that's an option. When you're so close to just manufacturing or procurement, you may not understand the bigger picture, and that's part of what we're able to provide our clients, given that we've been working in the space for decades. I see a real opportunity for us to get much more involved in investment recovery over the coming years. P

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Justin Kadis works in marketing and business development for Federal Equipment Company, a major supplier of used manufacturing equipment for a wide variety of industries. He graduated from Boston University with a bachelor's degree in business administration with a concentration in marketing.

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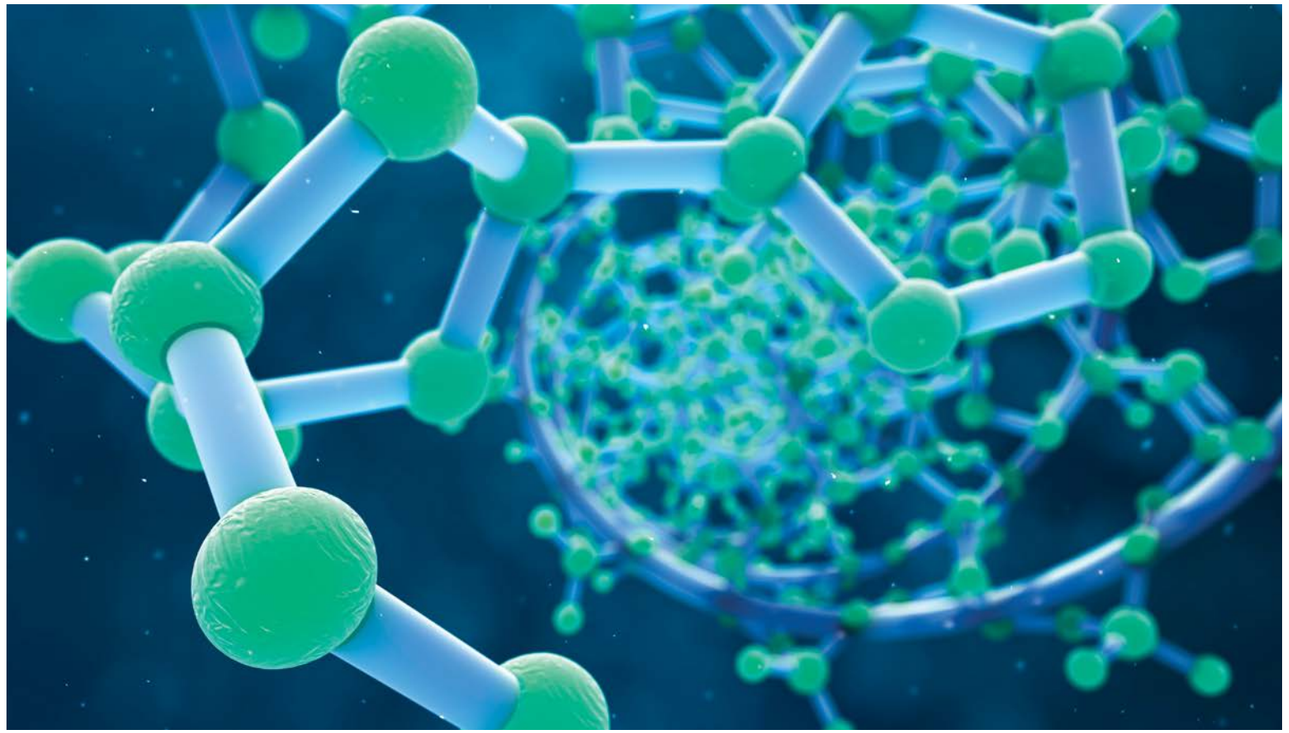
THE IMPORTANCE OF A GLOBAL LEADER IN SMALL MOLECULE MANUFACTURING DURING THE COVID-19 PANDEMIC

→ BY **PIERRE LUZEAU, Ph.D.,** SEQENS



Seqens was formed in December 2018 when Novacap merged with PCI Synthesis, PCAS, Uetikon, and Proteus. With 24 manufacturing plants and three R&D centers in Europe, North America, and Asia, we are an integrated global leader in pharmaceutical synthesis and specialty ingredients. During the COVID-19 pandemic, we have used our expertise in small molecule process development and scale-up to provide optimal routes to potential therapeutics and to reshore key compounds in short supply, as well as to produce isopropanol-based hand sanitizers for our local communities. Going forward, we will continue to invest in innovation to expand our onshoring efforts and increase our ability to produce the complex, next-generation molecules, including highly potent molecules, that will remain in demand for the foreseeable future.

RELOCATION TO ADDRESS SHORTAGES OF KEY MOLECULES

Even before the COVID-19 pandemic, the pharmaceutical industry was faced with a shortage of several important small molecule drug substances and drug products. The emergence of the pandemic highlighted this issue, particular for those molecules for which most manufacturing capacity has been located in Asia, especially China and India.

These shortages occurred for several reasons. In some cases, there were production issues, including those related to quality. In others, it was simply a capacity issue. Supply chain issues were also at play. These problems were further magnified by the shutdowns and limited operations of many facilities in Asia during the pandemic.

Our focus at Seqens has been to identify the small molecules that are in shortage and relocate production to the West. Relocation in this sense does not require building new plants. Our facilities, like many other contract development and manufacturing organizations (CDMOs) and pharmaceutical companies, are multipurpose and able to produce many different types of molecules. Modernization and expansion of capacity are needed to produce molecules in short supply.

The first step in this endeavor is to reevaluate the production processes and identify ways to improve the synthesis routes by leveraging newer, more efficient technologies that have been introduced since these molecules were first produced in India and China over the last two decades. Innovative approaches are ideally more cost-effective, environmentally friendly, and provide higher-quality products. Innovation is thus fundamental to successful reshoring.

BENEFITS OF SUPPLY CHAIN INTEGRATION

Even before the shortcomings of global supply chains became apparent in the context of the pandemic, Seqens was committed to providing an integrated, end-to-end supply chain for its clients. Seqens is capable of performing all necessary steps under one roof, from early intermediates in the early development process through commercial manufacturing, freeing our clients from having to manage inventory and logistics. While sourcing concerns appear more challenging than ever, Seqens' integrated supply chain has remained resilient, providing a simple, comprehensive solution to accelerate project timelines.

DIGITALIZATION AIDS RESHORING ACTIVITIES

One of the necessary areas of innovation for many parts of the value chain that wish to reshore pharmaceutical production is digitalization. For Seqens, digitalization can improve both the efficiency of research and development and the economics of commercial processes. Data mining can help identify older molecules that can be used for new applications, such as for synthethic routes.

Digitalization at Seqens enables us to accelerate our improvement and innovation processes, but also to reach new objectives thanks to the technologies we have implemented. The implementation of a wide range of digitalization tools and solutions has enabled the group to accelerate R&D, constantly improve production quality, guarantee operator safety, and ultimately ensure the satisfaction of our customers.

Our digital solutions range from automated mining equipment for the extraction of sodium bicarbonate to the use of digital platforms in our production facilities that enable better coordination production and maintenance scheduling and forecasting, quality assurance, and EH&S activities, as well as interactions with external partners. The Seqens Digiqual document and quality process management solution has been implemented at all production sites, ensuring a harmonization of practices while still allowing for customization to meet the unique needs at each location. We also invested in state-of-the-art analytical tools to optimize the efficiency of our analytical labs, including remote control of experiments.

Visualization of the supply chain has also been improved with the use of digital solutions. Seqens' QlikView solution provides a global, instantaneous, and exhaustive vision of activity across the supply chain, combined with a modeling capability to evaluate potential future needs. Users from the general manager to commercial operations through finance and supply chain members can readily obtain real-time data and assess the activity level of the company.

All of these efforts ultimately enable Seqens to better serve our customers. They are also supported by a new global customer relationship management platform (OneCRM) designed to strengthen the collaboration between our internal teams with the objective of improving the customer experience. These advances, which are gradually being rolled out to all Seqens sites around the world, are the first of many new solutions necessary for success of our recovery and relocation plan in France. Indeed, only an industrial tool that functions optimally through digitalization will enable a sustainable future for these investments.

INVESTING IN HIGHLY POTENT CAPABILITIES

One of the primary trends in the pharmaceutical industry today is the increasing number of potent or highly potent APIs (HPAPIs) under development. Approximately 40–50% of molecules in the pipeline fall in this category and require highly specialized facilities and equipment and skilled and trained operators for their safe production. These molecules often require complex chemistry for their synthesis. The containment systems required to protect workers and the environment are also complex technologies. From an investment standpoint, these systems are also costly. As a result, capacity has often not kept up with demand.

Seqens has carefully evaluated the risk of expanding our capabilities in the HPAPI field and concluded there will be a long-term need for these services going forward. In late August, we inaugurated an innovative HPAPI unit at our Villeneuve-La-Garenne site. This investment of $35 million (€30 million) in one of the three leading technologies in pharmaceutical synthesis, demonstrates the Seqens Group's ability to design, develop, and industrialize the most complex molecules while maintaining a high level of quality, safety, and respect for the environment. The construction of a second plant for HPAPIs in France is currently under consideration.

EVEN BEFORE THE SHORTCOMINGS OF GLOBAL SUPPLY CHAINS BECAME APPARENT IN THE CONTEXT OF THE **PANDEMIC, SEQENS WAS COMMITTED TO PROVIDING AN INTEGRATED, END-TO-END SUPPLY CHAIN FOR ITS CLIENTS.**

NOVEL BIOCATALYSTS ENABLE SMALL MOLECULE MANUFACTURING

Our greatest expertise at Seqens lies in developing and producing highly complex molecules using a unique skill set and a very broad continuum of technologies that encompasses both chemo- and biocatalysis. We bring together experience in enzymatic technologies and pharmaceutical route development with the development of optimized enzymes for specific transformations.

We also develop proprietary biocatalyst solutions. The most recent offering, launched in December 2019 by our Protéus subsidiary, are our SEQENZYM® Enzyme Kits, which contain enzymes selected among our extensive library of extremophile strains for fast early screening of biocatalysts. The seven different easy-to-use enzyme kits can accelerate screening of enzymes for molecular synthesis transformations by facilitating rapid assessment and identification of biocatalysts that afford desired conversion rates, selectivities, operating conditions, and kinetics.

AWARD-WINNING COVID-19 SUPPORT EFFORTS

During the COVID-19 pandemic, Seqens has been involved though partnerships with big pharma and biotech companies in the development of novel molecules with potential as COVID-19 therapeutics and more efficient routes to known compounds for repositioning, as well as the expansion of isopropanol production for the formulation of hand sanitizers. For the latter, we implemented the manufacture of hydroalcoholic and gel solutions for local communities at our plants in France, the UK, Canada and the United States in just a few months.

Indeed, Seqens' mobilization in response to COVID-19 has earned the company a 2020 European Responsible Care® Award for our project "Caring in Covid-19 Times." The special awards, issued by the European pharmaceutical trade group CEFIC, were based on the rapid engagement of our teams and workshops to propose and implement solutions to accelerate the fight against COVID-19 while adapting production lines to the market and providing support to local communities, populations at risk, and those in need by donating hand sanitizer.

To aid in antiviral candidate development, Seqens screened thousands of compounds in clinical databases and chemical abstracts, identifying both new chemical entities and existing drug substances with the potential to treat COVID-19. A smaller set of more than 100 compounds – for which Seqens was in a position to improve and accelerate by simplifying and reducing the synthesis stages and using innovative proprietary solutions – was then selected with the goal of providing the most effective solutions with the fastest routes to market in the context of this severe crisis

Seqens participates in the INOVA COVID-19 platform, which coordinates the achievements of the global players fighting against the novel coronavirus. Our researchers are collaborating at all levels across numerous areas of expertise (organic synthesis, analytical sciences, process engineering, process safety, thermodynamic and kinetic modeling) to develop robust solutions.

GLOBAL LEADER IN SMALL MOLECULE MANUFACTURING

Seqens has 24 plants worldwide, with a strong presence in Europe and in the United States. Our rapid growth will continue to be driven by ongoing investments in our plants. Despite the challenges experienced in 2020, we have additional investments planned in 2021 and 2022, and some announcements are forthcoming before the end of the year. In a nutshell, Seqens is on the path forward as a global key leader for small molecules.

Our dedication to this goal is reflected in the recent corporate social responsibility evaluations Seqens received from EcoVadis. Thirteen of our 24 operational entities have been assessed by EcoVadis, with five obtaining the Platinum level (top 1%), six the Gold level (top 5%), and two the Silver level.

SAFE AND EFFICIENT SYNTHESIS USING FLOW CHEMISTRY

Seqens has taken cues from other chemistry-based industries to leverage flow chemistry as part of an effort to make industrial processes safer. Continuous operation using flow chemistry approaches increase manufacturing efficiency by reducing reaction volumes, offering better control of reaction temperatures and exothermicity and a tighter residence time distribution than batch processes, and in many cases better selectivity. By minimizing secondary reactions and the formation of impurities, flow chemistry offers clear advantages in terms of quality while simultaneously reducing the environmental footprint. At the Seqens Lab in Porcheville, France, we systematically evaluate the feasibility of flow chemistry approaches for customer projects. Further investments in these capabilities are in the works, which by the end of 2020 will include a new GMP pilot plant designed for nitration-, diazotation-, or halogenation-type reactions and production of pre-commercial batches up to the ton scale. Bringing back activity in Europe to secure the supply chain will go also through this kind of safe and low environmental impact investments.

PREPARED FOR POST-PANDEMIC GROWTH

Seqens will continue to invest in innovation to maintain our competitiveness and gain access to markets that require specialized expertise and capabilities. We will build on our existing strengths in small molecule synthesis, focusing on HPAPIs and other challenging compounds we can positively impact.

Simultaneously, we will continue to focus on molecules that are in short supply in most Western countries. As an integrated player in the drug production chain, from the production of intermediates to the production of active pharmaceutical ingredients and from research and development to industrialization, Seqens has the technical and industrial capacities to relocate and increase the production capacity of essential and critical molecules.

We are committed to developing a skilled workforce and have already doubled the number of work-study students and apprentices, particularly in technical fields. In 2021, more than 150 young people will be welcomed to our sites to learn our businesses. At least 10% of the group's employees will continue to work on the development of new products and innovative processes. Our culture of performance, rigor, and continuous improvement enables us to provide quality products in compliance with the strictest quality, environmental, and safety standards. P

Case Studies: Improving the Synthesis of Small Molecule COVID-19 Therapeutic Candidates

Brilacidin was initially discovered by PolyMedic and is currently under development by Innovation Pharmaceuticals Inc. It is a next-generation, non-peptide antibiotic that mimics the structure of defensin, a category of host defense peptides. Several phase II clinical trials have been conducted in humans, targeting oral mucositis, ulcerative colitis, and acute bacterial skin infections, and Brilacidin is currently undergoing *in vitro* studies to assess its antiviral activity against SARS-CoV-2 and its ability to inhibit the excess production of cytokines (e.g., to prevent the cytokine storm associated with the most severe COVID-19 cases).

The established synthetic route for the production of Brilacidin involves one step requiring the use of reactive, corrosive, and dangerous reagents. Seqens has developed a flow-chemistry process to scale down the reaction and limit the quantity of reagents needed, addressing key safety concerns. Side reactions are also reduced in the new process, leading to high yields of purer product with a reduced environmental footprint.

In a separate step, Seqens has replaced a complex, difficult-to-synthesize chemocatalyst with a highly selective biocatalyst, reducing the cost of the transformation, which takes place in water under ambient conditions. The alcohol dehydrogenase used here is part of one of our SEQENZYM® enzyme kits.

Seqens' expertise in chemistry, biocatalysis, and, process engineering enabled the development of this more efficient, safer, and more environmentally friendly route to Brilacidin. These flexible tools enable us to increase the process robustness, improve the economics, and accelerate the scale-up and industrialization of reaction steps for many different drug candidates.

A second example is Danoprevir, another COVID-19 antiviral candidate. Discovered by Array BioPharma (now Pfizer) and first licensed to Roche for development and commercialization, this drug has been produced in China and marketed by Ascletis since 2018. The modified-peptidic–type macrocyclic structure of Danoprevir is built according to a 20-step convergent synthesis.

Seqens has developed an alternative route that leverages biocatalysis for the expedient synthesis of a key chiral intermediate and the cost-effective replacement of an expensive transition metal chemocatalyst. Our approach to Danoprevir highlights the benefits of integrating biocatalytic steps within API synthesis. It also provides a route that can be quickly scaled to commercial production without the need to rely on rare resources, such as precious metal catalysts.

ABOUT THE AUTHOR

Pierre Luzeau, Ph.D.
President and Chief Executive Officer, Seqens Group

Dr. Pierre Luzeau has been the President and CEO of the Seqens Group for 14 years. A chemist and physicist, Pierre began his career in the design of systems for superconductors epitaxy (used in electronics and defense) and then managed several international activities within Pechiney and then Rhodia. Pierre has also been Chairman of the Competitiveness Commission of France Chimie for more than 10 years. Pierre holds a Ph.D. in solid physics, two M.D.s in chemistry, and an MBA from CDI in Paris.

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CREATING QUALITY CONTENT FOR EFFECTIVE DIGITAL MARKETING

→ BY **RIZWAN CHAUDHREY,** RSK LIFE SCIENCE MEDIA

The evolution of marketing from print to digital was greatly accelerated by the COVID-19 pandemic. Social media is a powerful tool for reaching existing and potential customers if the messaging is done right. One way to cut through all the online noise is to offer easy-to-understand messages in the form of consistent, high-quality content.

EVOLUTION IN COMMUNICATION

The challenge for all marketers is how to communicate to the right people – and get them to listen. In the past, that communication was largely attempted via the printed word, mostly through magazine ads with massive circulations.

With websites, email marketing, social media platforms – the advent of technology platforms and the growing importance of personal electronic devices, businesses have adopted digital marketing approaches. These solutions allow companies to connect with existing and potential customers regardless of their locations, including people they would not have reached in the past.

Social media enables companies – whether a one-person start-up or an international conglomerate – to communicate with potential customers and build relationships. Sharing information and helping people stay informed is a tremendous way to build both a brand and customer relationships. The more valuable information you provide, the greater your following will be.

The challenge, of course, is the variety of available digital tools. Just as it isn't possible to rely on one exhibition to reach all customers, it is necessary to leverage all of the digital communications mechanisms available: LinkedIn, web advertising, Instagram, TikTok, Facebook, and so on. Although it may be the same overall message, it needs to be presented in different formats using different ways of communicating to reach the full range of people engaged with all of these different platforms, and in a way that resonates with each group and keeps them engaged.

SIMPLE MESSAGING

Resonating with people requires communication in a language they can understand. Often, marketing folks get overly locked into their own vernacular; they may focus on slogans and miss the main point of what they are trying to accomplish. The key is to communicate a simple message and target your demographic.

First, that requires understanding the perspective of your audience along with the problems they have. Next, it is necessary to understand the solutions currently offered. Highlighting the issues first attracts the people you want to reach because they can relate to them; talking about the solutions further maintains their interest. Sometimes the correct path requires reinterpretation of the marketing language into a form that will reach both scientists and nonscientists alike so they can both engage with the content.

There is a lot of noise out there, and it can be difficult to stand out and differentiate yourself. Often, there is too much focus, for instance, on special branding around video interviews. In my view, if the content is relevant, people will genuinely want to listen. They care far less, if at all, about a lovely logo or beautiful background.

THE LOCKDOWNS AND FORCED REMOTE WORKING HAVE REALLY CHANGED THE DYNAMICS **AND THE MARKET, WITH COMPANIES TRULY EMBRACING AND USING DIGITAL TECHNOLOGIES, SOME EVEN FOR THE FIRST TIME.**

Trade Shows – Will They Be Live Again?

Live shows have been converted into online exhibits and conferences for several months now. While not all have been successful, virtual booths are essentially all the same size. This removes the differentiating effect of having a very large stand in a conventional hall and random interest from foot traffic.

Due to the sudden changes caused by the pandemic, many organizers did not have time to entirely think through the mechanisms for interaction between virtual attendees and exhibitors or provide means for exhibitors to reach out to clients. A lot of this was the result of platform limitations that many event organizers are in the process of addressing. Many exhibitors have also failed to realize they need to be much more proactive at virtual trade shows; they need to do more to achieve the value that they are seeking.

Live events will return. We are already seeing announcements for some shows in 2021. However, organizers should be prepared to run a virtual event if necessary. I would recommend that they establish a digital platform and plan for a virtual event, and, if they find that some aspects can be held in-person, that would be a bonus — rather than the other way around.

While COVID-19 will eventually be mitigated, many companies that send attendees to trade shows have, during the lockdowns, been given the time to evaluate and assess the value of those they used to attend in person on a regular basis to the value realized at the virtual versions of those events. The result will likely be greater selectivity in the events they choose to attend in person. Participants will go to shows with excellent networking opportunities, while virtual participation will be leveraged if offered for those that haven't provided a definitive return.

Ultimately, there will likely be a mix of event types. Most will be hybrid events in which live and virtual options run concurrently. That might create the opportunity to offer new live events on different topics that haven't been covered in the past. Show organizers will have to make the determination based on their anticipated audiences and estimated revenue streams.

At this point, I have attended 20–30 of these virtual events on seven or eight different platforms. With that knowledge and experience, I am also able to advise clients — both organizers and exhibitors — how to maximize the virtual show experience. For organizers, I help improve the visitor and exhibitor experience, while for exhibitors I can help them make the most out of their virtual booths.

COVID-19 AND THE IMPACT OF LOCKDOWNS

The lockdowns that occurred as a result of the COVID-19 pandemic have accelerated the acceptance of digital marketing within the typically conservative pharmaceutical industry. The minds of senior managers within the life sciences have been opened, and they are allowing their thinking to broaden in new directions. The lockdowns and forced remote working have really changed the dynamics and the market, with companies truly embracing and using digital technologies, some even for the first time.

Overall, this tragic situation has created novel opportunities for many people. The companies that will survive and thrive are those that are willing to change, while companies that are waiting for things to return to normal may suffer.

Things will never go back to the "normal" we knew before the pandemic. To be successful going forward, companies must think about the future and find ways to solve the problems created by the need for remote operations, social distancing, and limited travel in new ways – both for themselves and for their customers.

DEVELOPING TRUST

One of the key drivers for holding in-person sales meetings and for attending conferences and exhibitions is to observe people's reactions during conversations. Face-to-face meetings provide an opportunity to get to know individuals as personalities. However, online visual meeting platforms provide the benefits of in-person meetings without the need for travel. Now that months have passed with people working virtually, casual dress has replaced traditional business attire and people are giving others actual views into their homes around them rather than using virtual backgrounds. As a result, they are providing a much greater window into their personalities, and as such allowing themselves to be seen as individuals rather than anonymous businesspeople. This also increases the opportunity to obtain getting more honest answers and opinions rather than the general company line, which can lead to deeper interactions and new and innovative ways of thinking.

Some of these elements that might have been considered "unprofessional" in the past are helping to make involved parties more believable, whatever positions they hold. This pays dividends in trust and is essential for effective communication. Particularly for people that aren't comfortable with online meetings, it helps to realize that the others don't mind looking somewhat silly and are relaxed while taking part in this new type of conversation.

CONSISTENT QUALITY CONTENT

With that trust established, it is possible to develop, for instance, relevant video content. Successful online messaging and communication cannot be achieved without consistent quality content. The right content is essential, and providing that content regularly is equally important. If the two go hand-in-hand, effective content delivered on a regular basis will grow and the appropriate audience will continue to expand. Add in appropriate marketing and sales cycle optimization (and other modern tools), and interest increases – that is when social media marketing is most powerful.

A BIT ABOUT RSK-SOLUTIONS

I started my business to help companies and event organizers, predominately within the life sciences industries, to leverage the power of social media, specifically on LinkedIn. My original vision was to work with people and companies who share the same values as I do; for instance, those who are honest and trustworthy, have integrity, are open to new ideas, are committed to helping others, have a sense of humor, and don't take themselves too seriously.

> THE COMMON THREAD CONNECTING ALL THE PEOPLE I INTERVIEW IS THAT **THEY ARE PASSIONATE ABOUT HELPING PEOPLE HAVE A BETTER LIFE.**

I have a large LinkedIn following of more than 8,000 industry members that was first established when I started working at *European Pharmaceutical Review*. Back then, I would attend shows and post pictures of the people I spoke with and describe the products and services they were offering or the trends and issues they felt were important on LinkedIn. When those pictures progressed to videos, my following on LinkedIn started to grow exponentially. And people – even those I wouldn't normally have otherwise spoken to – started to see me as a unique and reliable source of information.

When people started contacting me and asking what show I would be attending next and who I might be talking to, I realized that, while people love to go to shows, they can't go to all of them. They would like to know what is going on, but they are too busy to attend them all. There was an opportunity for me to be a conduit for them.

At RSK, I help them get that information. Between early September 2019 when I started the company and early March when travel became limited and shows were canceled due to the COVID-19 pandemic, I attended at least one event per week. At those shows, I conducted more than 80 video interviews with clients. This content was posted on LinkedIn and immediately made available to the industry at large.

I knew in January that COVID-19 could become a serious health threat and that trade shows would be canceled and the traditional in-person approach to sales and marketing would be totally upended, so I began focusing on helping clients with their digital marketing. While most people have experience with mobile phones, email, and the Internet, many do not have much experience reaching customers through social media and other digital platforms.

Since lockdown, my LinkedIn posts have evolved from news stories and articles to also publishing a weekly list of all the events running in life science across Europe and North America for this year and next year. This is very important, as events have been pivoting on a daily basis from live to virtual. I am also running ad hoc polls around issues related to life sciences and launching and producing my own interview series "#ChatsWithChaudhrey." I also have an RSK YouTube channel.

With my large LinkedIn following and experience creating consistent, high-quality content, I am in a great position to help companies. One of the most important things about my approach is that I always aim to keep things simple. There is so much noise out there, and it is critical for businesses to cut through that noise to reach their audience. Users are less interested in the branding and more focused on real content – how can the information help them meet their challenges? I (hopefully) help clients by giving them an honest perspective on their LinkedIn marketing.

I've proven that, by conducting interviews without fancy virtual backgrounds or branding around them but with good speakers that provide worthwhile content, people are genuinely interested and engaged. I help companies get their message out in a straightforward and trustworthy manner. I work hard to understand the problems my clients are addressing with their products and services and the solutions they are offering, and then find a way to communicate those concepts in a simple message so that the people they want to reach will want to listen to what they have to say.

I also have the advantage of being able to cover any topic related to the life science industry. My followers work in all stages of drug development, from discovery, to formulation and development, and to manufacturing and distribution, which means that I cover a wide range of topics. The common thread connecting all the people I interview is that they are passionate about helping people have a better life. Whether their companies focus on the early development stage or packaging, they are all trying to provide solutions so that people ultimately have better health and better lifestyles. Whichever part of pharma they are involved in, they've got passion behind their efforts, which is inspiring. I see that, not only in the interviews I conduct but also in the presentations and discussions that take place in virtual conferences and trade shows.

I am really proud to be working in an industry and with people, companies, and organizations who are at the forefront of not only finding a safe and viable vaccine for COVID-19, but also working on therapies and solutions for the many other diseases and illnesses humanity faces. P

ABOUT THE AUTHOR

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Having received his BSC (Hons) in economics/statistics with marketing in the late 1980s, **Rizwan** has worked for many of the UK's leading B2M media houses and brands across a diverse range of industries, including IT, healthcare, food & drink, social care, banking, construction, and pharma. He has worked with some of the world's biggest brands over the years. Apart from his wonderful wife and children, he loves comics (both varieties), travel, sports (The U, Fins, Manchester United), movies, reading, music, history, and the martial arts.

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CONTROLLING THE COST OF OWNERSHIP WITH MODULAR FACILITY CONSTRUCTION

→ BY **AARON STYLES,** ENVIRONMENTAL SYSTEMS CORPORATION

Biopharmaceutical manufacturers can only be competitive if they are nimble and agile — and that includes the design, construction, and operation of manufacturing facilities. With our proprietary, environmentally friendly modular cleanroom solutions, Environmental Systems Corporation can reduce the time and cost for constructing biopharma facilities that operate in a controlled and predictable manner.

GROWING ISSUES OF VERSATILITY, POTENCY, AND SPEED

There are several important trends in the pharmaceutical industry that are impacting the ways manufacturing facilities are designed and constructed. As companies bring outsourced projects in-house, they need to maintain the versatility afforded through contract manufacturers. They also require flexibility in scale-up from the lab/benchtop to pilot production through to commercial manufacturing.

Overlying these needs is the emergence of new modalities and next-generation products that require specialized manufacturing facilities in equipment, from cell and gene therapies to highly potent small molecule active pharmaceutical ingredients (APIs). Achieving the appropriate containment levels is essential for minimizing cross-contamination while also ensuring operator safety and protection from exposure to these highly potent compounds.

With the advent of COVID-19 vaccine approvals, there is also likely to be a shortage of aseptic filling capacity in North America, and biologics manufacturers – both biopharma companies and outsourcing partners – need to be versatile and adaptable enough to expand their capabilities to meet this growing demand.

In the end, working flexibility into business models is essential to remaining competitive. Drug developers must be able to move rapidly from development into production and scale-up in order to be the first to market. Indeed, timeframes are being drastically compressed for both pharmaceutical and biotech products with new facilities built faster.

ENHANCED CONCEPTUAL DESIGN

Construction of facilities for the production of new modalities and more highly potent compounds can carry significant uncertainties with respect to the specific design and equipment that will support still-evolving production practices. In many cases, decisions on the exact nature of the product and processes are delayed as long as possible, leaving less time to get to market.

To overcome these challenges, Environmental Systems Corporation (ESC) uses a process we call "enhanced conceptual design," which allows us to reduce the number of detailed reviews that are needed. We build a comprehensive team, bringing contractors and trade partners onboard early on so they can participate in initial discussions with the client. These teams bring a lot of great ideas on how to do things more efficiently and effectively from a construction and installation standpoint.

Taking this approach, it is possible even without having exactly defined the entire process to begin construction activities. With an understanding of a basic level of information and estimates for electrical power demand and cooling/heating loads, for instance, these components can be sketched in and confirmed once the process is further refined.

THERE IS ALSO LIKELY TO BE A SHORTAGE OF ASEPTIC FILLING CAPACITY IN NORTH AMERICA, AND BIOLOGICS MANUFACTURERS — BOTH BIOPHARMA COMPANIES **AND OUTSOURCING PARTNERS — NEED TO BE VERSATILE AND ADAPTABLE ENOUGH TO EXPAND THEIR CAPABILITIES TO MEET THIS GROWING DEMAND.**

The enhanced conceptual design approach provides clients with a better, more granular number when executing capital planning, forecasting, and seeking budget approvals. They can avoid the typically iterative and costly process of getting to the conceptual design stage, putting it out for bid tender, and then developing a detailed design, which leads to many changes and a need for further design revisions, and so on.

Of course, some clients already have a more sophisticated, complex project team in place to match the size of the project. We work within that type of environment as well. But we'll often try to implement the enhanced conceptual design–build approach.

ENHANCED CONSTRUCTION

When the enhanced conceptual design approach is combined with the use of modular construction and parallel process and facility engineering, it is possible to dramatically reduce the time required for facility construction. Modular construction is ideal for upfront pieces that can be decided on fairly quickly, allowing modules to be built in advance. These modules can then be bridged with a larger process room. While some clients elect to implement a fully modular solution, a hybrid approach often provides the best solution to meet their needs in minimal time.

Any systems that can be standardized and do not require detailed components specific to any one client's process can be modularized. Good examples include gowning rooms, anterooms, material handling spaces, airlocks, corridors, and laboratory, analytical, and QC spaces. If the traffic flow and number of people going into and out of a cleanroom are known, the gown room can be sized appropriately, for instance, predesigned standard modules can be put together like pieces in a puzzle.

ANY SYSTEMS THAT CAN BE STANDARDIZED AND DO NOT REQUIRE DETAILED **COMPONENTS SPECIFIC TO ANY ONE CLIENT'S PROCESS CAN BE MODULARIZED.**

What is very important at this stage is to understand how much space will be needed for the actual process operations so that appropriate room can be allotted during these initial stages when the modular systems are installed. Once the details for the processing and pilot suites are finalized by the client, they can be customized and installed.

With a completely modular solution, everything can be constructed in a controlled environment within a factory setting. Multiple spaces can be leveraged, with fabrication in one facility and the internal fit-out and infrastructure in another, to enable parallel processing and rapid sequencing of the modules. At the site, the only needs are the concrete padding/fittings/foundation depending on the size of the facility, and there is no waiting for a full building envelope to be enclosed.

Using a hybrid approach, the modules can be constructed in advance, and then the infrastructure is built into them. ESC typically adopts a two-storied approach for our modules, with personnel and processing areas in the ground floor modules and the infrastructure in the second-floor modules, including HVAC equipment, ductwork, and process piping, to maximize accessibility.

Using this approach, it is possible to fast-track construction and generate savings on project timing of anywhere from 15% to 30%, depending on the project. It also allows clients to identify which information has to be decided upfront to get construction underway and which decisions can be pushed out a little longer once greater process understanding is gained, and processes can be better defined.

In the face of the COVID-19 pandemic, modular construction also provides the advantage of dispersing work on a facility to multiple locations, rather than having everything done at the site. The fabrication unit works in its own "bubble," then the modules move to a different site where the electrical and mechanical components are roughed in a different "bubble." As a result, the risk of exposure and potential labor stoppages/shortages is limited because, if someone does get sick and people need to quarantine, only the immediate bubble is involved, and not everyone involved in the construction of the facility.

RELIABILITY AND PREDICTABILITY

Biopharmaceutical facilities typically operate around the clock every day for large periods of time. For instance, plants that manufacture the flu vaccine must operate for several months without stopping in order to produce the needed quantities of product to enable delivery and administration before the onset of flu season. During that time, all of the facility systems and equipment involved in those operations must be reliable and behave in a highly predictable manner.

To ensure that facilities can remain operational 100% of the time, ESC builds in reliability and creates redundancies for key systems. We are also looking to build facilities that no longer require summer or year-end maintenance shutdowns through the use of preventive and ongoing maintenance solutions that can be implemented while systems are operational.

CONTROL OF PROCESS PARAMETERS

In addition to providing predictability, modular systems from ESC can enhance the control of process parameters, such as temperature, humidity, and pressure. Controlling temperature, humidity, and pressurization is all about removing variables, which we achieve with our two-storied approach and avoiding the need to deal with an external building envelope.

Environmental controls are located in second-story, accessible modules. Each of these modules is designed specifically to support the operations/processes taking place in their corresponding first-story modules. As a result, clients can be confident that the right environmental conditions will be established. Even in cases where a single air handler may support two or three modules on the first story, the controls are installed in advance to meet the specific needs for each of those modules.

RECYCLABILITY

It is important not only to control the environment in biopharmaceutical production facilities, but to consider their impact on the surrounding environment. Recyclability of modular cleanroom components is one way to reduce that impact. All of the modular cleanroom components from ESC are constructed using aluminum-based materials. Aluminum has one of the most positive recyclability profiles from both content and demand perspectives.

ESC does not use any ferrous metals to avoid concerns about corrosion or quality. All cleanroom walls are aluminum. All structural components are high-quality aluminum. All scrap materials generated during the construction process and cleanrooms at the end of their life cycles are recycled at the processing facility.

DRIVING TECHNOLOGY DEVELOPMENT

ESC is continually seeking opportunities to develop novel solutions that will enable more rapid construction of highly efficient biopharmaceutical manufacturing facilities. Two important developments are in the works today.

The first is disposable, or at least semi-disposable, cleanrooms. These inflatable structures have liners inside them and are suitable for short-term (two or three months) campaigns, perhaps involving a highly potent compound or biologic. Rather than investing time, effort, and money in the validation of a more permanent solution with required cleaning processes, these cleanrooms can be deflated and compressed into a small package that can be incinerated.

ESC is also focused on developing solutions that leverage the Internet of Things and Industry (Pharma) 4.0, including both hardware and infrastructure, to enable more effective use of sensing and data analytics technologies. We are partnering with the technology group at our local college to determine the optimum solutions for capturing and analyzing data and providing the results, including how to maximally leverage artificial intelligence and machine learning in a biopharmaceutical manufacturing facility. This work is ultimately driving toward achieving net-zero facilities.

CREATING ENVIRONMENTS FOR SUCCESS

The guiding vision and philosophy of ESC is to create environments for success, not only for the company, but also for our clients, partners, vendors, and everyone we work with, including our own team members. As a full turnkey provider of critical environments and cleanrooms, we have developed our own products including our Aluma1 ceiling and floors system. We also work closely with clients to design and build custom cleanrooms that meet their specific needs. We build and manufacture the HVAC and other systems required to supply the critical environments for pharma manufacturing in our own facility, and we offer the final piece of integration around the controls and monitoring of those environments, right up to 21 CFR PART 11–validated monitoring systems.

Once we put the COVID-19 pandemic behind us, the biopharmaceutical industry will once again have the freedom to focus on bigger-picture issues: sustainability, energy consumption, the net-zero approach. How we use resources is going to become a bigger focus as we move forward over the next 20–30 years. We have to figure out how to drive down to that net-zero application or at least get as close to it as possible. But first, we have to truly set that target.

Net-zero is not a big part of the conversation yet, but ESC is beginning to drive the conversation, because there is room for improvement with respect to the carbon footprint of construction activities. We are starting to look at carbon footprints – and the larger environmental footprints – with a net-zero approach in mind. There are some new ways of approaching this that are already under development, the question is how to bring those technologies into the biopharmaceutical industry for their facilities.

ESC IS COMMITTED TO HELPING THE PHARMA INDUSTRY **ACHIEVE NET-ZERO PRODUCTION FACILITIES IN THE POST-COVID WORLD.**

ESC is committed to helping the pharma industry achieve net-zero production facilities in the post-COVID world. We are evaluating the environmental impacts and the operational and capital costs associated with the cleanrooms that exist today. This information will be used to design and build more environmentally friendly cleanrooms with the goal of realizing net-zero facilities. ESC wants to be a tangible part of the solution. To do so, we are looking at technologies that can actually contribute to a net reduction in carbon footprint and energy consumption.

For instance, we recently partnered with an emerging technology firm developing novel membrane dehumidification systems. This startup company, which stemmed from an incubation hub at a local university, has a new approach to this method of dehumidification. We have a scale-up demonstration currently in process and are hoping to have several clients piloting the technology in real-world settings by the second quarter of 2021. P

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Aaron is creating environments for success and value for clients, partners, and team members and applying his diverse industry experience to develop innovative solutions for Critical Environments and Cleanrooms. He has a Bachelor of Applied Science in chemical engineering from Queen's University and has worked in manufacturing, engineering, and operations management for 20 years holding several progressive positions.

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PREPARING FOR COVID-19 VACCINE DISTRIBUTION DESPITE TIGHT SHIPPING CAPACITY

→ BY **ANDREW T. BOYLE,** BOYLE TRANSPORTATION

Secure, validated cold-chain transportation is a scarce resource. Trends in the logistics sector and the emergence of the COVID-19 pandemic have created significant bottlenecks in the transportation market. Distribution of a vaccine for the novel coronavirus will create further demand for advanced shipping solutions. Logistics providers like Boyle Transportation that have continued to invest in systems, equipment, and personnel and established partnerships with temperature-controlled packaging suppliers are working with vaccine manufacturers and freight forwarders to ensure distribution of COVID-19 vaccines when they are available. Boyle Transportation Co-President Andrew Boyle spoke with *Pharma's Almanac* Editor-in-Chief David Alvaro, Ph.D., about the challenges ahead.

WHAT IS THE STATE OF DEMAND FOR TRUCKING SERVICES TODAY AND WHAT FACTORS ARE DRIVING IT?

The pandemic continues to have a direct impact on the demand for trucking services. Factory shutdowns in the spring led to reduced inventories. Retail sales have rebounded, resulting in the lowest inventory-to-sales ratio since 2014. Manufacturers and retailers are thus relying heavily on just-in-time transportation.

In September, the supply/demand imbalance was stark — some indices showed one hundred truckload shipments per available truck. With travel and entertainment curtailed, people can't spend on services, so they are buying things to enhance their lives as they stay at home. Unlike services, things must be shipped. People have also been cooking much more at home, and the demand for fresh food, which requires shipment at controlled temperatures, has risen. Shipments of medicines that require cold conditions have also increased due to the demand for COVID-19 treatments. Because of these trends, the demand for cold-chain storage and shipping has increased significantly.

IS THAT DEMAND BALANCED ON THE SUPPLY SIDE?

The supply side is short, leading to very tight capacity. After the pandemic hit, many motor carriers (but not Boyle) parked their trucks and didn't replenish their recruiting pipeline because business was down. Now that business has picked up again, they are short-staffed.

COVID-19 has also impacted professional truck drivers directly. Some have missed work because they contracted the virus. Others have voluntarily come off the road due to school closings or the need to care for family members. Indeed, we have hired more people to do even the same amount of work.

The driver shortage has been exacerbated by federally mandated use of the Drug & Alcohol Clearinghouse beginning in January 2020. While there is a formal return-to-work process drivers can follow after failing a drug or alcohol test, 78% have not elected to begin that process. Around 27,000 truck drivers have vanished from the pool since January, according to Freightwaves.

Insurance rates have also been rising drastically. According to the American Transportation Research Institute, the average jury verdict for a truck claim rose from $2.6 million in 2012 to $17.5 million in 2019. The financial strain on motor carriers, combined with the financial difficulties created by the pandemic, has caused a number of fleets to exit the market. Some of the fleets that remain are staying afloat by purchasing less insurance coverage, shifting more risk to the shipper.

The result of the increasing demand and limited supply has led to severe capacity tightness. The Logistics Managers' Index, a survey of leading logistics executives, indicated that transportation capacity in September fell to new lows. These low levels have occurred before the holiday season when peak demand typically occurs. Respondents to the survey expect capacity to continue to contract over the next year, but at a slower rate.

HOW MIGHT THAT TIGHT CAPACITY IMPACT THE DISTRIBUTION OF A COVID-19 VACCINE?

COVID-19 vaccine distribution is the most complicated logistical challenge since World War II. Many of the vaccines will require low or very low temperature shipment, and thus likely a combination of state-of-the-art active containers and temperature-controlled vehicles. It is essential that carriers be engaged months in advance.

ARE YOU WORKING CLOSELY WITH THE VACCINE DEVELOPERS TO ESTABLISH A COHESIVE LOGISTICS SOLUTION?

While the vaccine makers are understandably inward facing right now due to the complexities associated with developing safe and effective products, they have engaged with global integrators, freight forwarders, and carriers like Boyle to help us determine how we can best serve them. We have been doing test runs with them to prove logistical concepts in anticipation of vaccine approval. We all share the same concerns and want to plan as much as possible during a very fluid situation and a time of limited transportation capacity.

WHAT DO YOU SEE AS CRITICAL TO ENABLING THE SUCCESSFUL DISTRIBUTION OF A COVID-19 VACCINE?

We need a solution approach that accounts for the transportation vessels (aircraft and trucks) and the combination of active and passive shipping containers that will be required. The speed of the network must also be emphasized, because most containers will need to be replenished with dry ice or recharged in some way to maintain temperature control.

HOW DO YOU SEE THE PANDEMIC IMPACTING TRANSPORTATION DEMAND GOING FORWARD?

For the last 30 years, the supply chain has been moving to a global and "Lean" approach. The pandemic has exposed risks associated with that strategy. Whether driven by a government edict or corporate strategy, there will likely be more emphasis on supply chain resilience. We anticipate more "near-shoring" or "reshoring," whether to North America or specifically to the United States. That shift, combined with the trend of more products requiring temperature control, will drive healthcare transportation demand. So we'll continue to build out capabilities to meet that demand. We are also seeing a shift to the use of more software tools and mobile devices within the truck transportation sector. We expect to see more attention paid to the health and wellness and financial stability of professional truck drivers now that the general public realizes how important they are.

Boyle responded immediately following the emergence of the pandemic, implementing several measures to protect both our workers and our customers. We adopted physical distancing and engineering and administrative controls, increased cleaning protocols, required the use of PPE, and implemented contactless delivery per OSHA guidance. Rather than letting drivers go, we hired more people to ensure that all shifts were covered.

HOW CAN BOYLE ENABLE SUCCESSFUL DISTRIBUTION OF A COVID-19 VACCINE ONCE IT IS APPROVED AND AVAILABLE?

We already provide secure, validated cold-chain transportation for many vaccines. For COVID-19 vaccine manufacturers, Boyle Transportation offers a strategic approach to logistics and transportation that includes highly trained and experienced employees, advanced technologies to ensure validated temperature control and digital chain of custody from pickup to delivery, and extensive risk-management systems.

Our nearly 50 years of experience providing logistical support to government agencies and transporting defense materials led us to establish enhanced security protocols beyond what is typically needed to transport drugs, but which may be key if vaccine supply cannot keep up with demand. We are familiar with the many nuances associated with accessing facilities, security clearances for personnel, and transportation security standards, including or exceeding those established by BARDA.

We ensure uniformity, reliability, and high-quality delivery of crucial pharmaceutical products and provide our customers access to markets and people all across the United States. We have been making investments and our proud logistics professionals are prepared to support the distribution of COVID-19 vaccines when they are available. P

ABOUT THE AUTHOR

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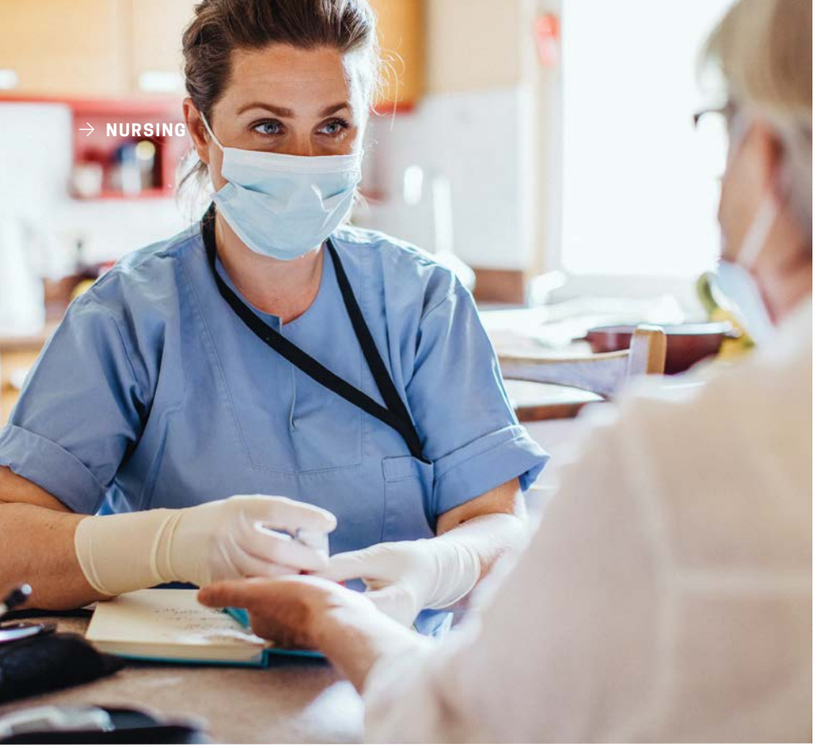

MOBILE RESEARCH NURSING: EVOLVING TO MEET PANDEMIC CHALLENGES

→ BY **JULES MORITZ**, ILLINGWORTH RESEARCH GROUP LTD.

