Drug Development & Delivery

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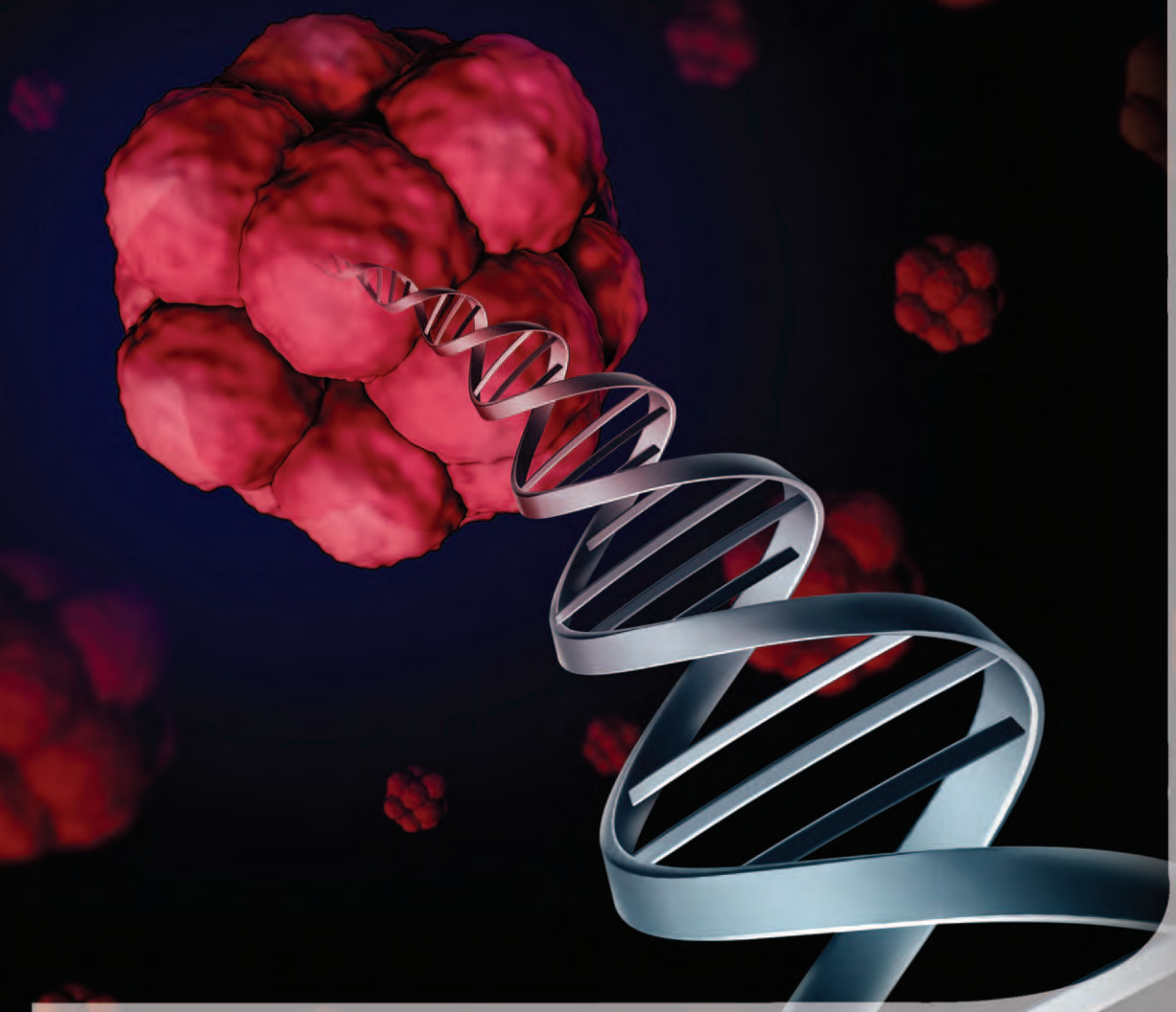
Where is C&GT Headed?



The Science & Business of Pharmaceutical and Biological Drug Development

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PRABU NAMBIAR, PHD

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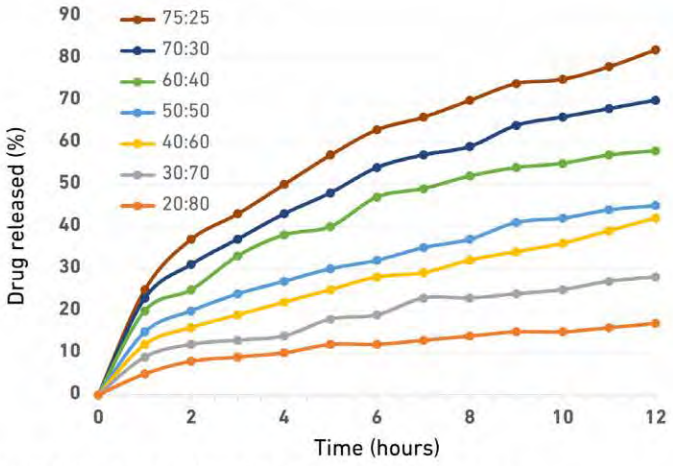

Effect of drug load on release from Niacin:Compritol® extrudates

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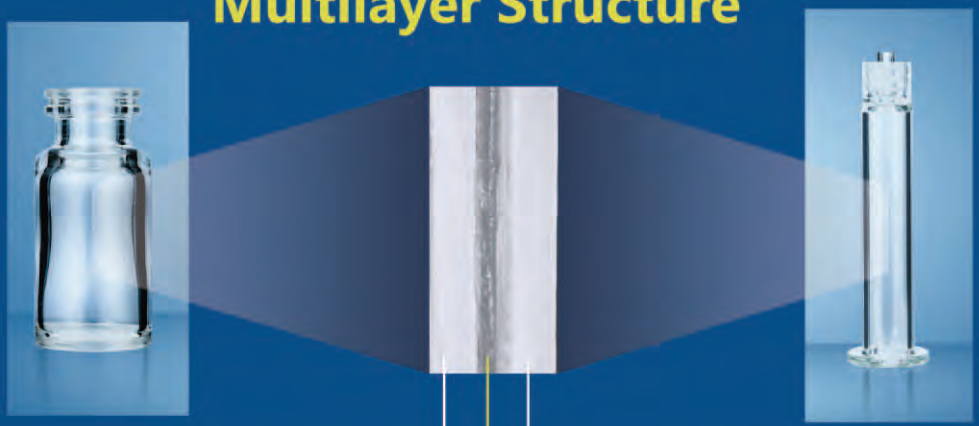

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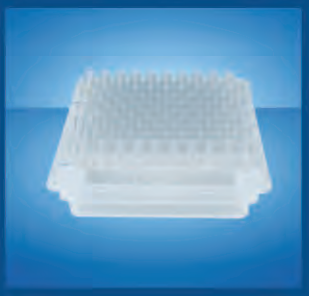
- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial



Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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"The Food & Drug Administration (FDA) has acknowledged that the lack of novel excipients is indeed a problem. In September 2021, the agency announced the Novel Excipient Review Pilot Program, which will select and review four novel excipients in the next two years using a new pathway. This will allow manufacturers to obtain an FDA review prior to the use of the novel excipient in a drug formulation."

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A TECHNOLOGY-DRIVEN CDMO DELIVERING END-TO-END PATIENT-CENTRIC SOLUTIONS

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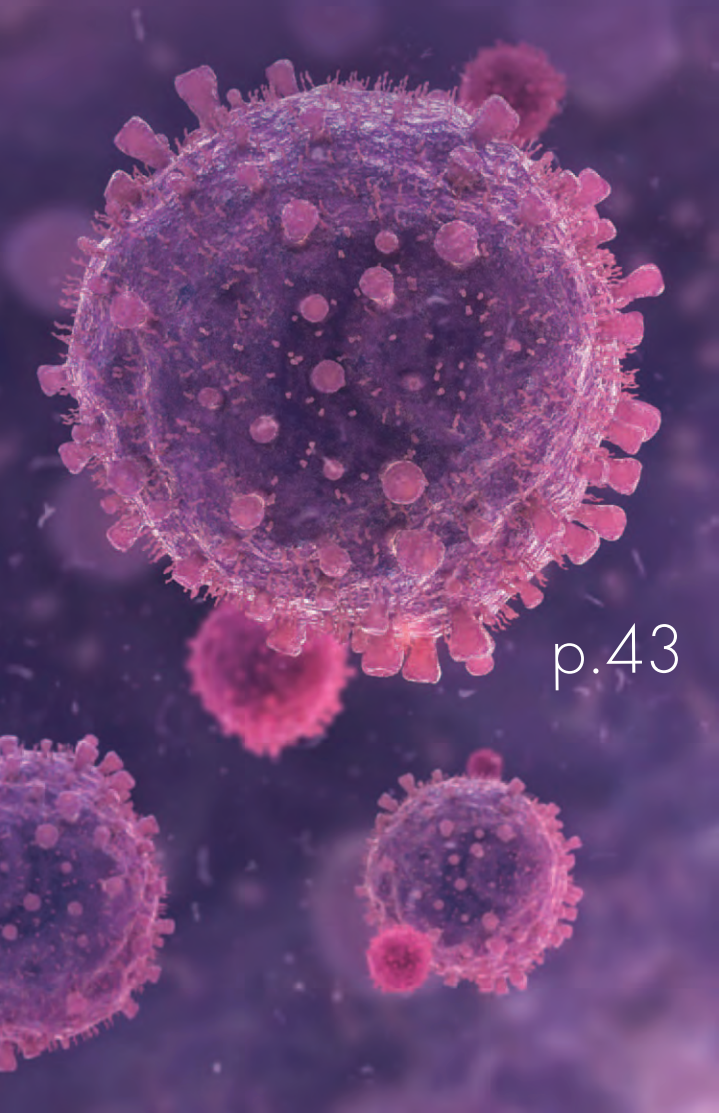
Where is C&GT Headed?

"If the industry wants to keep moving up the steep growth curve, then capacity and raw materials must be readily available. The innovations in therapies, platforms, and processes will all come with time, money and increasing availability of resources."



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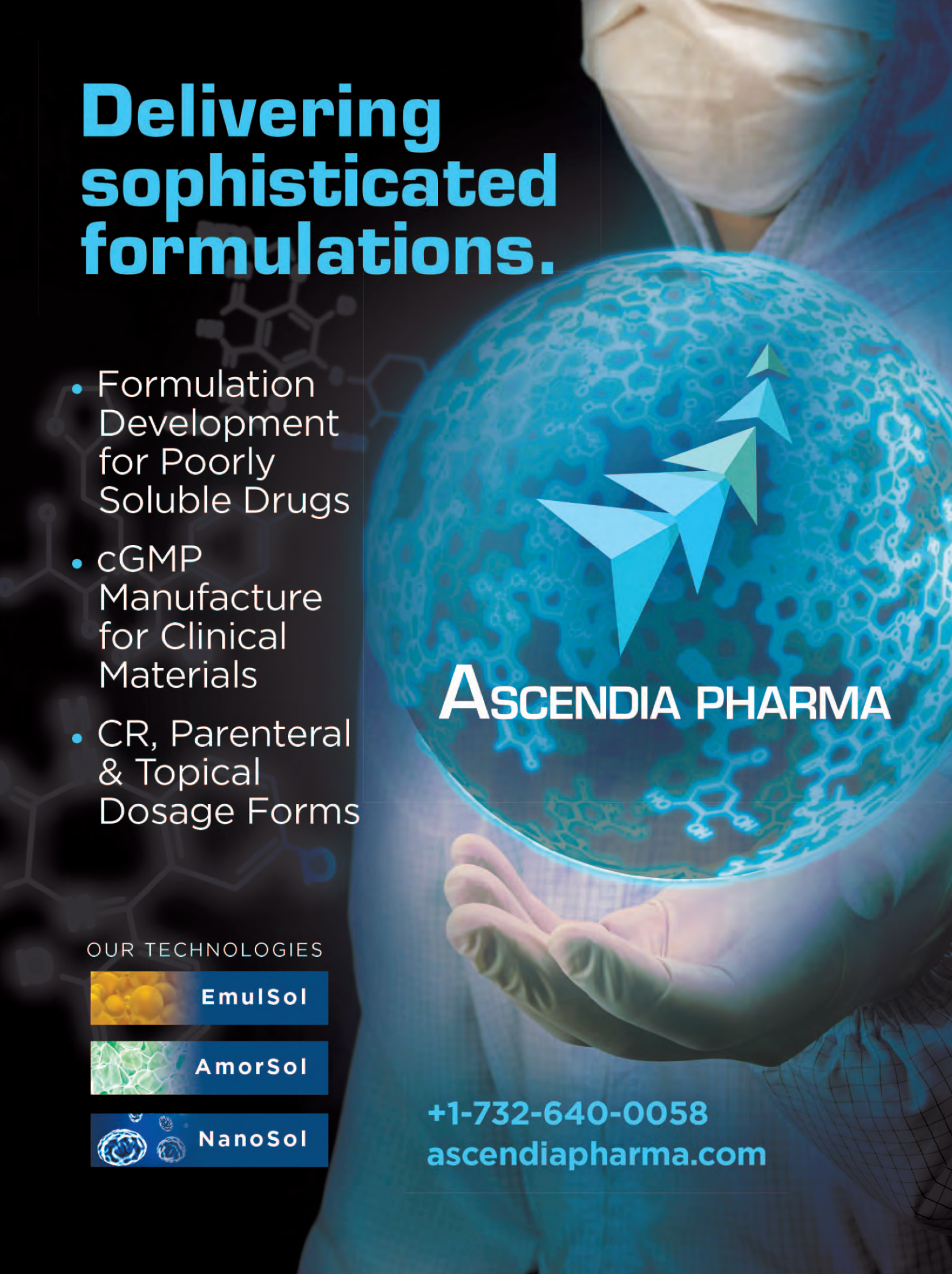
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Owen Mumford & Noble International Announce Collaboration

Owen Mumford Pharmaceutical Services recently announces its alliance with Noble International, an Aptar Pharma company and world leader in providing drug delivery training device programs for pharmaceutical companies and original equipment manufacturers.