In response to significant pandemic-related disruptions to clinical trial research, sponsors are seeking ways to adapt their studies so they can continue to be conducted safely and effectively without sacrificing data quality. One option is integrating experienced mobile research nurses into their site investigative teams, making it possible to operationalize studies that would not otherwise have gone forward during this challenging time. While COVID-19 has spurred growing interest in — and uptake of — mobile research nursing, these uniquely qualified professionals have been adding value to clinical trials since long before the pandemic.

With mobile research nursing, a skilled nurse goes to a study participant's home or other convenient location to conduct off-site visits and perform study-related assessments and data collection. Off-site visits lighten the burden of participation by allowing clinical trial obligations to be completed in the comfort of a familiar environment and at the convenience of the patient and their caregivers. These visits can also enhance retention and strengthen provider–participant rapport, particularly if the patient is visited routinely by the same nurse who is already familiar with their situation.

KEEPING STUDIES MOVING FORWARD

Pandemic-related site closures and travel restrictions caused many clinical trials to come to a halt. Even as sites reopened, patients and their caregivers may have been reluctant to go to clinical sites for fear of COVID-19 exposure. Mobile research nursing enables clinical research visits to be performed in a way that circumvents these obstacles — an attractive option in almost any study, as a majority of clinical trial participants live more than two hours away from designated clinical research sites.[1] By reducing or eliminating the need for long-distance travel, sponsors can expand the recruitment pool by making study participation accessible and attractive to those with limited mobility or who live far away from a site.

Mobile research nurses serve as an extension of the on-site study team and perform activities — including data collection — on behalf of the site. As such, selection of a mobile research nursing partner that is an appropriate fit for the study is critical. Importantly, mobile nursing is not a generic solution. Sponsors may want to seek out providers who offer licensed nurses with both clinical skills and trial experience in their therapeutic area of interest or to understand whether the provider has nurses in all the geographies covered by the study, how the provider trains nurses on the protocol and associated procedures, and what processes the provider uses to ensure the quality of the data captured by their nurses.

To ensure seamless integration with site staff, a best practice is to have every nurse approved by the site and named on the delegation of duties log, as these nurses perform activities on behalf of the site. It is critical for the nurses to build strong relationships with site staff and to establish a cadence of consistent communication. While in-person meetings with site staff are the ideal method for onboarding mobile research nurses, this practice has been adapted during COVID-19 to accommodate video conferencing as an alternative.

MAKING OFF-SITE VISITS SEAMLESS

In a recent survey of clinical trial participants, 38% of those who dropped out of a study said they did so because site visits were stressful.[2] Offering the option of off-site visits with a mobile research nurse can help to alleviate that stress by minimizing disruption of normal, daily routines. In addition to making study participation less disruptive for patients and their caregivers, mobile research nursing visits make it possible for site staff to assess the safety of their patients at more frequent, predictable timepoints, even if unforeseen circumstances — such as a global pandemic — arise.

The recommended approach for making the clinical trial experience seamless for study participants is for sponsors to include the option of mobile research nursing in the protocol and for principal investigators to explain the logistics of off-site visits. If the patient opts in, there would ideally be an onboarding process that gives the patient and their caregivers an opportunity to meet the assigned mobile research nurse in advance of the first visit, either in person or via telephone.

Before each visit, the mobile research nurse and the site team should connect to discuss details of the upcoming visit, including assessments to be performed, adverse events to follow up on, or medication changes to be made. The mobile research nursing team handles all the requirements of the visit, from coordinating with the pharmacy and the courier for delivery of the investigational product to bringing the necessary equipment for assessments to the off-site visit and transferring any samples to a courier for delivery to a lab. If a serious adverse event is noted during the visit, the nurse must immediately report it to the principal investigator and take any appropriate action.

ADAPTING TO MEET HEIGHTENED SAFETY REQUIREMENTS DURING COVID-19

Study recruitment and retention can be challenging, even outside the context of a public health emergency. Clinical trials often involve vulnerable populations who are most at risk from exposure to COVID-19, which further magnifies the obstacles of enrollment and ongoing study participation.

Just as sponsors have needed to adapt in response to pandemic-related challenges, mobile research nursing providers have been tasked with developing processes to protect both their nurses and the patients and caregivers they visit. In addition to mobilizing COVID-19 response teams, developing detailed safety protocols and symptomatology checklists for both nurses and patients has been crucial. An effective approach is to contact the patient and their caregivers the day before a scheduled visit to perform a symptom check. Having the nurses also perform a symptom check on themselves before the visit helps to ensure all parties involved in the visit remain safe. To limit unnecessary face-to-face contact, visits should also be preceded by phone calls between the nurse and the patient or caregiver to discuss the details of the visit.

It is recommended that nurses wear full personal protective equipment (PPE) at all visits, including face masks, gowns, and gloves, and all are supplied with disinfectant products for use during visits. Even more rigorous standards should be adhered to when the nurses are visiting with patients for extended periods of time, interacting with vulnerable patients, or performing procedures, such as pulmonary function tests, that increase exposure risk. Ensuring adherence to these heightened security precautions requires extensive training and situational testing. Strict policies regarding quarantining nurses who have been exposed to patients or other individuals with symptoms or confirmed diagnosis of COVID-19 are essential and should follow country-specific regulations for isolation and monitoring.

So long as COVID-19 remains a concern, it is incumbent upon mobile research nursing providers to continue to monitor what health agencies around the world are saying and to continually adapt their standard operating procedures so that nurses and patients and caregivers feel safe at every visit.

FUTURE-PROOFING CLINICAL TRIALS WITH MOBILE RESEARCH NURSING

This year of unparalleled uncertainty underscores the importance of proactively planning for unforeseen circumstances in every clinical trial. Clinical trials are the culmination of years of research and development, and they are resource-intensive endeavors. While sponsors of ongoing trials have successfully integrated mobile research nursing into existing protocols to keep their studies moving forward, sponsors of upcoming trials may benefit from incorporating the option of off-site visits at the outset to help future-proof (and pandemic-proof) their studies. P

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THE INNOVATION ISSUE FEATURE

The Future of Healthcare

By **David Alvaro, Ph.D., Emilie Branch,** and **Cynthia Challener, Ph.D.,** Nice Insight

PART 1

Wearable Technology: Innovation, Adherence, and Clinical Outcomes

Wearable technology is one of the fastest-advancing sectors in the broader technology industry, providing innovative solutions for patients and healthcare professionals alike. Eighteen percent of the people in the United States utilize digital health wearables to manage or monitor their well-being, with 35% using mobile applications.[1] With applications ranging from basic fitness trackers and smartwatches to devices designed for disease prevention and health maintenance, wearable devices are empowering patients and generating real-time data that could, in theory, provide critical updates to health practitioners on demand. The possibilities of the tech seem infinite, with implications that can potentially reduce patient costs while simultaneously improving both quality of care and clinical outcomes.

The vast data generated by wearable devices present tremendous opportunities for researchers who can apply machine learning and artificial intelligence to interpret, analyze, and manage it. However, the technology also poses challenges, such as user acceptance, data security, and ethical concerns. These issues must be mitigated for wearable tech to become usable for practical, everyday use within the healthcare industry.

Wearable technologies enable the continuous monitoring of human physical activities and behaviors, as well as physiological and biochemical parameters of daily life. The most commonly measured health data include vital signs (e.g., heart rate, blood pressure, body temperature, blood-oxygen saturation), as well as posture and physical activities. Wearable devices can be integrated into shoes, eyeglasses, jewelry, clothing, accessories, and, what is currently most widely used and accepted, into a watch interface. More highly integrated wearable technology is also in development, with applications ranging from skin to neurointegrated devices.[1]

Empowering Patients and Doctors Alike

Healthcare has become more connected in recent years, and wearable devices are paving the path toward an even more connected future. As patients demand higher-quality care that is more convenient and accessible at an affordable cost, wearable devices may play a pivotal role in keeping patients informed of their health while also providing aggregated physiological data to healthcare providers. Telemedicine and connected devices have emerged as technologies that can provide greater access and convenience and serve as a means to defer in-person treatment and consultation in favor of remote care experiences. Sophisticated sensors in wearable devices allow for the collection, storage, and management of a repository of patient data, which can then transmit to patients' healthcare providers to optimize tracking of key data points for various medical conditions. This allows for more accurate diagnoses and timely and personalized treatment plans, resulting in more favorable clinical outcomes.[2]

Wearable devices that offer reminders, allow users to set goals, and contain elements of gamification have been found to increase PA among those who wear them.

Wearable devices also have implications in reducing prescription costs and increasing efficacy, as data relayed to doctors can empower these medical professionals to avoid overprescribing drugs that are suboptimal and modify therapies without requiring patients to make a trip to the office – in this way, wearables can provide cost savings on appointments and drugs alike.

One in six adults owns a smartwatch, and sales continue to grow annually.[2] In 2019, sales of smartwatches increased by 60% from the previous year, and the market is projected to reach $31.3 billion by 2023.[2] While technological innovations typically appeal more to younger consumers, the benefits of being able to transmit real-time health data to physicians, as well as be acutely aware of one's current health parameters, have seniors adopting the technology at a similar rate as younger people.[2]

The Costs of Patient Nonadherence

Medication nonadherence not only affects clinical outcomes, but it also drives substantial healthcare costs. In 2010, the costs of healthcare in the United States exceeded $2.7 trillion and accounted for 17.9% of the gross domestic product, and it is estimated that 20–30% of U.S. healthcare spending is ultimately wasteful.[3] Providers and administrators must contain costs by reducing waste and improving the effectiveness of the care they provide.

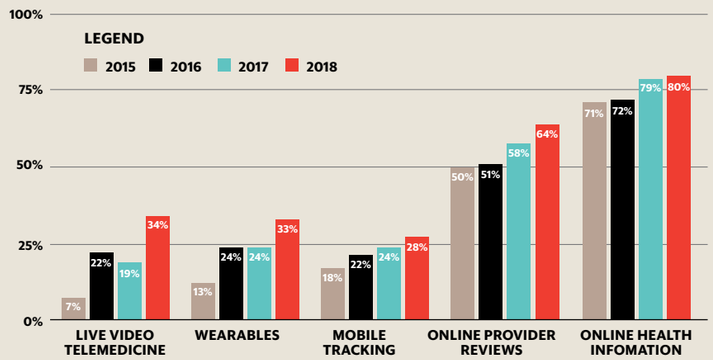
Patient nonadherence to prescribed medications is associated with poor therapeutic outcomes, disease progression, and billions of dollars per year in direct healthcare costs.[3] It is estimated that nonadherence alone costs the healthcare system $300 billion annually.[4] It is also estimated that 20–30% of prescriptions are never filled, and approximately 50% of medications for chronic diseases are not taken as prescribed.[5] This results in an estimated 10% of overall hospitalizations, costing between $100 billion and $289 billion annually, in addition to 125,000 deaths per year.[5]

Exercise Adherence Is Below Recommendations

The benefits of physical activity (PA) to manage health conditions of patients with chronic diseases are well known. However, adherence to PA guidelines in patients remains low.[6] Wearable technology presents a significant opportunity to increase exercise adherence to those who experience difficulties in participating in regular and substantial PA, and the technology could be supportive in increasing the success of exercise programs and interventions. The concept "exercise is medicine," as defined by the American College of Sports Medicine (ACSM), has been widely accepted for the prevention and in some cases the treatment of chronic diseases, such as cancer, type 2 diabetes mellitus (T2DM), and cardiovascular diseases, as well as for people with disabilities.[6]

Low, moderate, and vigorous activities have been linked to reductions in the risk of T2DM, as well as reductions of inflammatory markers in breast cancer survivors.[6] In cancer survivors, PA improves quality of life, cardiorespiratory fitness, and strength and alleviates fatigue.[6] In chronic obstructive pulmonary disease (COPD) patients, PA is associated with better respiratory parameters.[6] PA has a strong effect in reducing atherosclerotic factors, which are typical of cardiovascular diseases.[6] Moderate to vigorous PA is associated with lower severity of pain and fatigue in women with fibromyalgia, and graded exercise therapy has shown benefits for myalgic encephalomyelitis patients.[6] Exercise rehabilitation has also been shown to improve health-related quality of life for patients with heart failure, as well as to increase self-esteem and reduce stress in patients with chronic psychological disorders.[6]

ADOPTION OF DIGITAL HEALTH TOOLS 2015-2018



Source: Rock Health Digital Health Consumer Adoption Survey (n2018 = 4,000; n2017 = 3,997; n2016 = 4,015; n2015 = 4,017)

Despite the evidence showing the importance of PA in preventing and treating patients with chronic diseases, adherence to guidelines is still well below the targeted threshold. Patients with a serious mental illness were less active than the general population, with only 9% of them reaching the recommended PA guidelines.[6] A 2010 study found that, in Sweden, 84% of COPD, 74% of rheumatoid arthritis, and 72% of T2DM patients and 60% of healthy individuals did not adhere to PA guidelines.[6] In a UK cohort of seniors, only 15% of men and 10% of women met PA guidelines, while only 5% of all adults in the United States participated in the recommended amount of daily PA.[6]

A 2019 study from the Hannover Medical School in Germany found telemonitoring of exercise to be effective in treating patients with metabolic syndrome. Patients in the study were given Garmin smartwatches to monitor physical activity over a six-month period and were observed to have significant increases in overall health, work ability, and quality of life. The researchers conducted a randomized, controlled trial wherein participants were randomly assigned to either an exercise group or a control group. Those in the exercise group were given an exercise supervisor, nutritional counseling, and a smartwatch to monitor their activity.

The device measured their daily steps, heart rate, and general activity and reported the data back to the researchers. Baseline metrics, such as BMI, glucose levels, and lipid levels in the blood, were taken, as well as heart rate and blood pressure, while participants rode exercise bikes to measure exercise capacity. The researchers found that those in the exercise group averaged 9,612 steps per day and 147 minutes of exercise per week, with 48% of them achieving the recommended 150 minutes of daily exercise.[7] Among those who exercised, average waist circumference decreased by 4 cm, triglyceride levels decreased by 25 mg/dL, systolic blood pressure decreased by 2.7 mm Hg, and fasting glucose concentration decreased by 5.4 mg/dL.[7] The researchers concluded that these findings indicate the potential benefits of personalized and digitally monitored activity programs in treating patients with metabolic syndrome.

Smartwatches Increase Adherence in Heart Patients

Wearable devices that offer reminders, allow users to set goals, and contain elements of gamification have been found to increase PA among those who wear them. They can also provide a substantial lift to quantifiable metrics pertaining to both the amount of activity and positive clinical outcomes.[8] Patients with atrial fibrillation (AF) who received smartwatch notifications in addition to standard care have better adherence to oral anticoagulation compared with those who received standard care alone, according to data presented at the virtual Heart Rhythm Society Annual Scientific Sessions.[8]

In a multicenter, prospective, randomized controlled trial at the Beijing Chao-yang Hospital at Capital Medical University, doctors analyzed data from 160 patients with AF who were assigned a smartwatch reminder. Patients in the standard care group were scheduled for outpatient visits and received regular follow-up calls. Those in the smartwatch reminder group received daily intake reminders and nonadherence smartwatch notifications of missed or delayed doses in addition to standard care. These patients also had the ability to use an immediate telephone feedback function.

Adherence was assessed using the Morisky Medication Adherence Scale (MMAS), a self-reported measure, and the proportion of days covered, an objective measure. A score of 8 on the MMAS indicated adherence, in addition to a cutoff of 80% or greater for proportion of days covered. During nine months of follow-up, both groups were taking approximately four drugs each for antiarrhythmic and antihypertensive treatment. In patients assigned standard care alone, the percentage of those with an MMAS score of 8 decreased from 66.3% in the first month to 40% at nine months.[8]

A similar trend was noted for the proportion of days covered by 80% or greater in this group, which decreased from 75% in the first month to 30% at 9 months.[8] Conversely, the percentage of those with an MMAS score of 8 in patients assigned smartwatch reminders increased from 62.5% at one month to 77.8% at nine months.[8] The number of patients with a proportion of days covered with 80% or greater was more than 90% throughout the 9-month period. The study concluded that a smartwatch that can send medication reminders can significantly improve adherence to oral anticoagulation therapy in patients with AF.[8]

Cardiovascular disease (CVD) remains the leading cause of death in the United States, as well as in many countries around the world.[9] Vulnerable populations, including minorities, low-income groups,

and people living in communities with limited access to nutritious food and facilities to participate in physical activities (such as gyms) are especially susceptible to CVD.[9] Studies of these vulnerable populations show that behavioral interventions targeting one or more of these modifiable risk factors can improve overall cardiovascular health, albeit with challenges pertaining to patient adherence to clinical recommendations.[9] Wearable tech, including activity-monitor systems, are a promising modality for targeting physical activity in behavioral interventions, as they hold the promise of connecting patients to clinicians right when needed, without the need for face-to-face interaction. As consumer ownership of wearable devices that collect real-time behavioral data becomes more ubiquitous, opportunities for clinicians to promote behavioral adherence continue to expand.

A study conducted by Evidation Health and based on claims filed through Humana concluded that individuals who engage in activity tracking have significantly higher medication adherence than those who do not track their activities when controlling for age and sex across thousands of people with diabetes, hypertension, and dyslipidemia.[10] The results were not dependent on a specific condition or tracked activity, but the positive association with medication adherence extended to the frequency of activity tracking as well as to physical activity level, as measured by step count. The study evaluated medical and pharmacy claims from roughly 8,500 patients who use activity trackers like Fitbit, Garmin, Jawbone, and Apple products. According to the researchers, people using activity trackers were more compliant with medication adherence than those who weren't using mobile health tools.[10] Additionally, medication management improved as these people tracked their activity more frequently. Health systems like Cedars-Sinai in Los Angeles and the Dana Farber Cancer Institute in Boston have seen success using Fitbits and other devices to collaborate with patients and reinforce care management outside the hospital or doctor's office.[10]

Companies Driving Adherence Through Modern Innovation

In December 2018, Jason Oberfest, former CEO of the medication tracker startup Mango Health, joined Apple's health team to possibly help the company scope out opportunities in the medication adherence market. The Mango app helps patients track and manage their medications, and Oberfest's experience merged with Apple's other health efforts, such as the Apple Watch, which now offers two features approved for medical use.[11] In a related move into healthcare, Apple also hired M. Osman Akhtar, the former COO of the Minneapolis-based nonprofit hospital network Fairview Health Services. Since these hires, Apple has also recruited dozens of doctors to expand its digital health products, grown its employee health and wellness clinics, and rolled out a long-anticipated Apple Watch equipped with an electrocardiogram (ECG), combined with the watch's ability to detect and notify users of an irregular heart rhythm, and both features received FDA clearance.[12]

Apple's biggest venture into healthcare to date is its Health app, which it launched in 2014 and now comes preinstalled on every iPhone. The app includes features such as activity tracking, sleep monitoring, and mindfulness support, but those built-in features are only a starting point. Apple has also created three kits that help developers build health-related apps for the iPhone and Apple Watch – HealthKit, which allows developers to feed information to and from the app and provides a framework for connecting new apps; ResearchKit, through which developers can create apps for medical research or clinical trials; and CareKit, aimed at connecting patients with providers.

In January 2018, Apple rolled out a feature that allows users to download, store, and share elements of their medical records and, in turn, participating providers can send lab test results, medication regimens, and other data directly to a patient's iPhone. More than 39 providers have already opted in, including Cedars-Sinai, Geisinger Health System, Dignity Health, and Johns Hopkins Medicine.[12] At the same time, Apple also announced it was teaming up with several EHR vendors, including Athenahealth, Cerner, and Epic, to help users view their personal health records on their iPhones. Apple isn't the first company to try to bring health records to mobile devices – Google, Microsoft, and others have tried, but Apple is in a unique position: its Health app is already installed on the phones of 140 million Americans,[12] it has strong associations with consumers for safeguarding the privacy of its users' sensitive data, and it has a reputation as America's consumer technology leader, with whom industry-leading healthcare companies seek partnerships. Soon after Apple released HealthKit, it announced that partners, including Duke University School of Medicine and Stanford University Hospital, were already using the technology to allow chronically ill patients to remotely track and manage their symptoms.[12]

Because so many Apple users already use the Health app, the company can recruit patients rapidly and at a large scale for proposed medical studies – dramatically lowering costs for providers, pharmaceutical companies, and medical device manufacturers. One of the first examples is the Apple Heart Study, currently being conducted in partnership with Stanford Medicine, which compares Apple Watch's ability to detect AF to standard detection methods. The study recruited more than 400,000 participants via their iPhones.[12] As Alan Yeung, medical director for Stanford Cardiovascular Health, explained, "To get 10,000 people enrolled in a medical study normally, it would take a year and 50 medical centers around the country."

If you zoomed out into the future, and you look back, and you ask the question, 'What was Apple's greatest contribution to mankind?' It will be about health.

Duke University Health completed a study using the iPhone's facial recognition technology to screen young children for autism and other neurodevelopmental disorders. The app was downloaded more than 10,000 times, and usable data was collected on 88% of the videos that parents uploaded.[12] In January 2019, Apple announced a multi-year partnership with Johnson & Johnson (J&J) to run a randomized control trial testing if the combination of the Apple Watch's function with J&J's patient engagement app can help detect and diagnose AF earlier in patients over 65.[12]

The iPhone and Apple Watch are already sophisticated medical tools, offering features ranging from electrocardiograms (ECGs) to fall detection – creating an opening for providers to use the devices to involve their patients in monitoring and improving their health. As the iPhone and Apple Watch grow increasingly sophisticated, these partnerships could expand. The company has already provided Apple Watches for studies examining the device's ability to monitor migraines, blood pressure, adherence in psychiatric care, and even as a virtual therapist for arm recovery in stroke patients.[12] Apple has also filed patents suggesting that future versions of its devices may allow users to measure blood pressure, body fat, and heart rate simply by pressing their finger on the screen.[12]

This fall, the tech giant announced the release of the sixth version of the Apple Watch. In addition to the FDA-approved ECG feature, Apple Watch 6 also comes with a pulse oximeter or blood oxygen monitor, which does not carry FDA approval because it is designed as a general wellness feature, as opposed to being intended for medical purposes.[13] In an interview with *Mad Money*'s Jim Cramer, Apple CEO Tim Cook posed a rhetorical question about the future of his company: "If you zoomed out into the future, and you look back, and you ask the question, 'What was Apple's greatest contribution to mankind?' It will be about health."

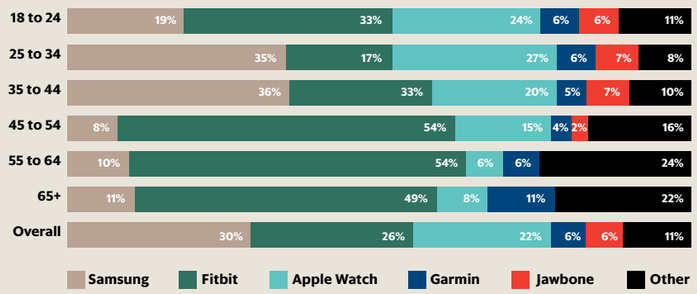
Adherence in Healthcare Retail

In June 2015, Walgreens officially launched its app for Apple Watch that assists people in taking medications as prescribed through its Pill Reminder and Refill Reminder features.[14] The Walgreens App for Apple Watch is designed to help patients manage their medications – from simple, once-daily reminders to multiple, complex drug regimens. The Apple Watch app connects with the user's Pill Reminders inside the Walgreens iPhone app, and Apple's "actionable alerts" allow the user to mark a medication as taken or skipped, as well as view which medications might have been missed or may be taken next. Refill Reminders predict when medication may be running low and offer users a one-touch method to initiate a refill. Users receive a follow-up notification when the medication is ready for pickup.

Walgreens competitor CVS has deployed a number of digital tools aimed at improving adherence and patient outcomes. The results of its first pilot of remote monitoring for patients with chronic myeloid leukemia (CML) found that participants in the two-way secure texting program were 22% more likely to be optimally adherent to their medications.[15] CML patients must maintain 90% or better adherence to their medication regimens in the first year after diagnosis to significantly boost their chances at remission.[15] In the program, patients were offered education and coaching on their medication through secure messaging. CVS's specialty pharmacy team is also targeting wearables to improve adherence and outcomes. It launched a pilot trial using smartwatches with 27 patients with multiple sclerosis (MS), with 90% of the test patients using the watches actively over the course of a year.[15] CVS found that 86% of participants regularly used the watches to report symptoms, and 75% took part in a walk test,[15] which is key in monitoring how well-managed an MS case is. P

WEARABLE ADOPTION

Percentage of adoption by age



Source: Rock Health 2016 consumer survey data (n = 4,015)

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PART 2

Wearable Technology: Targeting a Range of Uses and Indications

Products with Promise

As tech companies compete to bring game-changing devices to market, it remains unclear which types of wearable devices will become the gold standard in healthcare. While there are countless products in development or already available for consumer purchase, there remains a steep learning curve for consumers and health professionals alike, and choices for wearable devices in terms of features, practical usability, and value remain uncertain. However, for improving health, maintaining health, or managing chronic conditions, there is likely a device on the market that can make life better for many, or at least make one's body less mysterious.

Wrist wearables like smartwatches and fitness trackers have the deepest market penetration. Devices from Fitbit, Apple, Garmin, Polar, and Suunto, among others, all have the ability to track important metrics like heart rate, distance walked or run, and calories burned. For most consumers, purchasing decisions are made on the basis of how they will interact with their wristwear, as well the best option for connecting to other devices they own. Beyond smartwatches and fitness trackers, there is no shortage of innovative wearables designed to help users stay informed and motivated to maintain their health.

Diabetes Prevention and Treatment

Diabetes is a major health issue in the United States and the seventh leading cause of death.[1] Over 34 million people in the United States have diabetes, and one in five who have it are unaware of their condition.[1] Additionally, more than 88 million U.S. adults have prediabetes, which increases the risk for type 2 diabetes, heart disease, and stroke, and over 80% of people with prediabetes are unaware of their condition.[1] Australian start-up Nutromics is developing a Smart Patch device that combines sensors and stretchable electronics that attach to the skin on a user's arm. The patch tracks a user's health at a molecular level by measuring dietary biomarkers – biochemical indicators of dietary intake and nutritional status. The patch allows for a noninvasive and painless assessment that connects to an app allowing users to see how their bodies respond to various foods. By suggesting dietary modifications, it helps users reduce their risk for lifestyle-related diseases.

The V-Go Insulin patch is a 24-hour, patch-like wearable that delivers insulin. It features regular human insulin (RHI) in the patch, which has been found in at least one clinical trial to be just as effective and safe as the more modern rapid-acting insulin (RAI).[1] While RHI takes longer to reach the bloodstream, researchers found that using V-Go with RHI conferred similar blood-glucose control as the more expensive RAI counterpart.

A smart contact lens is in development by Pohang University of Science and Technology (POSTECH) to track glucose levels in diabetics. The wireless lenses remotely monitor sugar levels and can directly dispense medicine into the eye's membrane. This technology could provide an alternative to more invasive blood tests for diabetes, as it uses chip technology to track glucose levels through blood vessels behind the eyelid. It can also dispense medicine to treat diabetic retinopathy.

Stress

A watch-like device from Apollo Neuroscience, Inc. can be worn on either the wrist or ankle and uses gentle vibrations to help the body respond positively to stress. Developed by neuroscientists and physicians, it utilizes inaudible sound waves to change mindfulness and mood through sensory touch. Early adopters include doctors, patients, athletes, and those dealing with chronic stress, but Apollo Neuroscience aims to use this as a holistic alternative to mental health treatments that use prescription drugs. Apollo has a coordinated data-monitoring app for iOS and Android phones with seven different modes so users can achieve different goals by relaxing the body, clearing the mind, and restoring natural balance.

Another device aimed at reducing and managing stress, called PIP, is a tiny device designed to provide immediate feedback about stress levels. Its smartphone app helps users calm down through active relaxation, having users focus on various calming visual scenes. Users hold the PIP device between the thumb and index fingers to measure skin conductivity, and the app provides feedback on fluctuating stress levels throughout the exercises.

COVID-19

A wearable smart band created by the Instituto Italiano di Tecnologia research institute, affectionately named "iFeel-You," notifies users when their body temperature is higher than normal and when they get too close to someone else. It issues alerts when the wearer's temperature is above 37.5 °C (99.5 °F), with a sensitivity of 0.2 °C, allowing for quick identification of one of the main symptoms of COVID-19. The wristband reads the movement of the human body and releases radio signals to retrieve the distance from another bracelet. If two bands are too close, they vibrate and alert the users.

Ford Motor Company began testing a similar Samsung smartwatch that also aims to help users maintain social distancing guidelines. The watch vibrates and sends a color-coded warning to users when they come within six feet of each other, allowing factory workers to remain within the recommended social distancing guidelines. Ford plant supervisors also receive daily reports from the devices to ensure their employees adhere to the social distancing guidelines.

Researchers at Northwestern University have developed a patch designed to be placed at the dip on the base of a user's neck that can measure temperature, heart rate, body motions, chest wall movements, and respiratory sounds that indicate a cough.

Hackensack Meridian Health and Maimonides Medical Center are collaborating with Nanowear to test a cloth-based wearable technology called SimpleSENSE to track COVID-19 patients' conditions. The wearable contains nanosensors that can detect physiological and biomarker changes that may indicate that a patient's condition is worsening and alert hospital staff accordingly. Physicians can also use the wearable to remotely track patients' vital signs, including temperature, respiration and lung volume, and blood pressure. The wearable is able to collect 120 million data points per day for each patient and then transmit that data to clinical staff.[2]

As the world continues to adjust to life during the COVID-19 pandemic, companies will undoubtedly continue to innovate solutions to reduce its spread, monitor biometrics, and perform contact tracing.

Vitals Monitoring

The Withings smart blood pressure monitor consists of a wearable armband connected via Bluetooth to a smartphone app. The app measures heart rate and blood pressure and also counts weekly steps. The monitor features the ability to take three measurements and report the average, which is consistent with medical recommendations. Users can also set up reminders for various issues, including taking medications.

California Institute of Technology's professor Wei Gao developed an electronic skin that is applied to real skin with sensors that track data like heart rate, body temperature, blood sugar, and nerve signals. While most wearables use batteries, this e-skin runs on biofuel cells powered by sweat. The biofuel cells absorb lactate contained in sweat and combines it with oxygen from the environment to generate water and pyruvate. The fuel cells generate enough electricity to power the sensors and a Bluetooth device to wirelessly transmit the data.

AliveCor's FDA-cleared personal ECG takes medical-grade ECG recordings (detecting AF, bradycardia, tachycardia or normal heart rhythm) in just 30 seconds and delivers the results to a user's smartphone. This data can be tracked over time and shared with medical professionals for instant review. Users need only to put

their fingers on the sensors to measure and record results. The firm announced a partnership with Huami smartwatches, in hopes of making its heart healthcare platform a feature of the wearables of the future.

TempTraq monitors temperature for babies and children during an illness without interruption while they rest. It includes a Bluetooth sensor as a soft patch that can be placed under the child's arm, allowing parents keep a watch without having to take their temperature at different intervals in a day/night. The wearable is highly accurate and measures temperatures between 87.0 and 109.3 °F. Moreover, it has been tested to meet the ASTM E1112-00 standard, which is required for all the clinical digital thermometers.[3]

Air Quality

Researchers in China have developed ATMOBULE – a mask that purifies air particles using noiseless fans. The mask uses two fans to pull air through interchangeable HEPA filters that attach to the mask and can be used for over 150 hours, which is substantially longer than the commonly used N95 mask. The HEPA filters out 99.97% of air particles and generates air pressure inside the mask that is greater than the pressure outside, keeping contaminants out. The fans push purified air into the mask, allowing for normal breathing. It also features a silicone rim as an airtight seal to prevent air leaks.

BioScarf is a trendy alternative to standard air pollution masks. Beyond its stylish appeal, it is designed for individuals who want to protect themselves from potential respiratory health issues. A built-in N95 filter in the scarf helps strain over 99.75% of airborne pollutants, including pet dander, pollen, smoke, PM2.5, and other contaminants, offering protection against streptococcus, influenza, pneumonia, and tuberculosis.

Sleep

Ebb Therapeutics debuted a headband featuring its PrecisionCool Technology to target sleeplessness. It uses an intelligent cooling algorithm to cool the forehead, reducing metabolic activity in the frontal cortex. This reduction of brain activity allows users to fall asleep more easily, and an algorithm maintains an optimal temperature range throughout the night for more restorative sleep.

Philips SmartSleep is a wearable soft headband with sensors that help individuals identify their sleep needs. The wearable is also capable of producing audio tones that can help improve the depth and duration of REM sleep. A connected app logs sleep metrics and offers suggestions to improve overall sleep quality.

Fertility

The AVA sleep bracelet is a night-only wearable that provides insights to women about their fertility, pregnancy, and overall health. For pregnant women, it helps track weight, sleep, and stress levels. The wearable is known for its accuracy; a clinical study at the University Hospital of Zurich concluded that the device identified an average of 5.3 fertile days per cycle with an accuracy of 89%.[3]

Predicting the Future

While the market landscape remains largely unpredictable, there are trends and innovations that hint at future possibilities in the wearable tech space. Exoskeletons – effectively, robotic suits that humans wear – already exist and are used by some manufacturers to help human workers perform at optimal efficiency (e.g., lifting heavy weight without injury). Hyundai Motor Group has been testing its Hyundai Vest Exoskeleton, which helps to reduce pressure on workers' necks and backs in its factories. This tech could save money spent on worker's compensation, rehabilitation, physical therapy, and surgical procedures.[4]

Wearable technology also encompasses the new wave of prosthetics and robotic limbs that are increasingly becoming more intuitive (e.g., interacting directly with the nervous system and brain signals). MIT's Media Lab is involved in a research project that combines special amputation surgery with intuitive prosthetic development, where robot prosthetics are being designed for project volunteers to be able to operate their prosthetics via their nervous systems. If successful, intelligent prosthetics that respond to an individual's commands more intuitively may become the norm in the future.

Companies like Facebook are racing to develop wearable brain–computer interfaces that could allow users to type their Facebook status updates using only their mind. Similarly, Elon Musk's Neuralink company is working on a brain–computer interface that would help people with severe brain injuries.

62%
of consumers would choose virtual for health and wellness advisories.

55%
of consumers say "trusted healthcare professionals" would motivate them to take a more active role in managing their health.

11%
of consumers said that their regular healthcare provider recommended digital tools to manage health.

57%
of consumers are open to remote monitoring of ongoing health issues through at-home devices.

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PART 3

Wearable Technology: Their Future in Clinical Trials and the Real World

Can Wearables Be the Future of Clinical Trials?

Patient behaviors and key biological metrics are significantly easier to track with the multitude of wearables at the disposal of clinical researchers. The most frequently used consumer wearables include ActiGraph, Apple Watch, and Fitbit.[1] By February 2020, clinicaltrials.gov showed that ~460 wearables studies were underway,[1] and, according to Kaiser Associates and Intel, 70% of clinical trials will incorporate some type of wearable sensors by 2025.[1]

Pharmaceutical and medical device companies are empowered to take advantage of robust data sets to optimize trials and products to improve treatment efficacy. Wearable data can provide profound insights that can be leveraged in product development owing to the depth and breadth of the information that can be collected. Theoretically, wearables can be used across therapeutic areas for deep phenotyping, detection, and interpretation of adverse effects and for clinical trial recruitment.[1] Clinical trials depend on rich patient data, and collection in a physician's office captures only a snapshot of a participant's data, (e.g., one ECG or phenotype analysis). Conversely, wearables constantly track consumer and patient data over large periods of time, with the potential for real-time feedback, resulting in rich data sets and opportunities to gain more meaningful insights.

Early Adopters

Personal data collected in EHRs, as well as biological data collected via personal wearables and medical devices, are critical components in the success of clinical trials. AI tools can support analysis before and during a trial, and many life science organizations have started to see their value. Novartis has created a proprietary machine learning predictive analytics platform called Nerve Live. Novartis partnered with QuantumBlack, known for collecting data from Formula One races and using machine learning to optimize race operations. With QuantumBlack's help, Novartis piloted the platform to support its global drug development team's plan to simulate country allocation scenarios for clinical studies. The platform tracks all data points of the 550 clinical studies running in parallel and uses analytical software to predict issues in clinical trial execution.

Janssen Pharmaceuticals and Apple announced a collaboration in January 2019, culminating in the launch of a research study that focuses on the use of the Apple Watch's irregular rhythm notifications and the ECG app to improve AF outcomes and early detection.

Verily, a sister company of Google, kicked off Project Baseline in 2017. This was a collaboration with Duke and

Stanford universities to collect health data of participants over a four-year timeline. The collection of clinical consultation and survey data produced a large data set, creating a baseline for what it means to be healthy and the transition to disease. The success of the project resulted in a partnership between Verily, Pfizer, Sanofi, Novartis, and Otsuka in mid-2019. Using Verily's platform, patients and clinicians can actively engage in clinical trials that will increase the speed of clinical research. The program aims to map out the human health baseline and carry out clinical studies using technology developed under Verily to research a variety of diseases, including cancer, diabetes, and heart, dermatologic, and mental health diseases. The American Heart Association is using Verily's platform for the "Research Goes Red" registry, an initiative soliciting women across the country to participate in health research, particularly for heart disease. After launching its marketing campaign, it received more than 26,000 registrations, including 8,500 people who provided consent for specific clinical trials and are open to joining additional research opportunities through Project Baseline.[1]

Recruitment and retention in clinical trials can specifically benefit from AI tools, such as machine learning and natural language processing. These tools can find matches between specific patients and trials that are recruiting through integration with electronic health records (EHRs), medical devices, and wearables and recommend these matches to doctors and patients (either in real time at the clinical consultation or as a notification on the patient's wearable). In addition to recruitment, participant retention is a formidable challenge. The application of AI to rich patient data presents the opportunity to track a patient's compliance with a clinical trial's adherence criteria. The data can be presented to clinical trial administrators, allowing them to notify the patient of retention risks and take predictive and preemptive measures rather than practicing reactive management.

AbbVie, a biopharmaceutical company specializing in oncology, immunology, neuroscience, virology, and eye care, began integrating wearables into clinical trials in 2016.[2] The company wanted to deploy digital technologies but also wanted to improve the way it designed clinical trials to make them more data-driven. A center of excellence was created for clinical trial design that focused on using large data sets to help teams visualize the required patient population, the impact of their design decisions on patients, and the expected impact of geography and epidemiology. One trial was conducted using the Philips Actigraphy watch to measure sleep quality and itching in patients with atopic dermatitis. In another trial, patients with Parkinson's disease wore wearable devices that measured gait and sleep, which can be more difficult to measure using traditional methods with pen and paper. Patients wore sensors on their arms and legs that continuously and objectively measured Parkinson's motor symptoms and measured the quality of their sleep – something that greatly affects overall quality of life for patients who suffer from the disease. AbbVie subsequently replaced those devices with a wireless patch worn on an arm and leg. The patches are more comfortable and less intrusive for patients.

Broader Adoption

While wearables and AI tools create opportunities to simplify and streamline clinical research, they also elucidate the need to simplify existing processes, roles, and systems in life science companies. In advance of the broad adoption of wearables in clinical trials, researchers will continue to test and validate the feasibility of wearables in studies. Sponsors should also continue to partner with device makers to evolve endpoint data collection and validation. Studies have found that having clinical scientists directly involved in clinical study design and conduct is highly beneficial.[1] However, R&D scientists are generally not familiar with wearable devices, creating barriers to the adoption of wearable technologies in drug development clinical trials. Juxtapose this with the fact that device engineers lack knowledge and expertise as it pertains to drug development process and regulatory requirements for drug approvals, and collaboration seems necessary to streamline adoption and make wearable technology a standard in clinical studies.

Successful integration of wearables into clinical studies also hinges on meaningful collaboration with regulators to ensure that the scope of the clinical study is well defined and that outcomes can be achieved and implemented. Guidelines such as the Clinical Trials Transformation Initiative support such collaboration through recommendations for the use of mobile technology like wearable devices. One of its first recommendations is for R&D departments to start with a clinical trial endpoint and work backward to ensure that investigators select the right device. Consumer and medical device makers, researchers, technology data platform companies, and regulators must coordinate efforts in order to realize the full potential of this technology.

Perhaps the biggest challenge to full wearable integration is data privacy and security.

Growth Opportunities

A multitude of wearable devices are currently available for market consumption, and even more are in development, with promising implications for both overall health and cost efficiency. The global wearable computing devices market accounted for 181.5 million units in 2019, and it is expected to reach 520.1 million units by 2025, registering a compound annual growth rate of 19.9% over the forecast period between 2020 and 2025.[3] The product categories within the wearable tech market exhibit considerable diversity.

Smart clothing, including smart vests, smart bras, smart shoes, smart socks, and smart tights have a multitude of potential applications, including protecting the wearer from environmental hazards. Additionally, with an increase in the cases of chronic diseases worldwide, such as diabetes, cancer, respiratory disorders, and heart diseases, combined with the increase in the number of surgeries performed, the demand for smart fabric in the healthcare sector is expected to increase exponentially.[3] Edema ApS is developing a washable stocking to monitor and measure changes in leg volume for patients suffering from edema in lower limbs. Similarly, in March 2020, Powercast and Liquid X entered a joint venture to help manufacturers implement wearable sensors directly into garments, with potential applications for monitoring patients and athletes.[3]

According to Infopulse, over 80% of consumers are eager to wear fitness wearables, indicating interest and concern for monitoring various aspects of their health.[3] Augmented demand will also accelerate the development of personalized healthcare services, smart hospitals, and remote healthcare. In 2019, the FDA authorized the first wearable for hospital use, an AI-powered solution by Current Health.[3] This device traces a patient's health indicators with ICU-level accuracy and indicates threatening conditions, assisting healthcare providers in identifying deteriorating states and facilitating immediate provision of lifesaving services and procedures. Use of exoskeletons is anticipated to increase, as the North American population is slowly aging. In 2018, 16% of the U.S. population was 65 years or older, and by 2050 this number is expected to increase 20%.[3] The growing older population is expected to influence the demand for rehabilitation robots in the form of exoskeletons, something that once sounded like science fiction.

Real-World Evidence

As the healthcare industry focuses increasingly on outcomes, pharma companies are looking to sources beyond randomized clinical trials (RCTs) to measure and demonstrate the value they bring. Real-world evidence (RWE) has been in use for decades, but recent advances in technology and advanced analytics allow it to be employed in new ways. It allows for a better understanding of how patient characteristics and behaviors affect health outcomes, thereby helping to predict disease progression, patient response to therapy, and risk of adverse events – while also increasing the efficiency of R&D investments and accelerating time to market.

Cost and competitive pressures, scientific advances, digitally savvy stakeholders, progressive regulatory shifts, and the increasing breadth and interoperability of data and technologies are among many trends driving participants in the healthcare ecosystem to intensify their focus on value and patient outcomes.

Payers are gradually shifting to outcomes-based contracts, providers are working to gain privileged status with them, and patients are taking more ownership of their own outcomes. In this changing environment, insights from RWE are becoming more important in providing the right treatment to the right patient at the right time, measuring outcomes, and demonstrating the value of interventions. Given the significant disruption to RCTs and the need to rapidly understand burden by patient phenotype, as well as finding potential therapies for COVID-19, RWE is more prominent than it has been in the past.

Pharma companies have been using RWE for decades to inform their decision-making, respond to requests from external stakeholders, and improve their therapies' market positioning. More recently, growing regulatory acceptance, rising demand from payers and physicians, and increasing familiarity with digital and analytics have enabled some companies to derive much broader benefits from RWE.

An average top-20 pharma company that adopts advanced RWE analytics across its entire value chain for in-market and pipeline products could unlock more than $300 million per year over the next three to five years.[4] A typical cost base offers scope to save $100 million in development spending through the optimization of RCT design, the use of RWE studies rather than RCTs in some cases, and the implementation of synthetic trial arms.[4] Cost savings apart, the introduction of advanced RWE analytics could help companies identify new targets for molecules, accelerate time to market, improve formulary position and payer negotiations, and generate stronger evidence of differentiation and benefit/risk balance for in-market products. Analysis suggests that applying these actions to key assets could generate top-line value of $200 million or more.[4]

RWE may also support new uses for already approved drugs and/or help determine postapproval requirements for drugs. However, demonstrations of RWE from wearables are small in number to date. This is partially due to the deployment of digital and wearable technology remaining in the sphere of only a few multinational pharmaceutical companies.[5] Health insurance companies do not typically pay for digital medicine technology, because their coverage is based on data on patients and their claims. Healthcare systems largely do not yet see the value of wearables in clinical practice. However, multinationals like GlaxoSmithKline, Novartis and Lilly have chief digital officers overseeing integration of mobile and wearable technologies into their clinical trial programs.

These market issues are compounded by issues related to data collection, hosting, sharing, and management. Healthcare systems silos simply cannot handle the continuous stream of real-world data coming from wearable devices. Astonishingly, according to the American Medical Informatics Association, 75% of U.S. clinical centers still use fax machines to share EHRs,[5] and few are attempting to incorporate longitudinal real-world data from wearables with EHRs in a seamless environment.

Perhaps the biggest challenge to full wearable integration is data privacy and security. Strategies within the nascent direct-to-consumer wearables industry do not help. Although the American Medical Informatics Association has lobbied to update the 1996 U.S. Health Information Portability and Accountability Act to align wearables' data privacy policies with those in healthcare systems,[5] wearables companies are keen to protect their businesses. Consequently, their algorithms are proprietary, and their data cleanup is ill-defined or opaque, further exacerbating innate challenges with data privacy and perception of data security among users.

While wearable technology has seemingly limitless promise in potential applications for health awareness and medicine adherence, how it will be integrated into the provision of drug treatment and patient care in the future remains to be seen. However, despite a number of challenges, tech companies and life science researchers continue to innovate wearable tech solutions across all facets of the healthcare industry. P

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PREPARING FOR THE ADC EXPLOSION WITH END-TO-END SUPPORT

→ BY **JYOTHI SWAMY, Ph.D.,** AND **ELIZABETH MCKEE,** MILLIPORESIGMA

The pipeline for antibody–drug conjugates (ADCs) includes hundreds of candidates, with several expected to receive approval in the near future. Outsourcing of development and manufacturing for ADCs is common, owing to the complexity of these multicomponent drug substances, but few contract development and manufacturing organizations (CDMOs) have the relevant expertise to support the full supply chain, including the development and commercialization processes for ADCs. MilliporeSigma has deep experience in the relevant capabilities —monoclonal antibodies (mAbs), linkers, highly potent compounds, and conjugation technologies — and continues to build on its end-to-end capabilities. We are also excited to increase the number of commercial products produced at our U.S.-based facility, the first CDMO site approved for commercial ADC manufacturing in the US.

POSITIVE OUTLOOK FOR ANTIBODY-DRUG CONJUGATES

ADCs are complex, multicomponent drug substances designed to deliver highly potent pharmaceutically active agents to specific cells known to play crucial roles in various diseases. Their ability to effectively target disease-associated cells while minimizing off-target effects on healthy or non-diseased cells has drawn significant interest. Nine ADCs are currently on the market, and hundreds are in development, with seven or eight candidates expected to receive approval in the near future.

Most ADCs approved to-date were developed to target various types of cancer, but non-potent bioconjugates are also gaining prominence in non-oncology fields. We also expect ADCs, which are currently administered largely as second or third-line treatments, to soon begin to receive approval as first-line therapies. ADCs will also be used more often as components of combination therapies and for multiple indications. All of these trends will drive growth in demand for a new class of drugs. The global market for ADCs is projected to reach $10 billion by 2025.[1]

ADC TECHNOLOGIES STILL ADVANCING

Since the first ADCs were approved, much has been learned about the requirements for effective conjugation of cytotoxic payloads to antibodies. Conjugation was not site-specific in first-generation ADCs, resulting in multiple conjugated isomers that caused characterization challenges. That has led to the development of technologies that provide more control over the conjugation sites, and thus better safety profiles and more predictable *in vivo* results.

A variety of methods have been developed to enable site-specific conjugation and consequently improved therapeutic indexes. In some cases, the antibody is engineered or modified to enable site-specific conjugation. Linker technologies have also been introduced that do not require antibody modification but still achieve directed conjugation. A third approach involves enzyme-mediated conjugation technology.

In addition to advances in linker and conjugation technologies, MilliporeSigma has provided a solution to the manufacturing process with the application of single-use (SU) equipment. Using disposable systems eliminates the need for cleaning and cleaning validation, reduces changeover times between products, and lowers the risk of cross-contamination. The result is higher throughput with reduced risk.

We have worked with our internal resources who are already supplying Mobius mixers for mAb production and other processes to make these systems more suitable for ADC production, which involves the use of organic solvents. Those efforts have included the performance of solvent compatibility assessment and addressing questions about extractables and leachables so that our customers can be confident in the switch from traditional glass or stainless steel reactors to SU technologies. We have also shown that we can reliably transition from small-scale glass reactors at the development stage to larger-scale GMP SU reactors for clinical and commercial production.

UNIQUE MANUFACTURING CHALLENGES

The manufacture of ADCs is often outsourced, because production of these complex molecules requires expertise in biologics and small molecules, conjugation technologies, and the containment of highly potent compounds. It is also expensive to implement the infrastructure necessary for ADC manufacturing.

Pharma companies – both large and small – often elect to leverage the capabilities of a CDMO that has the infrastructure, in-depth technical expertise, and demonstrated success handing different ADC constructs at the development and commercial scales.

CDMOs such as MilliporeSigma, that have worked with multiple conjugation technologies and can use that knowledge when tackling new projects are preferred. Commercial experience is equally important, because the needs for early-stage development are significantly different from those during late-stage clinical studies and commercialization. Working with a CDMO that knows exactly what to do to get ready for customers' commercial regulatory filings is very important.

GLOBAL CONTRACT MANUFACTURING PARTNER

MilliporeSigma is a global CDMO offering support for biologic, small molecule, and biopolymer projects, including drug substances and excipients. MilliporeSigma offers a full line of ADC services, including process and analytical development, manufacturing, product characterization, GMP testing, and quality and regulatory support. We also provide testing and characterization services for mAbs as well as ADCs from one of the business units, Process Solutions Services. Our GMP facilities are located around the world and integrated with non-GMP facilities that produce starting materials for further processing at our other sites. Each project is assessed to determine, based on the customer's needs, which facility will be the best match.

Within each facility, our project management teams are led by managers that have a wide range of expertise, including

experience with both clinical and commercial programs. Different groups within each CDMO facility work closely together, with technical and manufacturing teams sharing information on a regular basis. There is also close interaction between the different CDMO sites, which is a great advantage in sharing lessons learned and for supporting customers when projects span multiple locations. Our project management organization is designed to ensure the comprehensive management of such projects, which is critical for projects with complex supply chains, such as ADCs.

LEVERAGING OUR EXPERIENCE FOR ADCs

With 35 years of experience in biologics and different types of bioconjugates at our St. Louis, Missouri site, and a facility in Madison, Wisconsin that specializes in highly potent APIs (HPAPIs), it was an obvious development for MilliporeSigma to enter the ADC space.[2] St. Louis was chosen as the main ADC production site because it was already established for small molecule manufacturing and also had biologics experience. With this dual expertise, we just needed to build the necessary infrastructure.

OUR APPROACH TO ADC COMMERCIALIZATION

Our journey to commercialization started with determining what was required and expected for commercial ADC manufacturing, including control strategies, risk assessment, process characterization, and validation.

Establishing microbial control is essential for biopharmaceuticals. Our approach involves setting in-process endotoxin acceptance criteria based on the worst-case raw material input and historical process data. As the process advances into commercialization, continuous process verification (CPV) is leveraged; acceptance criteria defined based on data gathered during qualification are monitored on an ongoing basis.

A quality-by-design (QbD) approach is leveraged to understand the inputs and outputs of the conjugation and ADC purification process needed to establish controls to ensure that critical quality attributes (CQAs) are consistently achieved. A step attribute matrix (SAM) is used to determine how material inputs and unit operations affect product quality attributes. A parameter attribute map (PAM) is then created to identify how variation within the process parameters could affect these quality attributes and to select those parameters that are critical to maintaining product quality. For example, the SAM/PAM exercise can help answer questions, such as the degree to which variation in the operating parameters of tangential flow filtration can affect impurity levels.

The process knowledge gained at this stage is then used to determine areas for investigation at development scale in order to characterize the process and provide a design space. Qualification of an appropriate scale-down model is essential to ensure that the bench-scale model will be predictive of the GMP scale. Qualification may include the utilization of equivalent raw materials, various mixing studies, and use of reference standards and controls where appropriate.

We also apply a range of experiments to understand how the process parameters – both independent and dependent of one another – affect quality attributes of the process. These experiments can include design of experiments (DoE) and one factor at a time (OFAT) experiments, among others.

Because ADCs combine the complexity of biologics manufacturing with the environmental controls required for highly potent compounds, we adopt a holistic view when building a detailed roadmap for commercialization that includes validation master plan scoping, risk assessment, and demonstration of process control and process performance qualification (PPQ). While many of the activities needed to move into process validation are completed as part of clinical ADC manufacturing, all potential risks and aspects of control and commercial requirements are formally reviewed.

As part of the validation master plan scoping, additional risk assessments needed for commercial manufacturing are also identified, and existing risk assessments are reviewed and updated to support additional controls for commercial manufacture. These risk assessments span all areas of the process, including process risks, operational and equipment risks, raw material risks, and microbial risks. Any necessary final studies or process changes are outlined before moving into validation, and critical process parameters are locked down.

OUR JOURNEY TO COMMERCIALIZATION STARTED WITH DETERMINING WHAT WAS REQUIRED AND EXPECTED FOR COMMERCIAL ADC MANUFACTURING, **INCLUDING CONTROL STRATEGIES, RISK ASSESSMENT, PROCESS CHARACTERIZATION, AND VALIDATION.**

To ensure commercial ADC manufacturing readiness, we also develop a detailed and robust commercial control strategy that incorporates risk assessment conclusions and mitigations, manufacturing process controls, critical process parameters (CPPs) and their relationship to product CQAs, rationale for acceptance criteria, process characterization data, and general quality management system controls. As a result, the commercial control strategy provides a complete outline of the process control space and clearly identifies how the manufacturing process is controlled to meet the CPPs. It is important to ensure that process control and knowledge are clearly outlined, as this is critical for supporting approval and the preapproval inspection audit (PAI).

Once the validation master plan deliverables required for PPQ are completed and the process is ready to move into validation, the PPQ protocol is developed to allow for the execution of the PPQ batches. The PPQ protocol outlines the validation strategy for the process and the test plans to be incorporated, including the required acceptance criteria. Once the batches are completed, a PPQ report is written to provide a summary of execution and adherence to acceptance criteria, and ultimately present a conclusion regarding the validation status of the process.

The PAI of our commercial ADC manufacturing facility was approached differently from how we had traditionally hosted inspections for small molecules at the same site. For non-biologics, the inspection was driven by the quality assurance team, with support from subject matter experts as needed. For ADCs, our subject matter experts were the core of the inspection team, given that much of the audit was focused on control strategies and the facility itself.

While the inspection was conducted according to Q7 (International Council for Harmonisation) guidelines, there are many different areas that the U.S. Food and Drug Administration (FDA) focuses on with regard to biologics. Scripts and storyboards, consisting of four to five slides, were used to describe complex processes. An example of a process that could benefit from a script is the raw material receipt process or any procedure at the site that would benefit from a very organized script to describe the workflow. Storyboards can also be used to describe complex gaps in the process, repeat deviations, or the validation narrative to the inspector. This approach ensures that the subject matter experts are comfortable with how they will relate the narrative of their department, their process, or the deviation that they helped investigate.

We also ensured the readiness of both our facility and staff. This is essential, as the inspectors may question staff members other than the subject matter experts when touring the facility; in many cases, the inspectors want to question the operators on the floor that are performing a particular action. Site-wide training reminds individuals how they may want to respond to inspectors and provides insight into the questions they may receive during the audit.

It was also beneficial to clarify the roles and responsibilities of each participant in the audit well ahead of time. Walk-throughs and mock audits were invaluable for helping subject matter experts become comfortable with the audit process and know what to expect. Team members were enlisted to play the role of inspectors and ask critical questions to ensure that our experts could explain their process effectively and concisely.

Finally, inspection logistics were coordinated and included establishing a timeline for preparation as well as the process flow and organization of documents. To ensure a robust and streamlined process flow, we had an audit team dedicated to each inspector or audit stream and a host who was well-versed in general quality systems at the site. The host answered general quality system questions and enlisted subject matter experts to discuss the individual process capabilities or any deviations. All of these efforts led to successful FDA approval of the site.

COMMUNICATING WITH REGULATORY AUTHORITIES

Regulatory guidance for ADCs continues to evolve. Given that ADCs combine the complexities of biologic and HPAPI manufacturing, current regulatory guidance pulls from both sectors. However, there are not yet as many specific guidances for ADCs as there are for biologics or small molecule APIs and formulated products. Complicating the situation for many ADCs is their receipt of Breakthrough and/or Fast Track designations from the FDA, resulting in the need to accelerate development activities.

Fortunately, the agency and other regulatory bodies have been very willing to work through the regulatory requirements with ADC developers to ensure that these novel therapies can reach the market as quickly as possible. Much of the information relating to expectations specifically for potent antibodies and conjugates, is gained via communication and discussions with the agencies.

As more ADCs are approved, we believe that greater clarity will be provided in the guidelines, and the expectations of regulatory authorities will become clearer. As an example, we anticipate that the FDA and other agencies will demand more thorough characterization of manufacturing processes and more control over both the manufacture and testing of ADCs.

EXPANDING CAPACITY

The progression of ADCs through the clinical pipeline is closely monitored by the industry, and both pharmaceutical companies and CDMOs are expanding production capacity in anticipation of the large number of approvals expected in the near future.

There is an acute need for CDMOs that understand how to execute late-stage studies to support a filing strategy. CDMOs with plans to support commercial-scale ADC manufacturing are establishing processes to handle challenging supply chains and investing in facilities and processes to ensure efficiency, quality, and security.

MilliporeSigma has proactively implemented several technologies to make sure that we are ready for customers when they need our support. We are also expanding capacity, not just for the production of final ADC products, but also for the production of linkers and payloads.

For instance, our ADC facility in St. Louis was constructed in 2008 for clinical programs, and in 2015 we expanded our capabilities to manufacture commercial programs. Additionally, we expanded our development capabilities in 2017 to enable production of larger development batches of ADCs. We recently announced a $65 million investment in Wisconsin for the production of HPAPIs and are already assessing what might be needed beyond that. There are many other projects in the works, all of which are designed to meet our customer's future needs.

FROM DESK TO CLINIC AND ONTO COMMERCIALIZATION

Those customers include big pharma as well as small and emerging pharma and biotech firms and virtual organizations with limited development, commercialization, and manufacturing resources and capacities. Big pharma companies often come to us with early-stage projects but then have the power and resources to take programs in-house if they advance to later stages. Customers that work with CDMOs such as MilliporeSigma are variable, ranging from big pharma to small and emerging pharma and biotech firms. While the rationale for collaboration

MILLIPORESIGMA HAS PROACTIVELY IMPLEMENTED SEVERAL TECHNOLOGIES TO **MAKE SURE THAT WE ARE READY FOR CUSTOMERS WHEN THEY NEED OUR SUPPORT.**

with MilliporeSigma may be different for each, it is clear that this collaboration offers many advantages, such as being able to utilize the extensive development, commercialization, and manufacturing knowledge and resources that MilliporeSigma can provide.

What is unique about MilliporeSigma is that we have the experience and capabilities to support ADC projects from the earliest stages to clinical programs and on through commercialization, including inspection and approval readiness and ultimately commercial manufacturing. For smaller companies just starting their ADC journeys, we can be a great partner, because we understand exactly what it takes to get programs to the commercial market.

ADC Express™ was developed to help companies with ADC concepts but lack the expertise and infrastructure to go forward. This service is designed to take a customer's concept all the way to the clinic. For instance, we can help a customer determine how a clinically active antibody will behave as an ADC. Our technical teams can prepare multiple ADC constructs with the antibody using different linkers and payloads, and the customers can screen constructs to select a lead candidate, which we can then help with development and GMP activities.

For ADCs with an established production process, the MilliporeSigma team of technical experts is equipped to support the transfer of that technology to our sites, whether they have processes that initially require scale-up or that have been optimized for commercial scale.

We can also transfer processes to our facility for companies that already have a commercial program but have discovered that the existing supply chain cannot meet rising demand. We conduct process transfer and validation activities and help customers file our facility as an alternate manufacturing facility with the appropriate regulatory authorities.

MilliporeSigma provides solutions across the entire ADC supply chain – from antibody production all the way to conjugation – including the testing services that are needed along the way. Some of the other CDMOs can only perform subsets of these services, so pharma and biotech companies engaging them must adopt a multi-CDMO model that can be challenging to manage.

ANTICIPATING MORE COMMERCIAL PROGRAMS

MilliporeSigma's experience with ADCs includes more than 65 unique development projects and more than 600 development batches spanning many ADC technologies from conventional antibody projects to bispecific and antibody fragments, as well as a range of cleavable and non-cleavable linkers and many types of cytotoxic payloads.

We built upon over 12 years of experience in clinical-scale supply of ADCs, as well as commercial-scale production of linker payloads, small molecules, and bio-organics and an extensive knowledge base in biologics manufacturing to establish commercial-scale ADC manufacturing capabilities. That extensive preparation led to the approval to manufacture commercial ADC batches.

Since first offering ADC manufacturing services in 2008, MilliporeSigma has produced more than 160 GMP batches, including more than 20 commercial batches. These batches have enabled more than 30 investigational new drugs (INDs) to enter the clinic.

Ten years from now, we will be continuing our investments in ADC capabilities to ensure that we maintain the ability to meet the growing demand for development and manufacturing support across the entire spectrum with respect to the value chain and the development to commercialization cycle. MilliporeSigma is the very first CDMO with an approved commercial ADC manufacturing facility in the United States. We are excited to work on more commercial programs as the first supplier for novel ADCs and as a second or third supplier for the existing, previously approved drugs that are experiencing growing demand. P

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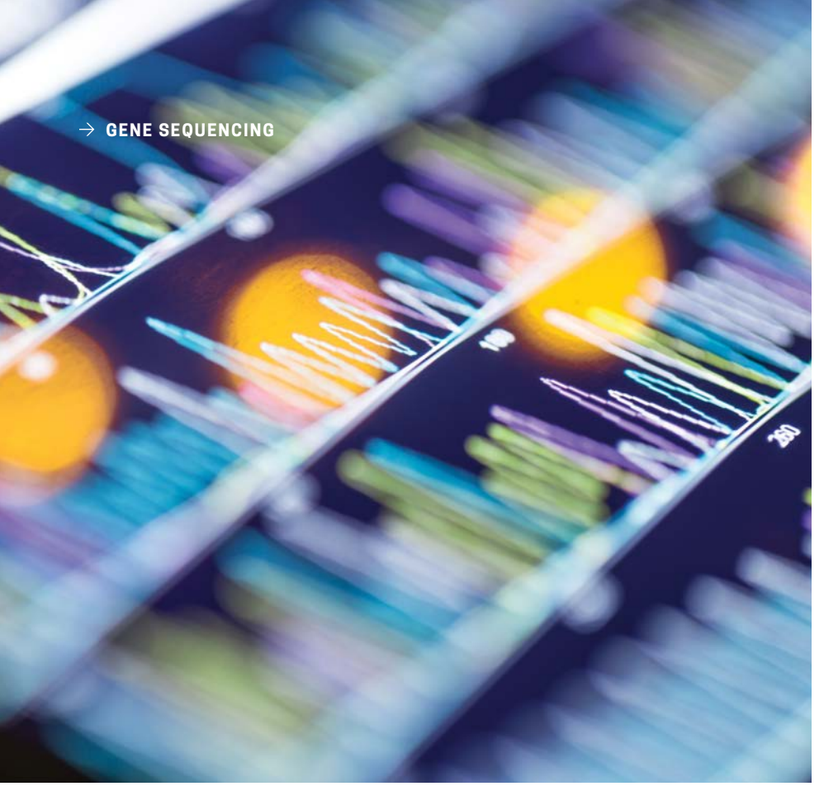

EXPANDING LABORATORY ACCESS TO GENE SEQUENCING

→ BY **GABRIELA SALDANHA,** PROMEGA CORPORATION

Genetic sequencing has traditionally required complex and expensive instruments, limiting the number of laboratories able to purchase them. With the introduction of an affordable benchtop instrument for Sanger sequencing and fragment analysis, Promega Corporation is enabling a wider range of researchers to take control of testing.

GOLD STANDARD

Genetic sequencing generally involves DNA extraction, PCR purification, and detection. Sanger sequencing is an established, widely used technique providing single-base resolution. Even with advances in next-generation sequencing (NGS), Sanger sequencing remains the gold standard; if a sequence determined using NGS requires confirmation, Sanger sequencing is performed. Similarly, Sanger sequencing proves that the desired insertion or deletion was achieved in applications of CRISPR or other gene-editing tools.

LIMITED ACCESS

Unfortunately, access to instrumentation to perform Sanger sequencing is limited, owing to the high costs and complexity of the capillary electrophoresis instruments required for this analysis. Buffers have to be prepared, the capillary must be flushed of the old polymer and the new polymer must be introduced. Instead of investing in an expensive machine and the time needed for training, most smaller labs send samples out to centralized labs.

Twenty years ago, it could take a week after a sample was sent to a central lab with Sanger sequencing capabilities to receive results; today, that time frame has been reduced to several days. However, granting researchers the ability to perform Sanger sequencing in-house presents a range of benefits. Researchers can set the run conditions of their assays and have direct control over quality during an analysis in case anything needs to be adjusted. Sometimes, the results are needed immediately, particularly with clinical case work or forensic analyses for high-profile cases. In such cases, there is also elevated concern about the chain of custody for samples, which makes sending samples out to external labs undesirable.

FROM CHEMISTRY KITS TO BENCHTOP INSTRUMENT

Promega Corporation has been offering reagent tool kits for laboratory tests in the fields of cell biology; DNA, RNA and protein analysis; drug development; human identification; and molecular diagnostics for nearly 50 years. We provide the chemistry solutions that enable gene sequencing for a host of different applications.

Examples include our PowerPlex® STR Systems used by forensic labs worldwide; GenePrint® Systems used for cell line authentication, mixed sample analysis; and other applications; and a microsatellite instability kit (MSI). We make robust amplification enzymes and understand master mixes. We offer a complex 24-multiplex system comprising more than 50 different primer combinations.

Customers who rely on this specialized chemistry expertise – and appreciate the service and support that we provide – frequently asked Promega to develop a single-base-resolution instrument that could be used with our chemistry solutions. However, this was not an easy instrument to develop – if it was, options would be on the market already.

In response, Promega had the vision of complementing our chemistry product line and offering a more complete workflow solution to our customers. To do that, we partnered with Hitachi High-Tech, which has been developing and manufacturing the larger-scale, expensive capillary electrophoresis instruments for genetic sequencing for many years. We talked with customers to better understand their needs, and then Hitachi contributed their instrument expertise and Promega brought its chemistry to the table. The end result was the Spectrum Compact CE system, a complete solution for our customers.

INTRODUCING THE SPECTRUM COMPACT CE SYSTEM

Our new compact gene sequencing system is very easy to install and use, requires only a small footprint, and provides results rapidly, making it a true personal benchtop sequencing machine. It is designed for use with existing sequencing chemistries using fluorescently labeled dideoxynucleotide triphosphate (ddATP) and 4-, 5- and 6-dye short tandem repeat (STR) kits from Promega, as well as other commercially available kits.

The consumables are pre-dispensed and designed to snap into place. There is no need to flush polymers or wash the capillary cartridge between runs. The software wizard provides a step-by-step guide to touch-screen operations including run set-up, consumables and an array usage of information, including system maintenance reminders. It is also possible to monitor run progress and view results during a run.

Many assays (at least 20 different dye set combinations) are preloaded and compatible with Sanger sequencing and fragment analysis (single-base resolution). It is also easy to make modifications to create customized run conditions. Export files (.ab1 for Sanger sequencing and .fsa for fragment analysis) are compatible with commercially available data analysis software. Promega is also developing a data analysis package called Gene MarkerHID® For Spectrum Systems. The instrument can also be connected to a separate computer on the same network so that setup can be completed in the office before going into the lab.

With on-site installation and operational training and in-depth training on the chemistry side for all assays and applications, the integrated and efficient instrument brings independence to the laboratory, placing Sanger sequencing and fragment analysis directly under the control of scientists and researchers, regardless of expertise.

BUILT-IN FLEXIBILITY

The Spectrum Compact CE system includes a barcode scanner, and all consumables used with the system have barcodes, the wizard-like workflow guides users through scanning and use of the consumables and keeps track of the number of injections performed and how many remain, the on-instrument expiration date, and warnings as the limit of uses and the expiration date approaches. Users have flexibility in how to use their consumables, which was an often-repeated request during development discussions with potential customers.

The benchtop CE system has just been launched, and Promega is focused on educating potential users about the benefits it offers and providing consumables for all application areas, including CRISPR confirmation. We are also planning features for a second version of the software based on input from customers who participated in early product evaluations. We will continue to listen to our customers with respect to their needs for different software, chemistry, or other capabilities.

DEMOCRATIZING GENETIC SEQUENCING

We are excited about the launch of the Spectrum Compact CE system after years of dedicated development efforts. Finally placing the instrument in the hands of customers so they can take full ownership of their sequencing needs gives them control and flexibility. It is easy to use and affords the opportunity to ensure chain of custody and the quality of the experiment for each sample. Promega is happy to help make capillary electrophoresis accessible to a broader customer base, thus democratizing the use of gene sequencing in a laboratory setting.

ADAPTABILITY CONTINUES TO BE KEY

Looking forward, adaptability will be essential in the testing arena. In 2020, when the COVID-19 pandemic emerged, we dropped our strategic plan and completely changed gears to support the development and implementation of diagnostics for the SARS-CoV-2 virus worldwide.

That type of agility will be required going forward. We expect a continued focus on viral research over the next several years to better prepare for the next epidemic/pandemic. With our expertise across the key fields of cell biology; DNA, RNA, and protein analysis; drug development; and molecular diagnostics in both chemistry and instrumentation, Promega is positioned to support and facilitate these critical efforts. P

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Gabriela Saldanha is a Senior Product Manager in the Sample Analysis Strategic Portfolio Management. Gabriela's career spans over 25 years in the laboratory and in product development, strategy and implementation related to nucleic acid amplification technologies, more recently leading the Spectrum Compact CE System launch.

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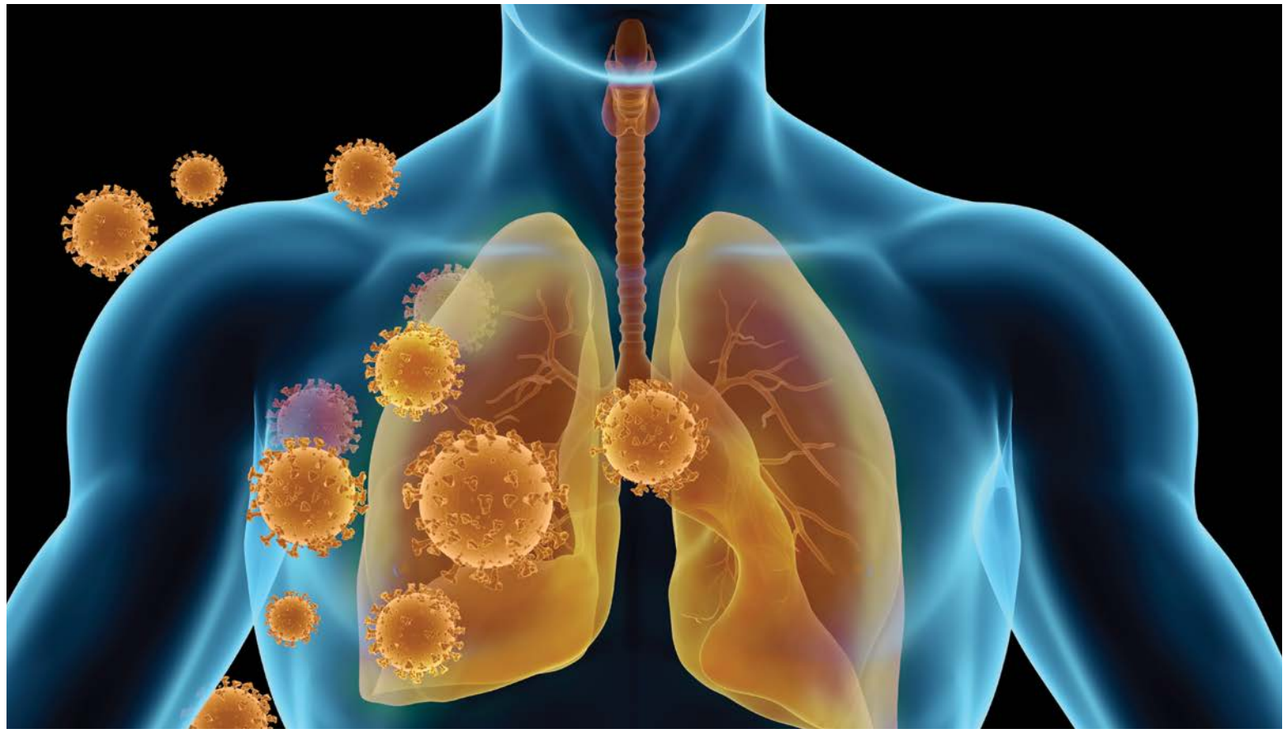
HOW AN AGILE COMPANY ADDRESSED THE PANDEMIC: MOVING FROM PSYCHIATRIC MEDICINES TO A COVID-19 THERAPEUTIC

→ BY **JONATHAN JAVITT, M.D.,** NEURORX, INC.



NeuroRx was founded to develop novel psychiatric medicines based on seminal research on the role of the NMDA receptor in psychiatric illness. However, the COVID-19 pandemic put enrollment in a phase III trial on hold. During that pause, the company pursued a potential treatment for COVID-19 based on the natural peptide VIP. VIP has demonstrated promising early results in phase II/III clinical trial for critically ill COVID-19 patients, and we hope that this drug candidate will prove to be an effective therapy for COVID-19 and other lung diseases. Simultaneously, we are excited to get back into the clinic with our game-changing treatment for bipolar disorder patients with acute suicidal ideation and behavior.

PANDEMIC CAUSES SHIFT FROM PSYCHIATRIC TO LUNG DISEASE TREATMENTS

Many people with bipolar disorder also suffer from acute suicidal ideation and behavior (ASIB). For that reason, people with bipolar disorder, particularly those with ASIB, are at particular risk if treated with traditional selective serotonin reuptake inhibitor (SSRI) antidepressants and have been excluded from clinical trials for these drugs. In addition, few pharma companies in the first two decades of the 21st century had any interest in developing new psychiatric drugs. As a result, the only treatment available for suicidal bipolar depression was electroshock (electroconvulsive) therapy (ECT).

NeuroRx was founded in 2015 to develop new therapies for psychiatric disorders based on research by Professor Daniel Javitt (my brother), which focused on the NMDA receptor in the brain. This receptor plays a role in regulating human thought processes in general and depression and suicidality more specifically. Our lead treatment regimen is NRX-100™/NRX-101™, the first sequential drug treatment for bipolar depression in patients with ASIB.

NRX-100™/NRX-101™ has been awarded breakthrough therapy designation from the U.S. FDA, and NeuroRx was actively enrolling patients in a phase III clinical trial when COVID-19 emerged in March 2020. Out of concern for patient safety, this clinical study was temporarily halted.

In the interim, investors in NeuroRx, the Global Emerging Markets (GEM) Fund, had proposed using the Swiss company Relief Therapeutics, which they had acquired, as a vehicle for taking NeuroRx public. GEM thought it had sold off all of Relief's assets, but one remained – VIP. This drug was originally discovered by the late Professor Sami Said of Stonybrook University, who found that it showed promise as a treatment for acute respiratory distress syndrome (ARDS). VIP had also been studied by Mondo Biotech (a precursor to Relief) and Biogen as a treatment for various lung diseases (e.g., sarcoid, pulmonary hypertension, pulmonary fibrosis), but Said's original work on ARDS was never pursued.

That changed when Yves Sagot at Relief pointed out to NeuroRx that COVID-19 lung injury was believed similar to lung injury in ARDS, and thus VIP could be relevant for the treatment of patients with SARS-CoV-2 infections. With the phase III NRX-100™/NRX-101™ trial on hold, we switched gears and focused on VIP.

STRAIGHT INTO THE CLINIC WITH VIP

Dr. Said's phase I study was the last time VIP was used intravenously. However, Biogen had established an extensive toxicology file for both intravenous and inhaled VIP, including a six-month study of the toxicity of inhaled VIP in non-human primates. No lethal dose of VIP was ever identified and, as a naturally occurring human peptide, VIP has a remarkable safety profile.

We satisfied the FDA's safety questions and quickly received approval from the agency for a phase II/III clinical trial of Aviptadil (RLF-100™), a synthetic form of human VIP, for the treatment of critical COVID-19 with respiratory failure, with the agency granting RLF-100™ Fast Track Designation. NeuroRx was also permitted to produce aviptadil in a formulating 503B pharmacy instead of a traditional GMP manufacturer, making it possible to start treating patients within ten weeks rather than 10 months.

The first patients were treated on May 15, and within two weeks we were receiving reports from different investigator sites about the rapid recovery of patients from respiratory failure in days. Nine patients out of the first 21 who were treated not only experienced rapid recovery, but also rapid clearing of chest X-rays. After examining data on the first 30 patients, the Data Monitoring Committee identified no safety concerns. An open-label study of patients with COVID-19 and severe comorbidity at Houston Methodist Hospital detected a statistically significant difference in recovery from respiratory failure in critical COVID-19 in those treated with Aviptadil versus a placebo.

We are eagerly awaiting completion of our double-blind study. We are hopeful that RLF-100™ can be applied as a broad treatment, though we initially focused on patients who were in critical condition without other options – there is still much to learn about the effects of the drug. The FDA has already granted NeuroRx permission to start a phase II/III trial for inhaled use in patients who have slightly less severe symptoms, and we feel it is appropriate to make this drug available to patients under the FDA's Expanded Access (EA) program. We have also asked the agency to turn the EA approval into an Emergency Use Authorization so that this potentially lifesaving drug can be given to people with a high likelihood of dying.

HANDLING THE CYTOKINE STORM

The initial positive results of Aviptadil in COVID-19 patients were difficult to explain with the view of VIP as a potent anti-cytokine agent alone. It turns out that the drug works via several pathways.

The primary cause of death in COVID-19 patients is acute respiratory failure. Some investigators, particularly those

associated with the development of anti-cytokine drugs, attributed this to cytokine storm, or the massive release of inflammatory cytokines as viral particles infect and then cause rupture of pulmonary epithelium cells.[1] However, the initial pathology of COVID-19 respiratory failure is increasingly attributed to alveolar collapse – that is, collapse of the air sacs that comprise the respiratory surface of the lung. That's what causes the "ground glass" signature of COVID-19 on X-ray. The alveolae of the lung are a bit like soap bubbles: the surface tension of the detergent, in the case the surfactant made in the lung, holds them open. Without the surfactant, the alveola collapse, and the lung cannot oxygenate the blood, which is called "respiratory failure."

All of the surfactant in the lung is made by a small population of cells, called alveolar type II (ATII) cells. The SARS-CoV-2 virus binds only to the ATII cells in the lung, because its spike protein recognizes the angiotensin-converting enzyme 2 (ACE2) on the surface of the ATII cell.

When the SARS-CoV-2 virus binds to the ACE2 receptors of ATII cells, the virus is able to enter the cell and take over its metabolism. Surfactant production is shut down and cytokines are synthesized. The virus then replicates and kills the cell, which ruptures and spreads the virus particles elsewhere in the lung where they cause more damage. This behavior only seems to occur in humans, because the surfactant-producing cells of other mammals lack the ACE2 receptors.

AS A RESULT, IF PROVEN EFFECTIVE AS A TREATMENT FOR COVID-19, **THERE IS A HUGE OPPORTUNITY TO READILY SCALE THE MANUFACTURE OF RLF-100™ AND MAKE IT BROADLY AVAILABLE.**

VIP has been protecting the lungs of mammals since the class emerged, and in fact, the amino acid sequences of mouse and human VIP are identical, suggesting that native VIP is evolutionarily optimized. In humans, VIP protects from smoke inhalation and inhaled vomit. Dr. Said published more than 300 papers about the role of VIP in protecting the lungs. Like SARS-CoV-2, VIP also binds to the ACE2 receptors of ATII cells in the lung, protecting them and the surrounding pulmonary epithelium by blocking cytokines, preventing apoptosis, and upregulating the production of surfactant.[2]

THE IDEAL THERAPEUTIC AGAINST SARS-COV-2

Further evidence for the importance of VIP in fighting COVID-19 infections was developed by researchers at the Oswaldo Cruz Institute in Rio de Janeiro. They reported that VIP blocks the replication of SARS-CoV-2 in human cell lines, specifically the Calu-3 cell line, which is essentially a human ATII cell. The Brazilian researchers also found that of 25 patients with critical COVID-19, the 13 who died had half the blood level of VIP as did the 12 who lived.

These findings coupled with our results suggest that VIP is likely to have effects in many places within the body. This COVID-19 therapeutic not only blocks cytokine production; it also blocks replication of the SARS virus itself. In addition, it increases surfactant production through well-understood genetic pathways. Furthermore, it blocks cytopathy (viral killing) of the type II pneumocyte.

Indeed, much remains to investigate. Many peptides are taken for granted (insulin is a good example); we have only a basic understanding of their mechanisms of action. VIP is no exception. We have learned that, as a treatment for COVID-19, it hits four relevant targets, but we may only be scratching the surface. Our hope is that researchers will return to the laboratory and use more sophisticated genomic and proteomic techniques to elucidate all of the functionality of VIP.

ADDITIONAL PROMISING RESULTS

In mid-October, top-line results from 45 patients assessed in the open-label prospective study where 21 patients were admitted to an ICU with critical COVID-19 and respiratory failure were treated with RLF-100™ and compared to 24 control patients treated in the same setting. All patients had severe comorbidities that rendered them ineligible for the ongoing randomized controlled phase IIb/III trial being conducted to ascertain the safety and efficacy of RLF-100™, and all patients were deteriorating despite treatment with approved therapies for COVID-19. The patients included in this study were representative of those who are too ill to be included in the clinical trials of any known treatment for COVID-19.

Overall, 81% of RLF-100™–treated patients survived beyond 60 days, compared with 17% of control patients. Patients treated with RLF-100™ demonstrated a ninefold increased probability of survival and recovery from respiratory failure, with a high degree of statistical significance. Importantly, the majority of these patients returned safely to their families

The results suggest that there may be substantial hope to mitigate the attack of the coronavirus on the delicate cells that line the lung with a natural peptide. While the number of patients that were treated at Houston Methodist Hospital is modest, the initial results in our nationwide expanded access program suggest similarly encouraging survival with RLF-100™. We look forward to the topline results from the randomized, placebo-controlled phase IIb/III study before the end of 2020.

READY SCALABILITY

The production of peptides like VIP via solid-based peptide synthesis costs approximately $6,000 a gram. Using yeast fermentation, however, the price is significantly lower. Synthetic insulin, for instance, currently costs about $200/gram, and insulin is twice as large a peptide as VIP.

As a result, if proven effective as a treatment for COVID-19, there is a huge opportunity to readily scale the manufacture of RLF-100™ and make it broadly available. Owing to its lack of toxicity and low cost of manufacture compared with proprietary biologics, VIP may be uniquely attractive to those focused on global countermeasures against COVID-19. VIP may also be the only candidate in human trials that could be produced at a cost structure that is compatible with the needs of the developing world.

VIP HAS BEEN PROTECTING THE LUNGS OF MAMMALS SINCE THE CLASS EMERGED, AND **IN FACT, THE AMINO ACID SEQUENCES OF MOUSE AND HUMAN VIP ARE IDENTICAL, SUGGESTING THAT NATIVE VIP IS EVOLUTIONARILY OPTIMIZED.**

TAKING NRX-100™/NRX-101™ BACK TO THE CLINIC

As the pandemic starts to come under control, we are hoping to get back into the clinic with our psychiatry portfolio before the end of 2020. NRX-100™/NRX-101™ was developed based on research conducted by Dan Javitt in combination with studies performed by Rob Berman at Yale.

Dan discovered that phencyclidine (i.e., angel dust), which causes psychosis, binds to the NMDA receptor and is critical to memory function. NMDA directly regulates a calcium ion channel that controls the rate of ideation (formation of new ideas) in the brain. Berman found that ketamine, which reversibly binds to the same receptor, had an unexpected antidepressant effect.[4]

Ketamine is a challenging drug because it is highly hallucinogenic, neurotoxic, and highly addictive – and it is difficult to control its binding to NMDA. Our goal at NeuroRx was to find a better option. That is when we identified D-cycloserine, an old tuberculosis drug that had previously been shown to be a potent antidepressant. Cycloserine is an NMDA inhibitor, but it has psychomimetic side effects. Treatment with D-cycloserine, therefore, requires administration with an antipsychotic to counteract these unwanted side effects.

The 5-HT2a receptor is a G protein–coupled receptor and a member of the serotonin family known for its role in mediating certain antipsychotic effects. Lurasidone is a 5-HT2a antagonist that is currently approved as an antipsychotic and for use in bipolar depression. Laboratory studies have shown that Lurasidone and other 5-HT2a antagonists have an unexpected synergistic effect with D-cycloserine, potentially enhancing the antidepressant effect while minimizing the potential psychomimetic (hallucinations) side effects. A phase II human study has shown results consistent with this finding.

Dan realized that many antidepressants cause suicidal thoughts because they cause akathisia in 10–15% of patients. He was the first to discover the synergy between NMDA and 5-HT2a-blocking drugs. Ketamine, a potent NMDA blocker, stabilizes these acutely suicidal patients in hours.

NRX-101™'s proprietary combination of D-cycloserine and Lurasidone is designed to be administered orally, daily for approximately six weeks following an initial, single infusion of ketamine (NRX-100™). We believe that this regimen may offer an oral, outpatient treatment with the potential to significantly extend ketamine's antidepressant/anti-suicidal effect, which could be game-changing.

VERSATILE TEAM

Our experience during the COVID-19 pandemic, in which we applied our same core skill set proven in development of a psychiatric drug to focus on a therapeutic against COVID-19, demonstrates that we at NeuroRx have built an incredibly versatile team. Robert Besthof started out in psychiatry drug development, first at Lilly and then at Pfizer. I met him when he was asked to lead Pfizer Ophthalmology. He went on to lead Pfizer's entire Neuroscience and Pain Division. Ellis Wilson, who leads our clinical development team, spent years in psychiatry drug development before leading COVID-19 studies for PPD. All those involved in the company were able to get up to speed on a new program quickly. They have demonstrated an appetite for taking on hopeless diseases, and their chief rewarded lies in benefitting patients.

Our corporate motto is taken from a first century philosopher and rabbi, who famously said: "The day is short, the work is endless, the wages are meager, the workers are inadequate, and the Master of the House is knocking on the door." P

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Dr. Javitt has played leadership roles in seven successful healthcare IT and biopharma startups with public exits. He has additionally led drug-development engagements for Merck, Allergan, Pharmacia, Novartis, and Pfizer. He was appointed to healthcare leadership roles under Presidents Reagan, George H.W. Bush, Clinton, and George W. Bush. In the latter role, he was commissioned to lead the White House policy for universal adoption of Health IT and establishment of the Office of the National Coordinator. He is a graduate of Princeton University, Cornell University Medical College, Harvard School of Public Health, the Wills Eye Hospital, and Johns Hopkins Medical School. Dr. Javitt has published more than 200 scientific works in the areas of health outcomes and pharmacoeconomics that have been cited by more than 16,000 people.

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IN CONVERSATION

COMBATING CANCER AND OTHER DISEASES WITH SUPERCHARGED NATURAL KILLER T CELLS MOBILIZED BY A NOVEL FORMULATION OF DEXAMETHASONE

→ WITH **THERESA DEISHER, Ph.D,** AVM BIOTECHNOLOGY

Natural killer T cells (NKTs) bridge the innate and adaptive immune systems and are increasingly being studied to treat cancer and microbial diseases. AVM Biotechnology is exploring its novel and proprietary formulation of dexamethasone to supercharge NKTs for a range of indications, including as a potential first choice for terminal, no-option cancer.

Theresa Deisher, Ph.D., CEO and Founder of AVM Biotechnology, spoke with *Pharma's Almanac* Managing Editor Emilie Branch.

AVM Biotechnology (AVM) was founded in 2008 to develop drugs to optimize stem cell performance in the human body.

Through years of experience working in the industry, it became widely understood that, if the body is not suitably prepared for regenerative treatment, cell therapy will prove ineffective. Traditional preparatory treatments such as chemotherapy also have high levels of toxicity. AVM set out to discover and understand how the body controls stem cell movement, as well as understanding how stem cells interact with controlling organs. In essence, AVM aimed to optimize regenerative medicine.

In 2015, following the loss of the founder's son Henry to Burkitt's lymphoma at the age of 14, the company began investigating pediatric cancer. Pediatric cancer patients generally do not have access to the latest biologics that have proven effective in many patients, and thus standard cancer treatment options like chemotherapy, with its high toxicity profile, continue to be the industry standard, with mixed results. This loss fueled the company-wide mission to deliver underserved populations with therapeutics that have a favorable risk-to-benefit ratio. Through its years of research and development, AVM has evolved and is currently positioned to meet its goal of providing hope to patients for whom all other treatments have failed through its lead product, AVM0703 – named in tribute to the date Henry succumbed to this illness.

AVM0703

AVM0703 is a novel and proprietary formulation of dexamethasone that is formulated to be provided at a high dose. AVM's research shows that the AVM high dose of dexamethasone mobilizes the body's natural, supercharged immune cells that are 10 times more activated than ordinary immune cells. The AVM formulation lacks the excipients that could be toxic if a high dose of currently available dexamethasone is administered. This formulation is designed to eliminate many of the stabilizing agents while maintaining an impressively long shelf life of at least 36 months.

AVM0703 is administered via a one-hour IV infusion, with a retreatment option, if needed, after 28 days. Having demonstrated activity in mouse models against aggressive, impossible-to-cure cancer models, AVM also showed that, when used as an adjunctive therapy, the dosage of common toxic chemotherapies can be reduced. Preclinical animal studies have shown AVM0703 to spare platelets, red blood cells, and stem cells, which chemotherapies are known to damage – and thus could reduce the need for blood transfusions. This may also be a cancer treatment option for people who do not want blood transfusions. AVM0703 has received FDA permission to proceed with clinical trials for the treatment of lymphoid malignancies, particularly relapsed, refractory non-Hodgkin's lymphoma, and will begin enrolling patients before the end of 2020. The trial's adaptive design will enable AVM to move through clinical trials as rapidly and as safely possible.

AVM0703 did not begin as a cancer-killing initiative. It was originally developed to prepare patients to receive regenerative medicine stem cell therapy, but these novel NKT immune cells entering the bloodstream were found during preclinical research as higher doses were examined. The novel NKT cells are programmed by nature to kill abnormal cells like cancer and virally infected cells. This epiphanic discovery facilitated a pivot away from regenerative medicine to focus on relapsed refractory and "no-option" cancer patients.

Additional Therapeutic Applications

The mechanism of action that enables AVM0703 to work against aggressive cancers may also prove effective against COVID-19 and other microbial diseases. To further that research, AVM has received permission to proceed with a clinical trial for the treatment of acute respiratory distress syndrome (ARDS) mediated by COVID-19 or influenza. The NKT cells that are triggered by AVM0703 are programmed by nature to kill abnormal cells. While AVM believed that HIV would be the first viral application, the COVID-19 pandemic presented a new opportunity to leverage AVM0703 in the fight to eliminate SARS-CoV-2–infected cells in severely ill COVID-19 patients for whom all other treatments have failed. AVM is also exploring AVM0703 as a therapeutic for type 1 diabetes with encouraging results and additional applications.

For patients who cannot enroll in the clinical trials, AVM provides AVM0703 through its compassionate use program (CUP), enabling physicians to treat patients that have exhausted other treatment options or do not meet the criteria to enroll in a clinical trial.

The AVM Team and Future Outlook

The team is comprised predominantly of female scientists and researchers who have come from all over the world since its founding – including Uganda, Togo, the Philippines, Vietnam, Japan, France, Germany, Pakistan, and India, with other employees from various regions in the United States. This diversity is paramount in achieving the company's goals, as leveraging different perspectives to overcome challenges is what has made AVM Biotechnology successful. They are thrilled to have assembled a team of strong, skillful professionals including COO Janet Rea, with over 35 years of experience in manufacturing, regulatory, quality, supply chain, and clinical trials. However, this strength is also a weakness – women-founded biotech companies are often faced with disproportionate challenges compared with more traditionally male-led biotech companies, who receive venture capital funds at a sevenfold higher rate. The company is hopeful that AVM's success to date and the success that they hope to achieve in clinical trials and eventual commercial launch will spur change in the way venture capital firms pursue opportunities with female-led companies.

The goal is to bring AVM0703 to the U.S. market within the next three years and to partner for worldwide development. AVM Biotechnology can envision an Initial Public Offering (IPO) within the next 3–5 years. AVM is an exciting company with an even more exciting drug and are confident that once they can prove safety and efficacy with AVM0703, they will also be able to go to market with other products that are currently in development.