Through this agreement, Noble will develop patient-focused training devices for Owen Mumford's safety syringe platform UniSafe. Noble will also develop and provide comprehensive training programs and materials to support and educate patients on their injection devices with the aim of improving therapy adherence and patient confidence.

Recent studies show that a staggering one-third of patients do not receive any formal training when they are prescribed a self-injectable course of therapy at their healthcare provider's office. For those patients who do receive training, the average training time is just 16 minutes, which discourages patients from practicing or asking questions.

"We understand the need for comprehensive training for drug delivery devices, especially for new patients or those with dexterity challenges. They will greatly benefit from having training on our UniSafe 1mL spring free design, which is already simple to use and has safety features such as a shielded needle and integrated plunger," said Michael Earl, Director of Owen Mumford Pharmaceutical Services. "We are excited about working with Noble and its extensive experience in providing a thorough training package will help to ensure that UniSafe patients are confident to deliver their medication and adhere to their drug regimen, therefore helping to achieve a positive impact on outcomes."

"This collaboration further strengthens both organisations' commitment to provide patients with the tools and resources to help them achieve better health outcomes," said Jeff Miller, Director of Business Development, Noble. "Noble's deep understanding of the anxieties and challenges that patients who self-administer face, combined with Owen Mumford's device experience and expertise, can better enable patients to begin their therapeutic treatment sooner and maintain their regiment longer."

Owen Mumford is a leader in the design, manufacture and advancement of medical technology, commercialising medical products in its own brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. It has pioneered the evolution of medical devices for almost 70 years with solutions for the ease and comfort of administering life-saving medication, safe and comfortable blood sampling and testing, and rapid professional and self-diagnostic testing kits. The company has a global presence across the UK, US, Europe and Asia and is a trusted partner to many of the world's biggest diagnostic and pharmaceutical companies.

Noble is an Aptar Pharma company and part of AptarGroup, Inc., a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions. A patient-centric global leader in medical device training solutions, Noble has expertise in human factors engineering, market insights, and device design and engineering to develop, manufacture and commercialize robust training solutions for patients who self-administer drug therapies.

DFE Pharma, Harro Höfliger & Sterling Announce Unique Partnership to Provide Formulation Services for Respiratory Products

Three leading companies in their respective fields – DFE Pharma (excipients solution provider), Harro Höfliger (equipment supplier), and Sterling (API manufacturer) recently announced a unique partnership with the establishment of Inhalation Together (INTO) in the field of dry powder inhalation (DPI).

This initiative provides R&D services to pharmaceutical companies in the respiratory field, making formulation development simpler, faster, and easier to manage. INTO offers a coordinated and aligned suite of services, leveraging the expertise and complementary skill sets of its three partners.

Developing a DPI formulation is a complex process, with a strong interdependency between process, powder, device, and patient. This increases the need for high-quality customer support. To address the specific customer needs, the INTO services range from initial consultancy and problem statement development to a stepwise formulation development program. The individual services include, among others, solid-state characterization and sono-crystallization of APIs and studies to optimize formulation, blending, and filling. The three INTO partners can also offer extensive consultancy services.

"I am very excited about the INTO initiative because it increases speed to market and reduces the complexity of formulation and process development. The three companies have a very good understanding of the critical aspects of development and manufacture of DPI products, therefore, adding significant value to our customers," said Martti Hedman, CEO of DFE Pharma.

DFE Pharma is a global leader in pharma- and nutraceutical excipient solutions. We develop, produce and supply high-quality functional excipients for use in the pharmaceutical, biopharmaceutical, and nutraceutical industries for respiratory, oral solid dose (OSD), ophthalmic and parenteral formulations. Our excipients are used in numerous medicinal and nutraceutical products, including COVID-19 vaccines and – treatments.

Our excipients play an essential role as fillers, binders, disintegrants, and in stabilizing active ingredients for release in a predictable and effective manner into the patient's system. With more than a century of experience and around 450 people worldwide, we are serving over 5,000 customers in 100+ countries worldwide. Headquartered in Goch, Germany, DFE Pharma is committed to supporting (bio)pharmaceutical and nutraceutical companies in their journey to improve patients' lives, driven by our purpose your medicines, our solutions. Moving to a healthier world.

Harro Höfliger specializes in the development of customer-oriented process and production solutions for pharmaceutical and medical applications as well as market-oriented consumer products. In addition to innovative machine platforms and packaging machines, customized turnkey system solutions for product assembly, processing of web materials, as well as dosing and inhalation technology are the company's core expertise.

Sterling founded in 1976 is a leading manufacturer of globally approved APIs with class leading facilities in Italy and Malta. Sterling delivers cost-efficient synthesis, process development, solid state science, material characterization, commercial manufacturing and life-cycle management solutions and has a proven capability to develop APIs for Respiratory sector (Rx & Gx) used in pMDI, capsule and complex DPI products. For more than 30 years Sterling has partnered with clients and supported successful complex inhalation programs providing advanced solutions for customers and in doing so supporting the world's population in the delivery of Respiratory Medicines.

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	Reduces manufacturing complexity	

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Gerresheimer Opens a New Plant to Produce Pharmaceutical Container Solutions

Gerresheimer ceremoniously took over a new building in Berlin, Ohio. In the future, the square plastic containers of the Duma Twist-Off Q brand with a 40-ml filling volume, child-resistant closure, and desiccant for filling with medications for the North American market will be produced here in a clean room. The new building is Gerresheimer's eighth location in total on American soil and is being built directly next to Gerresheimer's prescription packaging production facility. A major customer of the company has now audited the site for its orders.

"Many companies around the world produce bottles and closures from plastic. However, very few of them are produced in controlled areas and even fewer in classified cleanrooms like those at Gerresheimer. This is because it is the only way Gerresheimer can guarantee and ensure the quality and purity of the container solution used to package medicines. This is what Gerresheimer offers at each of its primary production sites for plastic packaging around the world. This project is a great example of successful knowledge sharing between the teams in the US and Denmark," said Niels Düring, Global Executive Vice President Plastic Packaging, who cut the blue ribbon at the dedication ceremony.

In the future, primary plastic packaging of the Duma Twist Off square brand with a 40 ml filling volume with a child-resistant closure and desiccant for filling solid medications will be produced at this new production facility in a clean room classified to ISO 8 standards.

Produced in a clean room using injection blow molding, the container is made of HDPE (high density polyethylene) and has a closure made of PP (polypropylene). The Duma Twist-Off square product family consists of seven products with volumes ranging from 30-200 ml. All bottles have injection-molded screw systems and are safety-packed. They are available with senior-friendly closures, which can also be supplied with child safety locks as an option. They are available with inserted or integrated desiccant. They can be additionally sealed with the Duma OneLiner closure. The containers have all the necessary approvals, in particular FDA, US and Canada Drug Master File.

As a specialist in plastic packaging solutions for the pharmaceutical industry, Gerresheimer offers a wide range of packaging solutions for solid, liquid and ophthalmic products. The leading brands Duma, Dudek, and Triveni for solid dosage forms, PET bottles of the edp brand for liquid dosage forms, and products for ophthalmic applications are part of the comprehensive and innovative product range.

The broadly diversified standard range includes a wide variety of containers and closures, PET bottles, eye droppers, nasal sprays, nebulizers, applicators, accessories, and countless customer-specific developments.

Gerresheimer is a leading global partner to the pharma and healthcare industry. With specialty products made of glass and plastic, the company contributes to health and well-being. prefillable syringes, injection vials, ampoules, bottles and containers for liquid and solid medications with closure and safety systems as well as packaging for the cosmetics industry.

eTheRNA Manufacturing Announces New LNP Formulation Development & Production Service

eTheRNA Manufacturing recently introduced a new Lipid Nanoparticle (LNP) formulation development and production service to support the discovery and early preclinical development of RNA-based therapeutics and vaccines.

This new LNP service uses eTheRNA's proprietary lipid libraries and proprietary formulations to facilitate targeted delivery and tailored biodistribution solutions. Combined with the expertise of its specialist team, the new LNP service has been devised to allow customers to maximize the delivery of their RNA-products.

eTheRNA Manufacturing's LNP formulation platforms employ a range of mRNA and lipid mixing technologies and will provide the market with differentiated alternatives to the LNP formulations in use currently. eTheRNA Manufacturing can also provide phase-appropriate analytical development in parallel with manufacturing process optimization to further assist customers with their RNA product development programs.

Bernard Sagaert, COO and Senior VP of Manufacturing at eTheRNA Manufacturing, said "The recent COVID pandemic has facilitated the rapid development and approval of the first-wave of COVID-19 RNA vaccines, which has led some people to underestimate some of the complexities of developing an RNA-based therapeutic or vaccine. Development of efficacious and safe RNA-based medicines requires a unique set of skills and resources to simultaneously advance both the active drug substance and the correct formulation required for the drug product. Through our long-established focus on RNA manufacture and delivery, and associated proprietary technologies, we have engineered libraries of custom lipids, which enables our LNP formulation team to design the most appropriate LNP for your mRNA application."

eTheRNA Manufacturing is a specialist RNA manufacture and LNP formulation division of eTheRNA. Our experienced teams, dedicated facilities and scalable proprietary processes provide expert support for your project from bench to clinic; initial drug substance to final drug product. eTheRNA Manufacturing provides services including plasmid development and production, research grade- and GMP grade-RNA production and a wide range of options for purification and QC analytics. Based upon experience in platform development at our parent organization, eTheRNA immunotherapies NV, we can also provide support in stability studies, purification and analytical method development and CMC report writing. For more information, visit www.ethernamanufacturing.com.

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Gb Sciences' Nanoparticle Encapsulation Technology Improves the Efficacy of Terpenes for Use in Chronic Pain Formulations

Gb Sciences, Inc. recently announced its sponsored study investigating the effect of nanoparticle encapsulation of three cannabis-based terpenes on their potential efficacy in pain management was published in the International Journal of Pharmaceutics on March 25. For the Gb Sciences-sponsored study, researchers at the University of Seville in Spain have developed time-released, oral nanoparticles to deliver Gb Sciences' patent-protected chronic pain formulations, which are based on synergistic mixtures of terpenes. Terpenes are normally highly volatile, highly lipophilic molecules that are difficult to formulate into stable drug products, so Gb Sciences and their colleagues believe that nanocarriers can improve their stability, solubility, and bioavailability.

"This research represents an important advance in the creation of novel terpene-containing pharmaceutical products for chronic pain, which have the potential to deliver relief over time in a safer and more efficient manner through our time-released delivery technology," said Dr. Andrea Small-Howard, President and Chief Science Officer of Gb Sciences, who co-authored the paper with researchers from the University of Seville in Spain and Chaminade University in Hawai'i. "There was a considerable technological challenge to developing a suitable drug delivery system for terpenes. This study demonstrates how nanomedicines offer an elegant solution for administering these efficacious molecules and opens up new opportunities for their use in chronic pain medicines."

In the US alone, chronic pain represents an estimated health burden of between $560 and $650 billion dollars, and an estimated 20.4% of US adults suffer from chronic pain that significantly decreases their quality of life. Despite the widespread rates of addiction and death, opioids remain the standard of care treatment for most people with chronic pain. Concerns over those issues have made novel chronic pain treatments such as Gb Sciences' therapies an important and promising field of research and development.

The Gb Sciences-sponsored study tested the effect of poly(lactide-co-glycolide) nanoparticles containing the three terpenes versus the effect of free terpenes in a cell model with TRPV1 receptors, which are known pain receptors. The study found that the encapsulated terpene nanoparticles produced significantly higher calcium responses alone or in combinations versus the free terpenes alone or in combinations. The elevated calcium responses through the TRPV1 channels indicate greater activation of these pain receptors, which can have an analgesic effect via desensitization of these important pain receptors.

In addition to its potential therapy for chronic pain, Gb Sciences has four other advanced preclinical-stage programs, including a Parkinson's disease treatment being prepared to enter a first-in-human clinical trial.

Gb Sciences, Inc. is a plant-inspired, biopharmaceutical research and development company creating patented, disease-targeted formulations of cannabis- and other plant-inspired therapeutic mixtures for the prescription drug market through its Canadian subsidiary, GbS Global Biopharma, Inc. The "plant-inspired" active ingredients in its therapeutic mixtures are synthetic homologues identical to the original plant compounds but produced under current Good Manufacturing Practices.

Prothena Announces FDA Clearance of IND for PRX012, a Subcutaneous Anti-Amyloid Beta Antibody Under Investigation for the Treatment of Alzheimer's Disease

Prothena Corporation plc recently announced the US FDA has cleared the investigational new drug (IND) application for PRX012, a potential best-in-class anti-amyloid beta (Aβ) antibody in development for the treatment of Alzheimer's disease (AD). Prothena has initiated the Phase 1 single ascending dose (SAD) study to investigate the safety, tolerability, immunogenicity and pharmacokinetics of PRX012 in both healthy volunteers and patients with AD. Prothena expects to initiate the Phase 1 multiple ascending dose study by year-end 2022.

PRX012 is a next-generation, high binding potency antibody, designed to enable subcutaneous dosing on a patient-friendly, convenient administration schedule, potentially providing greater accessibility for patients and caregivers. Preclinical data have shown that PRX012 binds to beta amyloid plaques and oligomers with high avidity, enabling effective levels of Aβ plaque occupancy at relatively lower dose ranges, which are optimal for subcutaneous delivery. Additional preclinical data demonstrated clearance of both pyroglutamate modified and unmodified Aβ plaque in brain tissue at concentrations of PRX012 estimated to be clinically achievable in the central nervous system with subcutaneous delivery. Compared to first generation anti-Aβ antibodies, PRX012 is expected to result in less variance of antibody concentrations in the brain.

"With Alzheimer's affecting more than 50 million people worldwide, we are committed to bringing a paradigm-shifting treatment to patients as quickly as possible. Having submitted our IND during this first quarter, we are excited to announce the initiation of this first-in-human study. PRX012's high binding potency and subcutaneous administration has the potential to serve as a foundational anti-Aβ treatment for Alzheimer's disease," said Gene Kinney, PhD, President and Chief Executive Officer. "We intend to leverage our multiple decades of experience and expertise in protein dysregulation together with clinical and regulatory learnings from first generation anti-Aβ therapies to maximize the probability of success for our PRX012 program to deliver a best-in-class treatment to patients with Alzheimer's and their families."

The Phase 1 single ascending dose (SAD) study of PRX012 is a randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, immunogenicity, and pharmacokinetics in healthy volunteers and patients with Alzheimer's disease. In this Phase 1 SAD study, healthy volunteers and patients will be randomized to receive a single subcutaneous injection of either PRX012 or placebo.

Prothena Corporation plc is a late-stage clinical company with a robust pipeline of novel investigational therapeutics built on protein dysregulation expertise with the potential to change the course of devastating neurodegenerative and rare peripheral amyloid diseases. Fueled by its deep scientific expertise built over decades of research, Prothena is advancing a pipeline of therapeutic candidates for a number of indications and novel targets for which its ability to integrate scientific insights around neurological dysfunction and the biology of misfolded proteins can be leveraged. Prothena's pipeline includes both wholly-owned and partnered programs being developed for the potential treatment of diseases including AL amyloidosis, ATTR amyloidosis, Alzheimer's disease, Parkinson's disease and a number of other neurodegenerative diseases.

Artizan Biosciences Announces Issuance of New US Patent to Cover Proprietary Discovery Platform

Artizan Biosciences, Inc. recently announced the US Patent and Trademark Office has issued US Patent No. 11,299,790 that broadens the use of the company's proprietary IgA-SEQ discovery platform. This is the fifth patent that Artizan has licensed in support of its technology.

Artizan's IgA-SEQ platform allows the company to interrogate microbial communities and identify individual bacterial strains and key virulence factors that elicit immunologic dysregulation and promote chronic inflammation. Artizan then develops small molecule and biologic therapeutics that inhibit these targets and thereby disrupt the root causes of pathological inflammatory cascades.

The new patent, issued to Yale University and licensed exclusively by Artizan, allows for additional use of the platform to identify specific bacteria implicated in inflammatory diseases, and methods of treating these bacteria. Deciphering pathogenic mechanisms allows Artizan's research team to develop disease-modifying therapeutic strategies. The platform is applicable to a broad range of diseases, including gastrointestinal, metabolic, autoimmune, neurodegenerative, and certain cancers.

"The award of this additional patent provides ongoing protections for our proprietary IgA-SEQ platform," said Bridget Martell, MA, MD, Artizan's President and CEO. "With our lead product candidate, ARZC-001, advancing toward the clinic this year, it expands the possibilities to leverage our unique technology and expand our portfolio for treatment of immune-driven inflammatory diseases."

Discovered internally and wholly owned by Artizan, ARZC-001 is a novel, oral, gut-restricted potent small molecule inhibitor for the treatment of inflammatory bowel disease (IBD). Artizan is advancing additional candidates into the late preclinical stage for IBD, each distinctly different in chemical composition and the target that it is aiming to inhibit. The company is also advancing its Parkinson's disease therapeutic discovery and development program in collaboration with Biohaven Therapeutics Ltd.

Artizan Biosciences is a biotechnology company creating a new class of transformative precision therapeutics that target and block the root causes of diverse, serious diseases triggered by intestinal inflammation. Founded with IgA-SEQ technology and preeminent immunobiology expertise from Yale University, Artizan's proprietary drug discovery platform identifies and characterizes microbial drivers of disease within precise patient subsets in certain cancers and gastrointestinal, metabolic, autoimmune, and neurodegenerative diseases.

In doing so, Artizan is creating multiple programs validated by strategic alliances that include Biohaven Pharmaceuticals, Brii Biosciences, and the Crohn's & Colitis Foundation. The Company's lead program, which is part of a portfolio of a new small molecule chemical class, is nearing the clinic in inflammatory bowel disease. Artizan is based in New Haven, CT. For more information, visit www.artizanbiosciences.com.

GeoVax Announces Issuance of Cancer Vaccine Patent

GeoVax Labs, Inc. recently announced the U.S. Patent and Trademark Office has issued Patent No. 11278607 to GeoVax, pursuant to the company's patent application No. 16/068,527 titled Compositions and Methods for Generating an Immune Response to a Tumor Associated Antigen.

The claims granted by the patent generally cover GeoVax's vector platform for expressing tumor associated antigens in virus-like particles (VLPs) from a Modified Vaccinia Ankara (MVA) viral vector and encompass GeoVax's Mucin 1 (MUC1) tumor-associated antigen immunotherapy candidate. The company uses its GV-MVA-VLP vaccine platform to express abnormal, aberrantly glycosylated forms of the cell surface-associated MUC1 protein that is associated with a wide range of cancers, including breast, colon, ovarian, prostate, pancreatic, and lung.

David Dodd, GeoVax President and CEO, said "The initial results with our MVA-VLP-MUC1 immunotherapy candidates have been encouraging and we recently began an IND-enabling animal study with Dr. Pinku Mukherjee at the University of North Carolina at Charlotte to define the optimal course and schedule of vaccination to define a protocol that can be evaluated in a Phase 1 clinical trial. We believe our MVA vector platform is well-suited for development of therapeutic cancer vaccines based on the expression of tumor-associated antigens such as MUC1 and Cyclin B1, among others. In addition to our work with MUC1, we are also developing Gedeptin, a novel patented product for the treatment of solid tumors currently in a Phase 1/2 trial evaluating its safety and efficacy in patients with recurrent head and neck squamous cell carcinoma (HNSCC). We are excited by the potential for GeoVax's growing immuno-oncology pipeline."

GeoVax Labs, Inc. is a clinical-stage biotechnology company developing human vaccines and immunotherapies against infectious diseases and cancer using novel proprietary platforms. GeoVax's product pipeline includes two ongoing Phase 2 clinical trials of GEO-CM04S1 (formerly COH04S1) for COVID-19 as a universal booster vaccine to mRNA vaccines authorized by the US FDA and as a primary vaccine for use in immunocompromised patients. In addition to GEO-CM04S1 for COVID-19, GeoVax is developing GEO-CM02 as a pan-coronavirus vaccine. The company is also conducting a Phase 1/2 clinical trial of Gedeptin for treatment of head and neck cancer. Gedeptin has been granted orphan drug status by the FDA. Additional research and development programs include preventive vaccines against Zika Virus, hemorrhagic fever viruses (Ebola, Sudan, Marburg, and Lassa) and malaria, as well as immunotherapies for multiple solid tumors. The Company's portfolio of wholly owned, co-owned, and in-licensed intellectual property stands at over 70 granted or pending patent applications spread over 20 patent families. For more information, visit www.geovax.com.

Blue Water Vaccines Announces Publication in Nano Research Supporting Novel S&P Vaccine Platform Versatility

Blue Water Vaccines Inc. recently announced its licensing partner, Cincinnati Children's Hospital Medical Center, or CCHMC, has published a research paper titled *Bioengineered pseudovirus nanoparticles displaying the HA1 antigens of influenza viruses for enhanced immunogenicity in Nano Research*. The company's lead vaccine programs are focused on developing transformational and novel vaccines against various infectious diseases, including influenza and gastroenteritis by norovirus or rotavirus infection.

The company's norovirus shell and protrusion (S&P) platform is currently being utilized to develop BWV-301, a vaccine for gastroenteritis caused by norovirus or rotavirus infection. This latest publication highlights the versatility of the S&P platform beyond norovirus/rotavirus application and supports BWV's exploration of utilizing the novel S&P platform to develop vaccine candidates against H1, H3, and Flu B infections.

According to Ming Tan, PhD, the principal investigator of this study, "Successful creation of HA1 influenza antigen PVNPs is a critical step forward in the development of a stable, durable flu vaccine. This platform will allow us to investigate the immunogenicity of pseudovirus nanoparticles (PVNPs) displaying various antigenic combinations and assess the potential effectiveness of each."

The research describes new technology developed to generate a unique HA1 norovirus based PVNP that displays the receptor-binding HA1 antigens of influenza viruses (IVs). These PVNPs displaying the HA1 antigens react with HA-specific antibodies and can be used as a new reagent for influenza virus studies. Moreover, the proprietary PVNPs provide a platform framework for designing multiple potential vaccine candidates in addition to influenza, including the norovirus/rotavirus vaccine candidate currently in the company's pipeline.

"This study is a great step forward for our S&P platform to develop novel vaccines across a wide range of infections, including influenza and gastroenteritis, which both represent significant global health burdens that need effective management through improved vaccines," said Joseph Hernandez, CEO of BWV. "With our partner at CCHMC, we look forward to the next stage of development of this novel platform and exploration of various vaccine development applications."

In July 2021, Blue Water Vaccines entered an exclusive, global licensing agreement with CCHMC to develop vaccines for multiple infectious diseases utilizing the latter's novel virus-like particle (VLP) vaccine platform. The platform leverages norovirus capsid proteins to present foreign antigens for immune enhancement. This synergistic partnership leverages CCHMC's scientific expertise for BWV's vaccine development.

According to the World Health Organization, there are normally more than 1 billion influenza infections leading to 290,000 to 650,000 deaths each year, even with available vaccination efforts. Current influenza vaccines are incredibly limited, relying on annual review and potential reformulation based upon the predicted circulation of specific strains. Additionally, the Centers for Disease Control and Prevention reports that viral gastroenteritis infections cause approximately 200,000 deaths in children worldwide each year. While there are available vaccines for rotavirus infection, there are currently no approved vaccines for norovirus infection prevention.

2021 Global Drug Delivery & Formulation REPORT

Part One of a Three-Part Series

Part 1: A Review of 2021 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals and Technologies of 2021

Part 3: Drug Delivery and Formulation Pipeline Trends

By: Kurt Sedo, Vice President Operations, PharmaCircle LLC

Introduction

The big question hanging over the pharmaceutical industry and healthcare professionals has been what impact COVID-19 would have on the development and approval of pharmaceutical products. Areas for concern varied widely from how pandemic-related public health restrictions might impact human resources, at the industry, patient, medical infrastructure, regulatory, and supplier levels, and how this might affect productivity. Given the lifecycle of product development and approval, it is likely the real impact of almost two "lost" years will only be revealed in the years to come. Once pivotal clinical trials are completed for a novel pharmaceutical product, a couple of years are required for the preparation of dossiers and review by regulatory bodies, both of which are less likely to be influenced by pandemic restrictions. The larger impact is expected to be related to the conduct of patient trials, particularly those that require regular patient and medical facility availability.

Some sense of the impact on industry productivity is offered by the 2021 FDA new product approval numbers. As suggested earlier, the impact is less likely to be seen in the new molecular entity (NME) products as these products have a longer development cycle and receive a greater sense of urgency from industry and regulatory authorities for commercial and public health reasons. Resources will be allocated by both groups as appropriate to get these products over the finish line. By contrast, products such as new dosage forms and especially new formulations and manufacturers are likely to receive less attention as they bring incremental patient benefits. At the bottom of the list are generic drug approvals. The figures bear this out. While NME approvals by the FDA were up slightly in 2021 versus 2020, generic (ANDA) approvals were down by a third compared with the previous two years. New dosage forms were down a quarter versus the previous year while new formulations were up a little.

The comparable figures for European and Japanese approvals are harder to reliably interpret. The European Medicines Agency (EMA) approvals relate only to specific classes of pharmaceutical products and don't capture the full range of products. The Japanese Pharmaceutical Medical and Medical Devices Agency (PMDA) published approvals are hard to access and properly assess. Taking these considerations into account, neither regulatory jurisdiction saw a drop in 2021 approvals compared with 2020, which might be considered a relatively normal year. The EMA approvals in 2021 were markedly higher than for 2020 and comparable to the 2019 approval numbers. For the European Union and the EMA, the challenge in 2020 was not limited to COVID-19 but also the reorganization and relocation arising from Brexit.

There seemed to be little impact of COVID-19 beyond approval numbers. Longer term trends in terms of dosage form, administration route, and molecule type were largely consistent with the two earlier years. Simple dosage forms continue to be preferred.

Biologics as a group continue to make inroads in terms of new molecular entities leading to a greater number of approved injectable products.

The impact of COVID-19 has not yet squeezed approvals. The pharmaceutical pipeline by development phase will be reviewed in Part 3 and may provide additional insights on what can be expected in the years to come.

Overall US NDA and BLA approvals were down in 2021, most notably generic product approvals

Table 1. FDA Therapeutics Approval Numbers by Classification[2] (2019, 2020, and 2021)

		2021	2020	2019
BLA (CDER*, CBER*)		**31**	**26**	**26**
CDER	Biologic, 351(a) & 351(k)	21	21	22
	- 351(a) (Innovator)	17	18	12
	- 351(k) (Biosimilar)	4	3	10
CBER	Biologic Therapeutics, 351(a)	10	5	4
NDA (CDER)		**111**	**122**	**117**
Type 1	New Molecular Entity	32	44	39
Type 2	New Active Ingredient	6	2	7
Type 3	New Dosage Form	19	25	26
Type 4	New Combination	7	7	8
Type 5	New Formulation or New Manufacturer	38	24	32
Type 7	Previously Marketed, Unapproved	0	0	1
Type 1/4	New Molecular Entity and New Combination	4	2	1
Type 3/4	New Dosage Form and New Combination	1	3	0
Other Type	Other Type or Not Specified	2	11	0
Medical Gas	Medical Gas	2	4	3
ANDA (CDER)	Abbreviated New Drug Approvals (Generic, Multisource)	**627**	**903**	**962**

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Modules

* - CDER (Center for Drug Evaluation and Research), CBER (Center for Biologics Evaluation and Research)

- Total human therapeutic product approvals by the FDA in 2021 were down in all areas except Biologics (BLA). The most notable decrease was seen in New Drug Approvals (NDA), with Generic, New Molecular Entity, and New Formulation approvals all down over 2020 and 2019.
- 2021's 31 Biologic approvals, 351(a) and 351(k), was a step up from 2020 and 2019. The increase was largely accounted for by an increase in CBER vaccines and gene and cell therapies approvals. Only one COVID-19 vaccine or therapeutic, Pfizer/BioNTech's Comirnaty, was among the 2021 BLA approvals.
- Biosimilar approvals in 2021, 4 in total, largely matched the total for 2020 (3) and represented a significant drop from the 10 approvals reported in 2019.
- 2021's 36 non-biologic novel drug approvals, including single active and combination products (Type 1 and Type 1,4), were a notable drop from the previous two years.
- New Dosage Form (Type 3 and Type 3,4) approvals totaled 20 in 2021, another notable drop from the previous two years. These products incorporated previously approved actives (PAA), often with the benefit of improved convenience or a focus on pediatric friendly formulations.
- New Formulation or New Manufacturer, Type 5, approvals bounced back in 2021 to exceed the approval numbers for both 2020 and 2019. These approvals are often associated with injectables, effectively generics that do not qualify for approval through the ANDA process and represent limited novelty.