More About AVM Biotechnology

AVM's team of scientists are wholly dedicated to changing what cancer, autoimmunity, and chronic infectious disease diagnoses mean to patients and their families. The company's mission is fueled by its passion to deliver drugs that work rapidly, safely, effectively, and affordably – treating life-threatening conditions when all other treatment options have been exhausted and seemingly failed. They serve overlooked populations – pediatric and adolescents, frail and elderly, and those who have failed all other options. AVM's products improve clinical outcomes without additional suffering in the form of side effects, because they believe that treatments should never be worse than diseases themselves. P

ABOUT THE PANELIST

Theresa Deisher, Ph.D.
Chief Executive Officer and Founder, AVM Biotechnology

Theresa A. Deisher, Ph.D., graduated from Stanford University School of Medicine with a doctoral degree in molecular and cellular physiology. She has 47 issued patents and four discoveries in clinical trials. Dr. Deisher has extensive scientific and management experience in the commercial biotechnology field at Genentech, Repligen, ZymoGenetics, Immunex, and Amgen. Since 2008, she has led a team of innovative scientists at AVM Biotechnology who have developed AVM0703, a drug with a novel mechanism of action that mobilizes the body's own natural immune cells to fight blood cancers, solid tumors, and infectious disease such as COVID-19 and influenza-mediated ARDS.

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NATIONALISM AND THE PHARMACEUTICAL SUPPLY CHAIN

→ BY **HAIG ARMAGHANIAN,** HAIG BARRETT

The COVID-19 era has, once again, positioned the pharmaceutical industry center stage before a global audience. On the one hand, the industry's awe-inspiring vaccine development work positions it to play a heroic role in helping to bring closure to these trying times. On the other hand, all stakeholders — the pharmaceutical industry, patients, the medical community, regulators, and governments — are at a crossroads. The pharmaceutical industry has become extremely globalized over the past three decades, with intricate supply chains winding worldwide. However, there is a growing cry from multiple nations, certainly including the United States, to bring pharmaceutical manufacturing "home."

For the past 75 years, the post-World War II global order has embraced the idea that interconnected trading relationships help preserve peace. After all, so the philosophy goes, nations are much less likely to attack and attempt to destroy trading partners on which they rely for their own prosperity.

Although nationalism has been on the rise for a handful of years now, the pandemic added rocket fuel to already simmering fires. The pharmaceutical industry is faced with the possible disruption of the postwar order along with key questions: What has the industry gotten right? Which areas of the pharmaceutical supply chain need to be reexamined and perhaps restructured?

Given that a full discussion of the global pharmaceutical supply chain is too ambitious for one article, this piece discusses supply chain issues primarily from a U.S. perspective; however, many U.S. supply chain concerns apply to other markets.

THE CURRENT PHARMACEUTICAL SUPPLY CHAIN

While not perfect, there is a reasonable picture of the finished dosage form supply chain. However, take just one step back in the supply chain to active pharmaceutical ingredients (APIs), and the picture gets a lot murkier. Take additional steps back to consider the supply chain of intermediates, key starting materials, specialty chemicals, excipients, packaging materials, drug administration components, and other materials, and the picture is utterly opaque. To begin addressing any problems in the pharmaceutical supply chain, we need a more accurate picture.

For years, many professionals in both the pharmaceutical industry and the press have cited that 80% of APIs come from China. Today, we do not know the exact API volumes coming from specific countries or facilities. However, we do know the number of FDA-approved facilities around the world. Globally, 28% of FDA-approved API manufacturing facilities are in the United States, 26% in the EU, 18% in India, 13% in China, 2% in Canada, and 13% in the rest of the world.[1] Although it is possible that 13% of API manufacturing facilities in China are generating large volumes of API, it is almost certainly untrue that these facilities are producing 80% of the total API volume used for U.S. market drugs.

Portions of the CARES Act, passed in March by the U.S. Congress, seek to address this lack of clarity. Under Section 3112(e), drugmakers will be required to report manufacturing volume data to the FDA, including the "amount of each drug … that was manufactured, prepared, propagated, compounded, or processed … for commercial distribution."

When enacted, these data will help the industry and regulators understand in which markets and in what volume API is being manufactured; nonetheless, the question of the U.S. pharmaceutical supply chain's security will be far from clear, given the assortment of materials required for API production.

"Players within the specialty and fine chemical industry are providing the starting materials, catalysts, and other materials needed for the drug industry to manufacture APIs," stated John DiLoreto, Executive Director of the Bulk Pharmaceuticals Task Force. "In terms of key starting materials, sometimes you have to source from where the starting materials actually are. On the specialty chemicals side of the equation, while I have not done a thorough analysis, specialty chemical industry suppliers are quite concentrated in China."

While the availability of API and the products needed to produce them are critical, the pharmaceutical supply chain's interconnectedness manifests in other, often unexpected ways. "When Hurricane Maria hit Puerto Rico in 2017, both the FDA and I were initially concerned about disruption in manufacturing on the island radiating out and causing widespread supply chain problems," commented Gil Roth, president of Pharma and Biopharma Outsourcing Association (PBOA). "But I did not anticipate the types of concerns my members actually had. For example, a CDMO manufacturer in the U.S. ships some product to a customer's warehouse in Puerto Rico for labeling, and then the product is shipped to customers worldwide. After the hurricane, there was no warehouse to ship to."

AS COUNTRIES WORLDWIDE PULL INWARD, **HOW CAN THE U.S. PHARMACEUTICAL INDUSTRY STRENGTHEN ITS EXTREMELY INTERCONNECTED SUPPLY CHAINS?**

Roth continued, "Another manufacturer used bioprocessing components sourced from Puerto Rico, and, as far as it knew, there was no other company importing this product to the U.S. – unavailability of this product would cause the production of its biologic products to cease. Ultimately, the FDA qualified an EU-based site to fill the need, but this was another illustration of how unanticipated problems can arise and how interconnected the supply chain is. It helps to think of it as nodes, rather than links."

Although progress in pharmaceutical supply chain understanding is being made, given the complexity of products and the highly global nature of the supply chain, a complete picture of the supply chain is not likely and arguably not practically possible.

U.S. PHARMACEUTICAL SUPPLY CHAIN — HOW DID WE GET HERE?

Why is the pharmaceutical supply chain so complex and globally distributed? First, it is important to understand that there are many pharmaceutical manufacturing facilities in the United States; as of 2019, 1,193 plants were producing FDA-approved products in the United States under GMP regulations, including API manufacturing plants.[2]

FOLLOW THE MONEY

Here is where things get interesting. The structure of the U.S. market has changed a great deal in a short period. As recently as 2005, 40% of prescriptions were for brand-name drugs, and about 50% were for unbranded generics. In 2019, only 10% of prescriptions were for brand-name drugs, and 86% were for unbranded generics.[3]

However, in 2019, brand-name drugs accounted for 80% of the total revenue spent on prescribed medicines in the United States – the remaining 20% was for branded and unbranded generics.[4]

Branded pharmaceuticals under patent protection are, in large part, sheltered from unforeseen pricing volatility. By contrast, generics very much contend with market pressures forcing prices downward. These pricing pressures often lead to pharmaceutical companies seeking lower-cost materials and manufacturing, opening the door to potential quality issues that can too often result in drug shortages.

"For a very large portion of the pharmaceutical industry, the U.S. public demands rock-solid supply chain security and high quality, and, at the same time, lower and lower prices," Roth shared. "This is not a sustainable approach. Ultimately, there are tradeoffs, and we need to have that conversation as an industry and as a nation." He noted that CDMOs work to provide their customers with high-quality manufacture of products but are outside the price-setting area. "Drug pricing, as I often tell Congressional staff, is literally above our pay grade," Roth remarked.

Cost control and pursuit of new opportunities are major factors that shaped the way the drug supply chain has developed over time. In the late 1990s and early 2000s, the industry started building and expanding manufacturing in growing markets. "Market growth in most developed, mature pharmaceutical markets like the United States, Canada, and Europe had flattened, but there was rapidly growing opportunity to serve the therapeutic needs of patients in China, India, and other rapidly growing markets," noted Sam Ricchezza, president of North American Operations at Bora Pharmaceuticals. "The industry started placing on-market plants to serve emerging market opportunities and to manufacture for established markets at a much lower cost"

A great deal of pharmaceutical manufacturing has moved to China and India for other reasons. "The industry didn't necessarily intend for a lot of pharmaceutical manufacturing to end up in these markets, but that's where the opportunities arose," shared DiLoreto. "The Chinese were quite effective at creating a business environment to attract pharmaceutical manufacturing. It was a dynamic similar to what state-level or regional economic development groups in the U.S. do."

It is nearly certain that the market changes that have evolved over the past 20 years cannot and will not change overnight, despite current political and popular pressures. "Due to regulatory restrictions and variances among different regulatory bodies, it's not easy to move pharmaceutical manufacturing around like you can for a computer chip or an auto part. Whatever supply sourcing changes take place in the market will take time to gain the necessary regulatory approvals," commented Ricchezza.

A MORE RESILIENT PHARMACEUTICAL SUPPLY CHAIN

Ultimately, every nation's pharmaceutical supply chain must be strong and resilient enough to safeguard the health and well-being of its people. So far, despite the challenges of the COVID-19 pandemic, the U.S. pharmaceutical supply chain (along with most advanced nations' supply chains) has proven to be strong and resilient. Regardless, there is room for improvement.

"In the early months of the pandemic, I regularly canvassed our members to see whether they were experiencing any shortages," shared Roth. "Most PBOA members operate in the U.S. and receive products from suppliers around the world, but not a single member company reported pharmaceutical ingredient shortages or anything else on the value side of the supply chain. Some were experiencing issues with consumables like PPE, but those shortages were hardly restricted to the CDMO space."

While the industry's supply chain has performed fairly well so far, the pandemic and rising nationalism have brought known vulnerabilities to the forefront. Perhaps a worldwide lockdown has encouraged the industry, regulators, and legislatures to consider scenarios previously viewed unlikely more seriously.

REDUNDANCY AND AGILE RESPONSE

While supply chain redundancy is simply good business, the pandemic has spurred a reexamination of the issue. Although redundancy is needed wherever possible, more than anything, the industry and regulators must be better positioned to manage the unforeseen swiftly.

"A colleague received approval for his generic drug in the early months of the pandemic," said Roth. "However, his API supplier was in India, and it was under lockdown. Fortunately, he had a second API supplier. Unfortunately, it was in Italy – also under lockdown. You can have a well-constructed, multicontinental redundant supply chain plan that still ends up facing problems. And there's no guarantee that if he would have had a supplier in the U.S., that site would have been operational."

DESPITE THE CHALLENGES OF THE COVID-19 PANDEMIC, THE U.S. PHARMACEUTICAL SUPPLY CHAIN (ALONG WITH MOST ADVANCED NATIONS' SUPPLY CHAINS) **HAS PROVEN TO BE STRONG AND RESILIENT. REGARDLESS,THERE IS ROOM FOR IMPROVEMENT.**

Regulatory constructs enabling agility could be a large part of the solution. "We have discussed with both Congress and the FDA that CDMOs have the ability to be backup suppliers. CDMOs could be prequalified with a streamlined tech transfer process in the case of a license holder–related shortage," shared Roth. "From a dosage form perspective, this approach would involve a streamlined way of either getting a product back on the market quickly or completely avoiding a shortage. This could also be part of a reshoring or manufacturing agility concept."

Global regulatory harmonization could also go a long way toward helping foster agility. "One of the biggest hurdles is there's not general harmonization in regulatory standards around the world," stated Ricchezza. "Increased harmonization would alleviate drug quality and safety concerns and would help us move processes around the world more easily. This would help us avoid drug shortages caused by both quality breaches and unforeseen events, like the pandemic."

BUFFER STOCKS, ESSENTIAL MEDICINES, AND THE NATIONAL STOCKPILE

For decades, manufacturers worked to reduce costs by applying as much "just-in-time" inventory control as possible. However, given the pandemic, just-in-time manufacturing has evolved into "just-in-case" manufacturing, reflecting the reality that highly efficient processes and inventory control are useless if the conditions that the efficient processes are designed for no longer exist.

"Pharmaceutical companies are looking at securing their drug supplies against potential shortages, including increasing their safety stocks," commented Ricchezza. "In order to mitigate the risks of drug shortages for critical drugs, companies have to develop better supply chain risk management and business continuity strategies by either developing or strengthening supplier relationships to reduce reliance on sole sourcing for their components or products. Many companies have taken proactive steps to either mitigate the potential for drug shortages or to be able to respond to unforeseen future events."

Moreover, a Trump administration executive order issued on August 6, 2020, mandated that the FDA create a list of essential medicines, then assure domestic production of those medications.

With the stated purpose of building the national stockpile and securing domestic manufacturing of essential medicines, Phlow, a brand-new corporation founded in January 2020, has been awarded as much as $812 million in grants and contracts from the Biomedical Advanced Research and Development Authority (BARDA), which is part of the U.S. Department of Health and Human Services.[5] Phlow's website states that it is "dedicated to manufacturing and securing our nation's most essential medicines, 100% in the U.S."

It is unclear exactly how Phlow will manufacture the therapeutics needed to fulfill its contracts. Perhaps it plans to build manufacturing facilities or possibly rely on a network of manufacturing partners for the long term. What is clear is that AMPAC Fine Chemicals, owned by South Korean conglomerate SK Holdings, will play a key role in API manufacturing at its Petersburg, Virginia facility. Additionally, Civica Rx, another Phlow partner, plans to build a finished dose manufacturing facility adjacent to the Petersburg AMPAC plant.[6]

PUBLIC–PRIVATE PARTNERSHIPS AND GOVERNMENT-CREATED MANUFACTURING INCENTIVES

Plenty of eyebrows have been raised over the generous funding of Phlow, a company new to the pharmaceutical industry, along with the loans granted to Eastman Kodak to manufacture pharmaceutical API for the first time in its history. It is important to note that the government loans to Eastman Kodak were suspended after the deal began experiencing intense scrutiny.[7] However, it appears as if the company plans to move forward with their API manufacturing plans with or without government backing.[8]

Despite these questionable endeavors, the private sector and the federal government clearly will need to work together more closely than ever to ensure the resiliency of the U.S. pharmaceutical supply chain. Mandates are unlikely to be embraced by the pharmaceutical industry or to be effective, but tax credits, long-term contracts, and other incentives to reshore production required for national security and supply chain resilience could be quite effective.

CLOSING THOUGHTS

The pharmaceutical industry, citizens, and global governments have much to consider. The pandemic has undoubtedly presented challenges and scenarios that most in the industry have never fully considered – at least not seriously.

Nonetheless, if a global pandemic can deliver good news, perhaps it is that the international pharmaceutical community will be forced to work in tandem to improve the security and agility of its supply chains. Virtually every country is pulling inward and determining how it can better secure its own pharmaceutical supply chain, but no country, including the United States, can operate in isolation. In an extremely globalized industry with production and raw materials spread across the planet, it will be simply impossible for any one country to operate alone.

Ricchezza gets the final word with his profound comment: "Any one country will not solve the security of the pharmaceutical supply chain. Improving patient health is a worldwide objective, and we need to solve it together." P

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With over 25 years of experience, **Haig** has accumulated a wealth of knowledge and experience in global business leadership and strategic facilitation and planning. Over the last 15 years, Haig has built Haig Barrett into a leading consulting firm with clients ranging from chemicals, automotive, energy, pharmaceutical and biotech sectors. Prior to founding Haig Barrett, Haig has led divisions for leading global Fortune 50 corporations including Rio Tinto. Haig graduated with a B.Sc. Honors in chemical engineering from Surrey University, England.

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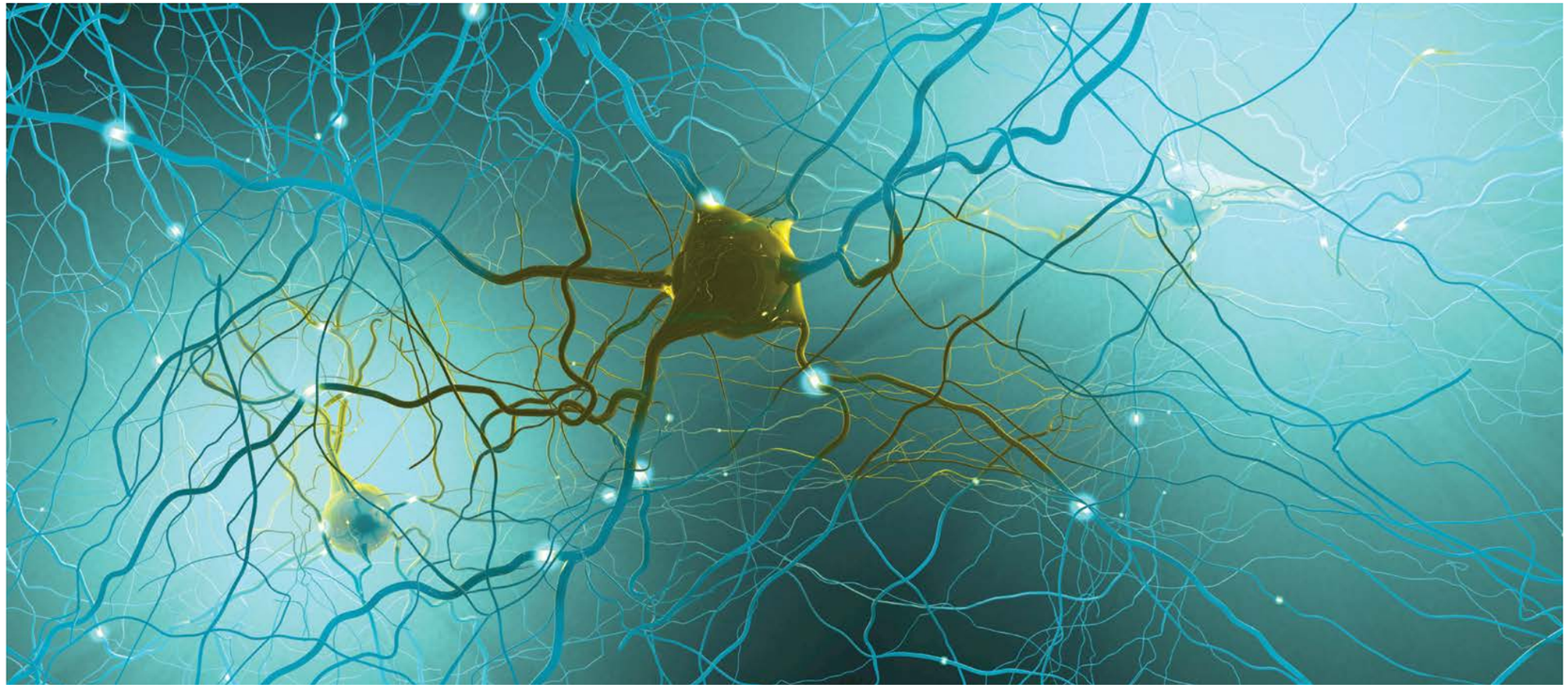
CHANGING THE PARADIGM OF STEM CELL TECHNOLOGY

→ BY **SANDY SOLMON,** CELAVIE BIOSCIENCES



Novel approaches to the treatment of neurodegenerative diseases that can address the multifaceted underlying mechanisms of disease are needed. Allogeneic, undifferentiated pluripotent stem cells developed by Celavie Biosciences react to the microenvironment into which they are transplanted, multiply and differentiate according to the nature and severity of the disorder, and repair structures and restore function.

CURRENT UNMET NEED

Neurodegenerative diseases include a variety of disorders characterized by progressive deterioration of the function of the central or peripheral nervous systems. Alzheimer's and Parkinson's diseases are two widely known examples. According to the World Health Organization, 7.1% of the global burden of disease stems from central nervous system neurological disorders and cerebrovascular diseases.

More than 6 million people worldwide live with Parkinson's disease (PD),[1] and the risk of developing this disorder is approximately 1% at age 60.[2] The cause is unknown, and there is no cure at this time. Huntington's disease is most common in populations of European descent and affects 25,000 to 30,000 individuals in the United States.[3]

Spinocerebellar ataxias (SCAs) include disorders associated with atrophy of the cerebellum and the spinal cord and involve progressive, symmetrical, midline, and limb ataxia, with characteristic loss of accuracy (dysmetria), rhythm (dysdiadochokinesis), and speed of movement, affecting eye movements, speech and swallowing, hand and foot coordination, station, and gait.[4]

Epilepsy is a central nervous system disorder in which nerve cell activity in the brain becomes disrupted, causing seizures. More than 23 million individuals worldwide suffer from epileptic seizures.[1] While treatment with medication or surgery can control seizures for approximately 80% of people with epilepsy, the remainder are in need of a new medical solution.

ADVANCING BEYOND MAINSTREAM STEM CELL TECHNOLOGY

Mainstream stem cell therapies involve the use of stem cells that are already matured and differentiated into specific types of cells. Celavie Biosciences has taken a different approach, advancing regenerative stem cell therapies for the treatment of Parkinson's disease and other disorders of the central nervous system (CNS) based on undifferentiated allogeneic pluripotent stem cells.

Undifferentiated stem cells are able to react to the microenvironment into which they are transplanted. These pluripotent cells respond to biochemical and genetic cues by becoming any cell type required to repair tissues that have been damaged by chronic disease, use, or trauma. Unlike commonly used predifferentiated cells, undifferentiated cells can address diseases with complex multifactorial deficiencies in their entirety.

Celavie has shown *in vitro* that our stem cells are capable of maturing into a wide range of adult stem cells that can be applied to a number of diseases:

- dopamine-producing neurons for Parkinson's disease,
- cardiomyocytes for myocardial infarction,
- tenocytes for tendon injuries,
- fibroblasts for ligament injuries,
- chondrocytes for joint injuries, and
- osteoblasts for bone injuries.

Celavie's undifferentiated cells may migrate to the site of the disorder, read the microenvironment into which they are transplanted, multiply and differentiate according to the nature and severity of the disorder, and repair structures and restore function.

In addition, Celavie's undifferentiated, pluripotent stem cells do not present concerns of tumorigenicity, which is an issue with embryonic stem cells and induced pluripotent cells, the other types of pluripotent cells that have high healing potential (but also require cells to be predifferentiated).

CLOSED-SYSTEM MANUFACTURING

Celavie's manufacturing process utilizes an industry-accepted, multitier cell banking system. Every bank of cells is required to meet stringent requirements for viability, genetic stability, and an absence of infectious agents before

being added to a cryobank. When required for treatment, Celavie cells are thawed, reintroduced to the transportation medium, and shipped to the clinical location overnight.

Clinical-scale manufacturing is performed by our contract development and manufacturing partner Comecer America at a cGMP manufacturing center in Oxnard, California. The sterility and the integrity of the manufacturing process are realized through the use of closed-system bioreactors and automated separation and dispensing systems in full compliance with GMP requirements. The proprietary isolation technology was designed in collaboration with Comecer America and ensures the production of large banks of undifferentiated cells with uniform, reproducible, and stable qualities. The cells are grown in a specialized patented medium that allows them to maintain their genetic stability over the course of the manufacturing process.

The manufacturing process is readily scalable for commercial-scale production and banking of our cells. Proprietary culture conditions defined by Celavie's media composition and strict environmental control allow for the production of large banks of homogeneous, genotypically, and phenotypically stable cells. A single cell line can produce up to 1 million therapeutic doses.

Our proprietary technology is also translatable among mammalian species and has been shown to produce human (OK99), equine (OK100), canine (OK200), and feline (OK300) cells that are all characterized by uniform stem cell marker expression, non-tumorigenicity, and hypo-immunogenicity, making it a true platform approach.

SUCCESSFUL RESULTS IN AN EXPLORATORY CLINICAL TRIAL IN PARKINSON'S DISEASE

Unlike embryonic stem cells, OK99 cells have not produced tumors when implanted into immunodeficient rats. An equine open-label study with 400 treated animals did not reveal any tumor formation during a three-year follow-up.

Most important, Celavie now has five-year follow-up data from the Company's first-in-human Exploratory Pilot Clinical Study conducted in Mexico City under the authorization of COFEPRIS (Mexico's FDA). This trial treated seven PD patients; there was no incidence of any lasting adverse events (no tumor formation, infection, or immune rejection), and no surgical complications associated with the stereotactic transplantation technique.

In addition, at five-year follow-up, Unified Parkinson's Disease Rating Scale (UPDRS) III scores demonstrated arrest of, and in some patients reversal of, the progression of PD.

Based on the results of this study, Celavie Biosciences is applying to the U.S. Food and Drug Administration for a Phase I double-blind, placebo-controlled, randomized clinical trial of OK99 stem cells in patients with moderate to advanced PD. The two-part study will involve a staggered-start open-label longitudinal trial (Part 1) and a randomized, two-arm, double-blind, controlled, longitudinal trial (Part II), the latter of which will be launched only if three-month follow-up of the patients enrolled and treated in Part I reveals no permanent, serious treatment-related adverse events. The primary and secondary endpoints are safety and variable neurological, neuropsychological, and radiological evaluations, respectively.

ADDITIONAL ONGOING PRECLINICAL STUDIES

Celavie researchers are in the process of collecting preclinical data for FDA submission for OK99 stem cells as an orphan drug for spinocerebellar ataxias, in collaboration with California State University, Northridge. Ataxic rats having received OK99 transplantation into the cerebellum displayed significantly higher motor activity scores, and sustained greater weights and longevity than control, non-treated ataxic rats. Microscopic examination of the treated animals revealed the transplanted stem cells displayed signs of purposeful migration, and neuronal development was observed in the degenerated Purkinje cell layer. These data support the initiation of a phase I clinical study in patients with spinocerebellar ataxia and other associated neurodegenerative diseases.

Considering the pathological mechanisms of most neurodegenerative diseases share fundamental features, these treatments have potential for use for Huntington's Disease, Friedreich's Ataxia (FA), Amyotrophic Lateral Sclerosis (ALS), Epilepsy and other disorders. Our research plan includes preclinical studies using OK99 stem cells for animal models of Epilepsy and Huntington's Disease.

STEM CELL THERAPIES AS VETERINARY MEDICINES

Celavie's subsidiary, Celavet, is applying our allogeneic, undifferentiated stem cell technology to the development of veterinary medicines using our equine, canine, and feline cell lines, which are derived in the same manner as human cells and express the same markers.

Celavet's product development is geared toward enabling injured horses to regain their fullest potential as competitors, performers, workers, and companions, with preclinical candidates targeting tendonitis (e.g., tendon injuries, bowed tendons) and musculoskeletal injuries via the transplantation of our allogeneic stem cells into ligaments and tendons. We are also developing treatments for osteoarthritis, ligament and tendon injuries, and wounds and burns in dogs. and kidney disease in cats.

To date, Celavet has treated nearly 400 horses in multiple trials at more than 35 veterinary centers around the United States. Our equine donor screening protocol and stem cell product characterization have been approved by the Center for Veterinary Medicine (CVM). Results have thus far been promising in horses with chronic tendon and ligament injuries, and disorders for which no existing treatments offer hope of recovery. We expect to obtain approval by early 2021 for Target Animal Safety (TAS) and clinical controlled studies: OK100 for the Treatment of Equine Musculoskeletal Injuries (INAD 011792).

Separately, in a pilot study conducted to evaluate the safety and efficacy of our canine OK200 stem cells for the treatment of chronic osteoarthritis and cruciate ligament injuries in dogs, both safety and the promise of efficacy were observed. In a compassionate-use case, an abused pit bull with severe third-degree burns to all four paws with no skin remaining was treated with OK200 stem cells. The cells were injected in a circular pattern around the rim of each pad, with a scaffold applied to hold them in place and provide a surface for attachment. The paws were then wrapped and bandaged. After just five weeks, nearly total restoration of the paws was achieved with no formation of scar tissue.

Based on these results, Celavet is committed to conducting a preclinical study on the use of OK200 stem cells for the treatment of chronic wounds and burns and will be submitting an Investigational New Animal Drug (INAD) application.

UNIQUE PERSPECTIVE ENSURES SUCCESS

It is not only Celavie's choice of undifferentiated stem cells that sets us apart from other stem cell therapy developers. We benefit from the unique perspective I bring as CEO of Celavie, as the Founder and CEO of Sweet Street®, the global leader in the manufacture of frozen gourmet desserts, employing 700 people worldwide and the holder of 17 U.S. copyrights and patents for the design of food products and packaging.

My experience overseeing a team of 15 QA and R&D managers at Sweet Street has been directly translatable from food to biotech. Both companies must comply with FDA and USDA guidelines participating in yearly inspections by those agencies, and both operate under a detailed system of SOPs and GMPs.

Speed to market is essential for success in each business. This becomes even more important when the technology is novel as it is with Celavie. Thus, we invested early on in our platform manufacturing system, allowing us to manufacture human, canine, or equine cell banks without needing to download our technology to a CMO. We are fortunate to have the inventor of our novel technology and co-founder of Celavie, Dr. Oleg Kopyov, MD, Ph.D., continuing to lead the discovery and direction of our science today in his role as CSO. One of his many talents is his ability to explain the science and technology to non-scientifically trained individuals. This has enabled me to envision potential novel directions for research and find the resources to pursue and execute on them.

My ability to coalesce the team to develop a strategy and resolve challenges is more important today, as Celavie has pending FDA IND applications for Cerebellar Ataxia (SCA1) and Parkinson's Disease, as well as the FDA CVM INADs for Equine and Canine Musculoskeletal Injuries. The trust we have built internally is proving to be a strong weapon in executing on the consistent work done over these past 14 years.

Our mission at Celavie is to deliver effective new restorative treatments for degenerative diseases, such as Parkinson's Disease and other disabling disorders, for which there are no cures. We believe our stem cells, with their restorative power and versatility to translate into multiple tissues, represent humanity's best hope for a cure for many unaddressed or underserved degenerative diseases and injuries. The next several years will be exciting for Celavie as we advance into larger and later-stage clinical trials, expand our range of preclinical studies, and demonstrate the full potential of our unique cell therapy platform technology. P

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Sandy Solmon is CEO, President and lead investor in Celavie Biosciences LLC, a private company whose mission is to improve lives and restore hope by advancing regenerative stem cell therapies for the treatment of Parkinson's disease and other central nervous system disorders. A dynamic entrepreneur recognized for innovation, philanthropy, and cutting-edge research, Sandy is also the founder and CEO of Sweet Street Desserts®, the world's largest manufacturer of frozen gourmet desserts reaching over 70 countries.

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→ SINGLE-CELL ANALYTICS

ENABLING PHARMA RESEARCHERS TO THINK DIFFERENTLY WITH EFFECTIVE DATA MANIPULATION

→ BY **MARILYN MATZ** AND **ZACHARY PITLUK, Ph.D.,** PARADIGM4

Pharma researchers are tasked with organizing disparate data, which detracts from time spent understanding disease mechanisms and enabling the development of more effective drugs. Paradigm4 is tackling this issue with a new platform based on a novel approach to data organization and elastic computing. Even companies with small budgets can access this amazing computational power at a very cost-effective price.

NEED FOR BETTER MANAGEMENT OF SCIENTIFIC DATA

For scientists, the traditional approach to storing, analyzing, and computing with data is inefficient and limiting. Scientific data is fundamentally different than business data, and, as such, it is not typically possible to effectively manipulate multi-dimensional and diverse scientific data using basic tables, files, or data lakes. Valuable scientific data must be simultaneously cleaned and curated on an ongoing basis so that researchers can continually augment it while also sharing it, reusing it, and collaborating. Additionally, scientists want to focus on their research and not have to learn complicated computer science methods to access and compute with large data sets.

FOCUSING ON THE LIFE SCIENCE VERTICAL

Paradigm4 is leveraging technology developed by Turing laureate and MIT Professor Mike Stonebraker for the life sciences vertical, addressing data manipulation challenges with a suite of end-to-end solutions. We synthesize knowledge at the cutting edge of computer science with an understanding of pharma and biotech research requirements. Experts in bioinformatics, biomechanical engineering, bioimaging, and statistical genetics collaborate with experts in machine learning and other emerging aspects of computer science.

SINGLE-CELL OMICS AND ANALYSIS

One of our focus areas is single-cell omics analysis. Single-cell sequencing within tumors can help oncologists understand the distribution of mutations and their co-occurrence within individual cells, potentially guiding precision medicine.

Single-cell studies involve not only RNA sequencing, but metabolomics and proteomics, examining genetic changes to consider their consequences for individual cells, such as morphology or protein expression, and adding additional layers of understanding essential for effective target identification and drug development.

We are facilitating the process by increasing the rate in which scientists can ask and answer questions to test hypotheses through appropriate data organization and elastic computing.

A UNIFIED, SCIENCE-READY REPOSITORY

The vision for Paradigm4 was to store diverse types of data, along with metadata, in a unified, science-ready repository. SciDB is our next-generation analytics platform, which enables scientific data modeling, storage, and large-scale computation. This all-in-one, enterprise-ready storage and elastic computing platform is a massively parallel, transaction-safe, array-oriented, analytics solution.

Data is organized into arrays that can easily be queried with scientific languages, such as R and Python. The old way of working – opening many files and bringing the data together into a matrix – is no longer necessary, because the data is ready for extraction, evaluation, and transformation. It is also easily parsable; specific data can be selected from the arrays without the need to open files. For companies that have tens of thousands of data sets, aggregation of that data in a usable format is tremendously empowering.

The elastic computing capability makes it possible for individual scientists to run their own algorithms at any scale without the help of an IT specialist. They do their normal work, and the software automatically expands the compute to match what they're doing. Any researcher can access the power of hundreds of computers from a laptop.

REVEAL™ TRANSLATIONAL INFORMATICS PLATFORM

Paradigm4's suite of REVEAL apps enables bioinformaticians and scientists to access a large quantity and diversity of public and proprietary multi-omics, behavioral, clinical, health outcomes, and environmental data to accelerate integrative, multimodal, longitudinal, population-scale data science exploration and discovery.

The REVEAL™ apps, or sets of use cases, are layered over the array data and compute engines, making it possible for scientists to answer questions in their own vernacular.

For example, the REVEAL: Single Cell™ app enables users to build a multidimensional understanding of disease biology; scale to handle more samples from patients with more cells, more features, and broader coverage; and readily assess key biological hypotheses for target evaluation, disease progression, and precision medicine. Our goal is to allow researchers to be as productive as possible by giving them an interface that is easy to use, intuitive, and understandable.

FOR SCIENTISTS, THE TRADITIONAL APPROACH TO STORING, ANALYZING, **AND COMPUTING WITH DATA IS INEFFICIENT AND LIMITING.**

Our other apps include the REVEAL: Biobank™ app, which brings together multiple data types, such as multi-omics data; practitioner, hospital, diagnostic codes and prescription history; and biometric and imaging data to support scientists in population-scale translational medicine and healthcare research. It leverages 70 terabytes of genomic data held within the UK Biobank, which contains the data for 500,000 people, including 100,000 participants' imaging data. Our app organizes analytical data from HPLC, UV, LC, mass spec, solubility, and other methods, which can also be terabytes worth of data, and makes it available to machine learning programs to improve processes.

The multi-omics REVEAL™ applications span 15 different data types from variance in copy number through proteomics. We also have experience working with wearables data through a collaboration with Pfizer on the Blue Sky Project, which led to our wearables app.

ENABLING AND EMPOWERING TECHNOLOGY

SciDB, combined with REVEAL™ apps, enables scientists to think differently by removing computational restraints, accelerating their ability to formulate and test hypotheses. Instead of spending most of their time organizing and accessing data, they can now spend time answering the real questions, including many that could never have even been asked before. Analysis of more comprehensive data sets also provides more accurate and much less approximate results.

Because we are leveraging spot instances in the cloud, we can provide this amazing computational power at a very cost-effective price, enabling nascent companies with small budgets to develop break through science.

A REVOLUTION IN UNDERSTANDING

Precision medicine will affect the treatments themselves, as well as dosing and the timing of administration. Underlying that will be a revolution in our understanding of physiology. We are just beginning to see cellular interactions at different scales.

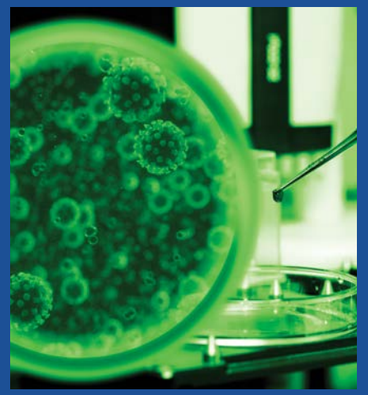
New instruments will afford the ability to see and measure things that weren't previously accessible, driving pharma to a new scientific plateau – but software tools and new methods are needed to be able to use the data that those instruments are generating.

To answer detailed questions about similarities between distal tissues, exosomal communications, the fragments of genetic material and proteins that play a role in knitting organisms together, and the role of microbiome metabolites, all of that data must be supremely organized in appropriate matrices so that it can be ready to analyze using machine learning and different types of algorithms. Having both new analytical technologies and data management capabilities like those offered by Paradigm4 will together revolutionize drug development. P

PARADIGM4 IS LEVERAGING TECHNOLOGY DEVELOPED BY TURING LAUREATE AND MIT PROFESSOR MIKE STONEBRAKER **FOR THE LIFE SCIENCES VERTICAL, ADDRESSING DATA MANIPULATION CHALLENGES WITH A SUITE OF END-TO-END SOLUTIONS.**

REVEAL: Single Cell and the COVID Cell Atlas

The first data sets entered into the REVEAL Single Cell™ app were from the HCA and the COVID-19 Cell Atlas. Questions such as "Where is the receptor for SAARS-CoV-2?" or "What are the tissue distribution and cell types that contain COVID-19 receptors?" can be answered in 30 seconds or less, with responses from 30 or more data sets (since expanded to ~100). More advanced questions can now be investigated, such as the causes for complications and sequelae seen in some patients. Rather than organizing all of those data, researchers can focus their attention on unlocking answers.



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Marilyn Matz is CEO and co-founder, along with Turing laureate Michael Stonebreaker, of Paradigm4. The scientific analytics solutions company enables scientists and data scientists to transform their research with an integrative analytics platform that powers massively scalable analytics and machine-learning. Prior to Paradigm4, after completing a MS degree at the MIT AI lab, she was one of three co-founders of Cognex Corporation, now a publicly traded, global industrial machine vision company. Marilyn was the recipient of the sixth annual Women Entrepreneurs in Science and Technology (WEST) Leadership Award; a co-recipient of the SEMI industry award for outstanding technical contributions to the semiconductor industry; and a 2020 NACD Directorship 100.

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Deborah A. Graham
Vice President & Site Director, Norman, Oklahoma
Avara Pharmaceutical Services

Avara Pharmaceutical Services: Specialization with a Client-Centric Approach

At Avara, our business is built upon the flexibility and adaptability that comes with centering our efforts around the needs of our clients. We view ourselves as true client partners, with collaboration, personal connection and attention to detail being at the forefront of everything we do. While we are continually integrating technological innovations, product offerings, and services on the manufacturing side, we believe that our core strength lies in our ability to integrate with our clients to ensure that their goals are met and their expectations are exceeded, thus building lasting relationships.

Our approach to business development aligns with our overall client services methodology, as we seek opportunities that fit our capabilities and processes. We are focused on working with clients that have needs we can meet and execute seamlessly, as opposed to pursuing or responding to RFPs for projects outside the proven scope of what has made our business successful. Our business model is also centered around repeatability – especially in terms of building processes and investing in equipment to meet the specificities of client projects—with our goal being to develop relationships by providing superior service.

Technological Innovation

As potent product categories become more prevalent in pharma, Avara has also outfitted our equipment to be ready for high-potency APIs. One of our core competencies is OSD manufacturing, which includes potent substances, spray drying, small batches, and over-the-counter (OTC) products. Our manufacturing and packaging capabilities include various forms of granulation, compression, extrusion, encapsulation, along with tablet and film coating. Both primary and secondary packaging services are available, along with global distribution and supply chain support. Our Norman, Oklahoma site also offers high shear, roller compaction, hot melt technology, automated cartoning and inspection and is also equipped with serialization technology.

Production scale at our Norman site generally ranges from 100-kg to 400-kg batches, but we also offer smaller batch sizes for clients, for example, those who deal with potent products. Tablet appearance is also very important, particularly in specific international markets, which is why Avara has vision inspection equipment in manufacturing, so that our finished product is also aesthetically consistent across every unit.

Many of our investments in new technology stem from specific client requests. We aim to partner with clients who have projects ready for tech transfer or products for which we are equipped to execute quickly and efficiently, such as scaling from phase III clinical trials to commercial manufacturing. We also engage in technical transfer work and the manufacturing of registration batches needed to complete filings, all the way through clinical trials and commercial product launches.

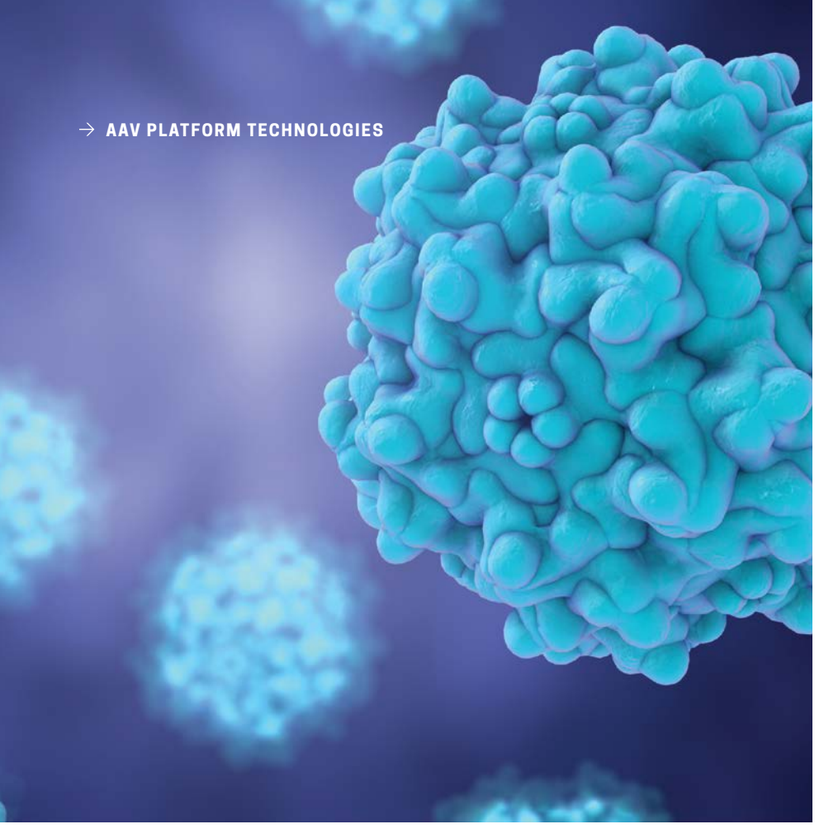
Avara Pharmaceutical Services is a contract manufacturing organization whose global operations are built around the needs, priorities, and objectives of our clients.

Looking Ahead

Avara has operated at our Norman site since 2016, and the facility itself has been there for 40 years. Throughout this time, the company has navigated pharma trends and the ebbs and flows of product development cycles. Our flexible, specialized approach allows us to adjust to evolving market conditions, which are typically very cyclical. As patents expire and new drug discoveries are made, the competitive landscape remains extremely dynamic, which is why client relationships and trusted delivery are as important as innovative technologies. We will continue to position ourselves as a client partner that can navigate market changes, leveraging our ability to evolve with our clients and maintain sustainable growth and marketability.

Avara's Commitment to the Industry

Avara Pharmaceutical Services is a contract manufacturing organization whose global operations are built around the needs, priorities, and objectives of our clients. With established facilities proven through decades of large-scale commercial supply within the pharmaceutical industry, we build on inherent long-term site expertise with an established company commitment to attentiveness, flexibility, and a fundamental focus on our clients. Our commitment to our clients is a cornerstone of our business, and this approach has enabled us to support various market and supply chain segments, with sterile fill-finish, oral solid dose drug product, and integrated packaging capabilities across each of our sites. P



INCREASING PREDICTABILITY WITH AAV PLATFORM TECHNOLOGIES

→ BY **FELIX HSU,** WUXI ADVANCED THERAPIES

To meet future demand for adeno-associated viral (AAV) vectors, platform technologies that offer greater titers, higher infectivity rates, and more efficient downstream processing operations are essential.

WHY AAV FOR GENE THERAPY DELIVERY?

AAV vectors are widely used in gene therapy, largely because they do not become integrated into the patient's DNA and are safe from an immunogenicity perspective. AAVs also offer great versatility, with different targets possible using different serotypes. Relative to other vectors, AAVs are also generally produced at higher titers, which reduces costs. In addition, they present long-lasting effects and tend to be more stable than other vectors.

BANKING ON IMPROVED TITERS

The market for AAV vectors is predicted to expand at approximately 20% annually over the next five years. In addition to more approvals of AAV-based gene therapies, this growth rate will likely only be maintained if innovations leading to improved titers continue. More efficient and effective production processes are needed to reduce the costs of gene therapy. For instance, a ten-fold improvement in titers could cut costs by at least 80%. Some advances have been made already, and we know from our experience with monoclonal antibodies (mAbs) that titers will likely continue to improve.

NEED FOR PLATFORM TECHNOLOGIES

When gene therapies first emerged, each process was by necessity customized for each product and customer. Working in this manner is highly inefficient, because additional time is required to develop each process, obtain or manufacture the myriad unique raw materials and get them approved, train the operators, design and install the equipment, and every other step in the program. Lead times can be extensive, and present a risk of derailing the program.

By taking a platform approach, common sources of problems can be minimized, with the process development strategy, raw materials, and equipment all standardized. Raw materials other than the plasmid for the gene of interest are maintained in stock, the batch record has been drafted, and the manufacturing team is already familiar with the process when the program begins. Because design-of-experiment studies were completed and a wide range of process parameters and conditions have been evaluated in advance, it is possible to troubleshoot novel issues that arise faster, so process optimization and scale-up proceed smoothly and rapidly.

In order for CDMOs to successfully demonstrate their ability to execute AAV vector programs at the quality and efficiency levels required, they must have established AAV manufacturing platforms. Only with a platform approach is it possible to demonstrate to potential customers that the CDMO has the knowledge, and expertise required for efficient process development and manufacturing, as well as the flexibility and agility needed to minimize disruptions and reach the clinic efficiently.

MOVING FROM ADHERENT TO SUSPENSION CELL CULTURE

Production of AAV vectors in adherent cell lines is difficult to scale – particularly in plasticware, but even in bioreactors – because adherent surfaces are needed to support the cells. It is easier to scale suspension cell culture processes, but suspension cell lines have been less productive.

At WuXi Advanced Therapies, we established an AAV adherent platform but over time realized that this technology was not sufficiently scalable to support our anticipated production levels/needs. The development of gene therapies for indications that are systemic or involve large parts of the body and/or the use of gene therapies in much larger patient populations, such as heart failure, driving the need to comprehensively scale AAV manufacturing.