Table notes: *Some multisource injectables are approved through the NDA rather than the ANDA regulatory process and can unintentionally skew the new drug approval figures.*

Injection route products represent the largest proportion of new product approvals

Table 2. 2021 Approvals by Administration Route

Route of Administration	US (n=170)	Europe (n=258)	Japan (n=82)
Buccal / Sublingual	-	**4** (2%)	-
Inhalation	**2** (1%)	**7** (3%)	**1** (1%)
Injection (All)	**93** (55%)	**93** (36%)	**48** (59%)
Instillation/Implantation/Irrigation	**2** (1%)	**1** (<1%)	**1** (1%)
Nasal	**4** (2%)	**9** (3%)	-
Ophthalmic	**3** (2%)	**20** (8%)	**2** (2%)
Oral	**55** (32%)	**102** (35%)	**26** (32%)
Surgical Insertion	**8** (5%)	**3** (1%)	**1** (1%)
Topical	**2** (1%)	**14** (5%)	**2** (2%)
Transdermal	-	**3** (1%)	**1** (1%)
Vaginal/Intrauterine	**1** (1%)	**2** (1%)	-

Source: PharmaCircle Pipeline & Products Intelligence module

- The approvals in Europe include both EMA and country level approvals for non-generic products. Not surprisingly, products using the Oral route were the most common followed by Injection (All). The Inhalation figures are skewed a little by the EMA practice of granting separate approvals for different brands of the same product. The Topical figures are remarkably high in part because of country level approvals for slightly differentiated formulations using previously approved actives. This also underlies the relatively high number of product approvals using the Ophthalmic route.
- The US approval population is consistent with earlier reports and represent new molecular entities and new novel formulations of previously approved actives. With this product set, Injection (All) significantly outpaces Oral. Inhalation is increasingly becoming a less common administration route for new products with effort being invested in Biologics that address respiratory diseases as common as asthma. In many cases, systemic injectables are being developed and approved to treat pulmonary conditions previously treated by inhalation.
- In terms of relative numbers, Japanese product approvals largely parallel the US, with Injection leading Oral.
- Nasal and Transdermal delivery continue to be associated with a very limited number of new approvals. For both Nasal and Transdermal delivery, the issue is largely related to the limited number of molecules suited for what is essentially "transcutaneous" delivery, be it mucous or dermal. The most interesting newer molecules pose increasingly significant demands on all delivery systems by virtue of drug size, lipophilicity and stability.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product.*

While intravenous remains dominant, subcutaneous injection is increasingly common

Table 3. 2021 Approvals by Injection Route

Injection Route	US (n=92)	Europe (n=69)	Japan (n=40)
Articular	1%	1%	3%
Intralesional	0%	0%	5%
Intramuscular	14%	13%	10%
Intramuscular, Subcutaneous	5%	1%	0%
Intravenous	39%	38%	38%
Intravenous, Intramuscular	2%	3%	0%
Intravenous, Intramuscular, Subcutaneous	0%	1%	0%
Intravenous, Intraperitoneal	1%	0%	0%
Intravenous, Subcutaneous	12%	9%	0%
Intravitreal	2%	1%	3%
Subcutaneous	20%	32%	43%
Subcutaneous, Intralesional	1%	0%	0%
Suprachoroidal	1%	0%	0%
Tissue	1%	0%	0%

Source: PharmaCircle Pipeline & Products Intelligence module

- There is remarkable consistency among the three territories with respect to the proportion of Injectable approvals in 2021 that used the Intravenous route of administration. Intravenous includes both bolus and infusion administration methods.
- The figures for subcutaneous administration at first glance seem varied, ranging from a high of 43% in Japan to a low of 20% in the US with the EU in the middle. The figures approach parity though when adding in the numbers for subcutaneous being approved as an administration option along with Intravenous and Intramuscular. In total, subcutaneous was the sole or optional administration option for 37% of approved products in the US, 43% in the EU and 43% in Japan.
- Using the same approach of adding together dosing options, dosing by the Intramuscular route was more varied between the territories. Intramuscular administration was approved for 21% of injectable products in the US, 18% in the EU, and 10% in Japan.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include Generics (All).*

Simple dosage forms, solutions, and tablets continued to be the norm in 2021

Table 4. 2021 Approvals by Dosage Form

Route of Administration	US (n=177)	Europe (n=247)	Japan (n=82)
Inhalation			
- Inhalation Powder	4	-	-
- Inhalation Solution, Suspension	4	-	1
Injection			
- Emulsion	2	-	-
- Lyophilized Powder for Solution or Suspension	19	10	9
- Solution	59	67	31
- Suspension	14	6	6
- Other	-	5	3
Nasal			
- Spray, Solution or Suspension	4	8	-
Ophthalmic			
- Emulsion	1	-	-
- Solution	2	20	-
Oral			
- Buccal or Sublingual	-	1	-
- Capsule	12	20	6
- Capsules, Soft Gel or Liquid Filled	1	4	2
- Lozenge	-	3	-
- Tablet or Powder for Solution or Suspension	3	3	1
- Sachet, Granules, Pellets	6	3	3
- Solution, Syrup	3	17	2
- Suspension	1	4	-
- Tablet	29	50	12
Topical			
- Cream, Ointment, Solution	2	8	1
- Foam, Gel	-	7	1
- Patch	1	-	-
Other			
- Intrauterine Device	-	2	-
- Implant	2	2	-
- Irrigation Solution	1	-	1
- Rectal Solution	-	1	-
- Stent	6	3	-
- Transdermal Gel, Patch	-	3	2
- Vaginal Gel	1	-	-

Source: PharmaCircle Pipeline & Products Intelligence module

- Simple and familiar dosage forms continued to be the norm for 2021 approvals. The most common injectable dosage form was a simple solution, with or without a dedicated delivery device. Oral dosage forms favored tablets and capsules with additional approvals of products that provided easier to swallow pediatric dosage forms such as granules and pellets. The higher proportion of oral dosage forms in the EU reflects the large number of dose-enhanced and proprietary formulations approved at the country level through the Heads of Medicines (HMA) procedures.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include Generics (All).*

Approvals by molecule type in 2021 showed the continuing ascent of biologics

Table 5. 2021 Approvals by Molecule Type

Molecule Type	**US** (n=170)	**Europe** (n=258)	**Japan** (n=81)
Antibody	23 (14%)	27 (10%)	16 (20%)
Antibody / Small Molecule	0	2	0
Carbohydrate	2	3	1
Cell or Gene Therapy	2	2	4
Natural Product	-	4	-
Oligonucleotide	2	-	-
Peptide	16 (9%)	5 (2%)	2 (2%)
Plasma or Tissue Derived	3	3	2
Polymeric	1	1	-
Protein	6 (4%)	11 (4%)	10 (12%)
Protein / Carbohydrate	0	-	1
Protein / Polymer	2	-	-
Small Molecule	108 (64%)	190 (74%)	42 (52%)
Vaccine or Virus	5	10	3

Source: PharmaCircle Pipeline & Products Intelligence module

- The Japan approval figures perhaps best represent the current trend with respect to Molecule Types and new molecular entities. The European data includes country- specific approvals (HMA) that largely represent reformulations of previously approved actives, generally small molecules. The same is somewhat true for the US where many approvals are Type 3 (New Dosage Form) and Type 5 (New Formulation or New Manufacturer), which generally relate to small molecules.
- Most notable perhaps are the inroads that peptides are making in terms of approved products, especially in the US. These molecules provide the eventual potential for non-injectable dosage forms while retaining the specificity of a macromolecule.

Table notes: *The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. Some products were categorized in two columns, for example Injection and Ophthalmic for a product delivered intravitreally. The figures above do not include Generics (All).*

References

1. Summary reports of 2021 approvals in all three territories are available at http://www.pharmacircle.com
2. NDA Classification Codes. https://www.fda.gov/media/94381/download

Formulation Forum

Oral Formulation Approaches for Different Stages of Clinical Studies

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INTRODUCTION

While we observe a rapid increase in new biological approvals in recent years, oral dosage forms still constitute a large percentage in terms of quantity. In fact, oral dosage products accounted for 45% (24 out of 53) of the new drugs approved by the FDA in 2020.

There are two main approaches to formulation development of oral dosage forms for human clinical studies, namely the fit-for-purpose, early phase formulation development and the late-stage commercial formulation development. For many biotech companies, it is the utmost important task to prove the principle in human for their new compounds as soon as possible, thus early phase formulation development has been using "the simple formulation approach" that demands a shorter development timeline, such as solution, suspension, drug in bottle, drug in capsule, liquid-filled capsule, powder for reconstitution, etc. However, in terms of compounds with solubility and bioavailability challenges, how to incorporate "enabling technologies," such as nanoparticles, amorphous dispersions, and nano-emulsions, into those "simple formulations" remains a challenging task for early phase development. Whereas the late-stage commercial formulation approach typically utilizes QBD principles and DOE experiments to develop a robust clinical formulation that is suitable for use as a commercial product, such as tablet, capsule, liquid-filled capsule, etc. Similarly, incorporation of advanced technologies into regular tablets/capsules dosage forms is a daunting task for late-stage development.

Even though it will be an ideal situation that a formulation can be used for both early phase and the late-stage clinical development and NDA registration, development for a market-image formulation is not initiated until Phase 2b for most of the clinical projects due to the fact that budgets and timelines are tight, and there is pressure to minimize development costs before proof of concept in human.

QUALITY TARGET PRODUCT PROFILES

It is critical to understand the compound's properties, indication, route of administration, disease model, patient population, and dose range, and to develop a phase-appropriate formulation that can meet QTTP and CQA criteria, including clinical requirements on the systemic exposure and PK profiles, label claim, content uniformity, dissolution, and stability, etc.

Per the ICH Harmonized Tripartite Guideline: Q8(R2) Pharmaceutical Development. August 2009, the quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." The QTPP is an essential element of a QbD approach and forms the basis of design of the pharmaceutical products. QTPP typically includes the elements such as dosage form, route of administration, dosage strength, and pharmacokinetics to ensure efficacy, safety, and stability, etc.

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute. All quality attributes are target elements of the drug product and should be achieved through a good quality management system as well as appropriate formulation and

process design and development. CQA for oral dosage forms typically includes identification, assay, content uniformity, dissolution, degradation products, residual solvents, water content, microbial limits, and container closure system.

CONSIDERATIONS FOR EARLY PHASE DEVELOPMENT

The main goal for early phase development is to test the compound safety and efficacy for the intended therapeutic indications in animals and humans. Tremendous efforts have been placed in improving the pharmacokinetic properties of compounds and ensuring bioavailability in animal models and human Phase 1 and 2 studies. Even though a simple formulation, such as solution/suspension, drug-in-capsule, is always desirable to allow for a fast transition to tox and human studies, a desired compound systemic exposure in testing subjects is a prerequisite to meet the goals of early development. Therefore, time and resources might have to be allocated for compounds with poor bioavailability to achieve a simple elegant dosage form that incorporates sophisticated formulation technologies. Otherwise, the drug program could be at a higher risk of costly failure in first-in-man and at the late stages.

Depending on compound permeability, body clearance half-life, GI absorption in the GI tract, dose, pH solubility, therapeutic window, and bioavailability, different types of dosage forms can be selected for development with the aid of modeling and simulation. When designing a clinical dosage form, ease of administration, dose accuracy, and swallowability should be always considered for the target patient populations. For example, pediatric and geriatric populations may demand liquid dosage forms with taste-masking properties, orally disintegrating tablets, or multi-particulate dosage forms, such as coated beads and powders for reconstitution, that help with ease of swallowing and accurate dosing.

DOSAGE FORM OPTIONS FOR EARLY PHASE CLINICAL STUDY

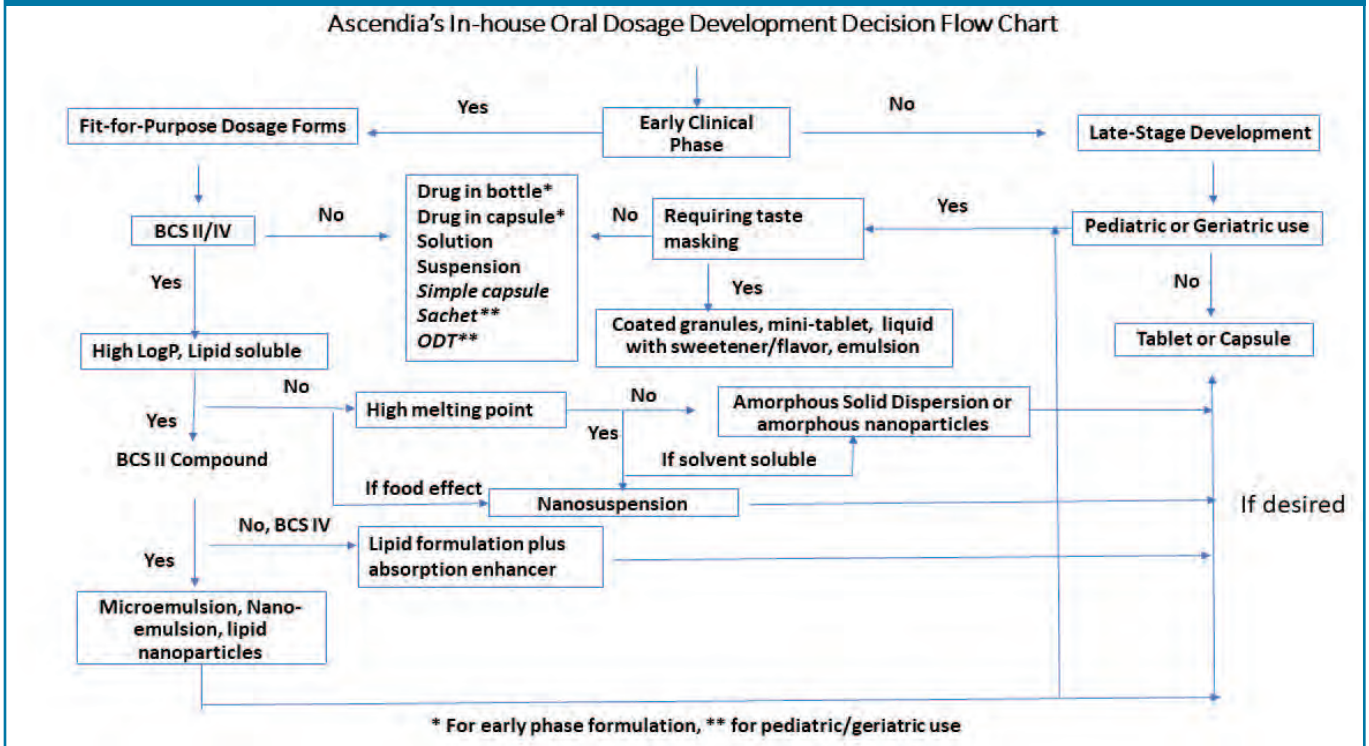
Drug-in-Bottle

API compound is supplied in a bottle for constitution into solution or suspension. The reconstitution is done at a hospital pharmacy. Commercial vehicles or their modified forms, such as "Ora-Sweet," could be considered for such purpose. The dose can be further diluted into filled bottles for different doses and for patients to take home. Dose flexibility is the advantage of the approach, and stability requirement is minimum. This dosage form is suitable for in-hospital dosing. In some cases, bulk amorphous solid dispersion formulations can be supplied in bottle and reconstituted by this approach.

Drug-in-Capsule

If the compound is readily wetted and dissolvable in GI fluids without the help of

FIGURE 1



Ascendia's in-house guideline in rational approach of oral dosage form selection for compounds at different stages of development.

"The main goal for early phase development is to test the compound safety and efficacy for the intended therapeutic indications in animals and humans. Tremendous efforts have been placed in improving the pharmacokinetic properties of compounds and ensuring bioavailability in animal models and human Phase 1 and 2 studies. Even though a simple formulation, such as solution/suspension, drug-in-capsule, is always desirable to allow for a fast transition to tox and human studies, a desired compound systemic exposure in testing subjects is a prerequisite to meet the goals of early development."

excipients, drug-in-capsule can be considered. Active compound is filled in hard capsules. Drug-in-capsule is suitable for out-patient dosing and for studies requiring blinding.

Solution or Suspension

If the compound is not suspendable or dissolvable in a commonly used suspending vehicle but is stable for a longer time period of at least 3 to 6 months, a formulated solution, suspension, and nanosuspension filled in bottle at a CDMO can be considered. This dosage form is desirable for out-patient dosing. In some cases, lipidic formulation (SEDDS or Nanoemulsions) can be formulated and filled into bottles or hard capsules (as liquid-filled capsule) by this approach.

Formulated Capsule & Tablet

For chronic dosing or a clinical program that is planned to fast progress to late-stage phase, formulated capsules or tablets may be desired. API compound can be simply blended with a diluting excipient, and the blend is filled in hard capsules, or in some cases, for API that has challenges in flowability, wettability, and dosage uniformity, a formulated capsule or tablet may be considered. For poorly water-soluble compounds, it is possible that the enabling formulations, such as nanosuspensions, lipidic formulations, and amorphous solid dispersions, can be further incorporated into the capsule and tablet dosage forms. Particularly, liquid-filled capsules that contain lipidic formulations have been used for both early and late-stage development.

CONSIDERATION FOR LATE-STAGE FORMULATION DEVELOPMENT

Oral formulation development normally goes through the following steps: 1) Definition of the quality target product profile (QTPP) and CQA; 2) Assessment of drug physical-chemical and biopharmaceutical properties that are relevant to oral dosage form design and that impact on CQA; 3) Modeling and simulation to define the dose and the simulated drug-absorption PK profiles; 4) selection of an appropriate formulation technology and in vitro test methods to evaluate formulations *in vitro;* 5) Identification of critical formulation variables that impact drug dissolution, bioavailability, and formulation stability; 6) In vivo study in animal or human models using prototype formulations for selection of a lead formulation; 7) Development of *in vitro/in vivo* relationship (IVIVR) or correlation (IVIVC) to aid product development; 8) Using QBD principle, conduct DOE experiments to identify critical process parameters; and 9) Scale up and manufacture for late-stage studies.

Oral dosage forms for late-stage and commercial production are preferably manufactured using conventional high-speed manufacturing processes. Traditional manufacturing processes for oral dosage forms include homogenizer for suspension, blending, roller compaction, comil for dry granulation, wet granulation by high shear granulator or fluid bed, drying by oven or fluid bed, milling, lubrication, encapsulation, capsule banding, tablet compression and coating, etc. To achieve a robust formulation and manufacturing procedure, it is important to understand the critical processing parameters (CPPs) that impact critical quality attributes (CQA). For tablet or capsule development, as a part of QBD, API properties (particle size, shape, crystallinity, solubility, drug loading, or flowability) that could potentially impact on the content uniformity, dissolution, compression, stability, and bioavailability should be evaluated together with critical process parameters (CPP), such as granulation volume/time, blending speed and time, impeller and chopper speed, lubrication time, drying time/temperature, and compression force and speed.

For compounds with solubility and bioavailability issues, the overall design and development process for late-stage dosage forms can be divided into the following steps: (1) to enhance the solubilities and dissolution rates using an enabling technology; and (2) to incorporate the drug intermediate with enhanced solubility in a traditional oral dosage form. Additional QBD and CPP should also be evaluated on the intermediate manufacturing process. For example, for nanosuspensions, the factors or combined factors such as milling speed, milling temperature, milling bead size, ratio of milling bead to formulation, drug concentration, milling time, etc., should be evaluated. For spray drying process, atomization pressure, spray rate, product temperature, solid content in spray solution, drug to polymer ratio, air volume, etc., are important to the formation of amorphous solid dispersion, particle size, dissolution, achievement of supersaturation, residual solvent level, yield, and product stability.

For formulation optimization, a DOE using factorial design may utilize 2-3 levels of critical excipients and their combination to evaluate their impact on CQA, such as dissolution, granule flowability, disintegration, hardness, etc. An optimum level of the formulation composition, such as drug loading, API particle size, filler, binder, disintegrant, glidant, and lubricant of a tablet formulation, can be determined from the DOE experiment. For the process optimization, once risk assessment is done in selection of CPPs and CQAs, DOE experiments using factorial design may select a few process parameters with three levels in combination with API of different particle size to evaluate their effects on granule flowability, compression, hardness, disintegration, and dissolution. Based on the statistical analysis, a design space will be identified to define the control strategy for large-scale manufacturing.

FIGURE 1

Ascendia scientist operating a Qualicap® F-40 liquid capsule filler with a speed of 40,000 units/hour in a solid oral cGMP manufacturing suite.

SUMMARY

Oral dosage forms still constitute a large percentage in term of quantity. It is of the utmost important task to utilize a phase-appropriate formulation development approach for early development and later-stage commercial development. Early phase formulation development has been using "the simple formulation approach," which, however, sometimes may require incorporating sophisticated technology for compounds with challenging properties in solubility and bioavailability, whereas late-stage development demands utilization of QBD principle and DOE experiment to optimize formulation and process parameters in order to achieve a robust commercial-viable formulation. ◆

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SUPPLY CHAIN MANAGEMENT

Are Supply Chains Up for the Post-Pandemic Challenge?

By: John Swift

INTRODUCTION

During the pandemic, medical technology businesses are likely to have identified stress points and vulnerabilities in supply chain infrastructures and operations that might otherwise have remained unnoticed. The struggles to address both peaks and troughs in product demand in a time of extreme uncertainty has helped bring weak links to light. These weak links, now that they have come to the forefront, must be tackled immediately in order to face any future pandemic waves or knock-on effects, and to prepare a solid front for any other unexpected events that may impact the market and supply chain.

Troubleshooting any weaknesses detected within the supply chain is key to preserving market dynamics from disruption to long supply chains, ensuring the immediate reprioritising of supplies critical for patient treatments, and preparing for the forthcoming flood of pent-up demand for postponed elective procedures. Failure in the medical device supply chain simply cannot be an option, as lack of stock may impact scheduling of future diagnosis and treatment, including drug administration, and ultimately put lives in danger. It is therefore urgent businesses update their policies to include plans for operational continuity,

disaster prevention, and business recovery in order to minimize the impact of future disruptions on product supply.

In addition to this, assessing supply chain risks should not be an ad hoc activity but an iterative process that is carried out periodically and continuously with the objective of keeping risk as low as reasonably possible. In fact, supply chain models come with risks by definition: the just-in-time (JIT) model for instance, while it has advantages, such as reduced storage fees, a reduction in waste and therefore carbon emissions as well as greater flexibility in inventory management, has a very slim margin of error and typically requires a series of back-up plans to prevent any problems. Whatever the supply chain model, however, a risk assessment can only be beneficial, and it might be well overdue.

THE MANUFACTURING MACHINE

The risk assessment process should ideally start within manufacturing plants. Here, it is advisable to review engineering spares policies, equipment, and assets usage and check that service level agreements are in place covering both the appropriate depth and frequency of service. Clear schedules and governance guidelines must be put into place to make sure that manufacturing controls are working as expected, and each key process in the manufacture of medical devices must be reviewed in light of recent pandemic experiences. It is vital to determine whether processes are still fit for purpose, whether risk parameters have changed, or a change in conditions dictates the need for new risk mitigation strategies. After completing this analysis, businesses will need to make sure their response is agile and flexible enough to deal with peaks and troughs in product demand. This may require additional investments, for example, execution of moulding or assembly capabilities for medical devices across alternative or multiple sites.

APPRAISING SUPPLIER NETWORKS

Supply shortages (15%), lack of alternatives (12%), and delays in production issues (12%) are some of the top post-pandemic concerns identified in a recent survey of supply chain professionals in the medtech industry.[1] One case in point is the polymer industry, which supplies medical device manufacturers; this sector has not yet recovered from the effects of the pandemic and as a result, downstream markets are experiencing longer lead times from suppliers and extended door-to-door shipping times for multiple routes and shipping lanes.[2] Reasons for these delays may include a surge in plastic products demand, a global shortage of shipping containers, and interruptions in production schedules.[3]

The same survey suggests that to prepare for potential natural disasters or other unforeseeable circumstances, manufacturers should improve the qualifications of multiple suppliers and of the review process (14%), try to source locally (16%), improve the visibility of supplier inventory, capacity, and lead times (13%), and endorse the restructuring of supply chains with second sources (12%). The availability of raw materials in different parts of the world of course impacts the ability of businesses to source locally, but they must also remain well aware of the exposure that source countries have to natural disasters, political instability, and other events that might impact the supply chain.

Keeping up to date with news and developments relating to the supply chain is therefore another critical activity for manufacturers. To do so, they will need a rigorous and comprehensive tracking and a management process that ensures early notification on potential disruption to supply and a consequent quicker implementation of mitigation activities to avoid or minimise future impact.

A CHECKLIST FOR SUPPLY CHAIN REVIEW

Based on the latest assessment of their supply chain, businesses may need to take action to mitigate issues caused by further and not yet known vulnerabilities among suppliers. The following dozen points in the checklist cover typical areas to keep under close control:

- Manufacturing suppliers' site changes, mergers, acquisitions, market volatility
- Regulatory compliance (current and future trends)
- Product lifecycle reduction, eg, obsolescence of raw materials
- Supplier constraints, such as capacity, capability, low volume challenges, and logistical risks
- Supplier solvency and financial health
- Risks due to supplier reliance on raw materials and concentration in countries likely to be impacted by climate change

- Supply chain disclosure aligned with appropriate policies, eg, regulatory, commitment to low carbon emissions
- Reliance on single-sourced key strategic items
- Supplier material/process changes and notification of change
- Uncertainty and level of understanding of the supply chain, role of distributors, upstream manufacturers, complex supplier networks, complete processes, and supplier maps
- Pre-screening and auditing of supplier quality
  - Organisation quality process assets
  - Manufacturing/processing equipment
  - State-of art health check
  - Potential internal process failures

SUPPLY CHAIN MAPPING

The results of the assessment should be used to draw up a supply chain map of the procurement path of tier one and sub-tier suppliers for key purchased and manufactured items. This type of graphical or tabular representation is ideal to ensure everyone in the business clearly understands the process and potential risks. It can prove a vital tool in today's post-pandemic recovery but should be part of regular best practice as it will support regulatory activities, such as tracking Economic Operator compliance under the EU Medical Device Regulation (MDR), which makes Manufacturers, Importers, and Authorized Representatives jointly and severally liable for nonconformities.

Supply chain mapping is particularly useful in highlighting:

- Supplier names, sites, and geographical locations
- Single source relative supply chain risk score
- Dual-source alternatives and preferences for primary and secondary sourcing
- Material demand chain: material type, processes, distribution, sub-tier suppliers (first level)
- Strategic and generic procurement, supplier agreements, including robust, active Notification of Change processes and aligned safety stock policies
- Validation level information and recovery time objectives
- Commercial engagement splits for dual-sourced, fully validated supply chains

ASSESSING NEEDS FOR NEW PRODUCTS

Finally, manufacturers should closely reconsider new products that are being developed, as they are, by definition, dynamic, and require an alignment between operational, business, and product strategies. New products also require an evaluation of the production and distribution model that needs to be built taking into consideration initial launch requirements and future demand. This may vary depending on each product and on whether the launch protocols are for a bespoke device for individual customers (such as a customized auto-injector) or a platform design for multiple customers (such as a safety device for prefilled syringes); the latter is likely to have a low-volume introduction but a forecasted growth to high volume. Businesses therefore need to identify potential risks to ongoing product supply to support product growth and meet

demand. A scale-up strategy is essential to make appropriate decisions relating to tool investment, tool cavitation, assembly investment, or transition from low-volume engineered fixtures to full automation.