We invested in the development of a suspension cell line and our AAV suspension platform was launched in January 2020. AAV 1.0 is a robust producer cell line with productivity comparable to conventional adherent cells. With the ability to readily scale processing using this suspension cell line, we will be better positioned to meet future customer needs.

AAV 2.0

Once we had a platform for manufacturing AAV, we knew there were opportunities to improve the new suspension cell line, the upstream process, and the downstream process, with the objective of further improving the titer and the infectivity rate.

By the end of 2020, WuXi Advanced Therapies will be launching AAV 2.0, an improved suspension cell line for AAV manufacture. The AAV 1.0 cell line was cloned, and the top clones presenting 2–3-fold improvements in titer were selected. In addition, we have further refined our upstream process. As a result, depending on the relevant serotype, we have been able to improve the titer from 3× to 20×.

INCREASING THE PERCENTAGE OF FULL CAPSIDS

There are some manufacturing solutions for improving the full-to-empty capsid ratio. Using ultracentrifugation rather than ion-exchange chromatography during down-stream processing generally provides a better ratio, but it is currently only feasible at smaller volumes. However, downstream purification only removes empty capsids, but what is really needed is a means to increase the number of full capsids produced upstream, optimizing the true yield rather than improving the separation of the empties.

EXPLORING ALTERNATIVE TECHNOLOGIES

Plasmids and HEK293 are not the only approach to AAV vector production. The use of insect (baculovirus) rather than human cells is attracting attention. The titers are better, the manufacturing process is simpler, and the times are shorter, which all lead to lower costs. However, the potency is often viewed to be lower, and thus support for this technology is split in the gene therapy community.

Completely nonviral methods for the introduction of genetic material into patient cells are also being explored, including electroporation and pressure. There is interest in moving away from viruses for both safety reasons and potential cost advantages. We are actively working with several different approaches, often in collaboration with customers.

We have found so far that these methods are less efficient, and most are not yet sufficiently advanced to displace viral vectors. It will be interesting to see, as AAV, lentivirus, and other vector technologies improve, whether these alternatives can advance as quickly.

PUTTING A "T" IN CDMO

In addition to reliably manufacturing AAVs – or any pharma product – CDMOs must also have the ability to develop process- and product-specific assays within the established timelines and perform those tests to support process development and product release. For AAVs, many CDMOs outsource analytical work to third parties, which can impact their responsiveness.

At WuXi Advanced Therapies, we conduct our testing in-house and have this capability integrated into our service offering. We have coined a new term for CDMOs that offer testing in conjunction with development and manufacturing support – CTDMO (contract testing, development, and manufacturing organization).

The testing capabilities are important, because it doesn't benefit a customer to have a CDMO manufacture a product that they are ultimately unable to release in a timely manner. In an emerging market like gene therapy, with so many candidates in clinical trials, access to third-party testing services can be challenging. Lack of analytical development resources is a key constraint in this industry. CTDMOs with the ability to offer integrated analytical support will have a distinct advantage. However, there will be a limited number of organizations that can claim to be true CTDMOs, because it is very difficult and time-consuming to set up broad testing capabilities that include analytical, molecular biology, virology, and other laboratories staffed by experienced technicians. P

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Felix Hsu is the Chief Commercial and Business Officer upon being promoted from Senior Vice President and Global Head at WuXi Advanced Therapies, located in Philadelphia, PA. He has nearly 31 years of experience in the life sciences industry and serves as an Advisory Board Member on the Jefferson Institute for Bioprocessing. He has also held executive and senior positions at WuXi AppTec and Medtronic. He studied at the University of Michigan – Stephen M. Ross School of Business, where he earned a Masters in Business Administration and Management.

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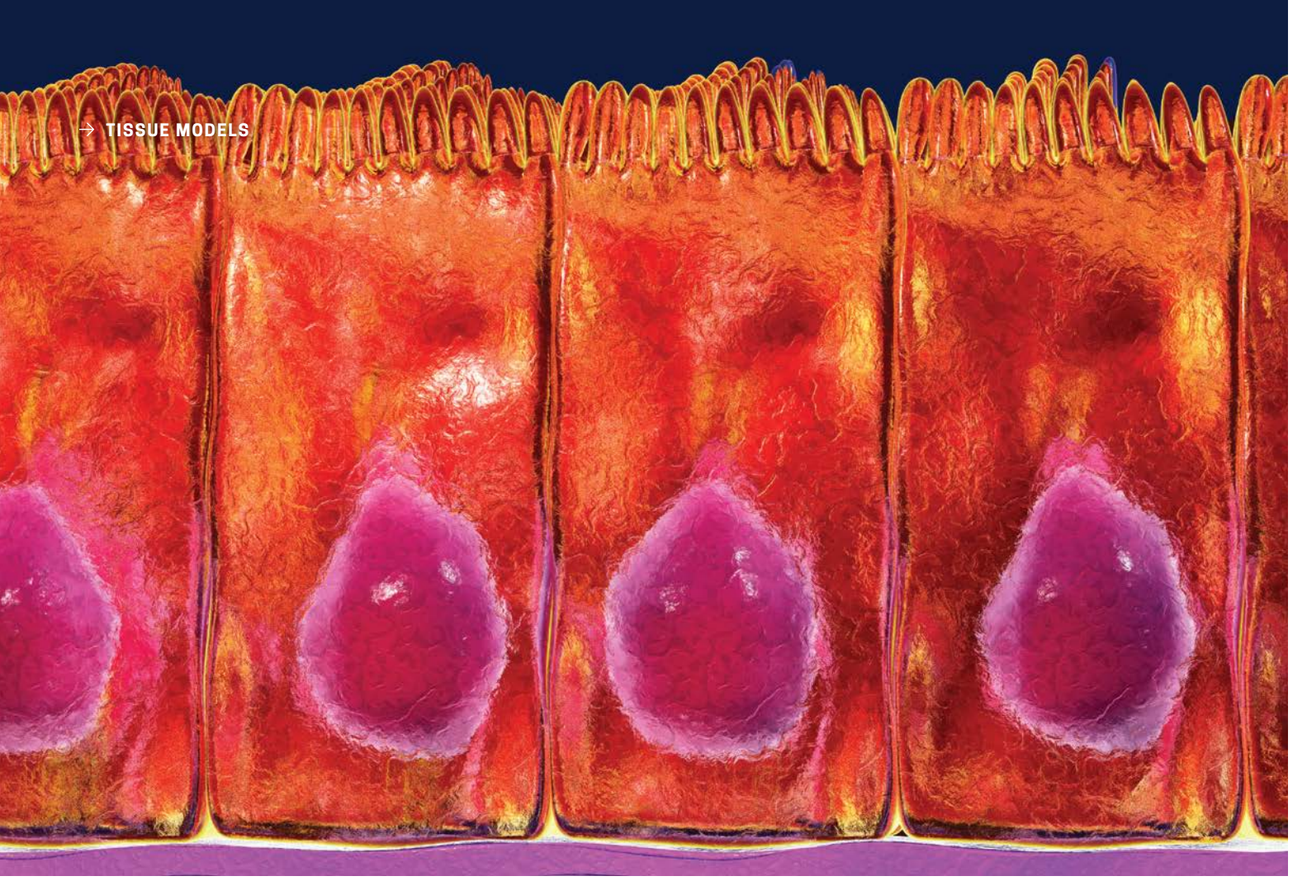

INCREASING THE EFFICIENCY OF DRUG DEVELOPMENT WITH PRECLINICAL TESTING USING HUMAN INTESTINAL STEM CELLS

→ BY **RON LAETHEM, Ph.D.,** ALTIS BIOSYSTEMS

Due to a lack of robust *in vivo* gut models, animal studies are generally required to evaluate gut toxicity. However, these studies can be lengthy and expensive and may not accurately recapitulate the behavior of the human gastrointestinal tract. Drugs are thus often developed with undesired gut side effects that are not apparent until clinical trials.

Organ-on-a-chip models are the closest *in vitro* options, but they still have many limitations. More efficient development of drugs with attractive side effect profiles requires robust, easy-to-use, cost-effective *in vitro* gut models that are physiologically representative of the human intestinal tract and thus predictive of *in vivo* behavior. RepliGut® tissue constructs have been designed to meet this need.

LACK OF ROBUST *IN VITRO* GUT MODELS

Very few *in vitro* models available accurately represent the gut. Some immortalized or cancerous cell lines, such as Caco-2 cells, are relatively simple to use and enable studies to be conducted fairly quickly. But the translatability of the data from *in vitro* to *in vivo* is always a question, especially since these are cancerous rather than normal cells. For studies of gut toxicity, animals are needed, and development timelines increase significantly when transitioning from the petri dish to *in vivo* evaluation. The higher up the evolutionary scale the model animal being used, the more that cost and timelines increase as well – it is much more expensive to conduct studies in non-human primates than in rats or mice.

The lack of robust *in vitro* gut models can be attributed to the complexity of gut biology, which makes it difficult to recapitulate. Even in animals relatively close to humans – such as dogs, a fairly popular species for tox studies – the gastrointestinal tract reacts quite differently than it does in humans. For instance, dogs are more prone to emesis (vomiting) and nausea. As a result, the translatability is questionable. While nonhuman primates are fairly good models for people, they are very expensive, and costs can skyrocket with these studies.

Intestinal organ-on-a-chip models are probably the closest *in vitro* options that exist today. While a few are commercially available, each has issues. Some are very expensive and require specialized equipment to implement. Throughput is typically the greatest limitation, and there are often challenges associated with sampling and analysis. The accuracy of predictions obtained using these models can also vary widely.

There is consequently a need for more robust, easy-to-use, cost-effective *in vitro* models that are physiologically representative of the human intestinal tract and thus predictive of *in vivo* behavior.

THE EXAMPLE OF GUT SIDE EFFECTS

To illustrate the difficulties, one good example is the potential for gut side effects caused by chemotherapeutic drug candidates. There are currently no robust *in vitro* models for use in frontline screening of compounds for potential gut side effects during discovery and lead optimization. Consequently, *in vitro* testing is employed to answer a host of questions about the properties of the candidates and how they will behave *in vivo*, but this issue is ignored.

In some cases, animal studies may be performed, but they may not be predictive regarding gut toxicities. As a result, the first indication that gastrointestinal adverse events (e.g., diarrhea, constipation, intestinal distress) could be a problem appears during human clinical trials. By that time, it is late in the development process, and it is not typically possible to go back and redesign the molecule to eliminate the issues and improve the side effect profile. This gastrointestinal distress often results in compliance issues that can compromise the benefits of therapy. The general solution is to prescribe palliative cotherapies to resolve the issue.

If potential gut toxicities could be explored using *in vitro* studies during the preclinical development stage, it would be possible to eliminate candidates with this liability early in the project timeline, saving both time and money. Clearly, fewer liabilities carried into the clinic will result in higher-quality drugs that reach the market more quickly.

AN EFFICIENT HUMAN CELL–BASED OPTION

RepliGut® tissue constructs from Altis Biosystems have the potential to address this critical need in pharmaceutical drug development. Based on human intestinal stem cells, RepliGut® eliminates the issues associated with the use of colon cancer cells. The polarized monolayers express tight junction proteins and recapitulate the barrier function of the intestine *in vivo*. Additionally, they can be tailored to consist of different cell lineages. Because they are healthy, normal (not cancerous) human cells, they provide more physiologically relevant results. Intestinal stem cells used for the RepliGut® system are harvested from transplant-grade human donor tissue for which there is no recipient match. As such, the stem cells are very high-quality with very low necrotic or ischemic damage.

Each tissue sample in a RepliGut® kit features a biomimetic scaffold that separates RepliGut® cells from the cassette's porous membrane and allows RepliGut® cells to survive for a prolonged period of time. Luminal and basal reservoirs allow compounds and additional cell types to interact with the epithelial cells for side-specific assays.

With this design, RepliGut® is able to more accurately model different behaviors in the intestine, such as the barrier function, which has been associated with diarrhea and other undesirable gut conditions. In some cases, it may be possible to eliminate the need for animal studies. The potential for efficiency gains and reductions in time and cost are therefore significant.

DEVELOPING DATA SETS

Achieving a high level of adoption of new assays, such as those based on the RepliGut® system, is challenging, even when the potential benefits are measurable. It is even harder when the methods being replaced are as well-entrenched as Caco-2–based analyses.

Typically, it takes the interest of a leading pharmaceutical company to drive movement within regulatory agencies. If a big pharma company takes data based on a new method to the U.S. Food and Drug Administration and shows the agency that the method is robust and reliable, the regulators will usually pick up the baton and investigate further. Small companies like Altis, even with tremendous positive data, typically cannot do it alone; they definitely need a buy-in from big pharma. Luckily, Altis works with half of the top-20 pharma companies and hopes to work with more in the future.

We are currently focused on developing extensive data for specific functionalities of the RepliGut® system. There are many potential applications, and we are taking a stepwise approach to test each application. Because the barrier function of the intestine is its key feature, we have initially focused on the development of a RepliGut® system useful in related assays. This system currently focuses on epithelial cells,

REPLIGUT® IS ABLE TO MORE ACCURATELY MODEL DIFFERENT BEHAVIORS IN THE INTESTINE, SUCH AS THE BARRIER FUNCTION, **WHICH HAS BEEN ASSOCIATED WITH DIARRHEA AND OTHER UNDESIRABLE GUT CONDITIONS.**

and RepliGut® offers a really robust barrier function on par with Caco-2 cells.

Altis has used RepliGut® to test a number of compounds in collaboration with AstraZeneca, but we need to conduct more in-depth studies and compare results obtained with RepliGut® to those obtained in the clinic to establish with confidence that the system accurately mimics what occurs *in vivo*.

Looking forward, there are many other aspects to intestinal biology that we could potentially assess with RepliGut®, and we will be taking a similar approach to determine if there is a robust correlation between the *in vitro* and *in vivo* data.

POTENTIAL APPLICATIONS FOR REPLIGUT®

RepliGut® has the potential for many applications, including screening of completely novel compounds with new modes of action or identification of derivatives that operate by known mechanisms but have the potential to offer benefits over currently marketed drugs.

In the latter case, new drugs that have the same mechanism of action but no gut toxicity that can lead to unwanted side effects like diarrhea would have a huge advantage and likely displace existing products on the market with those side effects. Afatanib is one example – the clinical incidence of serious diarrhea with this drug is approximately 96%, and it disrupted barrier function with RepliGut®. A new drug lacking that liability or with a reduced liability would be very attractive.

In addition to the cost savings achieved by eliminating non-representative *in vitro* and expensive, time-consuming and potentially non-correlative *in vivo* animal studies, the use of RepliGut® in gut toxicity assays has the potential to add immeasurable value in the form of improved health and quality of life. Both the patients and the drug manufacturer would benefit.

Elimination of animal testing also has a societal benefit. There is a strong push in the pharmaceutical industry to reduce and if possible eliminate animal testing for ethical reasons. As a result, there is a desire to recapitulate *in vivo* tests conducted with animals using *in vitro* and *in silico* models that have been proven to provide robust correlations.

GREATER LIFE SPAN WILL FURTHER BOOST EFFICIENCIES

There are many opportunities to expand the functionality of the RepliGut® platform, and Altis is working on many of these. Currently, most RepliGut® assays are fairly short-lived; after the stem cells are differentiated, there are no more dividing cells and the cells are all terminal. The lifespan of these mature, differentiated cells in the gut is only five to seven days. In our model, therefore, after about seven days of differentiation, the cells start to slough off just like they would *in vivo*. Since there are no stem cells to replace them, and the cultures die off.

In the human intestine, however, there is a mix of stem cells and differentiated cells, with cells present at different stages of maturity. The stem cells continue to divide and reproduce and then differentiate, replacing the ones that slough off.

Altis is working on models in which both proliferating stem cells and differentiated cells are present in the same well to lengthen the lifespan of our RepliGut® tissues and enable testing of drug effects on the entire system, rather than just differentiated cells.

In one of our prototype systems, we have maintained tissues for 30 days. We would like to extend that even further, so more detailed studies can be performed using an even more physiologically relevant model. This type of long-lasting model also presents the best opportunity to eliminate animal testing and increasing testing efficiency, because the system would be more complete and more reflective of the physiological gut.

DRIVING ADOPTION THROUGH PARTNERING

In addition to driving the interest of regulatory agencies, partnering with big pharma companies helps to build credibility in the eyes of other drug development companies of novel assays, such as those based on the RepliGut® platform. Large pharma firms tend not to institute or implement new methods that don't provide high-quality, reliable data. Attracting the attention of big pharma first requires extensive research and testing to demonstrate the robust performance and the method.

Altis has already done much internal work and will continue to pursue R&D programs designed to further build out our body of evidence supporting the use of the RepliGut® platform for drug screening and other applications. We will also continue to expand our existing collaborations with big pharma companies and actively publish and present the results of these studies. The focus is to make the models better for them with respect to both ease of use and performance. P

ABOUT THE AUTHOR

Ron Laethem, Ph.D.
Director of Biology, Altis Biosystems

Ron Laethem, Ph.D., is a drug disposition scientist with nearly 30 years of experience in the pharmaceutical and biotechnology areas with expertise carrying out *in vitro* ADME studies. Before Altis Biosystems, Ron was the Director of ADME Services Operations for BioIVT, responsible for setting up and overseeing the *in vitro* ADME group focusing on non-GLP drug–drug interaction studies for IND and NDA filings. Before BioIVT, Ron served as Associate Director with QPS, Senior Director of R&D for Triangle Research Labs, LLC, and in roles with BD technologies, HepatoTech, Inc, and GSK. Ron received a Ph.D. in biology from Case Western Reserve University.

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Tim Tyson
Chairman and CEO
TriRx Pharmaceutical Services

Product Diversification Through Expansion into the Animal Health Market

On September 1, 2020, TriRx Pharmaceutical Services, a global CDMO serving the biopharmaceutical market, announced its acquisition of a manufacturing site in Segré, France. The agreement between TriRx and Merck includes transfer of ownership and operations of a state-of-the-art facility that includes dedicated offices, production, sampling, warehouse areas, and a world-class staff, delivering products to all major global markets. The acquisition was predicated on an internal strategy to continually add high-demand capabilities, such as sterile injectables and animal health, to an already robust service offering.

The transaction also facilitated TriRx's expansion into Europe, by the acquisition of a best-in-class facility from Merck, one of the largest pharmaceutical companies in the world. This strategic move seamlessly aligns with our overall future plans. The Segré site offers a stable book of business, including a long-term supply agreement with Merck to continue manufacturing the animal health products formerly produced by MSD.

An Underserved Industry with Substantial Growth Potential

The production of animal health products serves dual segments – pet care and food supply. The global animal health market was valued at $47.1 billion in 2019 and estimated to be expanding at a compound annual growth rate of 5.8% through 2027.[1] Assuring animal health is a critical component to the world's food supply.

The regulatory rigors of animal health products, while not identical in terms of oversight, are fundamentally consistent with those for human health pharmaceuticals – much of the same regulatory scrutiny and current Good Manufacturing Practices (cGMPs) exist in both spaces. The capabilities at the Segré site supplement those at our Huntsville, Alabama facility. The acquisition of this site allows us to add sterile injectables to our existing capabilities in the liquids, creams, and ointments dosage forms with additional non-sterile liquids. Furthermore, the competencies needed to manufacture animal health products are analogous to those required for human pharmaceuticals, and we estimate that our animal health production will consume roughly 30–40% of our total production at the Segré site, enabling us to broaden our service offering to our existing clients who operate in both the animal and human health industries.

Entrance into Europe

The prospect of adding a centrally located, European facility with a sustained track record of high performance both in regulatory compliance and in delivery, as well as a highly competent, professional staff of around 130 people (we are pleased to have retained 100% of the site staff) that serve the international marketplace was extremely attractive. The facility fits our competitive growth strategy well, as the animal health market is rising at about a 6% compound annual growth rate (CAGR). The Segré site supplies North America, European and International markets, and is licensed to support roughly 120 markets worldwide. With very few of these types of facilities and capabilities currently in the CDMO market, acquiring a sterile injectable facility that specializes in high-quality manufacturing and development for one of the largest pharmaceutical companies in the world – with a history of significant and exceptional performance in both manufacturing and fill-finish – will meet a rapidly growing/underserved market demand.

Future Outlook

In the next three to five years, TriRx Pharmaceutical Services will continue to take a determined and opportunistic approach to expanding into additional delivery technologies; solid dosage form sterile human health, and biologics capabilities. We will also continue our search for an active pharmaceutical ingredient (API) facility that will facilitate a broad and integrated approach to satisfying market demand for our customers.

This site will transition to a worldwide center of contract manufacturing excellence in the fast growing animal health market and will continue to be a significant contributor to the local economy.

TriRx's Legacy

Founded and led by a team of pharmaceutical industry executives who have served as both contract service providers and customers, TriRx Pharmaceutical Services has a profound and multifaceted understanding of customer needs. We operate facilities that provide state-of-the-art laboratory, manufacturing, packaging, and warehousing capabilities, with a depth of understanding, commitment, and knowledge to deliver exceptional experiences on every project. P

Reference

1. *Animal Health Market Size, Share & Trends Analysis Report By Animal Type (Production, Companion), By End Use, By Product (Pharmaceuticals, Feed Additives, Vaccines), By Distribution Channel, And Segment Forecasts, 2020 – 2027.* Rep. Grand View Research. Feb. 2020. Web.

TARGETING RETINAL DISEASES WITH AN OPHTHALMIC FORMULATION OF BEVACIZUMAB

→ BY **LARRY A. KENYON,** OUTLOOK THERAPEUTICS

Although repackaged intravenous (IV) Avastin® (bevacizumab) is widely prescribed off-label to treat retinal diseases through intravitreal injection, bevacizumab has never been approved for these indications. There can be risks associated with the use of unapproved bevacizumab products from compounding pharmacies. Outlook Therapeutics is in late-stage clinical development with a version of bevacizumab formulated specifically for ophthalmic use in such retinal diseases as wet age-related macular degeneration (AMD). Outlook's compound, if approved, will provide a true on-label, cGMP-produced, responsibly priced ophthalmic bevacizumab, not only offering another safe and efficacious, on-label therapeutic option aross the spectrum of retinal care, but potentially expanding access to therapy to patients in markets where unapproved bevacizumab is not available and access to anti-VEGF treatments is limited.

FROM BIOSIMILARS TO OPHTHALMOLOGY

Outlook Therapeutics has an unusual history for a company focused on retinal diseases. We founded Oncobiologics in 2010 as a unique biosimilar company with in-house development and manufacturing. On our journey to develop an oncology biosimilar of bevacizumab for the branded oncology drug Avastin® (Genentech), we realized we could pursue a unique opportunity. Rather than compete with six or seven other potential biosimilar bevacizumab products in the oncology market, we could develop a novel ophthalmic bevacizumab formulated specifically for the treatment of retinal diseases.

In 2018, we pivoted to become an ophthalmology company and changed our name to Outlook Therapeutics. From that point forward, we have focused completely on our retinal strategy. Our lead asset, ONS-5010, is a version of bevacizumab we expect to call LYTENAVA™, if approved, and we hope it will become a widely accepted, new approved option for the treatment of wet AMD and other retinal diseases.

THREE INDICATIONS FOR ANTI-VEGF DRUGS

Within the ophthalmology space, anti-VEGF drugs like bevacizumab are used to treat diabetic macular edema (DME) and branch retinal vein occlusion (BRVO) in addition to wet AMD. This class of drugs has been considered the standard of care for retinal disease for nearly 15 years. There currently are three approved anti-VEGF drugs for treatment of these indications, all of which, like cancer, have leaky blood vessels as a major contributor of disease.

Anti-VEGF drugs, including Avastin®, target leaky blood vessels, which, in the case of retinal disease, proliferate behind the retina to cause vision loss and potentially blindness. Anti-VEGF drugs cause these abnormal blood vessels to dry up, thereby allowing vision to be improved if not restored. Anti-VEGF drugs for ophthalmic use are injected into the vitreous of the eye, on a dosing schedule that varies roughly from monthly to quarterly, depending on the patient's situation. In general they are probably dosed approximately six times per year.

BEVACIZUMAB MOST PRESCRIBED, BUT NOT APPROVED FOR RETINAL DISEASES

More than 34 million patients globally have retinal diseases that can be treated with anti-VEGF therapies, and the value of the global market for anti-VEGF treatments for these indications is estimated to be in excess of $13 billion in 2020. That figure does not include sales of unapproved repackaged IV Avastin®, which is used to treat up to 50% and 30% of wet AMD patients in the United States and Europe, respectively.

The driver behind the use of unapproved repackaged IV Avastin® is the cost. The currently approved therapies run nearly $2,000 per dose, compared with approximately $100 per treatment for unapproved Avastin®. We expect to market LYTENAVA™, if approved, under a responsible pricing policy that provides a win–win scenario for clinicians, patients, and payors.

MEETING A KEY UNMET NEED

There are some risks with the ophthalmic use of unapproved repackaged IV Avastin®. First, it was formulated for oncology indications, not for retinal diseases. Second, Avastin® is repackaged into syringes at a compounding pharmacy, where a single vial of IV Avastin® is repackaged into 70–80 doses in syringes, with 70–80 different needles dipped into that vial. There is no way to ensure complete sterility during the process, which is not performed in a cGMP environment. There also are no standards regarding the needles used for ophthalmic drugs, and generally the syringes into which the Avastin® is repackaged are not designed for use in the eye. Furthermore, there is no testing of the Avastin® in those syringes of any kind, including with respect to how long the syringe can be stored.

There is consequently a risk of syringe malfunction or contamination, as well as drug contamination or subpotency, all of which can potentially lead to severe complications, including infection of the eye (endophthalmitis) and even blindness or loss of an eye.

Bringing to market an FDA-approved, cGMP-produced, responsibly priced ophthalmic formulation of bevacizumab designed specifically for retinal diseases will eliminate the problems that can occur when using unapproved repackaged IV Avastin® from a compounding pharmacy. We believe that there is tremendous opportunity to greatly reduce the cost of care for patients while increasing patient safety.

Furthermore, in many parts of the world, even unapproved repackaged IV Avastin® is not available, and patient access to treatment is limited by the cost of the approved drugs. Our hope is therefore also to expand access to care on a global basis.

GOING FOR A BLA

Outlook intends to file a Biologic License Application (BLA) for our ophthalmic formulation of bevacizumab (ONS-5010/LYTENAVA™) as a new drug for the treatment of retinal diseases. We are able to pursue this path because Avastin® has never been approved for use in these indications. If approved, LYTENAVA™ will have 12 years of regulatory exclusivity.

VERY LATE-STAGE CLINICAL DEVELOPMENT

Our development of ONS-5010 for wet AMD is in the late clinical stages. We fully enrolled a pivotal study in early July and are expecting topline phase III data to be reported in early Q3 next year. We already have data from one completed clinical experience trial, and a third ongoing supplemental safety study will also be included in our BLA package. We intend to file our BLA with the FDA in late Q3 2021, with approval anticipated as early as mid-2022.

One of the reasons we have been able to accelerate the development of ONS-5010 is access to a wealth of clinical use data, since unapproved bevacizumab has been so widely used for many years. Additionally, there are strong data demonstrating bevacizumab's value in treating retinal disease from the National Eye Institute's CATT study, which found that bevacizumab was not inferior to LUCENTIS® (Novartis).[1]

In our phase III program, ONS-5010 is dosed monthly. The LUCENTIS® control arm involves three monthly loading doses of LUCENTIS® followed by quarterly doses thereafter. By using these two different arms, we are confident that monthly dosing of LYTENAVA™ will be shown to be superior to quarterly dosing of LUCENTIS®, which would result in a positive outcome for the study.

We also expect to pursue approvals for ONS-5010 in DME and BRVO. If all goes as planned, we will start those studies in mid-2021 and aim to get FDA approval on those indications a year or two after the first approval for wet AMD.

BUILDING A MIDSIZED OPHTHALMIC COMPANY

We believe that partnering with a life sciences company with commercial infrastructure would support our goals.. For the Asian market, we formed a joint venture with China-based Syntone Technologies to develop and manufacture LYTENAVA™ for Greater China.

We have been successfully raising funds as we move through the development process for LYTENAVA™, with plans to generate a next round with our future partners, allowing us to keep our infrastructure lean and focused as we look to develop a pipeline around ONS-5010 and build out the company into a successful, mid-size ophthalmic company. P

ABOUT THE AUTHOR

Larry A. Kenyon
President, Chief Executive Officer and Chief Financial Officer
Outlook Therapeutics

Lawrence A. Kenyon joined Outlook Therapeutics as CFO and Secretary in September 2015. In August 2018, Mr. Kenyon became the Company's President and CEO while still serving as CFO and as a member of the board of directors. He has more than 20 years of experience serving in executive and senior management roles at private and public biotechnology, biopharmaceutical, specialty pharma, and financial services companies. He holds a BA in Accounting from the University of Wisconsin-Whitewater..

LinkedIn www.linkedin.com/in/lawrencekenyon/

REFERENCE

1. *NIH study finds Avastin and Lucentis are equally effective in treating age-related macular degeneration.* National Institutes of Health. 28 Apr. 2011. Web.

Trip Tracker

TOTAL SUMMARY

DAYS	TRAVEL TIME
25	172:51
DISTANCE	**FUEL AMOUNT**
7766 mi	946 L

FINAL DESTINATION

13°C

East Molesey, England

TOTAL HEALTH SUMMARY

STEPS	CALORIES BURNED
329,150	57,063
AVG. HEART RATE	**WALKING DISTANCE**
89	178 mi

TRIP STATS

- A total of 27 countries visited
- September 26 – October 22, 2020
- Start and End of Trip: The Mall, London, UK
- 24 support staff in New York, London, and Los Angeles
- 2–4 hours of 4k video captured every day, with 100 pictures and two pieces of key art
- 2 chrome-wrapped Mini Coopers
- Only 7 pairs of shoes — picking under 10 was actually a challenge for shoe aficionado, Nigel
- **Car 1: Nigel Walker,** That's Nice Founder and Managing Director, English, New York; **Jordi Castan**, Director of Video, French, London
- **Car 2: Phill Neill**, Digital Marketing Director, Account Director, English, London; **Mark Gostick,** Photography & Director, English, London

ON THE ROAD TO 2021
THERE WERE NO PASSENGERS ON THIS JOURNEY

By Nigel Walker and Phill Neill, Nice Insight

After months of preparation and much more time spent loosely imaging what it would be like to travel through 25 countries in as many days, four select That's Nice team members decided to embark on an arduous trek in search to explore the future of healthcare across Europe – during a (hopefully) once in a lifetime occurrence. Despite COVID-19 ravaging the world, upending travel and daily life alike, Nigel Walker, Phill Neill, Jordi Castan, and Mark Gostick decided to take matters into their own hands and go directly to the source for a comprehensive, first-hand account of Europe's COVID-19 pandemic, unmet medical needs across the continent, and how pharma and biopharma are innovating to create a brighter future.

In addition to meeting pharma industry executives, students, investors, and healthcare workers, the team spent time with European and British nationals, asking for their honest take on the pandemic and other outstanding healthcare needs. The responses ranged the gamut from caution over COVID-19 to the feeling that the response was an overreaction, and even utter rejection of the disease's existence. Meetings with industry insiders generated several sophisticated takes, including how the pandemic will help to spur an emphasis on personalized medicine, the need for direct-to-patient trials, the ability to flexibly manipulate the supply chain for drugs to be delivered on time, and an emphasis on mental health – a focus that recurred throughout the month-long excursion.

The team traveled over 7,500 miles across the continent by planes, ferries, and a pair of Mini Coopers wrapped in chrome, facing tough weather and an uncharted landscape of a continent in the grips of a pandemic. Here's what happened each day on The Road to 2021.

September 26-27, 2020

TRIP KICKOFF AT HOME HOUSE IN KENSINGTON, LONDON

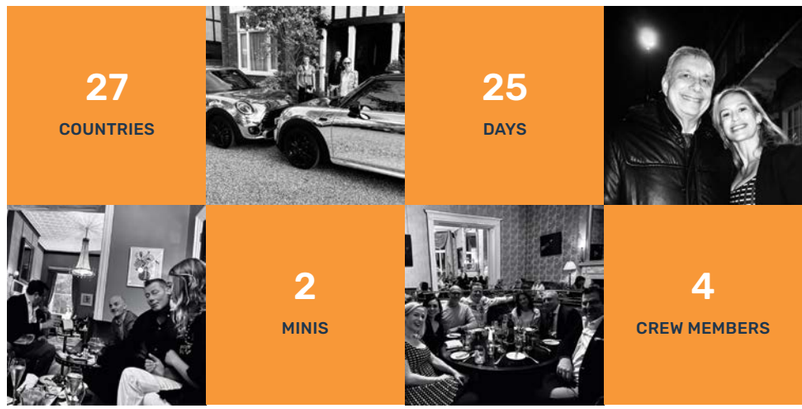
On the first official/unofficial day of the trip, there was excitement in the air. Though England had been locked down not long before, the most oppressive restrictions were presently lifted. There was the sense of an artificial celebration going on in the streets, as many relished their time together before the emergence of a possible second wave.

Nigel disembarked at Waterloo station, which was relatively empty, and traffic was additionally controlled through a soft barrier system, enforcing everyone to walk unilaterally. Though the party raged on outside, inside was a different story. England was enforcing the "Rule of Six" which meant no more than six people were permitted to gather together indoors. Though about 13 people had come out in support of the trip's kickoff at the Home House in Central London, they had to divide and meet with smaller groups, which was actually conducive to the design of the intimate space.

Fresh off their socially distanced event, Nigel was left enthusiastic and ready for what the next whirlwind of days would bring.

THE TEAM MET WITH:

Laura Towart and Alya Al-Johani, My Personal Therapeutics; **Don Phares,** *Manufacturing Chemist*; **Elisa Mantovani,** Graphic Designer; **Darragh Cullen,** Ocynovia Ltd.; **Russell Harris,** Centaur Biopharmaceutical Services; **Mallory Factor,** IntraBio; **Haig Armaghanian,** Haig Barrett Inc.; **Christina Georgallou,** Nutritional Therapist; **(Virtual) Rizwan Chaudhrey,** RSK-Solutions/RSK Life Science Media



2
COUNTRIES VISITED SO FAR

12°C

410 mi
TRAVEL DISTANCE

09:33
TRAVEL TIME

52 L
FUEL AMOUNT

Toughest Sequence of Days of the Trip: **Days 1–3**
Favorite Healthcare Worker of the Trip: **Laura Thomas**

September 28, 2020

SETTING OFF ON THE ROAD TO 2021

With considerable excitement, we hit the road for our first leg of travel. Departing London, we headed first for Stoke-on-Trent, where we met with Nigel's cousin Laura Thomas, a nurse at the Royal Stoke University Hospital, for our first interview exploring the impacts of the COVID-19 pandemic across the continent, learning about the challenges she and her colleagues have faced. Next, we zigzagged across England, reaching Gerrards Cross, where we were welcomed into the gorgeous and imposing sandstone home of Maliha Jaffer, the head of UK and Europe for Yourway, meeting with her and her colleague Hussein Pirbhai.

After enjoying their gracious hospitality, we got on the road to Wales a bit behind schedule, the first hint of a challenge that would stick with us throughout the trip. After an amazing drive through Welsh valleys, we arrived in Cardiff near the harbor in a heavy rainstorm, where we had a scheduled (and a bit tardy) meeting with Matthew Lakelin of TrakCel, with whom we discussed the future of supply chain and clinical trials logistics, particularly for smaller trials investigating things like cell and gene therapies.

The day also introduced us to one of the unique ways people are adapting commerce in the context of COVID-19: Phill needed to download an app to his phone in order to order a meal from a semi-portable kiosk. Although we were the only people there; they still required that we use the app! After that, we continued on a roughly 200-mile drive up to Holyhead, Wales, where we checked into a hotel to catch less than an hour of sleep.

THE TEAM MET WITH:
Maliha Jaffer and Hussein Pirbhai, Yourway; **Dr. Matthew Lakelin**, Trakcel; **Laura Thomas**, Royal Stoke University Hospital

HEALTHCARE IN WALES

POPULATION
3M *(4.5% of UK Population)*

LIFE EXPECTANCY
81.1 Years *(<1 Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2900 *(About €50 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 21%; Alcohol 22%

LEADING CAUSE OF DEATH
Heart Disease *(55.7% Decrease Since 2000)*

309 mi
TRAVEL DISTANCE

10 hr **6** min
TRAVEL TIME

"We Still Haven't Done a Guinness Brewery Tour": **Dublin**

September 29, 2020

EXPLORING THE EMERALD ISLE WITHOUT PUBS

On the second day of the trip, we woke up and caught a ferry from Holyhead to Dublin, experiencing our first border challenge of the trip, where we discovered that our honest story, that we were conducting interviews with local pharma and other businesses about COVID-19 and healthcare, satisfied the authorities.

Upon arriving in Dublin, we met with Graham Hogan, who runs a small, family healthcare business. Our primary takeaway from that conversation and our visit to Dublin more broadly was that the most important decisions made by Irish people – family and community decisions – are typically made at the pub, and the pandemic has taken that away from people, which is having an outsized impact on daily life. As a mark of respect, our next stop was the Guinness factory, where we were able to get some amazing pictures that would likely have been impossible in non-pandemic times. After that visit, we met with Gary McAuslan, who is looking to start a viral vector company in Dublin.

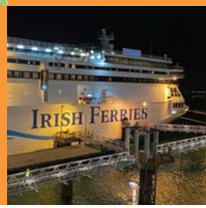
We then headed north toward Belfast, Northern Ireland, where we met outdoors with Kristof Szent-Ivanyi, COO of ChainbridgePharma, to discuss COVID-19's impact on supply chains and sustainable growth before boarding a ferry to Cairnryan, Scotland, finding ourselves an old hotel to crash for a few hours.

THE TEAM MET WITH:
Graham Hogan, Hogan Healthcare; **Gary McAuslan,** aCGT Vector; **Kristof Szent-Ivanyi,** ChainbridgePharma;

39 L
FUEL AMOUNT

4
COUNTRIES VISITED SO FAR

10°C



HEALTHCARE IN IRELAND

POPULATION
4M *(0.53% of Euro Population)*

LIFE EXPECTANCY
82.2 Years *(6 Yr Increase Since 2000)*

HEALTH SYSTEM
Hybrid: public, private, and out-of-pocket

HEALTH EXPENDITURE PER CAPITA
€3406 *(About €556 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 18%; Alcohol 32%

LEADING CAUSE OF DEATH
Heart Disease *(32.1% Decrease Since 2000)*

5
COUNTRIES VISITED SO FAR

11°C

291 mi
TRAVEL DISTANCE

5 hr **44** min
TRAVEL TIME

37 L
FUEL AMOUNT

Wettest Country of the Trip: **Scotland**

September 30, 2020

SCOTLAND, OUR COLLECTIVE FAVORITE STOP OF THE TRIP

We left our hotel on another day of intense rain, setting off on a gorgeous drive along the western coast of Scotland – with its pounding cliffs, weathered shoreline, and magnificent views – into the modern city of Glasgow, which felt totally deserted.

We arrived for a busy day of meetings and interviews at the Glasgow Science Center. This is a big statement, but we all agreed that Scotland was the country that embraced us the most, with many amazing people arriving excited to speak with us, many of whom had coordinated through Sandy Kennedy of Entrepreneurial Scotland. We met with representatives of eight companies: EOS Advisory, Talking Medicines, The Brain Tumour Charity, ClinSpec Dx, Glasgow Science Centre, Saltire Foundation, Entrepreneurial Scotland Foundation, and our local sponsor, Arranta Bio, as well as students and primary scientists.

After a long and invigorating day of meetings, we unfortunately had to hit the road without getting a chance to see much of the city, heading south across the border to Harrogate, England, a famous old Roman spa town, where we made up for the previous rough night by booking rooms at a big chain hotel. We ended what was probably the best day of the trip, having seen such amazing scenery, met with a large group of friendly and enthusiastic people, and actually got nearly eight hours of sleep, which was sorely needed.

THE TEAM MET WITH:
Dr. Mark Hegarty and Dr. Matthew Baker, ClinSpec Diagnostics Ltd; **Sandy Kennedy,** Entrepreneurial Scotland; **Kelly Glass,** Saltire Foundation; **Alice Russell,** The Brain Tumour Charity; **Jo Halliday and Dr. Elizabeth Fairley,** Talking Medicines; **Mark Beaumont,** EOS Advisory LLP; **Dr. Gillian Lang and Dr. Robin Hoyle,** Glasgow Science Centre; **Calum Stevens,** BDD Ltd.; **Nisha Middleton,** former That's Nice intern

HEALTHCARE IN SCOTLAND

POPULATION
5M *(7.5% of UK Population)*

LIFE EXPECTANCY
79.05 Years *(<1 Increase Since 2000)*

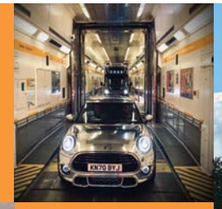
HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2900 *(About €50 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 21%; Alcohol 22%

LEADING CAUSE OF DEATH
Heart Disease *(50.7% Decrease Since 2000)*

447 mi
TRAVEL DISTANCE



8 hr **32** min
TRAVEL TIME

52 L
FUEL AMOUNT

7
COUNTRIES VISITED SO FAR

14°C

Two Mobsters on the Thames, London

October 1, 2020

SOUTHWARD THROUGH THE UK AND ACROSS THE CHANNEL TO EUROPE

Day four saw us making a few more stops in England before heading to continental Europe. We drove through the Yorkshire foothills, stopping briefly at a Royal Air Force base, before reaching the famous university city of Cambridge, where we had a meeting with Will Downie and Andreas Meliniotis of Vectura, a CDMO specializing in inhaled medicines, to discuss their recent rebranding, among other topics. We then returned to London to meet with our friend Russell Harris of Centaur Biopharmaceutical Services near his birthplace on the banks of the River Thames in Dartford.

Bidding goodbye to London, we drove to Folkestone, bought rail flexipasses, and drove our Minis onto the train that would take us across the English Channel to Calais, France. Having reached mainland Europe, we drove (now on the other side of the road) across northern France to arrive very late to spend the night in Brussels, capital of Belgium and de facto capital of the European Union, which felt like a suitable place to begin our exploration of the continent.

THE TEAM MET WITH:
Will Downie and Andreas Meliniotis, Vectura; **Russell Harris,** Centaur Biopharmaceutical Services

HEALTHCARE IN BELGIUM

POPULATION
11M *(1.47% of Euro Population)*

LIFE EXPECTANCY
81.6 Years *(4 Yr Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€3554 *(About €704 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 15%; Obesity 16%; Alcohol 27%

LEADING CAUSE OF DEATH
Heart Disease *(58.8% Decrease Since 2000)*

155 mi
TRAVEL DISTANCE

3 hr 07 min
TRAVEL TIME

20 L
FUEL AMOUNT

8
COUNTRIES VISITED SO FAR

13°C

Only Meeting on the Beach of the Trip: **the Hague**

October 2, 2020

A GORGEOUS AND RELAXING DAY IN THE BENE REGION

We began our first full day in continental Europe with more heavy rain, beginning with an outdoor interview with Thierry Durand of Minakem about highly potent APIs at the Université Libre de Bruxelles that turned out a bit funny, with us trying to stay professional while gradually becoming soaking wet.

We crossed over into the Netherlands for a stop in The Hague, where we first met with Maarten Pouw of Centrient Pharmaceuticals and chatted as we walked on the beach together, had a few beers, and shot some photos and videos using our drone. As an old friend of That's Nice, Maarten discussed the old days and the current situation in the Netherlands, including the country's response to the COVID-19 pandemic.

We ended our day of relatively light driving that exposed us to picturesque and historic scenery, not to mention modern, international centers of parliament, justice, and life sciences, with a stop in Amsterdam to meet an old buddy of ours, Stu Morrison, who works for Screen Europe, a digital printing company. After getting a bit lost and ending up driving on a tram line, we checked into a hotel in Amsterdam and had probably our first truly decent meal of the trip before hitting the sack, a bit regretful that we weren't able to see much of Amsterdam.

THE TEAM MET WITH:
Dr. Thierry Durand, Minakem; **Maarten Pouw,** Centrient Pharmaceuticals; **Stuart Morrison,** Screen Europe

HEALTHCARE IN THE NETHERLANDS

POPULATION
17M *(2.27% of Euro Population)*

LIFE EXPECTANCY
81.8 Years *(>3 Yr Increase Since 2000)*

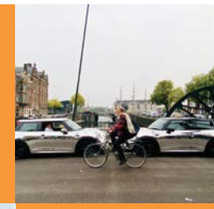
HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€3791 *(About €941 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 13%

LEADING CAUSE OF DEATH
Heart Disease *(64.9% Decrease Since 2000)*

715 mi
TRAVEL DISTANCE



14 hr 1 min
TRAVEL TIME

90 L
FUEL AMOUNT

10
COUNTRIES VISITED SO FAR

16°C

Two Speeding Tickets (Top speed: 135 MPH): **Holland**

October 3, 2020

A DAY OF SERIOUS DRIVING ACROSS GERMANY AND INTO DENMARK

Day six started early, as we departed Amsterdam before the sun had fully risen, capturing some great photos and footage of windmills, locks, waterways, and bridges before embarking on our first really big day of driving from a mileage perspective, which would ultimately take us across 715 miles from Amsterdam to Copenhagen, Denmark, passing across northern Germany on an auspicious day as the country marked the 30th anniversary of reunification.

After being stopped twice for speeding in the Netherlands, our first stop was with Fritjof Linz of Sartorius, meeting on the patio of his family home on the outskirts of Hanover, the capital of Lower Saxony to talk about the future of bioprocessing.

We then drove to Hamburg where we met with Marc Technow, a former intern at That's Nice and friend who recently completed his Master's Degree in Cologne, who deserves the biggest effort badge among our contacts, having embarked on a 9-hour round trip from his home to speak with us. While discussing unmet medical needs in Germany, Marc brought up mental health as a subject that is largely brushed under the carpet in Germany, the first of a series of similar responses we received in interviews across the continent, including in France.

Reaching the north German coast, we boarded a ferry for a short ride to Denmark, where we experienced the toughest border crossing scrutiny of the whole trip, but after providing information about our contacts in the country, the situation was resolved. We then drove the remaining two hours or so to the capital city of Copenhagen, where we called it a day.

THE TEAM MET WITH:
Dr. Fritjof Linz, Sartoris Stedim Biotech
Marc Technow, former That's Nice intern

HEALTHCARE IN DENMARK

POPULATION
5M *(0.67% of Euro Population)*

LIFE EXPECTANCY
81.1 Years *(4+ Yr Increase Since 2000)*

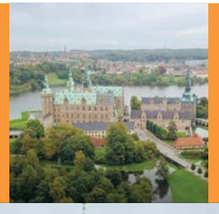
HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€4000 *(About €1100 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 17%; Alcohol 37%

LEADING CAUSE OF DEATH
Heart Disease *(65.5% Decrease Since 2000)*

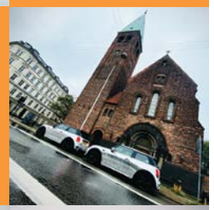
432 mi
TRAVEL DISTANCE



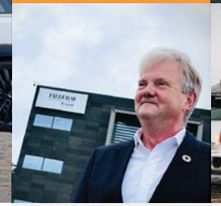
8 hr **34** min
TRAVEL TIME

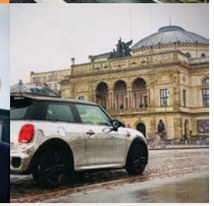
11
COUNTRIES VISITED SO FAR

14°C



54 L
FUEL AMOUNT





Sunday morning welcome from Morten: **Denmark**

October 4, 2020

HEAVY RAIN AND NOBEL PRIZES

Sunday began with more heavy rain (a running theme!), as we piled into the Minis for about an hour's drive to meet with Morten Munk at the FUJIFILM Diosynth Biotechnologies facility in Hillerød. The weather turned out to be so uncooperative that we conducted one of our few indoor interviews. It was great to catch up with Morten after a number of years, and we discussed his long history in the industry and FUJIFILM's impressive expansion plans for that site, as well as his interest in high-speed rollerblading.

In the increasingly heavy rain, we paid a visit to a local castle before heading to what we thought was going to be a bridge across to Sweden, only to arrive at our destination and discover no bridge existed, after which we immediately booked passage on a ferry to Malmo, Sweden (something that probably would have been impossible in pre-pandemic times).

We reached northern Europe's largest country on the same day that the Nobel Prize for Medicine and Physiology was announced – another fortuitous coincidence – and proceed to drive for six or seven hours across Sweden before finally reaching Stockholm.

THE TEAM MET WITH:
Morten Munk, FUJIFILM Diosynth Biotechnologies

HEALTHCARE IN SWEDEN

POPULATION
10M *(1.34% of Euro Population)*

LIFE EXPECTANCY
82.5 Years *(2 Yr Increase Since 2000)*

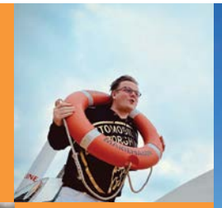
HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€1507 *(About €1343 Below the EU Average)*

PRIMARY RISK FACTORS
Smoking 10%; Obesity 13%

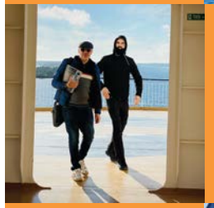
LEADING CAUSE OF DEATH
Heart Disease *(52.3% Decrease Since 2000)*

391 mi
TRAVEL DISTANCE



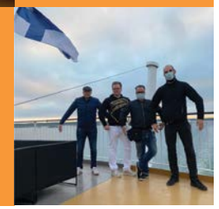
14 hr **35** min
TRAVEL TIME

28 L
FUEL AMOUNT



12
COUNTRIES VISITED SO FAR

14°C



Least Bugs on the Windscreen of the Trip: **Finland**
Most Peaceful Day of the Trip: **Sweden**

October 5, 2020

A RELAXING VOYAGE PAST THE FJORDS

Day eight was another hard traveling day with no scheduled interviews. After spending some time in the morning exploring Stockholm, we drove the minis onto yet another ferry, this one bound for Finland. The three-hour ferry ride gave us one of our longest stretches awake but out of the cars, as we relaxed and interacted with other ferry passengers while enjoying the beautiful weather that made up for the previous day's deluge. As the mostly empty ferry passed through fjords with their thousands of tiny islands, the team captured some amazing photographs.

After arriving in Finland, we had a few hours' drive to the capital, Helsinki. Nigel was very strongly struck – after over a week of periodic stops to clean graveyards of bugs off the windshields of the Minis – to not observe any bugs whatsoever in Finland.

HEALTHCARE IN FINLAND

POPULATION
5M *(0.67% of Euro Population)*

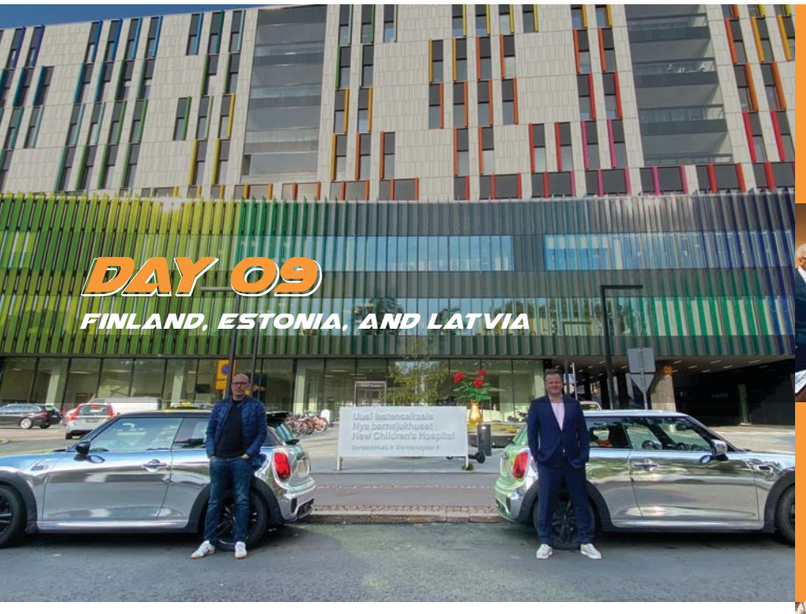
LIFE EXPECTANCY
81.7 Years *(4+ Yr Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€3036 *(About €186 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 14%; Obesity 20%

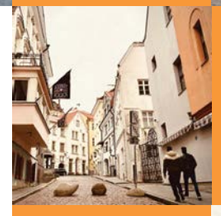
LEADING CAUSE OF DEATH
Heart Disease *(47.8% Decrease Since 2000)*



409 mi
TRAVEL DISTANCE

9 hr 32 min
TRAVEL TIME

52 L
FUEL AMOUNT



14
COUNTRIES VISITED SO FAR

14°C

Favorite Hospital Architecture of the Trip: **Finland**

October 6, 2020

ONWARD INTO THE BALTICS

Our morning in Finland began with some sightseeing there – in the northernmost city we reached on the trip, followed by a meeting with Marko Salo and Arto Toivonen of Fermion, the CDMO unit of Orion Corporation, the largest pharma company in the country, where we chatted about significant trends impacting the future of oncology. After stopping at an absolutely breathtaking hospital that looked more like a modern art museum, we headed to the waterfront to catch another ferry, which took us to Tallinn, Estonia.

As we traveled across Estonia and into Latvia – including a very fun stop at a graffiti-festooned cluster of derelict buildings – we were struck by the absence of real highways in the Baltic states, realizing that the good time we were making would be virtually impossible if not for the COVID-19–related shutdowns. We spent the night in the Latvian capital of Riga.

THE TEAM MET WITH:

Marko Salo and Arto Toivonen, Fermion, a unit of Orion Corporation

HEALTHCARE IN ESTONIA

POPULATION
1M *(0.13% of Euro Population)*

LIFE EXPECTANCY
78.4 Years *(7+ Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€1559 *(About €1291 Below the EU Average)*

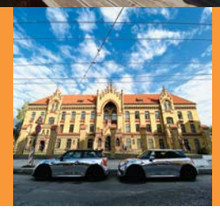
PRIMARY RISK FACTORS
Smoking 21%; Obesity 21%; Alcohol 23%

LEADING CAUSE OF DEATH
Heart Disease *(62.8% Decrease Since 2000)*

15
COUNTRIES VISITED SO FAR

12°C

208 mi
TRAVEL DISTANCE



4 hr 45 min
TRAVEL TIME

26 L
FUEL AMOUNT

Favorite Healthcare Image of the Trip: **Latvia**

October 7, 2020

POLICE ENCOUNTER AND SOVIET AIRCRAFT

Day 10 began with the team exploring the beautiful 13th century city of Riga, with its art nouveau architecture and 19th century wooden buildings. One thing that caught our attention was an enormous monument outside of a medical museum depicting a nurse in a white medical gown with a stethoscope and a face mask, which struck us as particularly poignant in these uncertain times. Unfortunately, Phill and Mark attracted some negative attention from local law enforcement for photographing the monument (apparently a faux pas).

We were taken on a tour of MGI Latvia's new R&D and manufacturing facility for its gene sequencing and multi-omics platforms by Rolando Delgado, after which we interviewed the General Manager, Andis Šlaitas, who provided a very personal take on the COVID-19 pandemic.

After leaving Riga, we stopped to conduct a Zoom interview with Vladas Bumelis, Chairman of the Board of Northway Biotech, which is based in Vilnius, Lithuania, precisely where we were headed. With over 40 years in the industry, few can match Vladas's experience, and he told us about the considerable expansion underway at the Vilnius facility.

Continuing on at dusk, the team was struck by coming across an airfield connected to a hotel that was full of MIG aircraft and large Russian helicopters. Crossing into Lithuania and finally encountering real highways again, we ultimately reached Vilnius late in the evening, where we were able to locate an elegant restaurant where we enjoyed a rare fine meal before calling it a night.

THE TEAM MET WITH:

Rolando H. Delgado and Dr. Andis Šlaitas, MGI Latvia; **(Virtual) Dr. Vladas Bumelis,** Northway Biotechpharma

HEALTHCARE IN LITHUANIA

POPULATION
2M *(0.27% of Euro Population)*

LIFE EXPECTANCY
75.8 Years *(5+ Yr Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€1500 *(About €1350 Below the EU Average)*

PRIMARY RISK FACTORS
Smoking 20%; Obesity 17%

LEADING CAUSE OF DEATH
Heart Disease *(18.7% Decrease Since 2000)*

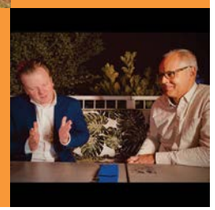
350 mi
TRAVEL DISTANCE

7 hr **22** min
TRAVEL TIME

44 L
FUEL AMOUNT

16
COUNTRIES VISITED SO FAR

12°C



Most Off-Road Driving: **Poland**

October 8, 2020

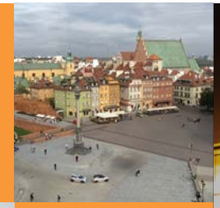
CROSSES ON THE ROAD TO WARSAW

We left Vilnius in the morning for another long day on the road, stopping briefly at the Northway Biotech facility in the city. Entering into Poland, Nigel noticed the hundreds of crosses the team observed dotting the highways, counting about 10 or more per mile, which are permanent markers of deaths from road accidents.

With no official interviews scheduled for the day, we arrived in Warsaw in the evening and had dinner with Eryk Krysztofiak, an old friend of Nigel's, and his wife, enjoying some hearty, traditional Polish cuisine. Having met in New York before moving their new family back to Poland, with one child born in each country, Eryk shared an interesting comparison between obstetric care between the two countries, contrasting Polish hospitals' willingness to let new mothers extend their hospital stays for several days with the hustle to discharge them within hours in New York. On the other hand, Eryk discussed the prejudice he experienced in Poland as a result of his leaving the country for an overseas education.

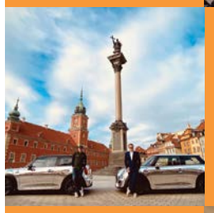
THE TEAM MET WITH:
Eryk Krysztofiak, Warsaw Property Management

467 mi
TRAVEL DISTANCE



7 hr **59** min
TRAVEL TIME

59 L
FUEL AMOUNT



17
COUNTRIES VISITED SO FAR

15°C

Statement of the Trip: **Gold**

October 9, 2020

A CHANGE OF PLANS LEADS US TO PRAGUE

We decided to change up our original route plan a bit and travel to Prague instead of Krakow. This was approximately a 350-mile drive. On the way, we decided to clean the cars, and took the opportunity to speak with the locals at the civic station and curiously received an offer from someone who wanted to buy one of our cars – but for his wife.

As we continued on our way, we noticed a facility that looked like something out of Mad Max or a massive Hollywood set. It was a huge power station with coolant towers that were nearly 300 feet tall, juxtaposed with a hydroponic greenhouse. We drove right up to the gates and took photos of the facility, despite a security guard lurking in the shadows.

After we secured our key art, we hit the road again and wound up in Prague, which has very picturesque, classic, Gothic architecture. We reached the hotel, which was rather decadent and totally empty because of COVID-19. The lobby was about 16,000 square feet, and we had it almost exclusively to ourselves.

HEALTHCARE IN POLAND

POPULATION
3M *(4.5% of UK Population)*

LIFE EXPECTANCY
81.1 Years *(1+ Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2900 *(About €50 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 21%; Alcohol 22%

LEADING CAUSE OF DEATH
Heart Disease *(55.7% Decrease Since 2000)*

HEALTHCARE IN CZECH REPUBLIC

POPULATION
10M *(1.34% of Euro Population)*

LIFE EXPECTANCY
80.9 Years *(4 Yr Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2096 *(About €754 Below the EU Average)*

PRIMARY RISK FACTORS
Smoking 18%; Obesity 20%

LEADING CAUSE OF DEATH
Heart Disease *(23.8% Decrease Since 2000)*

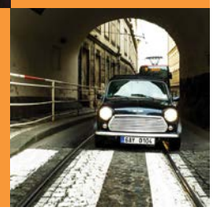
243 mi
TRAVEL DISTANCE

4 hr **33** min
TRAVEL TIME

31 L
FUEL AMOUNT

18
COUNTRIES VISITED SO FAR

13°C



Worst Breaking of the Rules of the Trip: **Prague**

October 10, 2020

LEARNING ABOUT PHARMACOVIGILANCE IN BRATISLAVA

Of course, we woke up to pouring rain, yet again. We decided to meet Alan by a famous bridge that would typically have 5,000 people on it but was totally empty at the time. The rain had stopped, and we decided to take advantage and conduct the interview on the bridge. Alan then took us back to the Arriello offices, where we chatted more about business and the impact of COVID-19 on pharmacovigilance, risk management, and compliance and admired their very cool wall of plants.

We reached our next destination, Bratislava, relatively ahead of schedule, a rare occurrence on this trip. We used the time to do our laundry in a mall. The hotel where we stayed had a retro, steampunk decor. It was time to eat again, so we went to probably the most crowded restaurant of the whole trip. They were less concerned about restrictions overall in Slovenia, though people were wearing masks.

This was the only time we were actually able to enjoy a few beers. We turned in around 9 pm to prepare for the big day ahead of us.

THE TEAM MET WITH:
Alan White and Anna Lukyanova, Arriello

HEALTHCARE IN SLOVAKIA

POPULATION
5M *(0.67% of Euro Population)*

LIFE EXPECTANCY
77.3 Years *(4+ Yr Increase Since 2000)*

HEALTH SYSTEM
Compulsory

HEALTH EXPENDITURE PER CAPITA
€1507 *(About €1343 Below the EU Average)*

PRIMARY RISK FACTORS
Smoking 25%

LEADING CAUSE OF DEATH
Heart Disease *(34.1% Decrease Since 2000)*

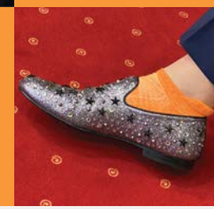
19
COUNTRIES VISITED SO FAR

13°C

19 L
FUEL AMOUNT

154 mi
TRAVEL DISTANCE

3 hr **35** min
TRAVEL TIME



Favorite Fixer of the Trip: **Uncle Alex**

October 11, 2020

MEETING TWO TRIP SPONSORS IN BRATISLAVA

It was a Sunday morning and we drove up to meet Andrew Mitchell from BioVectra, one of the sponsors, at a scenic castle with incredible views – you could see the whole of Vienna from this spot. We left Andrew and met with trip sponsor SanaClis's Alex Fetkovsky, who we nicknamed "Uncle Alex," because he fit perfectly into the role of the proactive doer and fixer. Alex invited us into his home, his offices, and the logistics warehouse, which is also serving as SanaClis' Bratislava location. In addition to being very accommodating and illuminating us about post-pandemic changes to clinical trials, Alex offered us to set us up with personal contacts in Croatia and Hungary.

The day led us to Bratislava's old town where we came across six students all from six different countries – Russia, Northern Africa, Egypt – all over the place. They were all Ph.D. and Master's level students, and it's doubtful we would have encountered them if not for Alex.

We headed off and traveled about three hours and thirty-five minutes to Budapest. We had been cautioned that crossing that border would be difficult though luckily encountered no issues. We emerged from this gorgeous tunnel that takes you into the city, and you then cross this beautiful bridge over the Danube River. The city is really picture perfect – it looks just like a postcard, especially with all the buildings lit up at night.

We threw our stuff down in the hotel as quickly as we could and left to meet Dr. Claudia Francesca, a contact of Phill's. The conversation shifted from life in Budapest to the healthcare system, and she informed us that public healthcare is actually preferable to the private sector – which doesn't have enough support to be viable. This was the first time where we heard about a public healthcare system trumping the private sector.

THE TEAM MET WITH:
Andrew Mitchell, BioVectra; **Alexander Fetkovsky,** SanaClis; **Dr. Klaudia Franciska Fodor,** Fodor Klaudia Law Firm

HEALTHCARE IN HUNGARY

POPULATION
9M *(1.2% of Euro Population)*

LIFE EXPECTANCY
76 Years *(4 Yr Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€1468 *(About €1382 Below the EU Average)*

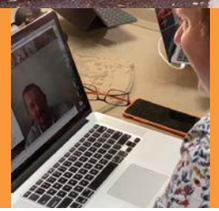
PRIMARY RISK FACTORS
Smoking 26%; Obesity 20%

LEADING CAUSE OF DEATH
Heart Disease *(16.5% Decrease Since 2000)*

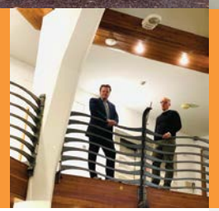
20
COUNTRIES VISITED SO FAR

8°C

239 mi
TRAVEL DISTANCE



4 hr **33** min
TRAVEL TIME



30 L
FUEL AMOUNT

Most Beautiful Architecture of the Trip: **Budapest**

October 12, 2020

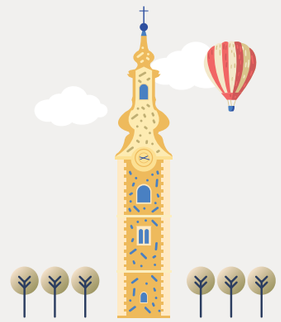
PRECLINICAL TRIALS AND PERSONALIZED DOSING

It was another wet day! We braved the weather and met with Liam Crow from FirstMed, a private English-speaking general health practice with a full range of services. Liam is originally from the United States, so he was able to speak candidly about healthcare in Hungary versus in his native New Jersey.

We jetted from that interview to meet with Stephen Collison a filmmaker, followed by Erno Duda, the founder of SOLVO. The company is focused on preclinical trials and was recently acquired by Charles River. Erno shared his insights on the future of healthcare, which he sees as patients being dosed differently – it makes no sense that the same dosage is used for mostly everyone, regardless of their specific size, age, or gender. We felt that was a very strong vision, though there's no telling how far into the future this would be from actualizing.

Our next stop was Croatia, where we stayed at a four-star city hotel. We were able to park the cars right outside, which would have been an impossibility under normal circumstances. The hotel had a Michelin two-star chef and we let the restaurant suggest what we should eat – it was off the chart good, good food. Totally satiated, we enjoyed a fabulous night's sleep.

THE TEAM MET WITH:
Liam Crow, FirstMed; **Stephen Collison,** filmmaker; **(Virtual) Erno Duda,** SOLVO Biotechnology, a Charles River Company



HEALTHCARE IN CROATIA

POPULATION
4M *(0.53% of Euro Population)*

LIFE EXPECTANCY
78 Years *(<3 Yr Increase Since 2000)*

HEALTH SYSTEM
Compulsory

HEALTH EXPENDITURE PER CAPITA
€1272 *(About €1578 Below the EU Average)*

PRIMARY RISK FACTORS
Smoking 25%; Obesity 18%; Alcohol 47%

LEADING CAUSE OF DEATH
Heart Disease *(34.3% Decrease Since 2000)*

190 mi
TRAVEL DISTANCE

4 hr **29** min
TRAVEL TIME

24 L
FUEL AMOUNT

22
COUNTRIES VISITED SO FAR

4°C

Best Food of the Trip: **Croatia**

October 13, 2020

PUBLIC HEALTHCARE TRUMPS PRIVATE IN EASTERN EUROPE

Our first meeting of the day was with Ljubisha Mitof Visurski, who works in media and brought his senior PR representative, Natalija Petkovic to the meeting. Our conversation focused on patient relations and how healthcare is administered. Again, the public healthcare system is very strong in Croatia and the private side of the business just doesn't exist. Instead, everybody's wellness is factored in through the sweeping healthcare system.

Uncle Alex had sorted us out with the hotel, which worked out wonderfully. We left to make our way to Slovenia, which we knew very little about, aside from it being the home country of Melania Trump. We were greeted by gorgeous, beautiful landscapes including mountain ranges, and ultimately walked away with the view that Slovenia is an underappreciated gem. We arrived at the capital city of Ljubljana at the end of the day and met with Jacqueline Stuart of Slovenia Invest, who taught us about healthcare and other industries in the county.

We then headed through the mountain ranges to our next destination, Austria. We stopped off at this enclave that was straight out of a Bond film, with castles hanging on cliff tops overlooking the water – like 200 feet in the air, and we took shots with the drone. We ended up in Bad Kleinkirchheim and met the proprietor of the hotel we were staying at, Gunther Raunig, and (finally) had a meal.

THE TEAM MET WITH:
Dr. Ljubisha Mitof Visurski and Natalija Petkovic; Jacqueline Stuart, Slovenia Invest

HEALTHCARE IN SLOVENIA

POPULATION
2M *(0.27% of Euro Population)*

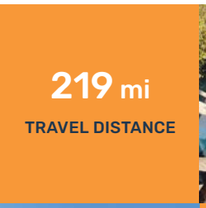
LIFE EXPECTANCY
81.2Years *(5 Yr Increase Since 2000)*

HEALTH SYSTEM
Compulsory

HEALTH EXPENDITURE PER CAPITA
€2060 *(About €790 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 19%; Obesity 16%

LEADING CAUSE OF DEATH
Heart Disease *(47.1% Decrease Since 2000)*



219 mi
TRAVEL DISTANCE

4 hr **57** min
TRAVEL TIME

28 L
FUEL AMOUNT

22
COUNTRIES VISITED SO FAR

5°C

Best Weather of the Trip, Best Driving Day of the Trip, and Best Views of the Trip: **Austria**

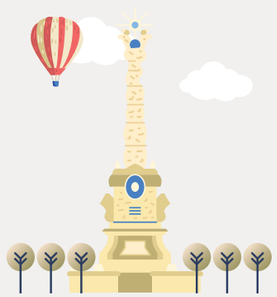
October 14, 2020

RECHARGING AT THE ALPINE PASS

Waking up high in the Alps, we spoke more with our hotelier, who introduced us to Jacob Forstnig, head of the tourist board of the resort town, which was the birthplace of Olympic alpine skier Franz Klammer, which made a lot of sense. After debating and ultimately deciding against a mountain hike, we instead proceeded by cable car up some of the mountains to the Alpine Pass, viewing breathtaking vistas, including changing leaves, without the usual crowds. Mark determined to return to Bad Kleinkirchheim sometime soon in his camper van. We did, however, observe some of the lowest levels of mask wearing we had seen across Europe.

Returning to the Minis, we headed down the gorgeous, winding Alpine Road through stunning scenery to ultimately reach our hotel in Linz. Austria.

THE TEAM MET WITH:
Jacob Forstnig, Bad Kleinkirchheim tourist board; **Guenter Raunig,** hotel proprietor



HEALTHCARE IN AUSTRIA

POPULATION
8M *(1.07% of Euro Population)*

LIFE EXPECTANCY
81.7 Years *(3 Yr Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€3900 *(About €1050 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 24%; Obesity 15%

LEADING CAUSE OF DEATH
Heart Disease *(39.4% Decrease Since 2000)*

318 mi
TRAVEL DISTANCE

6 hr **26**min
TRAVEL TIME

40 L
FUEL AMOUNT

24
COUNTRIES VISITED SO FAR

6°C

Smallest Country of the Trip: **Liechtenstein**

October 15, 2020

FOUR COUNTRIES IN A DAY, BUT FEW MASKS

Greeting the day in Linz, we decided we had to try some Linzer Torte, the first desert associated with a geographic place in history, but we were frankly underwhelmed. We explored the medieval city and had a brief meeting with a previous work colleague at a large CDMO that was acquired by a very large integrated pharma services supplier. We then left Austria behind and proceeded to Munich, Germany, a very impressive modern city that notably includes an English garden where the Eisbach, a small man-made channel of the Isar River has become a popular destination for river surfing.

Recalling Germany's early success in containing COVID-19, we were quite surprised by the low level of mask wearing that we observed in Munich, which may explain the recent surges in cases in the country.

We made a stop in Vaduz in the German-speaking principality of Liechtenstein, but we had been unable to arrange any meetings in the tiny microstate, making it one of only two countries where we came up empty. We then proceeded to Zürich, Switzerland.

HEALTHCARE IN GERMANY

POPULATION
83M *(11.1% of Euro Population)*

LIFE EXPECTANCY
81.1 Years *(3 Yr Increase Since 2000)*

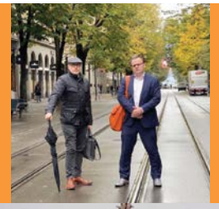
HEALTH SYSTEM
Nearly Universal

HEALTH EXPENDITURE PER CAPITA
€4300 *(About €1450 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 19%; Obesity 16%; Alcohol 33%

LEADING CAUSE OF DEATH
Heart Disease *(46.5% Decrease Since 2000)*

300 mi
TRAVEL DISTANCE

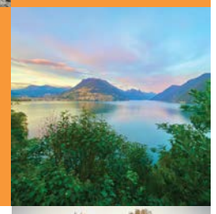


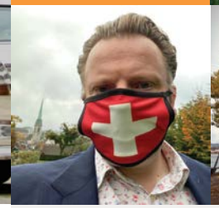
6 hr 49 min
TRAVEL TIME

25
COUNTRIES VISITED SO FAR

11°C

38 L
FUEL AMOUNT





Longest Life Span of a Citizen Along the Trip Route: **Switzerland**

October 16, 2020

UNDERSTANDING THE SWISS WAY

Nigel was very curious to meet with Swiss citizens, curious about their high standard of living, top-notch healthcare systems, and life expectancy that is among the highest in Europe. Waking up early in hospitable weather, we headed on foot to a meeting with Oriol Saludes, CEO and co-founder of Kemiex AG, a supply chain and sourcing company. By combining buyer and supplier perspectives, Kemiex built a very impressive platform that has expanded considerably over the last few years.

Leaving Zurich toward Basel, we took a pretty drive past a number of pharma facilities, including Novartis and Roche sites. We stopped at an old church and met outside with Brian Peasley, an American working for Integrated Project Services, LLC (IPS), another trip sponsor. In addition to discussing what pharma facilities of the future may look like, we talked about some of the differences he has perceived between Switzerland and the United States, in terms of healthcare and other concerns.

Heading south toward Italy, we drove past the pristine lakes that are major tourist destinations for the Swiss, Italians, and other Europeans, before reaching our final destination for the day, Milan, Italy.

THE TEAM MET WITH:
Oriol Saludes, Kemiex AG; **Brian Peasley,** Integrated Project Services, LLC (IPS)

HEALTHCARE IN SWITZERLAND

POPULATION
8M *(1.07% of Euro Population)*

LIFE EXPECTANCY
83.3 Years *(3 yr Increase Since 2000)*

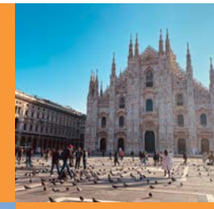
HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€5799 *(About €2949 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 25.7%; Obesity 19.5%

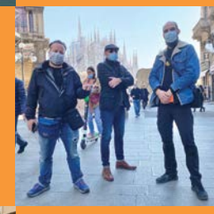
LEADING CAUSE OF DEATH
Heart Disease *(53.8% Decrease Since 2000)*

19.2 mi
WALKING DISTANCE



42,288
STEPS

865 kcal
CALORIES BURNED



25
COUNTRIES VISITED SO FAR

12°C

Most Beautiful City of the Trip: **Milano**
City Leader in Mask-Wearing Compliance: **Milano**

October 17, 2020

THE (PEDESTRIAN) ROAD THROUGH MILANO

Everyone started day 20 with a little spring in their steps, knowing that we wouldn't be doing any driving at all. We headed out on foot to explore the city and conduct two interviews. Although Scotland remained Nigel's favorite country overall owing to the enthusiasm of the people we met, Milano's beauty quickly earned it the rank of favorite city.

The first interview occurred against the backdrop of the magnificent Piazza del Duomo with Silvia Baldina and Simona Rivarollo of Tekno Scienze, an Italian academic publisher, with whom we discussed trends in life sciences publishing as well as Italy's tough early days with the COVID-19 pandemic.

After visiting Sempione Park and the Trienello Modern Art Museum, we headed to City Life, a new business park and commercial district, to meet with Luca Mantovani of specialty chemicals distributor Eigenmann & Veronelli, who spoke about supply chain changes in the wake of the pandemic. After the meeting, Luca was able to sweet talk our way into a very exclusive Argentinian steakhouse in the city for an unexpected but incredible meal, before finally turning in.

THE TEAM MET WITH:
Simona Rivarollo and Silvia Baldina, Tekno Scienze SRL; **Luca Mantovani,** independent

HEALTHCARE IN ITALY

POPULATION
60M *(8.02% of Euro Population)*

LIFE EXPECTANCY
83.1 Years *(3+ Yr Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2483 *(About €367 Above the EU Average)*

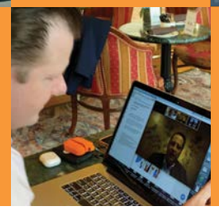
PRIMARY RISK FACTORS
Smoking 20%; Obesity 11%

LEADING CAUSE OF DEATH
Heart Disease *(33% Decrease Since 2000)*

339 mi
TRAVEL DISTANCE

6 hr 33 min
TRAVEL TIME

43 L
FUEL AMOUNT



26
COUNTRIES VISITED SO FAR

12°C

The Place We Want to Go Back to: **Monaco**

October 18, 2020

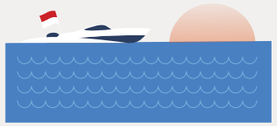
MONTE CARLO AND ALONG THE FRENCH RIVIERA

Day 21 began at our hotel with a virtual interview with Paolo Tubertini, CEO of Olon, another of our trip's sponsors, who discussed what to expect from Olon going forward, including a number of firsts for the company. He explained how the company is dealing with issues like validation batches in the context of the pandemic using cameras and virtual tools, without the physical presence of staff from a sponsor company.

After wrapping up the interview, we hit the road again, driving along sea cliffs and into the principality of Monaco. Once again, we experienced a kind of vertigo once we got to Monte Carlo, seeing the popular tourist destination looking a bit more like a ghost town. The weather was perfect for walking around a seafront city, and we soaked in the fresh air and blue skies.

At the famous marina, we met with Gilles Pagès, Director of Research INSERM at Roca Therapeutics to talk about the future of ocular therapies, as the company aims to close the gap of unmet needs for macular degeneration – with existing therapies offering a 50% chance of efficacy and a 50% chance the patient will end up going blind – to develop truly efficacious therapies. After saying goodbye to GIlles, we headed along the French Riviera, past Nice and into Marseille, settling in at a hotel in a fantastic location, but with lousy food.

THE TEAM MET WITH:
(Virtual) Paolo Tubertini, Olon; **Dr. Gilles Pagès,** Roca Therapeutics



HEALTHCARE IN MONACO

POPULATION
38K *(0.005% of Euro Population)*

LIFE EXPECTANCY
89.5 Years *(10+ Yr Increase Since 2000)*

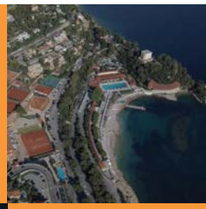
HEALTH SYSTEM
Compulsory

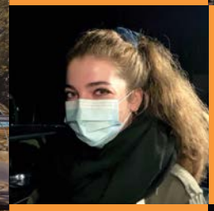
HEALTH EXPENDITURE PER CAPITA
€2932 *(About €100 Above the EU Average)*

PRIMARY RISK FACTORS
Physical Inactivity, Smoking

LEADING CAUSE OF DEATH
Cancer *(58.7% Decrease Since 2000)*

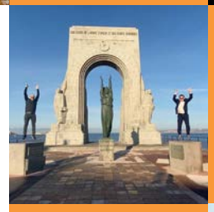
417 mi
TRAVEL DISTANCE





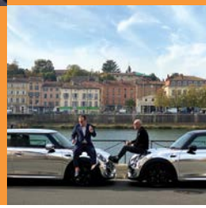
7 hr 42 min
TRAVEL TIME

53 L
FUEL AMOUNT



27
COUNTRIES VISITED SO FAR

8°C



Only Chateau We Visited on the Trip: **Mâcon**

October 19, 2020

HITTING OUR 27TH COUNTRY IN 22 DAYS

Our final Monday began with an interview with Margaux André, and oncology nurse at a private hospital and a friend of Jordi's. We discussed the challenges facing nurses during the pandemic and the dedication of nurses to their patients despite the heightened risks.

After that, we had a fun day driving around Marseille, exploring some of the gorgeous architecture and monuments, and launching our drone to capture some footage. We then hit the road in earnest in a seven-hour blur of miles through France, passing Lyon and Mâcon before reaching Luxembourg, passing our hoped-for country count for the trip – 27 countries – three days ahead of schedule.

THE TEAM MET WITH:
Margaux André, oncology nurse

HEALTHCARE IN LATVIA

POPULATION
1M *(0.13% of Euro Population)*

LIFE EXPECTANCY
74.9 Years *(4+ Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€1213 *(About €50 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 25%; Obesity 21%

LEADING CAUSE OF DEATH
Heart Disease *(31.6% Decrease Since 2000)*

279 mi
TRAVEL DISTANCE

5 hr **36** min
TRAVEL TIME

27
COUNTRIES VISITED SO FAR

13°C

35 L
FUEL AMOUNT

Most Impressive Healthcare Vision of the Trip: **Luxembourg**

October 20, 2020

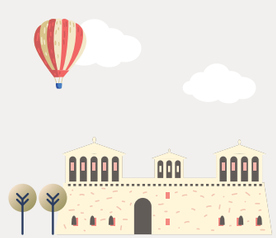
THE FUTURE OF PERSONALIZED MEDICINE IN LUXEMBOURG

While still in Luxembourg and noticing many similarities to our time in Switzerland, we met with Anna Chioti, Head of Pharmacy and Medicines at Luxembourg Health Directorate – Direction de la Santé, who confirmed similarities between the two wealthy countries' healthcare systems. Her description of the principality's work toward a centralized, digitized healthcare system – capturing all of a patient's interactions with the system, from doctor visits and hospitalizations through prescription adherence – sounded like the kind of distant fantasy we have in the United States about the promise of personalized medicine. Anna was something of the trip's unicorn, with experience in R&D, as an innovator, on the commercial side, and now public service.

Our next meeting was with Jens Schwamborn of Organo Therapeutics, who told us about the company's cutting-edge work on minibrains exploring therapies for Parkinson's disease and dementia. Next we met with Marc Jacobs – an engineer, not the designer – from Molecular Plasma Group (MPG), in the Technoport Hall innovator hub in Foetz, where MPG has their facility. Marc explained how the company uses plasma to coat objects, including automobile parts and now face masks, and even exploring ways to use polymers to coat APIs.

We then hit the road to reach our final destination, Paris, France. We arrived late that night in heavy rain (no surprise), when the city's curfew was in effect, with some trepidation that we would not be allowed into the city but were surprised to see it more bustling than any other metropolis we had visited, with a lot of people on the street without masks. Exhausted from the day, we found a lousy hotel and settled in.

THE TEAM MET WITH:
Dr. Anna Chioti, Luxembourg Health Directorate – Direction de la Santé; **Dr. Jens Schwamborn,** Organo Therapeutics; **Marc Jacobs,** Molecular Plasma Group (MPG)



HEALTHCARE IN LUXEMBOURG

POPULATION
596K *(0.08% of Euro Population)*

LIFE EXPECTANCY
82.1 Years *(4+ Yr Increase Since 2000)*

HEALTH SYSTEM
Hybrid

HEALTH EXPENDITURE PER CAPITA
€4936 *(About €2086 Above The Eu Average)*

PRIMARY RISK FACTORS
Smoking 16%; Obesity 16%; Alcohol 35%

LEADING CAUSE OF DEATH
Heart Disease

7 mi
TRAVEL DISTANCE

0 hr **45** min
TRAVEL TIME

1 L
FUEL AMOUNT

27
COUNTRIES VISITED SO FAR

17°C

Biggest Interview of the Trip: **Paris**

October 21, 2020

PARIS SITES AND DIGITAL SOLUTIONS

We awoke in our tiny rooms excited for another walking day. We started at the Place de la Concorde, and then followed the park all the way along the Seine to the Louvre. During the day, we did see most people wearing masks, in keeping with local orders. The team checked in with Gwenaël Servant, who runs That's Nice's European office in Paris.

We had quite a few dynamic interviews planned for the day in the city. First up was David Guez, Executive Director of Servier WeHealth, who taught us about digital and connected e-health solutions and how they will transform patient care. Next up was Manuel Gea of BM Systems, with whom we discussed predictive integrative biology and how it will enhance our understanding of disease in the coming years. Alexis Paul told us about how Cenexi is evolving its vision to grow to meet the challenges of the future of healthcare.

Finally, we spent some time with Jacques Brom and Géraldine Gorgol of Sanofi AIS, exploring the long-term impacts from the COVID-19 pandemic, including shifts in the global supply chain, the rising demand for domestic/regional sourcing, and changes in outsourcing or partnership models, as well as the increasing importance of emerging markets.

THE TEAM MET WITH:
Dr. Gwenaël Servant, That's Nice; **David Guez,** Servier WeHealth; **Manuel Gea,** BM Systems; **Dr. Alexis Paul,** Cenexi; **Dr. Jacques Brom and Géraldine Gorgol,** Sanofi AIS

HEALTHCARE IN FRANCE

POPULATION
66M *(8.83% of Euro Population)*

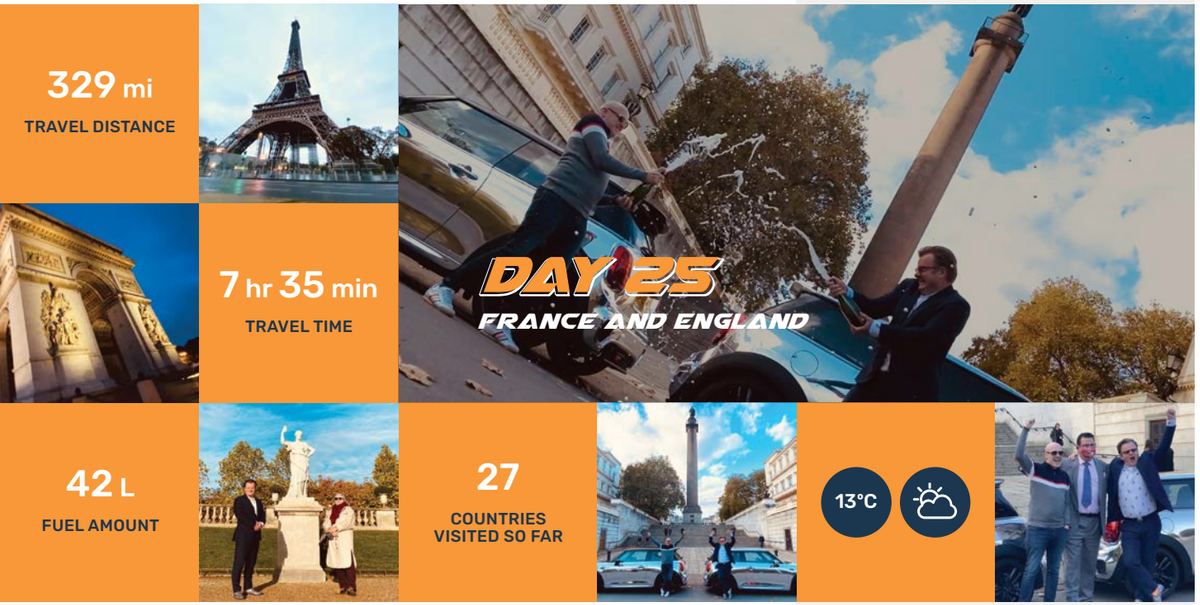
LIFE EXPECTANCY
82.7 Years *(2+ Yr Increase Since 2000)*

HEALTH SYSTEM
Near Universal

HEALTH EXPENDITURE PER CAPITA
€3626 *(About €776 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 25%; Obesity 14%

LEADING CAUSE OF DEATH
Stroke *(85.2% Decrease Since 2000)*



Only Person We Met Twice On The Trip: **Haig Armaghanian**

October 22, 2020

IT'S THE END OF THIS JOURNEY, BUT THE START OF THE NEXT ONE

On the final day of the trip, Nigel met with his old college friend Mina Alessandri in the Jardin du Luxembourg, behind the Palais du Luxembourg, before leaving Paris for good. Mina is American and married to a Frenchman, but like Nigel's friend Eryk in Poland, has had experiences having children both in New York and France. Similar to Eryk's family's experience with childbirth – and consistent with what we learned throughout the trip about European healthcare systems – she agreed that the French system was far more caring and patient centric. However, when discussing what healthcare needs were not being adequately addressed, she brought up mental health, a subject raised by a number of our interview subjects, as well as in person-on-the-street interviews.

After that last interview, we headed over to the Eiffel Tower and through the surprisingly scary Arc de Triomphe and captured some hero shots before heading back to Calais, the Channel Tunnel, and ultimately the United Kingdom.

After reconnecting, we took the Blackwall Tunnel under the Thames into central London. We started getting excited just as we were coming back to the Trafalgar area, where you come out of the tunnel and suddenly you've got all these huge, glistening, silver skyscrapers – the Swiss Re Building and the London Eye – as a backdrop to the Tower of London. It's a brilliant juxtaposition of the old and the new, and it's quite dramatic, but it also felt like a suitable bookend for the entire journey.

We headed down Trafalgar and turned left toward the Mall, passing Buckingham Palace before meeting up with our old colleague Haig Armaghanian of Haig Barrett and his film crew for a mini-interview at the same spot where we began our journey 25 days earlier. We opened some bottles of champagne, before retiring to the Mitre Hotel for a couple hours of debriefing before ending the night – and the trip.

THE TEAM MET WITH:
Haig Armaghanian and Sarah Flindall, Haig Barrett

HEALTHCARE IN ENGLAND

POPULATION
56M *(84.02% of UK Population)*

LIFE EXPECTANCY
81.1 Years *(<1 Increase Since 2000)*

HEALTH SYSTEM
Universal

HEALTH EXPENDITURE PER CAPITA
€2900 *(About €50 Above the EU Average)*

PRIMARY RISK FACTORS
Smoking 17%; Obesity 21%; Alcohol 22%

LEADING CAUSE OF DEATH
Heart Disease *(56.2% Decrease since 2000)*

Special Thanks To The Trip's Remote Crew: Wei, Yiyi, Divya, Eugene, Lulu, Albert, Guy, Gwenaél, Shiouwen, Nathan, Lucas, Adama, Mark, Jenna, Samantha, David, Emilie, Tj, Young, Melissa, Nataliya, Cory, Jaren, and Parth

Our **ROAD TO 2021 SPONSORS** discuss how they are preparing to face the future of healthcare.

INNOVATING FOR THE FUTURE OF HEALTHCARE

Enterprise Sponsor
CRO

SanaClis
CONTRACT RESEARCH ORGANIZATION

SanaClis remains one of the most recognized full-service CROs with integrated clinical supplies in the industry, offering a boutique, one-stop shop for sponsors and their clinical trials, which ultimately impacts the deliverables of their biopharma clients. SanaClis has all services in-house, including solely owned, state-of-the-art GMP/GDP-certified and compliant depots. SanaClis holds a near perfect track record of on-time delivery, with approximately 95% of projects delivered on or before the set timeframe and within budget. With such a commendable track record, SanaClis has established long-term relationships with both large pharma and biotechs across the world for their studies, building partnerships based on transparency, trust, and quality. Clients especially value the dedication of staff working on their projects in combination with a near-zero turnover rate on assigned projects: this is facilitated by the company's strong focus on employees, offering a pleasant and healthy working environment and a wide range of company benefits.

Stare Grunty 130
841 04 Bratislava Slovakia
www.sanaclis.eu

Over the coming decade, SanaClis believes that patient centricity will become the central focus for the entire industry, with individualized treatment regimens and personalized treatments fast becoming the dominant therapeutic paradigm. A patient-centric approach, with personalized medicine supported by robust technology-enabled RBQM, will become the new norm following COVID-19, upending the traditional but outdated business models in the clinical trials industry.

Clinical trial protocols during the pandemic, and most likely post-pandemic as well, will be dominated and designed around home care for patients – both in terms of clinical trials and commercialized medicines; a trend that seeks to ease access to medication for patients while reducing the patient burden. As the COVID-19 pandemic makes hospitals, clinical trials sites, and treating physicians less accessible, particularly for immunocompromised patients or those with other underlying health conditions, it is imperative to design studies with a patient-centric focus, in order to significantly reduce disruption in clinical studies as seen throughout 2020. With growing uncertainty as to the required duration of pandemic measures aimed to mitigate COVID-19, the industry needs to seek new ways to conduct procedures in patients' homes, assisted by nursing networks, with the ability to conduct more complex home care treatments, such as administration of investigational medicinal products (IMPs). SanaClis – in collaboration with many large pharma companies – is proud to be instrumental in pioneering development and implementation of such home care approaches into ongoing studies, as well as new studies planned to start in 2021.

Mindful of the changing needs in clinical trials of the future, SanaClis continues to analyze and implement newly emerging and disruptive technologies with the potential to transform how clinical trials are conducted, with a particular focus on digital technologies enabling adoption of decentralized or hybrid clinical trials as a new norm. Rapid and smart adoption of AIML at scale and powering next-gen RBQM through real-time data interoperability hold great promise to address the growing dilemma as to how to handle increasing volumes of study data without adverse impacts on study duration.

In the context of the evolving adoption of home care procedures and treatment administrations that will transform patient experiences, it is important to consider the impact upon the supply chain and realize changes necessary to support it. The industry must seek to improve quality and accountability in regard to the transportation, dispensing, and storage of clinical trial supplies for effective home care delivery. While this paradigm shift may initially pose a strain on the existing supply chain, it will in practice create new efficiencies.

SanaClis is at the forefront of change to mitigate the impacts of the COVID-19 pandemic, as we develop patient programs and designed Patient Compliance and Protection Kits to support safe conduct of clinical trials for hospitals, doctors, site staff, and, importantly, the patients.