PROACTIVE PLANNING

Each medical device manufacturer will discover different patterns of risk as a result of COVID-19. It is therefore imperative that businesses carry out an in-depth and urgent re-appraisal of their supply chain, as failing to do so may cause commercial damage. Some of the changes we are now experiencing may become permanent, and the pandemic has alerted businesses, governments, and regulators alike to risks in the medtech supply chain, which were previously under-recognized or even invisible. Setting up best practice systems and processes to ensure the supply chain is critically assessed regularly is not only an important practice to face the current challenges, but will stand a business in good stead for any future unexpected changes in the supply chain. Manufacturers that begin their appraisal sooner rather than later are more likely to be well prepared, capable of weathering future storms, and able to grasp competitive advantage. ◆

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BIOGRAPHY

John Swift is Head of Supply Chain at Owen Mumford Ltd. He is an experienced operations program manager with a successful track record working throughout the supply chain, covering procurement, supplier management, invention, development and manufacture, as well as promotion, sales, and distribution. He is experienced in applying and adapting skills across both large corporations – such as Abbott, Abbvie, and Tyco – and SMEs, and has worked in multiple industries, including medical device, aerospace and defence, rail, chemical, automotive, and printing.

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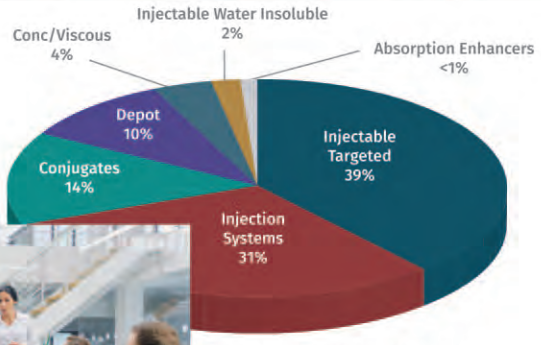
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
TITANIUM DIOXIDE **(Tablet/Capsule coat)**	7 mg
FD&C RED NO. 40 **(Tablet/Capsule coat)**	
FD&C BLUE NO. 2 **(Tablet/Capsule coat)**	

Evaluate New and Promising Technologies



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Special Feature

Excipients: Exciting Expansion & Innovation

By: Cindy H. Dubin, Contributor

The global pharmaceutical excipients market was valued at $7.7 billion in 2020 and is expected to reach $11.2 billion by 2026. Functional excipients are witnessing a strong demand as companies supply a wide range of functional excipients that help manufacturers produce cost-effective, high-quality, finished pharmaceutical product.[1] Many industry experts point to a widening demand and use of organic pharmaceutical excipients. These organic excipients include oleochemicals, petrochemicals, proteins, carbohydrates, and others. Additionally, binders and functional excipients are witnessing a strong demand. Regarding delivery route, it is the topical segment that is witnessing fast growth in the global pharmaceutical excipients market, as topical drug delivery is witnessing a significantly stronger progression because of its ability to surpass the metabolism pathways of the stomach and liver.[2]

However, the high cost associated with the drug development process will impede the growth rate of the pharmaceutical excipients market. Additionally, strict government regulations have hindered the pharmaceutical excipients market growth. Safety, quality concerns, and lack of awareness will further challenge the market in the forecast period mentioned above.[3]

Evonik Health Care is a development partner and solutions provider to the pharma industry.

This is particularly true for novel excipients, which do have technical, therapeutic, and commercial benefits in oral drug delivery. Despite their formulation-enhancing benefits, novel excipients are sacrificed early in development because of a lack of precedence of use.

"Without an independent pathway to allow new excipients or new uses for existing excipients into drug products, except when associated with a drug filing, there are limited tools available for pharmaceutical companies to formulate better performing, and in many cases, life-saving drugs," says Shaukat Ali, PhD, Technical Service Manager, BASF. "Meanwhile, drug manufacturers are reluctant to use new excipients and take on the additional layer of scrutiny from regulatory agencies to demonstrate full excipient characterization, safety, quality, function, and appropriateness of use."

The Food & Drug Administration (FDA) has acknowledged that the lack of novel excipients is indeed a problem. In September 2021, the Agency announced the Novel Excipient Review Pilot Program, which will select and review four novel excipients in the next two years using a new pathway. This will allow manufacturers to obtain an FDA review prior to the use of the novel excipient in a drug formulation.

"FDA's recent stance and acceptance that the novel excipients are critical in development of new drug candidates, the perceptions around the novel excipients are being changed as the Agency continues to embrace the facts that the pharma industry is in dire need of new excipients for bringing the innovative drugs to the market faster," says Dr. Ali. "This is the first time in history that the agency is opening doors for novel excipients to be freely evaluated and used in the innovative formulations for NCEs."

"Note, though, that this is not an excipient approval process; the novel excipient would still be evaluated as part of the overall drug product approval," says Dr. Iain Moore, Head of Global Quality Assurance, Croda International. "In the next three to five years, we can expect to see an acceleration in the examination of the composition and purity of excipients."

In this exclusive annual report, *Drug Development & Delivery* presents a unique look at how excipients are being used to support today's and future innovative active pharmaceutical ingredients.

Aceto: Custom Raw Material Development

Novel excipients, compressed excipients, and modified excipients are growing in demand globally. The industry as a whole is evolving at a rapid pace to different methods for dosage and delivery — such as targeted immunotherapies that require unique solutions that in many cases cannot be provided by IID-listed excipients. For parenteral delivery, there is a need for excipients that can improve solubility and chemical and physical stability. The need for novel excipients is increasing as well as current excipients listed in the IID, but those intended to be used for a new route of administration, at a higher dosage level, or modified in some way is ever increasing.

Novel excipients are increasing, but with longer development time lines, higher cost, and higher risk of regulatory rejection. "We at Aceto have witnessed a higher demand for modified excipients with low impurity profiles required for parental and biopharmaceutical applications," says Gearoid O'Rourke, Vice President of Global Marketing at Aceto.

He adds that well-known excipients with established quality standards can be modified with regard to their impurity profile or their physical properties. High purity grades of excipients that have a reduced level of reactive impurities are desired to increase the stability of sensitive active ingredients.

"Examples of these modified excipients and critical raw materials manufactured at Aceto's North American GMP facilities would be PMSF, Phenol red and, most recently, our new low endotoxin Sucrose with endotoxin levels <2EU/g," says Mr. O'Rourke. "Aceto understands the growing demand for novel or custom/modified excipients and offers custom raw material/excipient development through a practical process approach at one of our R&D centers of excellence around the world, with all manufacturing performed at our North American, European, or Indian GMP facilities."

BASF: Opening the Door to New NCEs

BASF has launched several excipients due, in part, to many new chemical entities (NCEs) being either poorly soluble and less bioavailable;

highly bitter, requiring taste masking, particularly in pediatric formulations; or highly incompressible in direct compaction with individual physical blends of excipients. To address these issues, BASF has introduced several excipients:

- Kollicoat® Smartseal 30 D (dispersion), or its powder form Kollicoat Smartseal 100P, is comprised of methyl methacrylate and diethylamino ethyl methacrylate (7:3), is a taste-masking polymer for bitter drugs, and is used as a moisture barrier for sensitive APIs. Its lipophilic nature prevents the degradation of highly sensitive drugs.

"For formulators interested in identifying the polymers with multiple functionalities, such as taste masking and moisture barrier coating, Kollicoat Smartseal opens the door to many new NCEs," says Shaukat Ali, PhD, Technical Service Manager, BASF.

- Kollitab® DC 87 L is a lactose-based, co-processed excipient for direct compression of APIs, also amenable to continuous manufacturing processes. It is compatible with acidic or basic APIs, and is highly compressible with increased drug loading for tableting and compatible to stability.

- Soluplus® is a polymeric solubilizer (HLB 16) comprised of grafted polycaprolactam and polyvinyl acetate on a polyethylene glycol chain. It is widely used for increasing solubility and enhancing bioavailability. It has been marketed globally in several drugs and several others are in clinical development.

"The reasons for introducing these excipients are multifold," says Dr. Ali. "In the recent past, over 80% of the NCEs are poorly soluble and bioavailable. Thus, developing those molecules as drug candidates remains challenging, and requires the innovative, novel excipients to expedite the development process for improving solubility and permeability of these molecules as well as compatibility to formulation technologies, especially processing at higher temperatures and conditions."

As an example, Soluplus possesses a lower glass transition temperature (Tg) 72°C, making it suited for hot melt extrusion at 130°C or higher temperatures without plasticizers for high melting crystallized drugs and converting them into amorphous solid dispersions (ASD) to help improve the solubility and bioavailability. Soluplus is also a polymeric solubilizer with HLB values of 14, is used in development of several ophthalmic and topical formulations, making it just one of BASF's multifunctional excipients.

"Multifunctional means they are not used only in oral, but can be used in parenteral, topical or ophthalmic formulation," says Dr. Ali. "Therefore, the quality of these excipients is of utmost importance critical because of their impact on the development of drug products."

Other examples of BASF's multifunctional excipients are:

- Kollicoat IR for immediate-release coating is comprised of polyvinyl alcohol grafted with polyethylene glycol (3:1), and has been marketed in several drug products and is monographed in the USP and *Pharm. Eur.*, as well as being listed in the IID. It has low viscosity with higher solid content in coating suspension, can expedite processing time, and save cost as opposed to cellulosic excipients, says Dr. Ali. In addition, it is a peroxide-free binder, and is well suited for drugs susceptible to oxidative degradation. It is also used as seal coat for many of the weakly acidic or alkaline drugs incompatible to pH-dependent functional polymers. Kollicoat IR is also used in 3D printing by fused deposition model (FDM) when combined with the appropriate polymers.

- Kollidon® VA64 is used as a dry binder in direct compression and roller compaction in tableting, but it is also used as a polymeric solubilizer for poorly soluble drugs in hot melt extrusion and spray drying for amorphous solid dispersions of crystalline APIs.

- Kolliphor® HS15 (HLB 16), is a solubilizer, used in parenteral drugs and ophthalmic formulations. It can be used alone or with other solubilizers like Kolliphor P188 parenteral and in self-emulsifying drug systems (SEDDS) for several insoluble molecules.

"Poloxamers such as Kolliphor P188 and Kolliphor P407 also bear multifunctional characteristics for innovative and generic marketed drug products in which they have been used as solubilizers for increasing solubility,

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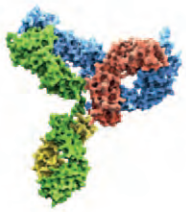
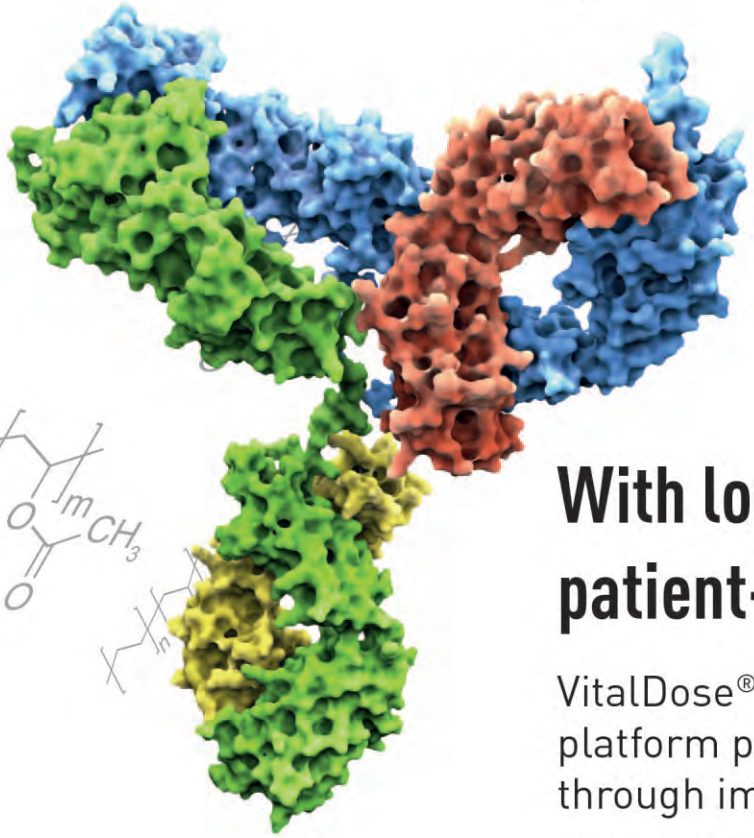
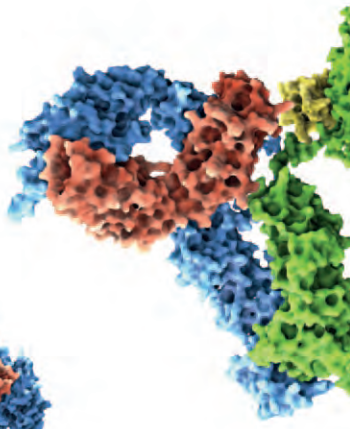
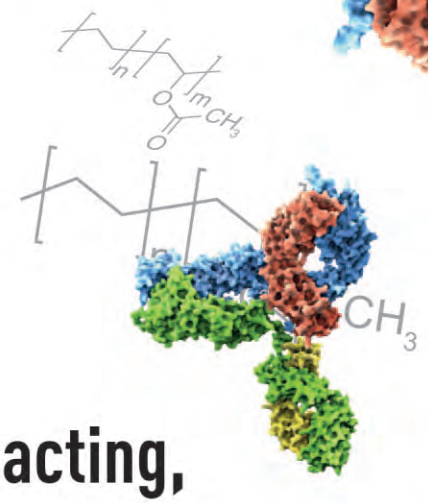


Sustained Drug Delivery







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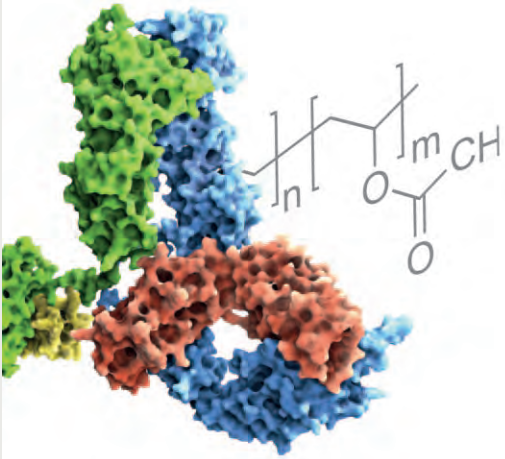

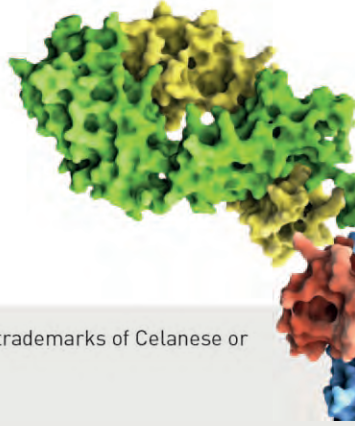

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wettability, and bioavailability of poorly soluble drugs in oral, parenteral, topical, ophthalmic, and biologics formulations," says Dr. Ali. "Such enabling diversity in the excipients' chemistries and functionalities are typical hallmarks of many BASF excipients that bears their acceptances in innovative nanotechnologies for development of drug molecules."