SanaClis remains committed to promoting and supporting implementation of patient-centric decentralized clinical trials. SanaClis's core belief is that the patient remains at the very heart of everything we do and how we innovate; the COVID-19 pandemic has only reinforced that belief, and, with the combination of strong cross-industry collaboration, research, teamwork, and adaptability, SanaClis welcomes the opportunity to overcome current and future challenges of such magnitude. P

Enterprise Sponsor

MAMMALIAN BIOLOGICS

THE NEXT BIG DEVELOPMENT AMONG CDMOS IS THE INTEGRATION OF END-TO-END SERVICES AND THE ABILITY FOR ONE CONTRACT COMPANY TO SUPPORT A PRODUCT FROM DISCOVERY THROUGH TO FILL-FINISH AND COMMERCIAL SUPPLY.

If there has been a single outcome from the COVID-19 pandemic for drug developers, it is the realization that, through innovation and collaboration, the industry can work faster. At the time of writing, Oxford University/Astra Zeneca's COVID-19 vaccine "ChAdOx1 nCoV-19" has entered phase III clinical trials after less than 10 months. Typically, the industry standard to reach this stage is 4–8 years. While this is an unprecedented situation with an almost unlimited budget and the priority of governments and regulators internationally, there will almost certainly be lessons learned on how to accelerate drug development aside from COVID-19.

There continues to be an ongoing shift of early-stage biologics development work away from big biotech organizations to small and mid-size private biotechnology companies. Approximately 50% of new phase I clinical trials are now being initiated by private biotech firms that rely heavily on contract development partners. It is imperative that these CDMOs lead the charge in finding innovations to accelerate drug development and become more involved in working directly with regulators and clinical trial bodies. There are multiple ways in which Polpharma Biologics is already achieving this.

Accelerating Drug Development

We are accelerating the development process through investment in new technology and equipment, such as our recently purchased Cyto-Mine® in cell line development that will reduce timelines and enable the production of manufacturing cell lines in 4–5 months – reduced from 9 months – with no effect on productivity or quality due to the automation of a previously time-consuming manual step.

Another step is the investment in high-throughput automated bioreactor system equipment, which replicates the conditions in industrial bioreactors at microscale, allowing the anticipation of process problems much earlier and thus further reducing process timelines. Our switch to single-use equipment also significantly speeds up production. Converting a production suite from one product to another can now be done in as little as a day; the cleaning process previously took weeks between batches in stainless steel bioreactors.

Integrating Services

The next big development among CDMOs is the integration of end-to-end services and the ability for one contract company to support a product from discovery through to fill-finish and commercial supply. An integrated provider significantly reduces timelines by eliminating process transfer between organizations. It also facilitates easier communication, as adjustments can be immediately implemented into facility schedules. Integration also enables the overlap of processes, such as starting upstream development while stability studies in cell line development are finishing, and removes the time-intensive and risky process of transferring knowledge between contractors.

Polpharma Biologics possesses this full-service integration but has also taken a further step and combined regulatory, IP, and clinical services into the company offering – including for preclinical, clinical strategy, and clinical operations. With one partner who believes in being open, flexible, and collaborative becoming so involved with a product's development, the passion the team has for delivering the drug to the market matches that of the developer. This leads to motivated teams, who all care about their common goal of getting products to patients as safely and quickly as possible. P

Polpharma Biologics is a biopharmaceutical company with state-of-the-art facilities across Europe. Polpharma Biologics has multiple international centers of excellence specializing in cell line development, product and process development, clinical manufacturing, commercial-scale production, and regulatory affairs. They work with their partners to advance their biological pipeline (biosimilars and novel biologics) by providing top-quality contract development and manufacturing services to the industry.

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Technology Sponsor

COLD CHAIN LOGISTICS

Yourway is an integrated biopharmaceutical supply chain solutions provider offering a full range of primary and secondary clinical packaging, logistics, storage and distribution services for the global pharmaceutical and biotech industries. Headquartered in Allentown, Pennsylvania, with additional strategic locations worldwide, Yourway specializes in time- and temperature-sensitive clinical drug product and biological sample shipments. Yourway is a flexible and reliable logistics partner committed to the safe, efficient and on-time delivery of clients' high-value, high-priority clinical materials.

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www.yourway.com

With the industry facing an uncertain future as we continue to work to move forward past the COVID-19 pandemic, some changes that will impact the future of clinical trials seem clear.

First, we can anticipate that clinical trials going forward will rely much more on decentralized, virtual, and hybrid models, with direct-to-patient (DTP) and direct-from-patient (DFP) logistics services becoming critical. These evolving approaches to clinical trials were already gathering momentum owing to their patient-centric benefits, as well as their potential to simplify recruitment and retention for clinical trials for rare diseases with geographically dispersed populations – and in 2020 became indispensable to allow trials to continue while assuring the safety of participants and site staff during the pandemic. With sponsor companies that had previously been hesitant to adopt these new approaches seeing their benefits during the COVID-19 crisis, we believe that many will continue to pursue them even once it is possible to return to traditional, site-based clinical trials. This will expand the demand for clinical trials service providers who can fully support these trials, including via comprehensive DTP/DFP services.

The second likely trend resulting from the pandemic and its response will be an even-greater emphasis on finding new ways to accelerate clinical trials. Again, even before the pandemic, sponsor companies and regulatory agencies were motivated to find ways to speed up clinical trials and get drugs to market as quickly as possible, reflected in the increasing embrace of Fast Track and other accelerated approval designations. The rush to approve vaccines and therapeutics for SARS-CoV-2 and growing evidence that it is possible to do so much more rapidly than traditionally believed are changing expectations regarding clinical timelines, a shift that is likely to continue for the foreseeable future. Sponsor companies will be looking for clinical trials providers who are sufficiently agile to maintain the same high standards of quality and transparency while moving more quickly than ever before.

Yourway has built a reputation on excelling during challenging times when other providers cannot. We have pioneered DTP/DFP services for a variety of complex protocols to create reliable, successful strategies to support decentralized or virtual clinical trials, whether that means transitioning trials originally planned to be held at centralized sites, rescuing decentralized trials initiated by other providers who were not able to provide sufficiently robust solutions to ensure trial continuity during these challenging times, or planning truly decentralized trials from their inception.

Yourway is also well positioned to support clients as we collectively work to reduce clinical timelines, owing to our integration of a range of key services. We do not simply offer a suite of discrete services – logistics, warehousing, and packaging support – but take a solutions management approach to all projects, combining project management support, planning and optimization guidance, comparator drug and ancillary supply sourcing, forecasting, and returns/reconciliation management, to provide customized solutions for each client's need. Integration of this full range of clinical supportive services translates into unmatched quality, speed, and operational efficiencies.

Regardless of the uncertainty ahead and new needs that may emerge over the next few years, Yourway is ready to support our clients and overcome these challenges to face the future of healthcare. P

Technology Sponsor

GENE THERAPY

OUR VISION FOR INCEPTOR BIO IS 20:20 IN 2020 — WE WANT TO LAUNCH 20 BIOTECHS IN 20 YEARS STARTING IN 2020.

INCEPTOR BIO

Inceptor Bio is taking a unique approach to accelerating disruptive synthetic biology platforms. The company is focused on changing the healthcare landscape by creating 20 companies over 20 years to significantly advance progress for curing cancer and neurodegenerative diseases.

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We believe that the biotech industry is in the early stages of a 50-year healthcare transformation led by gene and cell therapy. With the advent of a host of synthetic biology platforms, such as RNAi, CAR-T, gene editing, and viral vector delivery, we are beginning to unlock the secrets of addressing difficult-to-treat, intractable diseases. We anticipate an ongoing wave of approvals for cell and gene therapeutics — up to 10 approvals per year over the next decade — which will have many downstream effects on the rest of the life sciences ecosystem, particularly manufacturing, which is a well-known bottleneck.

The biotech industry's rapid response to the COVID-19 pandemic will have an outsized impact on humanity. It's quite remarkable that biotech companies were able to develop a therapeutic approach two months after the COVID-19 sequence was deciphered. The biotech community's renewed sense of responsibility and ability to function as a positive agent for society is the most important trend from 2020.

New Technologies on the Horizon

Biopharma is in the early stages of discovering approaches to synthetic biology and leveraging these approaches to treat areas of critical unmet need. We are particularly encouraged by advances in fourth-generation CAR-T programs, DNA editing, RNA editing, gene therapy for rare diseases, and novel TCR approaches. While there are a number of approved drugs that validate these synthetic biology approaches, the greatest innovations are forthcoming.

Artificial intelligence (AI) and machine learning (ML) are still widely misunderstood. Many biotechs talk about their AI/ML capabilities, but when we look at the underlying approaches, they're using relatively simple models. A number of leading companies are doing very interesting work in this field but — for the majority of early-stage companies — it's currently more aspirational rather than truly impacting their company's development.

Upcoming Innovations

Our first platform is a novel CAR-T technology, which addresses the large unmet needs in solid tumors. CAR-T has shown great applicability for B cell lymphomas. The work in solid tumors has been limited due to the immunosuppressive tumor microenvironment, trafficking issues, tumor antigen escape, and tumor heterogeneity.

These issues lead to T cell exhaustion, which our novel platform addresses. We have compelling *in vitro* data and *in vivo* data for renal cell carcinoma. Additionally, we're researching ovarian cancer and triple-negative breast cancer. These three indications have high incidence and prevalence in the United States and poor current treatment options.

Transforming the Patient Experience

Autologous CAR-T therapy, while transformational, has many limitations, including cost, manufacturing challenges, quality control, and other factors. The rise of allogeneic ("off the shelf") CAR-T therapy will enable more patients to afford life-changing therapies at a more realistic price.

Lasting Impact of COVID-19 and Predicted Growth

One lasting impact of the pandemic is that work from home will remain popular in the United States for years to come. One of our core values at Inceptor Bio is maintaining an entrepreneurial spirit, which we applied when assessing how the COVID-19 pandemic would impact our short-term, day-to-day approach.

Our vision for Inceptor Bio is 20:20 in 2020 — we want to launch 20 biotechs in 20 years starting in 2020. We're well on our way to this goal. We've already launched and funded two biotechs so far in 2020. There is no shortage of technologies to invest in. Our goal is to progress science to find cures for cancer and for neurodegenerative and rare diseases. P

Enterprise Sponsor

STERILES

Pii
PHARMACEUTICS KNOW-HOW™

Pharmaceutics International, Inc., (Pii) is a contract development and manufacturing organization (CDMO) with a passion for solving problems efficiently with the highest quality standards. Pii's Hunt Valley, Maryland campus includes 70 manufacturing suites with 4 integrated aseptic filling lines delivering quality, safety, and efficiency. Our professionals have extensive experience with small and large molecule compounds, developing and manufacturing complex parenteral drugs, extended-release formulations, non-aqueous injectable drug products, and lyophilization.

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HEALTHCARE INNOVATIONS, DRIVEN BY ADVANCEMENTS IN CLINICAL PHARMACOLOGY, ARE BEING INTRODUCED AT AN UNPRECEDENTED PACE.

Currently, there are two great forces at work that are disrupting traditional models for advancing drug therapies from discovery to commercial production and distribution. This transformation, when complete, will impact the biopharmaceutical supply chain significantly and potentially achieve outcomes that were considered impossible a short time ago.

The first is scientific innovation, which the industry has been talking about for a while. Healthcare innovations, driven by advancements in clinical pharmacology, are being introduced at an unprecedented pace. The quantity and quality of encouraging early-phase drug therapies are challenging the traditional pharmaceutical supply chain and demanding far more agility from biopharma companies, contract development and manufacturing organizations (CDMOs), clinical and contract research organizations (CROs), and regulatory bodies like the U.S. FDA and the EMA.

The second is not something we anticipated — the urgency with which treatments and vaccines are being developed to combat the COVID-19 pandemic. If a vaccine is ready by early 2021, as many experts believe, it will be on a timeline like nothing we have experienced. Commercial biopharmaceutical development timelines have always been measured in years, not months. If the anticipated COVID-19 vaccine timeline is achieved, it will be difficult to accept a return to the traditional timelines.

CDMOs will play a critical role as healthcare supply chains are transformed, and the changes are happening faster than anyone could have predicted. CDMOs have long possessed the agility to quickly repurpose facilities and production lines for emerging market needs and the requirements of specific drug sponsor clients.

At Pharmaceutics International, Inc. (Pii), we were expecting this transformation. We began modernizing our facilities and analytical labs precisely for the kind of change now underway, one that demands a more responsive biopharmaceutical supply chain. Additionally, we recognized that, to deliver a better organizational response, we needed to develop some additional skills. We went to work becoming more collaborative, flattening our organization for quicker decision-making, and placed a premium on professional project management to deliver client outcomes on time, or even early. These organizational changes also enable us to manage our capacity better and more predictably and be ready to flexibly respond to drug shortages when they are experienced by healthcare providers.

Pii is a U.S.-based CDMO located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on solving difficult problems; it is part of their DNA. In addition to knowing how to innovate for the future needs of the biopharmaceutical industry, Pii has expertise in developing and manufacturing complex parenteral drugs and possesses a wealth of analytical testing, formulation development, and manufacturing capabilities across a variety of dosage forms. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities, and the talented professionals at Pii stand ready to help! P

Enterprise Sponsor

USED PHARMA EQUIPMENT

Federal Equipment Company

Federal Equipment Company is a reliable resource for pharmaceutical processing and packaging equipment, with over 60 years of expertise buying and selling used equipment. They take away the headaches when you need to sell equipment, offering deep knowledge of equipment values and accurate appraisals. Federal Equipment Company optimizes the value you recoup, and expertly removes equipment, protecting your facility. When you need equipment, the company has a broad, on-hand inventory of reliable equipment from leading OEMs. Their experienced staff ensures you buy exactly what you need and with a fast turnaround — they also offer expert training & troubleshooting.

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www.fedequip.com

FOR THE LAST 20 YEARS, WE'VE GROWN OUR PHARMACEUTICAL BUSINESS INTO THE LEADER IN THE USED PHARMACEUTICAL EQUIPMENT INDUSTRY.

Over the next decade, we anticipate a great deal of innovation and development in pharmaceutical and chemical manufacturing. Major pharmaceutical companies will want stronger control of their supply chains and the ability to respond to emergencies like COVID-19 with quicker speeds with both new and existing manufacturing processes. Federal Equipment Company offers those companies the ability to source equipment for their development or existing manufacturing projects at greatly reduced purchase prices and with immediate access.

Due to the pandemic, the used process and packaging equipment industry, and many others, accelerated plans and actions to facilitate doing business in certain ways more virtually. We have come a long way from taking instant Polaroid photos of equipment and sending them to customers in a courier's envelope. We are now doing many equipment inspections with FaceTime and discussing deals through Zoom meetings. While some things may return to normal in 2021, we could very well see some of these changes remain going forward.

We plan to increasingly use technology to improve communication and receive rapid feedback, both internally and externally with our customers and clients. This will allow us to iterate our digital platforms and presences and tailor our investment recovery programs, service offerings, and how we present equipment for sale to meet the needs of our customers.

Disruptive Innovations

Federal Equipment Company sponsored and actively developed the hugely popular Virtual Expo Series. With two online Virtual Pharma Expo events in 2020, we reached thousands of people in the industry with live discussions about equipment and process technology development. Our format allowed users to hear from a wide range of experts from equipment suppliers and service providers in a short period of time. We feel that this virtual trade concept will continue into the future as people are able to learn about new innovations remotely, and the suppliers were able to reach a large number of people with relatively low production costs. We certainly miss seeing our customers in person, but we see value in continuing to offer remote and mobile device–friendly events that allow us to show up where our customers can meet us.

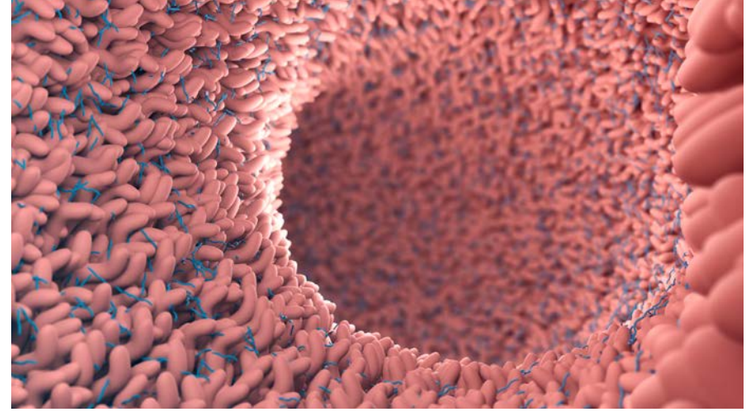
People are using mobile devices more than ever, and there is no doubt that usage will continue to rise. Our challenge is to continue to include engaging and informative content that helps our customers improve their decision-making on a mobile-ready platform. Imagine, from an equipment purchasing perspective, being able to see the equipment you're considering purchasing placed virtually on your production floor and being able to view equipment in 360 degrees. Another area is parts.

We have acquired many parts from liquidations over the years, including machines that are probably more valuable as a source of spare parts than they are as a complete machine. Inventorying and marketing these lower-value units of inventory was cost-prohibitive until recently. Look for a launch of PharmParts in Q4 of 2020, and you can achieve significant cost savings by purchasing original equipment parts at a huge discount. We plan to offer parts for a wide variety of equipment, primarily focused on solid-dose manufacturing to start. The parts will range from brand new to parts that have some wear but may be enough to get your machine running until a new part arrives.

For the last 20 years, we've grown our pharmaceutical business into the leader in the used pharmaceutical equipment industry. We've added complementary services, like manufacturing process training, decontamination, and now parts and virtual shows. We will continue to be aggressive in providing equipment solutions within the entire pharmaceutical industry. P

Enterprise Sponsor

MICROBIOME



ARRANTA BIO

Arranta Bio is a CDMO specifically established to focus on serving companies seeking to develop and commercialize therapies targeting the human microbiome. Headed by a management team and technical experts with a proven track record, they offer the knowledge and resources necessary to help you to develop and manufacture promising new microbiome-based therapies to meet the needs of patients.

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ARRANTA BIO IS BUILDING ON OVER A DECADE OF EXPERIENCE IN MANUFACTURING LIVE BIOPHARMACEUTICAL PRODUCTS AND IS POSITIONED TO LEAD IN MICROBIOME DEVELOPMENT AS IT GROWS.

Increasing evidence points to the gut microbiome playing a larger role than previously thought in health and disease. Over the next year (and beyond), we will see more investment into the microbiome, as pioneer companies advance live biotherapeutic products (LBPs) in their pipeline and key clinical data becomes available.

Transformative Technology

Analytics in the LBP arena are outdated. A full battery of analytical assays needs to be developed, to eventually become the regulatory standard in the industry. Four distinct areas need to be improved:

1. Characterization: Routinely, isolates are taken from fecal matter and are the basis of potential therapies. The exact origins where these isolates thrive and function within the lengthy gastrointestinal tract remain largely unknown, and the assays/techniques to predict those origins are largely unavailable. Phase-appropriate qualification is paramount during early clinical trials; once a better understanding is achieved for the analytics, we can convert those assays to quality-indicating assays for routine characterization and stability-indicating testing.

2. Quality indicating: Colony-forming units (CFUs) are the common assay to-date to determine potency. However, CFUs are not always the best predictor of potency. For LBPs targeting indications within the small intestinal tract (GIT through the small intestine is 4–6 hours), lag phase may be just as important, if not more important, as CFUs. Other potency tests that can be employed include assays that measure microorganisms' ability to metabolize a target analyte, to measure its potency.

3. Speed: Growth-based assays can be very lengthy, ultimately slowing the decision-making process. Therefore, there is a true need to be able to test and potentially release in hours instead of days to weeks. The speed of release of a product is rate limited by USP <61> Total Yeast and Mold Count (TYMC) analysis, as the minimum incubation is 5 days. Molecular methods and the speed they bring can be huge in the assessment of formulation changes and optimization.

4. Efficacy indicating: Assays to better predict clinical efficacy (engraftment, host/organ interactions, etc.) are currently lagging. Not only are current assays lacking or deficient, larger, validated animal models that have more representative human GIT are not there. Innovations in these areas will speed the development and assist in creating better products for our innovators.

Trend Acceleration

COVID-19 accelerated trends already underway. On a fundamental level, we have seen clearly that the rapid adoption of technologies and collaboration tools have made effective, flexible work possible, while continuing to allow us to build an organizational culture of mission-driven teamwork.

Arranta Bio is committed to being a best-in-class CDMO supporting pioneering companies in the microbiome sector. Over the next decade, this area is expected to mature with products commercialized and diseases within larger populations addressed. Arranta Bio is building on over a decade of experience in manufacturing live biopharmaceutical products and is positioned to lead in microbiome development as it grows. P

Enterprise Sponsor

ORAL SOLID DOSE (OSD)

AT AVARA, WE HAVE BEEN SUPPORTING CLIENTS BY DELIVERING ON EXPEDITED TIMELINES AND REMAINING RESPONSIVE TO THEIR REQUESTS AND NEEDS.

avara
PHARMACEUTICAL SERVICES

Avara Pharmaceutical Services offers commercial-scale manufacturing, packaging, and supply of oral solid dose and sterile drug products. Avara's global footprint has been built through acquisition of established pharmaceutical companies with demonstrated records of the highest quality and regulatory standards. With years of experience gained by delivering high-volume commercial products to multiple geographies, Avara's teams offer in-depth understanding of clients' needs.

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www.avara.com

As pharmaceutical companies look to maximize efficiency of operations in order to invest in the research and development of new products, we see the desire to form strategic partnerships with CMOs like ours becoming even more prevalent. At Avara, on-hand leadership teams and streamlined processes allow us to develop more timely responses and solutions to our clients' needs. This, in turn, helps us nurture these relationships into long-term partnerships, as client and CMO objectives become more aligned.

Today, Avara is investing in enhancements to existing capabilities and service offerings. For example, we are expanding our capacities for blending, granulation, compression, and coating of OTC products at our Aiken, South Carolina, facility. In Arecibo, Puerto Rico, we recently completed serialization on our high-speed bottling line to support the release of Rx products for international markets. In Norman, Oklahoma, we are further improving our suite of spray-drying capabilities and have added encapsulation equipment to the facility. In our sterile service offering in Liscate, Italy, we have introduced new cartoning equipment for integrated packaging to support new business.

The COVID-19 pandemic has challenged businesses worldwide to adjust the way they interact. We've seen a greater reliance on video conferencing and have provided solutions to our clients by offering virtual site visits and audits as opposed to more traditional, in-person customer collaboration. While we believe that in-person meetings will resume after the pandemic – especially in the introductory phase – we anticipate that the practice of more frequent, remote conferencing will become more standard as projects progress.

Looking Beyond 2020

This year has presented a multitude of challenges to businesses worldwide, resulting in changes being driven to a broad range of processes. In particular, we have seen a higher number of discussions around Emergency Use Authorizations with our clients, as the effects of the COVID-19 pandemic create urgency in the sector to advance drug regulatory approvals. At Avara, we have been supporting clients by delivering on expedited timelines and remaining responsive to their requests and needs. As we move toward 2021, we have fine-tuned many of our processes, resulting in optimization across all departments – from Supply Chain to Finance – to support "speed to market" in our industry.

For the wider community, awareness of the importance of accelerating the introduction of new products to the market has grown significantly as countries around the world support collaborative efforts to remove obstacles within drug research, clinical trial, and drug approval processes. The engagement with regulatory authorities during 2020 has been key, and we believe that these industry and politically motivated changes will have the most lasting impact to the R&D and pharmaceutical manufacturing sectors, as companies are encouraged to fast-track critical drug supplies to the patients who need them.

As Avara continues to grow through the next decade, we envision broadening our services and offerings to complement our core capabilities of OSD (Rx and OTC) and sterile commercial manufacturing and packaging, thus enabling Avara to engage with our clients earlier in the product life cycle. We look forward to continuing to evolve and adapt our business to meeting the needs of our clients and the industry as a whole. P

Technology Sponsor

GLASS

SGD PHARMA BELIEVES THAT THERE ARE SEVERAL MAJOR TRENDS CURRENTLY MOTIVATING THE PHARMACEUTICAL MARKET, WITH THE UNIFORM GOAL OF DRIVING PATIENT CENTRICITY AND, BY EXTENSION, IN-HOME SELF-CARE.

SGD PHARMA

SGD Pharma is a leading provider of glass pharmaceutical packaging. Formerly part of Saint-Gobain, SGD Pharma has more than 100 years of experience in the production of pharmaceutical glass primary packaging. SGD Pharma manufactures over eight million vials every day from five plants in France, Germany, India, and China, all of which employ cGMP standards and ISO 8 cleanrooms and are certified to ISO 15378, the standard for pharma packaging systems. The company's mission is to improve and protect patient health by supplying high-quality, reliable, and innovative glass primary packaging. Through continuous improvement and innovation, SGD Pharma is committed to reinforcing patient safety by improving the physical, chemical, and cosmetic properties of its products.

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The industry will certainly change over the coming decade, with several trends structurally modifying how people are cared for and how manufacturing is conducted. The pandemic is accelerating multiple existing trends.

One such example is the switch to ready-to-use (RTU) vials: this trend began over the last decade in vials, but demand has significantly increased during the last six months for vaccines, while bulk filling is becoming obsolete, even for high volumes.

Packaging materials, especially tubular glass vials, are becoming scarce, driving adoption of complementary alternatives, such as molded glass vials, which offer higher chemical and physical characteristics.

The pandemic has also increased needs for home care, which has driven demand for diagnostic facilities, which need to be closer to populations for testing, as well as online medical consulting. Packaging strength is thus becoming increasingly important, as are innovations that facilitate ease of use.

In addition, we have observed growing demand for sustainability and natural products. SGD Pharma launched its first CSR report last year and will further expand it this year.

On a global level, China is predicted to internalize production even more, which may be to the detriment of Western customers.

Patent-Focused Innovation

SGD Pharma believes that there are several major trends currently motivating the pharmaceutical market, with the uniform goal of driving patient centricity and, by extension, in-home self-care.

Flexibility is key for this to come to fruition, as companies strive to develop more personalized therapeutics. Added-value drugs are on the rise, along with growth in biologics and large molecules.

There is an increased regulatory focus on quality and compliance.

New technologies are driving the push toward in-home care, including e-health, telemedicine, and "Uber health" equivalents. This is matched by a push for sustainability in production and affordability.

Lasting Developments

Partnerships that have developed over the last year will have a lasting impact. At SGD Pharma, we have prioritized better molded glass vials that have higher quality and better inspectability and are resistant to breakage.

As an additional product range, we can now offer 13-mm amber molded glass vials as a complement and alternative to tubular glass vials. This special product offering is available immediately.

This past year has also brought about a digital transformation, an increase in demand for RTU vials, and a range extension of our Sterinity offering.

We have also seen an increase in demand for tubular vials, especially for vaccines.

In terms of market trends, cannabidiol (CBD) has grown in popularity as an alternative to traditional pain medication; consumers are also looking for medicines derived from natural sources. Most recently, we launched Ensiemo, a high-quality range of clear and amber bottles and dropper assemblies ideally suited for oil product formulations. The droppers are child- and senior-friendly; they feature pharmaceutical-grade glass with precise and accurate dropper dosage, resulting in virtually no product waste.

In addition to Ensiemo, we also offer a full product range, including Clareo injectable vials, EasyLyo injectable vials in molded glass, and the Sterinity platform, which features a selection of secondary packaging configurations and boasts a diverse glass vial portfolio.

SGD Pharma's vision over the next decade is to further increase our presence in pharmerging markets.

We intend to develop more value-added products. Sustainability and digitalization are definitely must haves, and SGD Pharma is taking these trends very seriously. P

Technology Sponsor

CLEANROOMS

THE COVID-19 ENVIRONMENT HAS REALLY ACCENTUATED THE VALUE OF THE DESIGN–BUILD APPROACH, ALONG WITH THE FULLY INTEGRATED SERVICES THAT AES OFFERS.

aes Clean Technology

Providing cleanrooms and critically controlled environments has always been **AES Clean Technologies**' sole focus. With over 35 years of experience, we have witnessed the changes in regulations, as well as the challenges that our clients face in getting their products to market faster and more efficiently. Many of our life sciences and biotech cleanroom customers have been with us from being a small start-up operation to world-recognized leaders in our own right. We value their partnership, and their repeat business continues to be one of our greatest compliments.

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Over the coming decade, we anticipate continuation of the trend within the industry to quickly deliver safe and effective patient-specific therapies. The biggest evolution within the industry is to develop and produce these targeted treatments at a more affordable cost to increase their accessibility.

We are already seeing these therapies influencing the way facilities are designed. Given the smaller batch sizes of the products being produced, the traditional large ballroom cleanrooms with large stainless steel vessels and piping have become a thing of the past. The cell and gene therapy applications of today are smaller in scope, less infrastructure-intense, less costly, and quicker to deploy. This has significant and beneficial implications, making it possible to expedite bringing manufacturing capacity online quicker and more affordably than ever before.

Companies are taking advantage of the standardization of manufacturing platforms (e.g., single-use bioreactors, columns) and techniques to produce drug substance and drug products, and thus it is becoming much easier to develop and provide standard facility options that meet the needs of the vast majority of the market. Rather than reinvent the wheel for every manufacturing application, there are designs available that can be quickly deployed to minimize costs and timelines. To leverage these benefits, AES has developed three standardized turnkey cleanroom options with our Faciliflex Express line of standard facility options. Faciliflex Express standard cleanroom sizes are 5,000, 15,000, and 30,000 square feet to accommodate a wide range of client needs.

We are excited to see ongoing developments with respect to contamination-control technologies that further eliminate bioburden risk within cleanrooms and the potential implication this brings to product quality and reductions in costs and downtime associated with cleaning within the cleanroom. Many of the technologies will introduce repeatability and thus a high level of quality assurance to the cGMP environments. This will enhance product quality and patient safety.

One of the things that AES is always focused on is innovating technologies and services that bring our cleanroom facilities into reality quicker and provide long-term value to our customers. Among the many near-term products or services that we will be launching to the market is our Performance Assurance Program (PAP), which is an added layer of service support for existing AES cleanrooms, additional enhancements to AES' best-in-class proprietary cleanroom system, and a further expansion of AES' Faciliflex product line (stay tuned!).

Looking Past COVID-19

The COVID-19 environment has really accentuated the value of the design–build approach, along with the fully integrated services that AES offers. The pandemic has made managing multiple service providers to deliver a cGMP facility very complex and challenging, with a variety of unknown COVID-related complications. AES' clients have found that working with a company like AES that provides their own engineering, manufacturing, and field installation services reduces known and unknown risks to projects and provides reliable project outcomes.

If anything, COVID-19 has further demonstrated that AES' design–build approach to providing fully integrated cGMP facilities is the least risky approach. We have been proud to have been part of many Project Warp Speed applications in the United States to provide cleanrooms supporting COVID-19 vaccine production at an extremely aggressive pace. We have successfully delivered on all these projects and are excited to be part of the world's response to this menacing global pandemic. P

Technology Sponsor

COMPARATOR DRUG SOURCING

OVER THE NEXT DECADE, GLOBYZ WILL ESTABLISH ITS PRESENCE IN MAJOR MARKETS GLOBALLY BY ENHANCING THE REGIONAL TEAM AND ADDING LOCAL RESOURCES.

GLOBYZ Biopharma Services

Globyz Biopharma Services is dedicated to sourcing and supplying commercial medicines for analytical research, drug development, clinical trials or bioequivalence studies across all therapeutic areas. Globyz Biopharma Services include comprehensive solutions for global comparator sourcing and storing and distributing pharmaceuticals, materials, and ancillary supplies for clinical trials, as well as GMP storage, packaging, labeling, kitting, controlled drug services, importer of record and QP services, and global GxP temperature-controlled logistics.

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www.globyz.com

Globyz Biopharma Services provides a one-source solution for comparator and reference drug sourcing, clinical trial materials, ancillary supplies, clinical packaging/labeling, storage, and distribution of investigational medicinal products, placebos, pharmaceuticals, and more.

Our expertise in managing the regulatory, logistics, and supply chain challenges of sourcing, storing, and distributing comparators for global clinical trials makes Globyz Biopharma Services the ideal partner for small and medium-sized pharmaceutical and biotechnology sponsors, CROs, CMOs, and CDMOs that don't get the attention they deserve from larger providers. We offer comprehensive clinical trial logistics services, from supply consulting to packaging, labeling and kit preparation, storage, and distribution in validated thermal shipping containers through a worldwide network of GMP-compliant warehouses and depots with the capability to handle temperature-sensitive materials. With offices and state-of-the-art GMP depots strategically located in the United States, Canada, Germany, India, Singapore, and Brazil, we have a presence in major markets across the globe and can provide end-to-end temperature-controlled logistics solutions from any point of origin to any destination, in any size and within any temperature range.

A More Virtual World

At Globyz Biopharma Services, we foresee that virtual trials and direct-to-patient trials will shape the industry over the coming decade. In terms of other significant trends changing the face of the industry, research in the area of cell and gene therapy, as well as the development of biosimilars, will drive innovation and change in pharma through 2030. Though they might not be available soon, 3D printing of medicines and tissues are positioned to be potentially transformative.

Virtual meetings with existing and potential clients, as well as virtual teams working from home, have had the most lasting impact on how business is conducted over this last unique year.

Current and Future Growth

Globyz is currently working on tracking packages with GPS and monitoring the internal temperature of shipments in transit to detect temperature excursions. This will be helpful in ensuring compliance, prompting proactive actions during potential exposure to temperature shifts in transit. This will also minimize the loss of packages in transit.

At Globyz, we predict an increase in the usage of Internet of things (IOT)-enabled devices will be most impactful in transforming the patient experience. In terms of the lasting impacts of the COVID-19 pandemic, trials will increasingly move away from hospitals and formal trial sites to patients' homes, as much as is possible, which may aid in trials participant recruitment, retention, and compliance. In general, virtual trials will increase, supported by evolving televisit and digital solutions.

Over the next decade, Globyz will establish its presence in major markets globally by enhancing the regional team and adding local resources. Globyz will build enhanced services in biosimilar, injectable, and cell and gene therapy trials. To achieve these goals, we will work on expanding our team, hiring personnel with specialized expertise in these areas. P

Enterprise Sponsor

EXCIPIENTS

SPI PHARMA PLANS TO FOCUS ON THOSE SPECIFIC PARTS OF THE MAJOR PHARMA TRENDS THAT WE BELIEVE WE CAN IMPACT USING OUR BROAD SET OF INNOVATIVE TECHNOLOGICAL TOOLS.

The pharmaceutical industry, as a part of the larger healthcare system. has seen and will continue to see explosive growth in product innovation and diversity of therapeutic offerings. Looking into the future, the advancements will not just be in small molecules and biologics, but will expand into targeted therapy, genomics, digital therapies based on artificial intelligence, and so forth. Some of the new models being adopted to achieve expedient and successful drug launches: fragment-based screening (FBS) processes used in the discovery of lead molecules resulting in significantly fewer compounds for screening, machine learning to identify patterns enabling design of effective clinical trials, and biomonitoring. When it comes to disruptive technologies, there are several being pursued. Some of the noteworthy ones are DIY genome sequencing, body sensors, an end of human clinicals, and nanorobots in blood.

While several of these will end up being used to create new, cutting-edge therapies, at the ground level, pharmaceutical regulators and government agencies will most likely force the drug developers and other technology enablers to go beyond just successful therapeutic outcomes. These new technologies will need to be focused on patients, not just outcomes. They should consider patient-centric drug designs and apply technology to address patient experience, accessibility, affordability, and adherence for individual patients.

Simply put, what good is cutting-edge therapy if a high level of patient compliance to the regimen cannot be achieved for any one of the reasons cited above? As is well known, the current level of noncompliance is a significant cost to healthcare systems and negatively impacts people's lives around the world. In the coming decade, we expect personalized medicine to become more mainstream, based on continuous monitoring, while patient-centered therapies will be practiced more broadly.

SPI Pharma plans to focus on those specific parts of the major pharma trends that we believe we can impact using our broad set of innovative technological tools. They are in the areas of IP-based patient-centric dosage forms, especially for pediatric and geriatric patients, buccal and sublingual delivery systems for peptides and vaccines, bioenhanced cannabinoids for pharmaceutical indications, microencapsulation of APIs to enhance functionality, and an elegant solution to issues surrounding syrups and suspensions, to name a few. In the category of the disruptive model, SPI Pharma is pursuing patient-centric initiatives with a view on ease of administration and personalized medicine. SPI Pharma continues to develop and pursue IP in this field and the technical/commercial feasibility of this hypothesis to underpin further development. P

SPI Pharma™
Making a Difference
An ABF Ingredients Company

SPI Pharma provides formulation innovation and support to pharmaceutical clients in more than 55 countries. Its products include antacid actives, excipients, taste-masking and fast-dissolve technologies, drug delivery systems for tablets, and a variety of other innovations for patient-friendly dosage forms. The company's functional excipients can be used in a wide range of customer applications, including soft chew, chewable, swallow tablets, lozenges, orally disintegrating, and soft gel dosage forms. SPI Pharma is headquartered in Wilmington, Delaware, and has locations across the United States, France, and India.

SPI Pharma is a leading supplier of solutions to pharmaceutical formulation marketers worldwide. The company's primary objective is to engineer functional materials that enable their customers to solve formulation problems, achieve differentiation, and gain speed to market. Through collaboration with our customers, SPI uses proven processing skills and formulation expertise to deliver value-added and cost-effective solutions to their customers' problems.

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Technology Sponsor

VENTURE CAPITAL & PRIVATE EQUITY

WE ARE ACTIVELY INVESTING IN ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML), WHICH HAVE ENORMOUS POTENTIAL IN THE DISCOVERY AND DEVELOPMENT OF NOVEL THERAPIES.

DYNAMK CAPITAL

Dynamk Capital is a venture capital and growth equity firm investing in life science companies. Dynamk's investment strategy is centered on Life Science Industrials: companies developing disruptive technologies, tools, and services that enable the full biopharma continuum across discovery, development, and manufacturing of therapeutics. The Dynamk team includes experienced life science entrepreneurs, investors, advisors, and subject matter experts and is headquartered in New York City.

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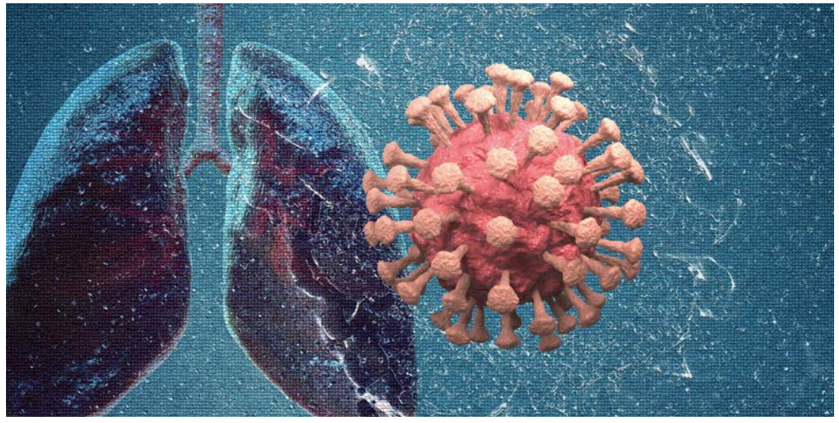

Our team is incredibly proud of the part we play in life sciences and the work we do in support of partner companies that supply critical technologies that biopharma innovators rely upon. This is ingrained in our culture as entrepreneurs — whether we are supporting recruiting, product development, outsourcing, or positioning for a strategic acquisition — we live and breathe life sciences. Our growth plan includes building our own teams in key markets to support our mission and ensure that Dynamk Capital is the go-to sponsor for life science industrials.

Every day, we look for ways to help our partner companies add value by solving the toughest challenges facing biopharma innovators to bring life-enhancing and life-saving therapeutics to patients.

We are closely monitoring the integration of drug substance and drug products in-house with drug development and manufacturing, a shift from the traditional approach that generally involves outsourcing to third-party fill-finish. The underlying trend is for innovators and producers to continue to outsource non-value activities to third parties, such as CDMOs and fill-finish partners. We believe that CDMOs that continue to speed timelines from gene to manufacturing to delivery of released product have a competitive advantage.

Monitoring Innovations

We are actively investing in artificial intelligence (AI) and machine learning (ML), which have enormous potential in the discovery and development of novel therapies. Envisagenics, one of Dynamk's earliest portfolio companies, is using ML to address genetic diseases caused by RNA splicing errors with their SpliceCore™ platform. AI and ML will come into play as digitally identical process models (i.e., digital twins to actual manufacturing processes) become a reality. We are already seeing this in early stages and expect significant focus in this area through 2021 as manufacturers plan for the coming decade.

We are also exploring new technologies, several being commercialized by our portfolio companies, that are using non-viral–based mechanisms to introduce gene-editing payloads. This could potentially eliminate the need for viral vectors in certain applications.

We recently invested in Lucid Scientific, who launched their RESIPHER smart handheld readers that sense real-time metabolic changes in response to potential therapeutics. The device provides valuable insights into cellular metabolism that are key for therapeutic discovery and drug safety considerations.

Ongoing Impacts of COVID-19

Owing to our focus on life science industrials, our overarching investment thesis has not changed as a result of the pandemic, but there have been tactical shifts necessary to adjust to our new reality. As COVID-19 hit initially, our priority was ensuring that our portfolio companies were well-positioned and funded to ride out any potential adverse effects and to take advantage of programs where their technologies could make a difference. We saw that very clearly with our partner company RoosterBio supplying critical MSCs and optimized cell culture media and development services to those actively developing therapies for ARDS (acute respiratory distress syndrome) and related COVID-19 complications.

It quickly became obvious that life science leaders were proving their resilience. COVID-19 underscored the importance of tools, technologies, and services already critical to biopharma; biopharma is relying on these innovations and technologies with increased intensity. The industry has more immediate needs, from development and supply of diagnostics, to therapeutics and potential vaccines. In the short term, it was critical that supply chains, production, and quality teams were able to meet these increasing demands. P

Technology Sponsor

SEMI-SOLIDS

TriRx PHARMACEUTICAL SERVICES

TriRx Pharmaceutical Services is a global CDMO serving the biopharmaceutical market. Headquartered approximately 50 miles outside of New York City in Norwalk, Connecticut, TriRx operates facilities providing state-of-the-art laboratory, manufacturing, packaging, warehousing, and technical service capabilities.

Founded and led by a team of pharmaceutical industry executives who have served as both contract service providers and customers, TriRx has a profound and multifaceted understanding of customer needs. This depth of understanding and commitment provides TriRx with the knowledge and know-how to deliver an exceptional experience on every project, consistently meeting or exceeding quality standards, regulatory requirements, on-time-in-full (OTIF) commitments, all at a fair price.

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The industry is facing revolutionary change – the cost of healthcare is the single largest socioeconomic issue in every country around the world. The industry continues to be one of the leading sources for preventing disease and improving quality/longevity of life while reducing per capita expenses. Pharma will continue to evolve by advancing gene therapy, progressing individualized medicines, improving speed to market, and reducing the price of medicines.

Trends Going Forward

Manufacturing and supply chains will be an ever-increasing component to the costly delivery of care. To become more efficient and significantly reduce costs, there will be increased use of CDMOs and outsourcing, with integrated project teams between customers and suppliers being key to success. The few CDMOs who are most effective at providing access to facilities, open lines of communication, and real-time information will set a higher standard of industry performance and deliver the critical requirements of on-time, in-full delivery, compliant with regulatory requirements and at a fair price

Collaboration among all components of the supply chain is crucial to timely, cost-effective delivery. The ability to integrate systems, projects, and communication lines between suppliers and customers is more important than ever. The industry now expects dedicated CDMO project leaders that provide stewardship for each customer's product as if it were their own. Increasing visibility of available capacity and increasing capacity utilization will also be key to rapid response. Regulatory cooperation to reduce bureaucracy will reduce response time and make lifesaving medicines available quickly.

There are a number of critical disruptive technologies under development: continuous flow processing, 3D printing, parametric control/release, CAR-T technologies, other individualized processing technologies, drone delivery, single-use technology, and the IoT. Improvements in drug development that significantly reduce adverse effects and increase effectiveness, including making drugs more bioavailable through controlled release, will transform the patient experience. Though they may yet remain far off, regenerative medicine and medicines by design will revolutionize the industry further.

CDMOs Remain Critical

CDMOs are a critical link to increasing efficiency and capacity utilization and reducing per-unit cost of medicines. At TriRx, we apply Lean Six Sigma processes to everything we do. Standardization of systems and processes is a goal, so we are constantly integrating as we acquire new sites to ensure that all of our operations are on the same system. We especially focus on a quality systems approach to operations to assure consistency and to meet (or exceed) regulatory requirements.

The COVID-19 pandemic has transformed the industry, including more efficient collaboration with regulatory authorities and better interactions with customers. We are constantly challenging ourselves to find ways to use technology in a more customer-centric manner, and virtual meetings and tours provide our customers with real-time access to our people, our sites, and our events. The pandemic has also led to better delivery through renewed supply chain relationships.

We continue to grow organically and through acquisition to become an industry leader providing a cost-effective, secure source of supply for the world's medicines. We will be investing in critical capabilities and dosage delivery technology to be a winner in the consolidation activities afoot and to continually increase productivity and efficiencies. We will always focus on delivering on our commitments to our customers and the patients they serve. P

Technology Sponsor

PLASMA PROTEINS

WE BELIEVE THAT OUR INNOVATIVE MANUFACTURING TECHNIQUE WILL ALLOW US TO FURTHER ADVANCE THE QUALITY AND AVAILABILITY OF PLASMA-DERIVED THERAPEUTICS AND TO MORE EFFICIENTLY EXTRACT A BROADER RANGE OF PROTEINS AT HIGHER YIELDS, AS COMPARED WITH TRADITIONAL MANUFACTURING TECHNIQUES.

evolve biologics

Evolve Biologics is a new kind of biologics company. We're built around a next-generation technology for bringing critical therapeutics to the people who need them. We believe our patented next-generation technology, PlasmaCap EBA®, is the first major advancement in the field since the 1940s. We believe it will help us deliver critical plasma-derived therapeutics at higher levels of purity, efficiency, and quality than conventional methods can.

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Originally founded and based in Canada, Evolve is a new kind of biologics company built around a patented next-generation technology that brings critical plasma-derived therapeutics to patients in need.

There are many patients with rare diseases around the world who rely on therapeutics made from the many valuable proteins extracted from human blood plasma. Unfortunately, for more than 75 years, these proteins have been captured through a largely unchanged, yet expensive manufacturing process.

Breakthrough Technology

We believe our patented next-generation technology PlasmaCap EBA® is the first major advancement in the field since the 1940s, allowing us to deliver these critical plasma-derived therapeutics at higher levels of purity, efficiency, and quality than conventional methods. Ultimately, Evolve's vision is focused on improving patient lives while building a broad and innovative product portfolio in the process. This portfolio would include both existing plasma-derived therapeutics and other proteins not currently commercially available. This would be particularly important where such therapeutic options are currently limited or non-existent, which could include hyperimmune globulins, some of which are currently in development for the potential treatment of COVID-19.