Croda Intl., Plc: Supporting Global Excipient Development

Concerns, such as drug stabilization, surface adsorption or agglomeration are found throughout the drug development process, especially within biopharma, which reinforces the need to utilize novel and highly functional excipients. It is crucial that the right excipient is adopted to assist in preventing these common issues from occurring. The current palette of excipients has its limitations, and novel excipients, which aid in the delivery of these new therapeutic agents, must be introduced.

"Truly novel chemical entities that have been designed and manufactured as pharmaceutical excipients are exceptionally rare," says Dr. Iain Moore, Head of Global Quality Assurance at Croda. "Recent examples have incurred large development costs, not least in the demonstration of patient safety, and have been generally underutilized by the pharmaceutical industry."

Dr. Moore asks: Why would a scientist formulate with a novel excipient knowing the regulatory scrutiny of the marketing authorization dossier may trigger additional questions and delays when using a traditional excipient which would not incur such questions, even if it did not perform as well? He says that, during the COVID-19 pandemic, the acute need for a successful vaccine outweighed any reluctance to use novel excipients, driving the use of the polar lipids developed to encapsulate the mRNA in the COVID-19 vaccine.

Croda supports global excipient development through Empowering Biologics Delivery.

"Croda recognizes the difficulties when using and developing novel excipients and the barriers all parties face," he says. "Excipient suppliers, excipient users, and authorities can collaborate effectively to bring new novel excipients to market. With a delicate precedent set after the development of the COVID-19 vaccine, we see some significant movement in support of the creation of novel excipients."

In addition, excipient purity comes into play, as the level of functionality

can, in many cases, be a direct function of the impurity levels. As the acceleration of examining the purity in excipients heightens, Dr. Sreejit Menon, Research and Technology Manager at Croda, states, "It is important to take all considerations of an excipient into account in its selection to ensure it not only does the job it's supposed to, but does it at the highest possible level. Thus, high purity versions of existing excipients can help bridge the gap caused by the lack of novel excipients."

Croda's proprietary purification processes, which are used to develop its range of Super Refined™ excipients, align with the expanding regulations and investments in innovation seen throughout the industry. "Developed to support the most sensitive of formulations, our growing range of Super Refined™ excipients will continue to support our customers and the growing need to formulate with the purest excipients available, both today and in the future," says Dr. Menon. "Innovation is at the forefront of our business, and novel excipients play a crucial part in that."

Daicel: Co-processed Excipients Offer Unique Advantages

A co-processed excipient is a processed excipient with multiple ingredients listed in monographs without chemical bond, providing new functions that cannot be achieved with individual ingredients. Dr. Yukiko Suganuma, Pharma Solutions, Daicel Corp., says co-processed excipients offer unique advantages. First, the safety of co-processed excipients is linked to the safety of each individual ingredient included as a raw material. This offers advantages in terms of safety compared to a novel chemical substance, and results in fewer barriers to apply novel co-processed excipients to drugs.

Second, co-processed excipients are applicable to continuous manufacturing. "In order to achieve continuous manufacturing for high quality drugs, high quality ingredients are required," says Dr. Suganuma. "There is concern that slight lot-to-lot variations of multiple ingredients may affect product quality in a continuous man-

Daicel's co-processed excipients, GRANFILLER-DT™ and HiSORAD™, are applicable to continuous manufacturing, while maintaining good compactability and rapid disintegration for orally disintegrating tablets.

ufacturing process. We are confident that co-processed excipients could contribute to stabilizing quality in continuous manufacturing because they are designed to adjust the lot-to-lot variation."

Daicel's co-excipients, GRANFILLER-D™ and HiSORAD™, are suited for orally disintegrating tablets. "These co-processed excipients are applicable to continuous manufacturing, while maintaining good compactability, and rapid disintegration," he says.

Evonik: Polymeric- and Lipid-Based Platforms Address Current Excipient Problems

Many excipients are opening exciting opportunities for drug developers. One area that has been catapulted into the spotlight thanks to the Covid-19 vaccines are the lipid drug delivery platforms used for transporting mRNA and nucleic acids. Among the lipid delivery platforms, most innovation is taking place with ionizable lipids. However, other lipids such as cholesterol – which Evonik offers as the plant-derived PhytoChol® – has a crucial role in improving the stability of LNPs and can improve the overall encapsulation payload. There are also structural lipids, such as DSPC and PEG-lipids, which are particularly important for supporting the stability of the LNPs. Furthermore, the PEG lipids help to stabilize LNPs during particle formation and control the size of the particles. For many types of lipids, Evonik has development and manufacturing capabilities.

In addition to lipid drug delivery platforms, there are other exciting opportunities regarding excipients. For example, customization is a valuable approach when aiming to expand existing excipient options. "The wide range of standard polymers are good for screening broad material properties, but product realization often requires further tailoring of functional excipient properties," says Jay Stone, MS, Global Product Manager, Excipients, Parenteral Drug Delivery Solutions, Evonik Health Care.

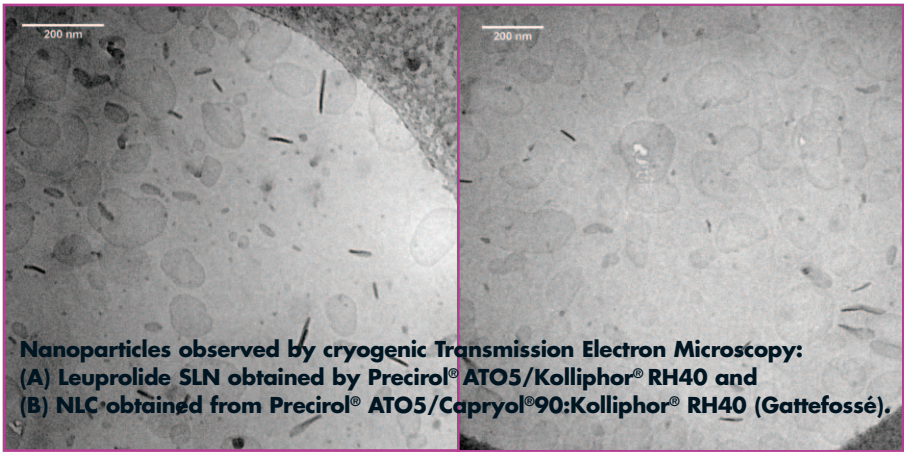
Evonik can customize its LACTEL® and RESOMER® polymers to address limitations of standard excipients. And, over the past 10 years, Evonik has expanded the RESOMER portfolio to address many formulation challenges. RESOMER Zero offers a virtually tin-free excipient enabling formulation with actives that are sensitive to degradation with residual tin catalyst. RESOMER Sterile provides formulators with the option to process formulations aseptically where typical terminal sterilization methods are not feasible.

RESOMER Select allows for full polymer customization. Various options include copolymer composition, molecular weight, and end group chemistry. Furthermore, the degradation properties can be tuned to increase hydrophilicity by incorporation of PEG segments. These polymer properties can be tailored to create a design space for the formulation and defining critical quality attributes.

Also interesting, says Mr. Stone, is the blurring of the lines between polymeric and lipid-based excipients. One example is the Charge Altering Releasable Transporters (CARTs) that have been developed by Stanford University. "These molecules have a polymeric biodegradable backbone, but with lipid-like behavior that can be used to complex nucleic acids, such as mRNA, and deliver them to various tissues – not just the liver as is the case for the mRNA-LNPs," he says. "We anticipate continued and growing research and investments in these types of excipients that can address problems that current excipients cannot solve."

Gattefossé: New Chemistry Innovation

Like novel excipients, co-processed excipients are in need of a pathway for regulatory approval. Gelucire® 59/14, for example, is obtained by blending two known IID



Nanoparticles observed by cryogenic Transmission Electron Microscopy: (A) Leuprolide SLN obtained by Precirol® ATO5/Kolliphor® RH40 and (B) NLC obtained from Precirol® ATO5/Capryol®90:Kolliphor® RH40 (Gattefossé).

listed excipients. "To address this challenge, excipient providers have introduced excipients with certain modifications, but that still conform to existing monographs (i.e., Gelucire® 48/16)," says Ron Permutt, Senior Director, Pharmaceutical Division, Gattefossé.

On the other hand, well-characterized multifunctional excipients, which have global regulatory and safety acceptance, are indispensable tools in the development of novel drug delivery systems. Examples include versatile excipients like Compritol® and Precirol®, used in direct compression as lubricants and in prolonged-release systems, solvent-free coatings, melt congealing, and granulation systems. Other key applications in which Compritol and Precirol are used include development of solid lipid nanoparticles and nano lipid carriers, and when combined with other solid and liquid excipients, deliver peptides like leuprolide.

Gattefossé excipients, notably Labrasol®, Labrafac®, and Labrafil® series, are currently in commercial products and late-stage clinical development projects to enhance small-molecule drug solubility and permeability across biological barriers as well as peptides via inter- and intracellular pathways.

Over and above excipient quality, safety, and regulatory acceptance is need for innovation in the form of new excipient chemistries and modified existing excipient chemistries, says Mr. Permutt. "Excipient innovation is key to shaping the way drug products are developed, as in the case of charged lipids, which help encapsulate mRNA in COVID-19 vaccines."

Lubrizol: Novel Polymers Enable Efficient Solubility Enhancement with Established Techniques

Poor aqueous solubility is an established and growing challenge in formulation development. While there are several approaches to addressing poor solubility, many novel techniques involve complex manufacturing processes that are difficult to optimize.

"Novel excipients for solubility enhancement are an appealing option because they leverage established formulation techniques, giving drug products a clear path to scale-up and commercialization," says Nick DiFranco, Global Market Segment Manager for Oral Treatments, Lubrizol Life Science Health. For example, Lubrizol's Apinovex™ Polymer enables highly loaded, stable oral amorphous solid dispersions via spray drying. In a case study, Apinovex™ formed a homogenous amorphous solid dispersion of itraconazole at 80% loading, which was two times the highest loading reported in literature, says Mr. DiFranco. "Efficiency gains like this may allow formulators to develop smaller, easier-to-swallow tablets, use less expensive API per dose, or develop differentiated, patent-protected formulations."

Another example is Lubrizol's Apisolex™ Polymer for use in injectable drug products. A simple mixing process followed by filtration and lyophilization results in a stable drug product that can increase the solubility of drugs by up to 50,000-fold, says Joey Glassco, Senior Global Market Manager for Parenteral Drug Delivery, Lubrizol Life Science Health.

The polyamino acid-based Apisolex Polymer is a novel chemistry that serves as a non-toxic, non-immunogenic, biocompatible, and biodegradable alternative to PEG, explains Ms. Glassco. The polymer enables up to a 50,000-fold increase in API solubility and results in drug products with reconstitution times of less than 30 seconds in saline. "Using novel excipients such as Apisolex, formulators can not only achieve technical benefits such as solubility enhancement and high drug loading, but they can also improve the overall patient experience," she says.

After learning of Boehringer Ingelheim's (BI's) open innovation collaboration effort with its opnMe program,

Putting Lubrizol's Apisolex™ Polymer to the Test

API	Solubility in Water (µg/ml)	Solubility in Formulation with Apisolex Polymer (µg/ml)	Solubility Increase with Apisolex Polymer (Fold)
BI-001[1]	20	2,000	100
BI-002[1]	8	2,000	250
BI-003[1]	0.4	20,000	50,000
BI-004[1]	1.2	10,000	8,333
BI-005[1]	4	5,000	1,250

[1]APIs for this study were provided by Boehringer Ingelheim Pharm. Inc.

Results of experiments conducted with Lubrizol's Apisolex™ Polymer and opnMe APIs provided by Boehringer Ingelheim Pharm., Inc.

Lubrizol reached out to BI to explain the benefits of injectable-grade Apisolex to increase the solubility of active pharmaceutical ingredients by nano-encapsulating the APIs in micelles. BI provided Lubrizol with five APIs, BI-0001 – BI-0005, which were known to have low aqueous solubility.

"Lubrizol formulated the five APIs with Apisolex and six other solubilizing excipients showing that only Apisolex polymer was able to consistently solubilize the BI actives to produce viable drug products," says Ms. Glassco.

Further, Lubrizol analyzed the increase in solubility that the polymer was able to provide and found that Apisolex was able to increase the water solubility of these APIs by up to 50,000-fold.