Looking forward to 2021 and beyond, the demand for many of these important plasma-derived therapeutics will continue unabated, especially immunoglobulins based on both existing and future therapeutic indications. We believe that our innovative manufacturing technique will allow us to further advance the quality and availability of plasma-derived therapeutics and to more efficiently extract a broader range of proteins at higher yields, as compared with traditional manufacturing techniques. This efficiency drives reliability and consistency of supply, which is important considering the frequency of product shortages, especially for immunoglobulins.

Phase III Clinical Trials and Beyond

Evolve is currently in the process of completing its phase III clinical trial for intravenous immunoglobulin (IVIG) in both the United States and Canada, as well as building a new fully dedicated commercial facility in North America. The facility will allow the manufacture of plasma-derived therapeutics, initially for the U.S. market. Going forward, we see our scalable and cost-efficient technology becoming available in smaller countries, allowing plasma collected locally to be used to manufacture plasma-derived therapeutics for their own population. The time has come to advance the way plasma-derived therapeutics are delivered, and Evolve is doing just that! P

Technology Sponsor

PATIENT SAFETY

DAY IN AND OUT, ECRI STUDIES WHAT CAN GO WRONG WITH THE USE OF MEDICAL DEVICES AND PHARMACEUTICALS; THIS NEW MIGRATION OF TECHNOLOGY IS A GAME-CHANGER FOR THE HEALTHCARE INDUSTRY, PATIENTS, AND OVERALL SAFETY.

ECRI's passion for safe, effective, and efficient care is deeply ingrained into the fabric of the trusted nonprofit organization. For more than 50 years, the people of ECRI have been unyielding in their work to protect patients from unsafe and ineffective medical technologies and practices. With the affiliation of the Institute for Safe Medication Practices (ISMP), ECRI has created one of the largest healthcare quality and safety entities in the world. Part of ISMP's mission is to work with the FDA and pharmaceutical companies to avoid medication safety problems. ISMP's wholly owned for-profit subsidiary, Medication Safety Board (MSB), works directly with the pharmaceutical industry to identify and help prevent errors related to packaging and labeling, further assuring patient safety.

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The biggest change in the evolution of healthcare is point-of-care delivery. Care is rapidly moving out of hospitals and into ambulatory settings and homes. The COVID-19 pandemic has accelerated this seismic shift. The rapid adoption of telehealth and remote care during the pandemic is going to continue to escalate. Treatments and procedures that used to take place in hospitals with overnight stays are now often in-and-out procedures at ambulatory care centers. More and more patients receive complex treatments at home, such as chemotherapy infusions, dialysis, and cardiac monitoring. In most cases, these devices have alarms to alert personnel when something is wrong, but, when complex technology is used in the home setting, patient safety can be at risk.

Additionally, treatments are becoming more complex with new drug/device combination therapies. That's one reason why ECRI, an independent nonprofit patient safety organization, joined forces with the Institute for Safe Medication Practices, the world's leader in medication safety. By creating one of the largest healthcare quality and safety entities in the world, we can closely monitor an evolving set of issues that could lead to errors and patient harm. For example, rather than oversight by a trained clinician, devices and drugs used in the home are now in the hands of an aging lay population who bring new risks to the use of that technology. Day in and out, ECRI studies what can go wrong with the use of medical devices and pharmaceuticals; this new migration of technology is a game-changer for the healthcare industry, patients, and overall safety.

Patient Safety in All Settings

Patient safety is paramount in all care settings, now and in the future. ECRI's more than five decades of medical device and patient safety experience has been instrumental in establishing safe and effective clinical pathways and guidelines. We have been overseeing medical device safety since the late 1960s, when ECRI reviewed and evaluated lifesaving devices in hospital emergency departments. We established the National Guideline Clearinghouse in 1998 for the federal government, and now our ECRI Guidelines Trust vets guidelines' adherence to the highest standards for trustworthiness. This assures clinicians that treatment pathways are supported by science and the best available evidence. Every day, ECRI scans the horizon for new drugs, devices, treatments, and interventions that show promise to improve care by disrupting standard practices. ECRI is well qualified to advance safety and quality into the next dramatic shift as care moves into the home setting.

ECRI and ISMP promote patient safety by sharing adverse events, near misses, and unsafe conditions across all healthcare settings, including ones associated with a pharmaceutical product and medical device use. ISMP's wholly owned for-profit subsidiary, the Medication Safety Board (MSB), works directly with the pharmaceutical industry to identify risks upstream and help prevent errors related to packaging and labeling from happening.

COVID-19 has changed the way the world delivers healthcare. ECRI, ISMP, and the medical device and pharma industries all need to change, too. For us, it is evident that hospitals and pharmacies are consolidating. Care is shifting to ambulatory, aging, and home care settings. To remain viable, we need to broaden our attractiveness to nontraditional healthcare providers, understand how they operate, and then develop services targeted to their needs. Cost savings is just one element in that equation. The ultimate value we provide must be improving patient safety in all care settings. P

Technology Sponsor

BIOANALYTICAL SERVICES

Altis's mission is to develop, manufacture, and sell innovative services and research tools to accelerate drug development. Their goal is to reduce the time and cost of drug development with *in vitro* platforms that more accurately reflect native human biology. Altis considers its intestinal platform to be the next generation for *in vitro* testing during drug development.

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THE ALTIS SYSTEM USES PRIMARY HUMAN STEM CELLS TO GENERATE A PLATFORM THAT MIMICS REAL HUMAN INTESTINAL BIOLOGY FAR MORE ACCURATELY THAN MODELS USING iPSCS.

There is a growing need to address the high failure rate of drug candidates as they progress through clinical trials. Altis Biosystems aims to bring its technological advances to the forefront, enabling the drug development process to more effectively translate results from preclinical experiments to late-stage clinical trials.

Breaking the Conformity of Inadequate Testing Platforms

The struggle for companies to successfully transition promising preclinical research to late-stage clinical trials has existed for decades. Roughly 85–90% of drug candidates either display toxic side effects or fail to show efficacy once they are tested in real-world conditions. Rectifying this issue would lead to a massive growth in efficiency for pharmaceutical companies, reducing costs and freeing resources to invest in other innovations. It is here that Altis Biosystems can enhance the robustness of preclinical research, improving the quality of predictive models so that researchers can have increased confidence in the viability of drug candidates as they progress into clinical trials.

Typically, preclinical studies are conducted using either tumor tissue cell culture lines or whole-animal studies, but only include limited experiments employing primary human tissues. By underutilizing primary human tissues, it is unsurprising that many of these experiments do not accurately reflect human biology and disease states or translate well into clinical studies. We believe that, with an improved platform to undertake these initial experiments, developers can move forward with greater conviction concerning early results.

In the past, experts may have balked at the cost and difficulty of using primary human tissue: its limited viability; its need for multiple donors and the inconsistency this can bring; and its poor proliferative capacity. However, with new stem cell technologies, it is now possible to use primary human stem cells and induced pluripotent stem cells (iPSCs) to create cell lines and tissues in the lab. iPSCs are a cutting-edge technology with a wide range of applications, but they have drawbacks in achieving a physiologically accurate intestinal model. Donor cells can be easily obtained, but then they must be genetically modified to create a stem cell bank, which must then be differentiated under very strict protocols – with complex and time-consuming logistics – to create the desired lineage(s) that also possess a fetal gene expression pattern. Human intestinal stem cells, by contrast, are already epigenetically modified to limit them to a range of differentiated types but are then free to form the appropriate diversity of intestinal epithelial cell types. As such, the Altis system uses primary human stem cells to generate a platform that mimics real human intestinal biology far more accurately than models using iPSCs.

Unpacking the Complexity of *In Vitro* Intestinal Models

Most human diseases involve a combination of effects from multiple environmental factors and multiple genes. This complexity is more pronounced with gastrointestinal studies, which must also account for the microbiome. The future of increasingly accurate intestinal models is dependent on identifying and replicating a number of specific features, including selection of primary human tissues exhibiting the target disease or disease susceptibility, co-culturing additional relevant tissues, accounting for the microbiome and the anaerobic conditions present in the lumen, and modeling the physiological mucous layer. As we model each of these factors more accurately, we will move toward an ever-more refined and effective testing platform that will enable consistent translation of preclinical results to real-world successes.

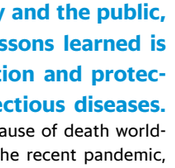
Our current foci are threefold: first, to expand our possible tissue variety, creating a biobank of donor stem cells from individuals with intestinal related diseases; second, replication of the anaerobic conditions of the intestinal lumen; and, finally, to pursue a model that recapitulates the intestinal mucous layer. We appreciate the immense difficulty of the task ahead, and our vision will require uniting experts across multiple disciplines. This challenge may not be simple, but it is certainly worthwhile. P

COVID-19 IMPACTS

What do you think is the greatest lesson learned from the COVID-19 pandemic, and what lasting impacts do you foresee over the next 5–10 years?

The COVID-19 pandemic itself will have lasting impacts on the industry and the public, but one of the greatest lessons learned is the importance of prevention and protection when it comes to infectious diseases. Infectious diseases are a leading cause of death worldwide, and, as we have seen with the recent pandemic, they present an ongoing global unmet medical need. Safe and effective prevention methods must be explored that mitigate the spread of infectious diseases and protect the entire global population from contracting these types of illnesses. Preventative methods to control the spread of infectious diseases for the entire population, including the aging and immunocompromised, are also cost-effective public health tactics that help save many lives each year.

At Cidara, we have learned the importance of leveraging our capabilities and being nimble enough to adapt in times of crisis. Having a platform technology allows us to create a broad range of therapeutics for various viral diseases. We have decades of experience in the infectious disease space, so pivoting our efforts toward the coronavirus represented a natural extension of our capabilities. We have initiated programs to identify and develop a potential protective agent against SARS-CoV-2 (the virus causing COVID-19) and its complications. Our fundamental programs in development include a novel, long-lasting antifungal candidate called rezafungin and our Cloudbreak® antiviral platform, yielding a new class of drug candidates called antiviral conjugates (AVCs). Our philosophy has always centered on the development of long-acting drugs, a necessary concept for protection from serious infections.

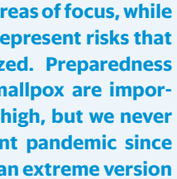


Jeff Stein, Ph.D.
CEO, Cidara

The greatest lesson is the fact that our national preparedness areas of focus, while important, historically represent risks that we have not yet realized. Preparedness for risks such as anthrax and smallpox are important because the threat remains high, but we never expected that the first significant pandemic since the flu pandemic was going to be an extreme version of the common cold.

The lesson learned is one of pandemic preparation and responsiveness, both domestically and internationally. Our preparedness must be much broader in scope, with more innovative ways of preparing, to ensure accelerated responses. One of the unique aspects of the COVID-19 pandemic is the urgency with which we have had to respond. No one envisioned that we would have to develop and manufacture a vaccine from the ground up in such a short period of time.

Over the next 5–10 years, I expect the focus on domestic preparedness to intensify. There will be novel ways to enable and incentivize the onshoring of our manufacturing capability as well as a heightened focus on risk mitigation across the global supply chain owing to our dependency on foreign suppliers. There will be fundamental changes to how we interact on a personal level. Hand shaking may go away, and the traditional way of working will be challenged, as our society has demonstrated in many different settings our ability to work remotely. Fundamentally our society will change in terms of interpersonal relationships and physical interaction, as well as workplace norms.



Sean Kirk
EVP, Manufacturing & Technical Operations, Emergent BioSolutions

Flexibility. As a global organization, it is vital to be flexible to respond as necessary to whatever circumstances the ever-changing situation presents. Our business continuity plans, which were well established and well-rehearsed, were enacted at the very beginning of the outbreak. Given the nature of the pandemic and the pace at which it spread, we immediately established an emergency response team to effectively and efficiently assess, amend, and cascade actions right across the business.

Our ability to be agile, implement changes, pivot as necessary, and, most importantly, communicate often, enabled Almac to ensure the integrity of our supply and the safety of our employees throughout, meaning that our service levels were not impacted in any way.

It is also evident that flexibility in terms of conducting clinical trials will be required if clinical development is to continue during the pandemic. An annual global survey conducted by Almac Group, designed to keep abreast of key trends in the industry, revealed that a majority of organizations (64%) are starting to rely on technologies from outsourced service providers allowing them to conduct trials in a decentralized manner. Almac has launched a number of innovative solutions that offer clients the flexibility required without compromising on quality of service. Our Simplify™ platform was introduced during the pandemic and is an advanced IRT solution enabling faster clinical trials start-up and empowering trial sponsors and CROs to conduct patient randomization and site and drug supply management in half the time of traditional solutions. In addition, our new innovative direct-to-patient (DtP) solution offers our clients the option to ship clinical trial material direct to patients' homes, offering more flexibility, and aiming to improve patient compliance.

Additionally, respondents expect to reduce their attendance at trade shows and workshops by approximately two-thirds for the remainder of 2020 and are most likely to rely on virtual 1:1 meetings, followed by educational webinars, in place of face-to-face events during the COVID-19 pandemic. Almac has responded to this shift by digitizing our conventional on-site audits and meetings to ensure continued quality and regulatory compliance for our operations.

The next 5–10 years will bring a sea-change in how "normal" working practices are carried out across the globe. Telecommuting, virtual meetings, increased emphasis on digital methods of conducting business, and reduced business travel could become the norm well beyond 2020.

Michael Cannarsa, Ph.D.
Director of Business Development, Almac Sciences

The greatest lesson we have learned is that cumulative ability, expertise, and knowledge offer the best path forward in developing new drugs and therapies.

We have seen the industry come together, with collaborations being forged between companies from the outbreak of the crisis, and the pharma industry has been lauded from all sides for the efforts that it has taken to mobilize quickly to try to help contain and treat the coronavirus.

Going forward, I hope that this level of openness, decisiveness, and will to collaborate on projects continues. This pandemic has seen companies re-evaluate molecules from previous programs against the new COVID-19 disease threat, and this is a model that could continue into the future. Whether a molecule has been launched or shelved during development previously, the opportunity to repurpose and reposition drugs offers the prospect of a faster route to patients than a discovery project for a new molecule, which is both expensive and lengthy. Given the time invested in the countless projects by pharmaceutical and biotech companies over the decades, the work undertaken during this pandemic to find a solution is a key reminder for medical scientists and the industry that, before embarking on new expensive discovery projects, we should look at what is in our existing medicinal arsenal.

Antony Fitzpatrick
Executive Vice President Operations, Vectura

The biggest lesson learned from the COVID-19 pandemic is how interdependent and global the pharmaceutical supply chain is.

Interdependencies affect every aspect of the industry, from the discovery of a new active pharmaceutical ingredient (API) to the efficient manufacturing of an established and mature generic drug. The pharma industry is only as strong as its weakest part, and each participant in this space needs to understand and comply with the most stringent quality and regulatory requirements. Pharma needs to develop robust and resilient supply chains based on the principles of transparency, open dialogue, and collaboration across chain participants — something that will help the industry improve in the long term.

Dago Caceres
Global Strategic Marketing Leader for the Pharma Solutions Platform, DuPont Nutrition & Biosciences

Q: What do you think is the greatest lesson learned from the COVID-19 pandemic, **and what lasting impacts do you foresee over the next 5–10 years?**

ROUNDTABLE

We knew a pandemic would happen; we just didn't know when and what the virus would be. Although we were trying to be prepared, we obviously weren't prepared enough. Hopefully, we will not forget the COVID-19 pandemic anytime soon, and we can increase our preparedness efforts.

The COVID-19 pandemic has taught us how much collaboration can impact results. Traditionally, a vaccine would take 10 years to create, but now, because so many groups within the industry are working together, we are looking at a timeline closer to 12–18 months. In the next 5–10 years, we anticipate that this increased level of collaboration will continue as we prepare for future pandemics.

In order to foster this high level of collaboration, effective communication among vaccine developers, manufacturers, and regulatory bodies should be a priority, and we must put protocols in place to help facilitate this. When these protocols aren't working, they should be analyzed and improved upon immediately.

It's also important that different groups that may not traditionally work together pair up so that differing areas of expertise can be leveraged. We've seen that the leading vaccine candidates come from diverse groups that pull together many complementary but different areas of expertise, such as small biotechs or universities that work together with established developers. These groups can then collaborate with contract manufacturing organizations that have the production capacities and with life sciences suppliers that bring with them robust supply chains and funding.

We have also learned how much strong industry associations, such as the Coalition for Epidemic Preparedness Innovations and other non-profit and expert groups that are focusing on pandemic preparedness, can help move the field forward. In the future, we believe it is important to strengthen and properly fund these groups so they can be prepared for the future.

Amélie Boulais
Marketing Manager within the Vaccine Segment, Sartorius

First, the importance of our industry: both the ability of biopharmaceutical companies to directly address the challenges of COVID-19 and the fact that our sector has remained so strong in such turbulent times. In an era when so many discretionary activities have been paused, the continued development of new medicines for people with cancer, neurodegeneration, and other serious diseases — by us and others — is as essential as ever.

During these uncertain times, a new priority has been placed upon logistical agility while also focusing on the importance of geographic diversification. We have achieved this through partnership with smaller, highly specialized CROs (across several geographic locations) without compromising our ongoing commitment to data reproducibility or robustness. This approach has enabled our drug development team to remain highly productive while staying interactive and remaining safe, despite spikes in viral transmission around the world.

Another significant impact is in how people work. As a company that uses computational technology for drug discovery, we have been fortunate that 100% of our full-time employees can do their jobs from home. We do miss in-person interaction and discussion, but since we have remained fully productive, we are able to avoid pushing our employees back to the office until the level of risk is exceedingly low.

Ben Zeskind, Ph.D.
CEO, Immuneering

With respect to cell therapy clinical development, we see an impact on our logistics operations. The mere fact that the number of flights has decreased by more than 70% complicates the logistics of blood-derived products with time limited viability.

We have also experienced slower recruitment into clinical trials caused by the COVID-19–related restrictions at the clinical sites. The situation caused by COVID-19 was not anticipated, and it caused a significant effort to adjust operations and keep the trials active. We will certainly plan for this kind of situation for the visible future, as there is very little visibility on the duration of the COVID-19 pandemic and related restrictive measures.

Radek Špíšek, Ph.D.
Global CEO, Sotio

Over the past three decades, the pharmaceutical supply chain has grown more complex and international to meet policies focused on aggressively decreasing drug prices. Though this worked from a pricing perspective, it also impacted the global supply chain. Many drug manufacturers were pushed to outsource APIs and other manufacturing steps to China and India. Today, it is estimated that 80% of all drugs sold in the West contain some form of precursor, whether basic or advanced, from either country.

At the start of the pandemic, we saw the level of vulnerability this approach has created as trade restrictions and logistical complications arose. Now, Western societies are seeing the strategic and operational chaos this reliance could have if essential ingredients or drugs are again restricted in the future. As a result, myself and many other industry experts predict a trend towards a reverse of this approach with onshoring efforts for pharmaceutical manufacturing supported by national production incentives.

Politicians can no longer argue that complete globalization is a "necessary thing" because we now see that the core theory underlying the concept of globalization has been proven wrong. Wealth has not transformed dictatorships into democracies; rather, it has threatened democracies at their core, causing a rise in populist authoritarian regimes. And while pharma remains a global industry, business as usual will have to transform to ensure that access and quality drugs are maintained across the globe during a crisis. A new approach to sourcing and securing supply with a more realistic cost structure is needed.

Andrew Badrot
CEO, C^2 PHARMA

To me, the greatest lesson learned from the COVID-19 pandemic is resilience: the CDMO industry has proven to be capable of outstanding resilience over the past months.

When governments decided to prioritize the supply chain for the health industry, there was a lot of uncertainty. Nobody knew for sure whether we could meet our engagement. But we have a very honorable mission as a CDMO: our mission is to produce APIs and, in the end, to contribute to help save people's lives. That is the reason why, when half of humanity was on lockdown, our employees have continued to operate our plants, even though they knew there was a risk for them. And I would like to thank them again for their commitment and resilience.

We had to face several operational challenges during lockdown. First, we had to work under degraded conditions: there were many people in telework. But it didn't prevent us from reaching our objectives, and it made us realize that we can work in a more efficient way in order to be even more competitive.

We also suffered from the fragility of the supply chain in Southeast Asia. Therefore, one of the lasting impacts I foresee over the next years is a rebalancing of our supply chain towards Western countries. And we now know that we can do this while remaining very competitive.

Jean Bléhaut
President of the Synthesis Solutions Business Unit, Novasep

COVID-19 has drawn attention to a critical step in the drug development process that has typically been behind the scenes: safety testing. Because safety testing happens long before a drug ever touches a human patient, this is often unknown to the general public. Safety testing isn't about finding the cure for a disease — it's about ensuring that the treatments people receive are safe and effective. As more consumers track the accelerated development of COVID vaccines, there is an increasing awareness of and emphasis on the importance of safety testing. Though timelines may decrease, the focus on safety and quality remain the highest priority.

At the same time, from an organizational perspective, COVID-19 has shown companies that it's imperative to focus on their people. For Charles River, the pandemic shifted our employees' perception of us as "just an employer" to an integral part of their lives. We've seen many of our employees step up to face the challenges of COVID-19. We have listened to our people to provide the resources and support they needed to succeed both professionally and personally.

COVID-19 has taught us that we must be ready to shift demand based on priority — priorities that can dramatically and quickly change. We as a CRO — and as an industry — have to be agile and adjust our own priorities to be able to react to something like this in the future. Moving forward, companies will continue to make investments to ensure more flexibility in handling similar situations and supporting our employees during stressful times.

Shannon M. Parisotto
Corporate Senior Vice President, Global Safety Assessment, Charles River Laboratories

Q: What do you think is the greatest lesson learned from the COVID-19 pandemic, **and what lasting impacts do you foresee over the next 5–10 years?**

ROUNDTABLE

As the world leader in serving science, Thermo Fisher Scientific has been involved in virtually every aspect of the fight against COVID-19, including more than 200 projects in vaccines, antivirals, and treatments. Over this time, there are several important learnings for pharma services businesses to keep in mind:

1. **Robust business continuity planning is crucial.** You will need to adapt over time, meaning your business plan should be flexible and agile. Be proactive, not reactive — this plan needs to be tested and in place before a major event happens.
2. **Reinforce the supply chain.** It is more important than ever to work closely with supplier partners and monitor and reassess your supply chain. It is equally critical to validate alternative sources of supply and expedited transportation modes wherever possible to ensure critical inventories for both COVID-19 and vital non-COVID-19 medicines. The pandemic has underscored the need for redundant capacity to eliminate single points of failure. Businesses should continue to prioritize second sources within a single network or leverage multiple supply organizations.
3. **Continue to invest.** Despite the uncertainty created by the COVID-19 pandemic, continue to invest in your business. For pharma services, this means growth in capabilities, capacity, and supply to ensure that critical medicines are never delayed.
4. **Innovate and leverage digital.** The adoption of digital technologies is critical to ensure business continuity and connectivity with colleagues and customers in new, virtual ways. For example, VR/AR technology can provide virtual site visits and inspections for regulatory agencies and customers.

Leon Wyszkowski
President, Commercial Operations,
Pharma Services, Thermo Fisher Scientific

All of us benefit from the tremendous expertise, infrastructure, and investments that exist in the United States to deliver lifesaving medicines. We have come to appreciate this more as a result of this pandemic.

In addition, the COVID-19 response has highlighted leading indicators of a new era in the pharmaceutical industry, one in which we will develop therapies that leverage nature's information-encoding schema (the genetic code) to turn genes and their resultant proteins on or off, as appropriate, to address most diseases at their root cause. The traditional method of testing libraries of chemicals against targets in the hopes of stumbling onto something that works is inefficient and slow, as we cannot predict target engagement or off-target effects reliably. We see this industry transformation evident in the vaccine trials for SARS-CoV-2. The platform technologies that embrace a genetic approach to design were among the first to generate viable candidates, some of which are now leading the race.

In my mind, the ultimate goal is to develop transformative, scalable platforms that could provide us with an entirely new arsenal of tools at our disposal for current areas of unmet need in monogenic disease, cancer, and common disease, as well as in infectious disease. Beyond the next 5–10 years, we believe that there will be increased reliance on scalable, high-Impact platforms that employ a digital approach to design and development. At NeuBase, we have such a platform that has the potential to create a limitless pipeline through this exact strategy.

Dietrich Stephan, Ph.D.
CEO, Neubase Therapeutics

The COVID-19 pandemic has clearly demonstrated the need for decentralized, low-cost, rapid point-of-care testing. Before the pandemic, the diagnostics industry was producing around 2 billion lateral flow tests per year for testing everything from HIV and malaria to pregnancy and allergies. Right now, for COVID-19 testing in the United States alone, we're talking about testing 300–400 million people, 2–4 days per week. That equates to 600 million to 1.6 billion tests per week — over 10 times more than what the market was making to test for every disease combined. The scientific community is in agreement that COVID-19 is not the last pandemic we will experience in our lifetimes, and it is clear that the capacity we're building to meet testing demand will be vital not only to continue battling COVID-19 even after a vaccine is developed, but also for future outbreaks and pandemics of viruses known and unknown.

BioDot, which makes automated, ultra-low-volume, non-contact dispensing platforms that are used to produce COVID-19 tests, began expanding its manufacturing capacity in the earliest days of the pandemic, anticipating that diagnostic companies would need to start sending in orders for the equipment that would be needed to ramp up test production as quickly as possible. To ensure that it could meet demand, BioDot strengthened its supply chain, began production at a new facility, and hired additional personnel, reducing prior lead times for most orders.

Anthony Lemmo, Ph.D.
CEO, BioDot Inc.

The COVID-19 pandemic has been a great proving ground for our ever-evolving technology. Before the COVID-19 pandemic, we were able to deliver pharmaceuticals with less than 0.1% temperature excursions, but the real test came when lockdown happened — and a recent audit of shipments made since global lockdowns found that we have retained that level of proficiency. This has shown us that furthering the integration of new technology into pharmaceutical logistics is vital if we are to efficiently deliver products around the world with near-zero spoilage rates.

The proliferation of biologic pharmaceuticals, which form the base of a number of COVID-19 vaccines, means the maintenance of stable conditions in transit will become even more vital if we are to deliver these lifesaving treatments around the world in viable condition, especially as these specific types of treatments are more vulnerable to changes in external conditions where limited temperature stability and their side effects are known, and therefore will require better hardware and software to keep them within usable parameters during transit.

Moving forward, COVID-19 will undoubtedly have lasting impacts on the industry. Over the next 5–10 years we will see greater importance placed on minimizing spoilage rates in transit. The industry still accepts that as much as 12% of pharmaceutical payloads will be not immediately released due to temperature excursions, which lead to hundreds of millions of additional inventory, express shipping costs, and quality assurance costs. The pandemic has shown that we need to be aiming to bring that rate down to as close to zero as possible.

Richard Ettl
CEO and Founder, SkyCell

The coronavirus crisis definitely taught the world many lessons, and within BASF I would like to highlight the learnings around collaboration, automation, and digitalization. During the crisis, we felt that it was more important than ever to stay close and communicate often with our employees, customers, and the entire value chain. We remained in close contact with our customers, suppliers, and logistics service providers in order to find practical solutions, regardless of the situation, and to maintain the supply of critical ingredients to our customers as fast as possible, even with increasing challenges and uncertainties within the global supply chain. Automation was already efficiently integrated into our manufacturing processes, which was strategic during the crisis, and because of this preparation the BASF Pharma Solutions production sites operated without major disruption and continued supplying pharmaceutical companies around the globe. Finally, the COVID-19 pandemic offered an opportunity to accelerate the use of digitalization: first and foremost, a quick pivot to virtual meetings and digital collaboration spaces, but then an increasing reliance of our customers on our Virtual Pharma Assistants, ZoomLab™, RegXcellence®, and MyProductWorld, providing technical, regulatory, and quality services to our customers instantly and online. Each of these initiatives will continue to impact our business in a positive way for years to come.

Dave Freidinger
Vice President, Business Management,
BASF Pharma Solutions

RISK MITIGATION

Although there is no such thing as a truly "crisis-proof" organization, how are you working to mitigate risks for future crises like the COVID-19 pandemic?

Our company has always prized agility and the ability to work across geographies. We had been operating offices in Boston, New York, and San Diego for some time, making us well-equipped to manage and direct the transition from in-office to in-home easily. Our team was already expert with Zoom meetings and Slack well in advance of COVID-19.

We have also always prioritized hiring highly self-motivated individuals, which enabled continued rapid growth when we all went remote. For example, Immuneering's dual-RAF/MEK inhibitor is now less than a year from the clinic, and our KRAS modulator is now in hit-to-lead. Immuneering's neuroscience team also launched a collaboration with Astex during the pandemic.

In addition, we have maintained strong lines of communication with our employees, ensuring them that their safety and comfort comes first. Providing this strong support to an already highly motivated workforce has helped enable us to be productive and successful despite the many changes encountered by the pandemic.

Ben Zeskind, Ph.D.
CEO, Immuneering

Throughout the pandemic, we have had to contend with flight cancellations and localized lockdowns, the need for emergency shipments of lifesaving vaccines across great distances (one such shipment going from Tokyo to Frankfurt), and misplaced cargo on the tarmac. Despite these mounting challenges, the tracking technology in our smart containers has allowed easier management of cargo and better communication with ground crews across the globe when shipments have been misdirected or lost. The self-charging capabilities of our containers mean that — no matter where they were and no matter the external conditions — they were always at the correct temperature to ensure that products arrive at their destination unspoiled.

The company's hybrid solution of hardware and software has allowed for smooth operations to continue throughout the crisis, and this should continue in the future. SkyCell's innovative product design and innovative IoT technology has allowed us to continue to perform at pre-pandemic levels throughout the pandemic — even in March and April when countries were locking down airports and flights were being cancelled at short notice.

Beyond the technology in the actual delivery, we have been successful in remaining efficient while part of our workforce worked from home. As critical suppliers to governments such as the EU and Switzerland, we already had this contingency planning in place, and the transition was smooth. Collaboration, both internally and with external stakeholders, is vital to the work we do, and we were quickly able to move our operations to remote working without any loss of performance. The pandemic has shown all companies in all industries the importance of being able to work remotely, and this will be something that companies will have to look at moving forward.

Richard Ettl
CEO and Founder, SkyCell

Because we're a leading supplier for end-to-end bioprocessing products, our sector has been greatly impacted by COVID-19. Our customers developing and producing a SARS-CoV-2 vaccine or therapeutic need the necessary technology immediately, thereby increasing its global demand.

While these changes have caused a significant increase in demand, Sartorius has been able to maintain its performance level thanks to its robust manufacturing strategy and further mitigation actions. Some of these steps include:

- Strengthening safety regulations at the manufacturing sites to keep risk of cross-contamination to a strict minimum in case somebody is infected;
- An established global manufacturing network enabling load balancing across sites, thereby ensuring optimized capacity utilization and limiting risk for site-specific bottlenecks;
- A long-established strategy of a minimum of dual manufacturing capabilities of key product families;
- A fully operational demand-planning structure in close contact with our global customers, including the COVID-19 vaccine developers, to anticipate future demand, which is translated in our routine S&OP process to anticipate future capacity needs.
- A core-carrier program with strong partnerships with our key forwards to ensure a strengthened logistical network, even at times when transportation possibilities are limited;
- Increased manufacturing output through process optimization, additional personnel, production equipment, and production shifts for key technologies;
- Stock review and increase both for finished products as well as raw material; and
- Ensuring that we can maintain our supply chain and product quality outside of COVID-19–related products, so organizations producing other vital products aren't disrupted.

Amélie Boulais
Marketing Manager within the Vaccine Segment, Sartorius

To me, there's no such a thing as "crisis-proof" organization. However, there are companies with more capacity to utilize crisis situations as a catalyst for change and a chance to do things differently. At BASF, we were able to build upon our strengths: a diversified and backward integrated portfolio, a global production footprint, the company's solid financials, and flexible and motivated employees.

BASF's diversified portfolio offers numerous advantages, especially in difficult times. Not all of our customer industries were and continue to be equally affected by the pandemic, and each showed different degrees of resilience in this environment. The pharma segment, for example, was expected to perform even at levels higher than before the pandemic, as many of our ingredients were utilized in the race for treatment and vaccine options for COVID-19, as well as the countless other essential medicines that patients rely on — quite simply, supply continuity was crucial.

As part of an overarching contingency plan, BASF has had a pandemic preparedness plan for a long time. The company has set up crisis teams in all regions to coordinate and communicate all measures. The crisis teams evaluated current information from external and internal experts and decided on a daily basis which measures are appropriate for BASF at the respective sites and globally. Our objective was and is to secure both the continuity of our business operations and to protect our employees, contractors, visitors, and the communities in which we operate.

We know that many of our products are indispensable for the continued production of essential industries, such as pharma, hygiene, and food. This awareness gives our employees extra motivation to continue strong contributions to their role within the business and the industries that we serve.

Dave Freidinger
Vice President, Business Management, BASF Pharma Solutions

Although there is no such thing as a truly "crisis-proof" organization, **how are you working to mitigate risks for future crises like the COVID-19 pandemic?**

At Charles River, business continuity plans (BCP) are in place to help our sites prepare for a variety of situations and crises. During COVID-19, these plans enabled us to continue operations and exceed client expectations, especially during a time when our services are so critical to clients and the industry. During this time, our BCP enabled us to have 70% of our people, who are considered essential, continue to be on-site in our facilities. It also provided us with the framework to ensure all client meetings, communications, and audits shifted to an entirely virtual model.

Additionally, we have carefully examined our suppliers and know exactly how their process and routing works. Our procurement team has been monitoring changes very closely and helped significantly in sourcing the required supplies to support our businesses. This combination of staying close to our clients and managing our supplies allowed us to continue to deliver for our clients. This coordination would not have been as successful without our well-tested BCP.

As the pandemic evolves or new challenges arise, the key is to remain agile, always monitoring the situation and advising with our internal and external experts on the impact on employee safety and business operations. With proper planning, we can achieve our goals of both protecting our employees while still meeting clients' needs for research products and services.

Shannon M. Parisotto
Corporate Senior Vice President,
Global Safety Assessment,
Charles River Laboratories

While the advent of the COVID-19 pandemic brought about a tumultuous period across industries, we demonstrated operational resilience and established ourselves as a "crisis-proof" organization. It was a priority to act, rather than react. We seamlessly adjusted operationally by introducing initiatives, such as flexible work-from-home policies, and investing in technology and infrastructure to support remote work and virtual collaboration capabilities. As we embraced adaptability, we were able to continue to achieve important company milestones, such as dosing our first patient in Part B of phase I/Ib study of IL-15 superagonist SO-C101, in combination with PD-1 inhibitor pembrolizumab for the treatment of advanced/metastatic solid tumors, as well as acquiring rights to the BOXR CAR-T platform and products from Unum Therapeutics. Our ability to pivot accordingly allowed us to focus on our mission to develop the next generation of immunotherapies for patients with cancer.

Radek Špíšek, Ph.D.
Global CEO, Sotio

C² PHARMA is a virtual manufacturing and distribution company specialized in establishing high-quality, redundant supply chains for complex active pharmaceutical ingredients (APIs) from natural and synthetic origins. Our business model is rather unique for this industry, with a focus on building quality, reliability, and sustainability throughout our supply chain.

Rather than pouring money into owned production facilities, our time and money are invested in creating a supply network that manufactures quality APIs from sustainable, reliable sources under contract for us. We also work with affiliates for preferred access to services that further complement our goals.

To ensure that our goals are met, we have implemented a proprietary quality oversight model to fully validate CMO (contract manufacturing organizations) for end-to-end API life cycle management, and all CMO and testing laboratories are under comprehensive QAAs (quality assurance agreements) with audits conducted annually. Our unique approach to doing business requires a level of full transparency on activities that is built on deep partnerships. And this approach has paid off during the pandemic with no delays or gaps in the supply chain.

2020 has been a challenging year mentally, but from a business perspective, our team has stayed committed. We are getting ready to submit more than ten regulatory filings in the United States, Europe, and Asia before the end of 2021, and I am very proud of what we are achieving. We are setting a new standard across the industry.

Andrew Badrot
CEO, C² PHARMA

With all of the standard protocols that are necessary to maintain the smooth running of clinical trial operations to meet the necessary regulatory requirements, crises such as the COVID-19 pandemic demonstrate the need for organizations to be flexible, responsive, and above-all professional, so that studies can continue.

Obviously, the safety and well-being of trial participants and staff remains the top priority of any organization conducting clinical studies, but it is absolutely imperative that the quality and integrity of data from trials remains at the highest standard.

To this end, we must look to the regulators for guidance in times of crisis, and this pandemic led to the FDA, EMA, and MHRA releasing guidelines to ensure that trial facilities could operate safely, and studies could continue. Alongside this guidance, national and regional instructions and regulations needed to be adhered to, so that we could resume activities in our Clinical Pharmacology Unit (CPU) in Antwerp.

With some adaptions to procedures, and the adoption of new methodologies, as well the commitment and flexibility of staff and investigators, the CPU has continued to run effectively. Visits to the unit are carried out by individually scheduled appointments and are streamlined to reduce the time subjects spend at the facility, minimizing contact with staff and other study participants. Technology has been adopted that allows for data to be collected and reviewed remotely, further reducing staff contact with subjects.

The nature of crises makes events unique, but as a company we learn from them and look to use them to inform future planning.

Nariné Baririan, PharmD
Clinical Pharmacology Expert,
SGS

What we have seen over the last six months is unprecedented and has tested every company's resilience. At the beginning of the pandemic, Vectura initiated its crisis management procedures, which cover a range of scenarios, and quickly began establishing priority actions to ensure that the safety of employees, business continuity, and delivery of critical products were unaffected.

There are probably two key areas that can be identified as being important to be resilient in this time. First, in our supply chain and our network of logistics operations, we had identified options that minimized risks, both to us being able to manufacture products and ship them to patients throughout the crisis. Second, using technology to its optimal efficiency was crucial to ensure that communications, both internally and externally, throughout the pandemic were swift and decisive. Without face-to-face contact, we have had to adapt our methods of communication, and this has been important both for business needs and to maintain the well-being of employees.

One specific point about resilience should be reserved for the staff and the efforts they have gone through to ensure that business was unaffected. Teamwork has been vital, and the cross-functional teams that were established out of necessity have brought people together. People have also learned new skills because of them, which makes us stronger going forward.

Antony Fitzpatrick
Executive Vice President
Operations, Vectura

I'm not sure any organization is completely "crisis-proof" — we never know what is around the corner; however, implementation of the appropriate policies, processes, and structure for communication throughout a crisis can ensure any eventuality can be managed effectively.

With over 5,600 employees operating globally, Almac must act swiftly to assess the situation, agree on the appropriate actions, deploy a strategy to implement agreed measures, and immediately communicate to all key stakeholders across the business. This takes careful planning and decisive action, ensuring preventative measures are implemented where possible, and a flexible approach is adopted to adequately manage all situations, something which we were able to clearly demonstrate throughout the COVID-19 situation.

Michael Cannarsa, Ph.D.
Director of Business
Development, Almac Sciences

Although there is no such thing as a truly "crisis-proof" organization, **how are you working to mitigate risks for future crises like the COVID-19 pandemic?**

While completely "crisis-proof" is a high bar, as an organization, Cidara fosters an adaptive and agile corporate culture, as well as sustaining a strong balance sheet and maintaining continuous dialogue with our employees, board members, and shareholders.

During the pandemic, we actively managed our business operations, while also taking measures to protect the well-being of our employees, their families, and local communities. We transitioned many of our employees to work virtually, and, for positions that required onsite work, we implemented safety measures that aligned with local and state guidelines. Having our own labs in-house also streamlines communication and generates open dialogue. During the COVID-19 crisis, it's often been our heightened sense of corporate mission to prevent and treat serious infectious diseases, which translates to getting things done no matter what.

Despite the impact of the pandemic, our stock (NASDAQ: CDTX) has gone up 165% over the past year. This is a testament to our experienced management team that not only knows the infectious disease space inside and out, but also has gone through a previous recession together in 2008 and knows how to effectively handle times of uncertainty.

Our team is built around the core values of collaboration, integrity, accountability, urgency, and courage. These values are the basis of our corporate culture and help us to handle adversities. By authentically living out our mission statement, we are equipped to communicate internally and externally in a timely and effective manner, adapt quickly, react purposefully, and work with reliability.

Jeff Stein, Ph.D.
CEO, Cidara

Like every global organization, Catalent has crisis management plans in place for various scenarios. Surveillance and communication are key and help identify threats quickly to enable timely response.

It is not easy to anticipate everything needed for any crisis. The COVID-19 pandemic is, we hope, a once-in-a-hundred-years crisis. We had no roadmap, but our mission and values provided a compass to guide our actions.

First, we looked to secure the safety of our employees before assessing the impact on 40+ facilities across four continents. Our work is essential in protecting the health and well-being of millions, so we had to ensure reliable supply of medicines to patients and consumers.

It sounds like a cliché, but the strength of our response has undoubtedly been our people. We focused on putting employees and patients first. Above all, we listened to deep expertise from our teams and the needs of our sites. Our facilities remained open, and we are responding to 50+ diagnostic, treatment, antiviral, and vaccine programs against COVID-19.

Effective communication internally and externally has enabled strategic assessment of capacity, equipment, and resource allocation; and, alongside careful planning, proactive investment has been expedited where necessary to ensure that we can deliver on our future commitments. Critical projects were even expedited "at risk," before contracts were formalized, with a view to saving time.

This ongoing pandemic gives Catalent the opportunity to reflect and re-evaluate the crisis management plans that were in place and refine them for future scenarios.

Kay Schmidt
Senior Vice President, Technical Operations, Catalent

ROUNDTABLE

Sean Kirk
EVP, Manufacturing & Technical Operations, Emergent BioSolutions

I don't believe any organization is crisis proof, because you can't foresee what the crisis is going to be.

There's a big difference between an organization dealing with the crisis of a global pandemic versus the crisis of a natural disaster like a tornado, hurricane, or wildfire. A crisis can manifest in many different ways. Speaking specifically in the context of the COVID-19 response, we've done an extraordinary job leveraging our historically established business continuity programs that were written years ago and then brought to bear in the COVID-19 emergency in order to protect our employees, solidify our supply chains, and enable our organization to continue to provide a variety of critical products. This has been possible because of the tremendous amount of effort put into proactive planning around business continuity in the past, which has in many ways saved us. We weren't "creating the will" in the midst of an emergency. Thankfully, it was already created.

I wouldn't go as far as to say that we are crisis-proof, because we never know what can happen in the future. However, we have shown great flexibility and managed to be responsive from the beginning of the COVID-19 pandemic.

We had to adapt and transform our organization to react quickly and minimize the impact of this pandemic on our business. We decided to put in place a dedicated governance, on two different levels:

- A crisis unit with daily calls of the executive committee to make swift decisions, and
- A task force composed of mixed profiles: some people from the top management, as well as employees from various departments within Novasep.

This organization has helped us to take rapid decisions and to set up and disseminate new procedures in the most effective way. We managed to stand by our commitment to customers and patients despite the crisis. It is certainly a best practice that we could duplicate if we face other critical situations in the upcoming years.

Jean Bléhaut
President of the Synthesis Solutions Business Unit, Novasep

We've learned this year to expect the unexpected, and I don't think any organization can be 100% "crisis-proof." Still, at Alcami, we work very hard to be proactive and prepared for anything that may come our way. This effort applies beyond natural disasters and force majeure events to anything that may not go as planned. I'm confident anyone working in drug development would agree; unforeseen challenges will inevitably arise somewhere along the way.

At Alcami, our size enables us to adjust quickly and adapt to crises. For instance, this year we have embraced remote working and virtual solutions. Alcami employees have been amazingly creative and persistent in overcoming other challenges like supply chain issues that have come with the pandemic. We've maintained operations at all sites and even have a new sterile facility in RTP, North Carolina, on schedule to be operational in October.

A huge part of Alcami's ability to be "crisis-proof" is the willingness of our employees to go above and beyond to ensure that our work can go on. We are a small cog in the giant machine responsible for providing lifesaving medications, and that is a big responsibility. Across all departments, we keep in mind the patients that our work is benefiting in the end, and that always provides the motivation needed to overcome whatever crisis we may encounter.

Casey Franklin
Senior Manager of Sales & Business Development, Alcami

The key to overcoming any crisis is robust planning, eliminating single points of failure, adapting quickly, and building a culture of creative problem solving. We spend an enormous amount of focused effort planning our objectives and key results (OKRs) on a quarterly basis, which align with the company's long-term goals.

Thereafter, we review them from the perspective of risk, so as to deeply understand the fragile points and then shore those up. Many risks fall into the category of single points of failure. In these instances, we build redundancy if possible. In addition to redundancy, we make sure that we monitor potential risks closely and in real time to ensure that we have the earliest visibility into the need to adapt. Adaptation must be done quickly and decisively, and rigorous advance planning allows us to think about how we might adapt should we be required to do so. Early data points indicating a manifesting risk are evaluated unemotionally, followed by a set of diverse inputs from our team and finally decisive decision-making. All failures and resolutions are captured and allow us to keep getting better.

When the pandemic first began, we quickly responded and implemented measures to protect our employees while still pressing ahead with our work. We adjusted schedules, made all of our meetings virtual, and implemented strict safety guidelines. The entire process was surprisingly seamless, and we believe that many of these new practices streamlined our process and will continue well past the pandemic.

Dietrich Stephan, Ph.D.
CEO, Neubase Therapeutics

For the pharmaceutical industry, it's critical that their strategic suppliers and partners are companies with a robust financial position, a responsible management structure, a long-term view of their business, high ethical standards, a focus on making high-quality and safe ingredients, and credible and up-to-date business continuity plans to ensure a reliable and consistent delivery of the product. DuPont's alignment with these needs and our decades-long commitment to the industry allow us to maintain and grow our participation in this space even during these difficult times.

Dago Caceres
Global Strategic Marketing Leader for the Pharma Solutions Platform, DuPont Nutrition & Biosciences

▶ Nice Insight and the *Pharma's Almanac* editorial team would like to thank all the companies participating in this quarter's edition. The following are the profiles of the industry-leading companies that have appeared in this issue.

Arcturus Therapeutics is a clinical-stage mRNA medicines and vaccines company with enabling technologies: (i) LUNAR® lipid-mediated delivery, (ii) STARR™ mRNA, and (iii) mRNA drug substance along with drug product manufacturing expertise. Arcturus' diverse pipeline includes self-replicating mRNA vaccine programs for SARS-CoV-2 (COVID-19) and Influenza, and other programs to potentially treat ornithine transcarbamylase (OTC) deficiency, cystic fibrosis, and cardiovascular disease, along with multiple diverse partnered programs.

Founded in 2013 and based in San Diego, California,

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RSK LIFE SCIENCE MEDIA

RSK-Solutions/RSK Life Science Media was launched in Sept 2019 and has two main strands: blogging on all things life science on LinkedIn, sharing news and information which is of benefit to the life science community; and consultancy services to help companies and event organizers make the most of their events and marketing on LinkedIn, as well as advice on marketing, media, events, and publishing.

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