"With excipient-led approaches to solubility-enhancement, formulators can simply integrate new options into their existing screening programs, saving time and resources during development," says Mr. DiFranco. "In addition to processing benefits, excipient suppliers are also able to adjust polymer properties to better serve specific APIs. Formulators equipped with several customizable excipient chemistries in early development have more flexibility in addressing solubility and bioavailability challenges." ◆

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CELL & GENE THERAPY

State of the Industry – Where is C&GT Headed?

By: Bill Vincent

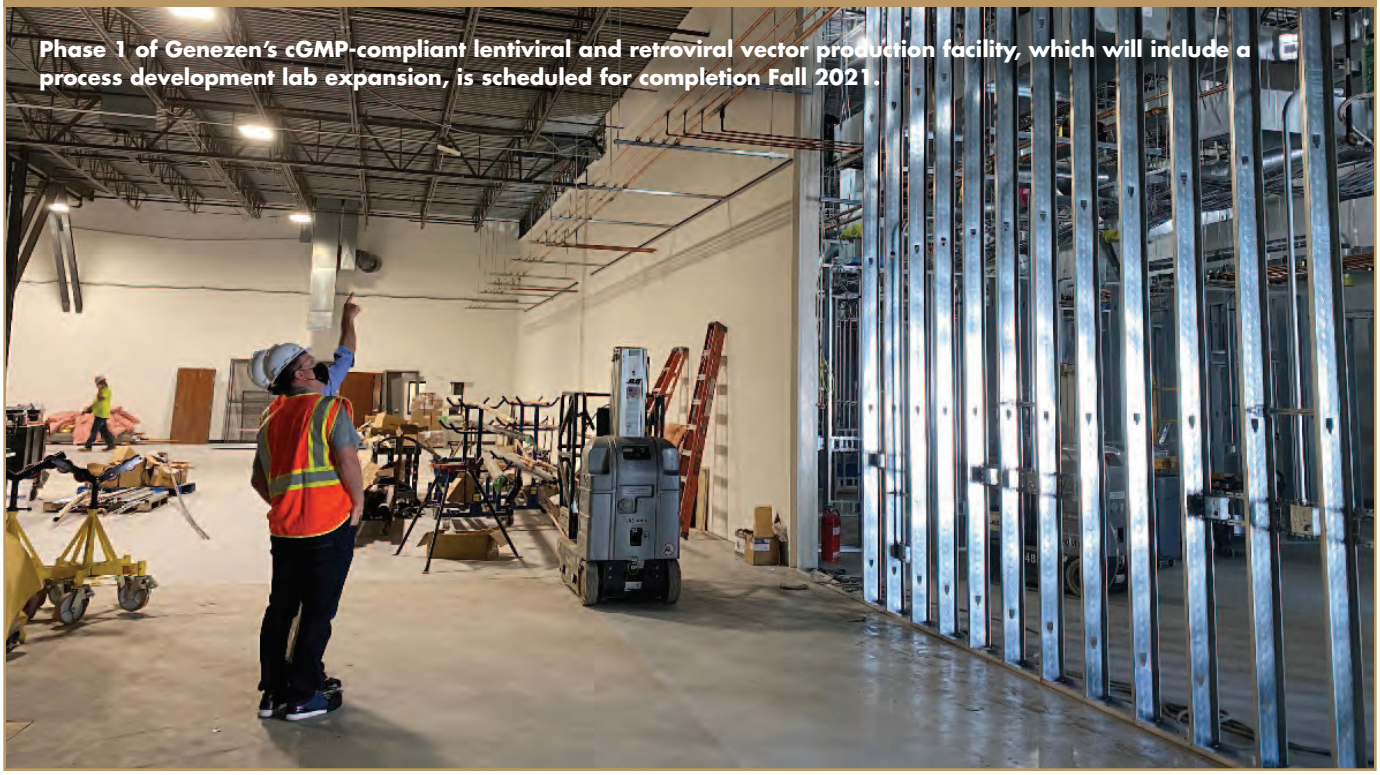
INTRODUCTION

Cell and gene therapies (C&GT) continue to be at the very center of healthcare innovation and are the fastest-growing areas of therapeutics, having already contributed to some of the most significant disruptions in the pharmaceutical and biotech industries. Continuous advancements in C&GT are transforming how certain diseases are treated and potentially cured, and significantly changing healthcare outcomes. So, what's next? Where is C&GT headed? The following explores the industry dynamics that will shape the C&GT space throughout the next decade.

COST VERSUS VALUE

The US Food and Drug Administration has approved seven cell and gene therapy drugs, but the new product pipeline has approximately 1,200 experimental therapies, with more than half of these in Phase 2 clinical trials. CAGR estimates are about 15% for cell therapies and nearly 30% for gene therapies, and the Alliance for Regenerative Medicine points to a rapid rise in cell and gene therapy developers, with 1,100 such ventures in 2020, an increase of about 10% from 2019.[1-3] The industry is still transitioning out of the early development phase and sits at the very start of the rapid growth phase with a lot of opportunity ahead.

FIGURE 1



Phase 1 of Genezen's cGMP-compliant lentiviral and retroviral vector production facility, which will include a process development lab expansion, is scheduled for completion Fall 2021.

Showing the therapies are providing a lifelong cure and not just another type of ongoing treatment will be key to justifying the pricing and gaining acceptance from patients, providers, and payors, be they insurance or governmental. Unfortunately, when new cell and gene products hit the market, the discussion in media often focuses on the price tag instead of highlighting the availability of a new therapy with the potential to cure instead of simply managing what may have been a previously untreatable disease.

This is creating increased pressure to drive down manufacturing costs – a common challenge across the pharma and biotech industries. In C&GT, this effort will be focused on several fronts, such as increasing batch sizes, standardizing and streamlining processes, and reducing the cost of the materials used in manufacturing. This will go hand in hand with developing processes that provide high yields of consistent product.

The markets will also have an influence. Where there is a broader market upon which to spread the development costs, such as cancers, where there is usually a larger patient population, therapies can hit a lower price point. For the rare or orphan diseases, it will be harder to spread out costs. But there is potential to achieve lower costs in the long run, as in these cases, it may be fruitful to have a platform, such as a particular viral vector, upon which multiple therapeutics can be more easily developed, thereby reducing some of R&D costs.

VIRAL VECTOR DELIVERY SYSTEMS

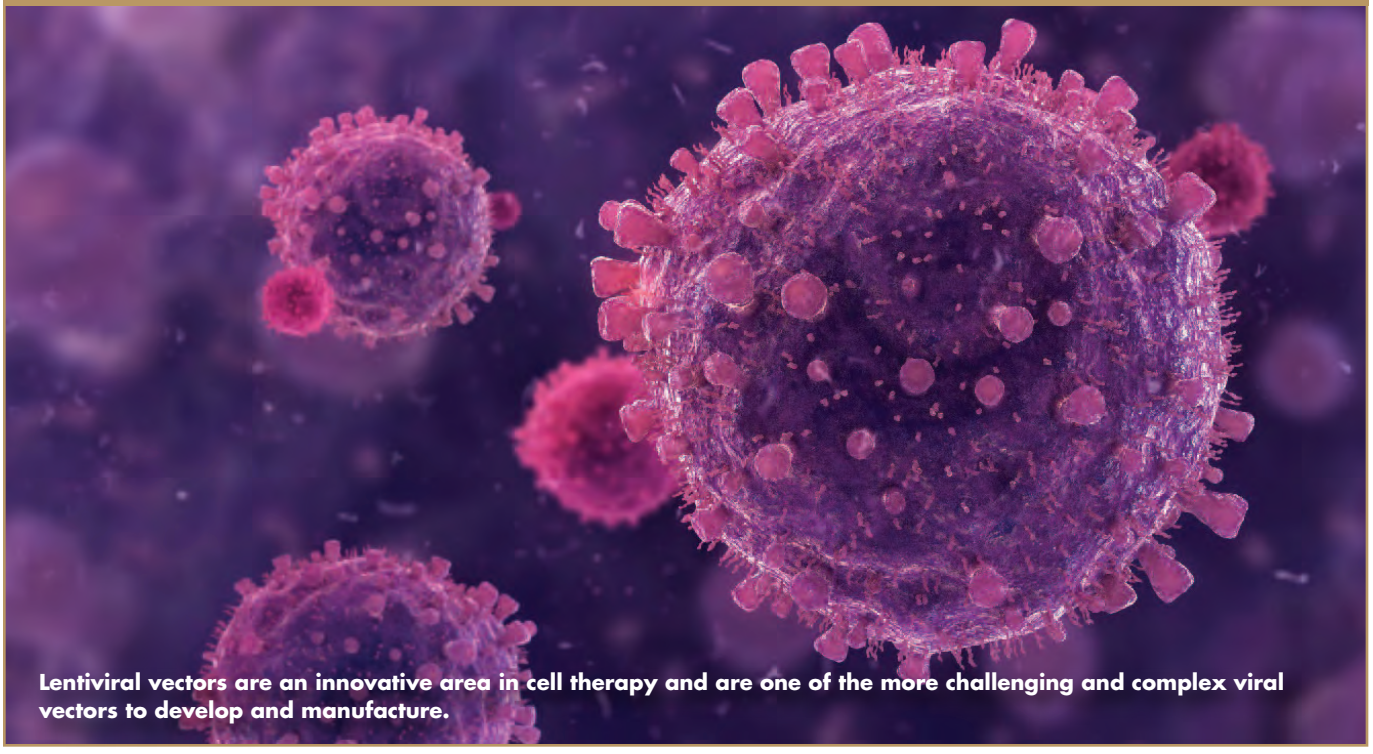
The efficacy of a gene therapy depends on the delivery vehicle and its ability to effectively deliver a gene into target cell populations. A variety of delivery vehicles have been employed throughout the years attempting to improve the effectiveness of gene therapy, such as DNA nanoparticles, naked DNA, liposomes (DNA and cationic), polyplexes, and non-viral biological delivery.

However, most clinical trials to date have employed viral vectors for the delivery of genetic material as they are capable of efficiently transducing cells and can achieve long-term expression of the desired genes to deliver sustained therapeutic effects. There are further decisions to be made around the optimal vector platform; the pros and cons of each need to be carefully weighed from a holistic viewpoint of the therapy's developability, scalability and end-use.

Lentivirus (LV)

Lentiviral vectors are best used for therapies in which the patient's cells are going to be transduced *ex vivo*. An example would be in delivering a target gene into bone marrow stem cells to treat a disorder originating in the bone marrow. This technique has been used in treating disorders like Severe Combined Immuno Defi-

FIGURE 2



Lentiviral vectors are an innovative area in cell therapy and are one of the more challenging and complex viral vectors to develop and manufacture.

ciency (SCID), also known as the "bubble boy disease". This works well for CAR-T therapies in which a patient's T-cells are transducing and expanded ex vivo before being administered back to the patient. It is simply a difference in the cell type being transduced, T-cells versus bone marrow stem cells.

Lentivectors have an advantage in that they can carry a larger transgene or target gene for delivery, compared to most other viral vector delivery platforms. It is also an integrating virus, so the gene is incorporated into the DNA of the cell and is transferred to progeny cells that originate from the treated cell. Many viral vectors can only enter a cell when the cell is dividing, but this is not the case with LV vectors as they can deliver their transgene into the cell when the cell is "resting".

The downside is that because LV vectors are large, the immune system recognizes it as foreign. Therefore, it is not a good choice for in vivo use and thus not currently a good option for treating systemic or organ-based disorders. These vectors are still largely produced using transient transfection of 293T cells. There have been several attempts at developing a producer cell line from which clones could be developed, allowing the vector to come from a consistent source for each production. One of the biggest issues is that the VSVG protein envelope used with LV is toxic to the producer cells and thus, these cell lines have met with varying degrees of success.

Retrovirus (RV)

When people talk about retroviruses, they are generally referring to gamma retroviruses – we should note that Lentiviruses are a type of Retrovirus, there are however notable differences both in production and method of action between them. With RV, it is currently feasible to make a producer cell line and develop clones to use for all subsequent productions to give a consistent product from one batch to the next. It is also a large virus capable of delivering a large transgene, so like the LV, it is suited to mainly ex vivo applications. Also, like the LV, it is an integrating virus, however, in the case of RV, they tend to integrate the transgene near oncogenes. When there is a strong promotor on the transgene, it can trigger the oncogene and, in rare cases, this has resulted in patients developing leukemia. So it has largely been replaced by LV vectors with a few applications still using it for treatments such as CAR-T therapies in cancers.

Adenovirus (AV)

The adenovirus has mainly been used for in vivo applications. It cannot carry as large of a transgene as the retro- and lentiviruses. The most notable problem is that most people have been exposed to an AV at some point in their lifetime (common cold), and the immune system recognizes it and puts up a defense before transfection can take place in most cases. It should be noted though there has been work done using Adenoviruses as the viral vector platform for vaccines such as the J&J Covid-19 vaccine

FIGURE 3

As viral vectors become increasingly important delivery systems in the booming cell and gene therapy sector, the rising demand in a qualified workforce becomes a challenge.

Adeno-Associated Virus (AAV)

Throughout the past few years, AAV has been the shining star in C&GT. It is small so it doesn't carry as large a transgene. However, its size means it can often slip past the immune system without eliciting a major response, at least when first used. This makes it ideal for in vivo treatments in specific organs or for systemic disorders. The downside is that it is not an integrating virus. The plasmid that is delivered generally stays free of the cellular DNA and thus is not passed on to the cell's progeny. In theory, over time, the therapeutic benefits decrease, it remains to be seen just how much of an impact this has over the life of a patient. Some have suggested that subsequent rounds of treatment could be done; however, some attempts have resulted in significant immune responses - time will tell if longevity of the therapy is really an issue. One other item that has been seen, at least in the laboratory, is that over time, some of the transgene plasmids do end up integrating into the cellular DNA. The problem is that much like the RVs, they seem to be integrating near oncogenes. Again, it remains to be seen if this is an issue long-term or if it is just unique to the animal model and the laboratory setting.

WHAT'S NEXT?

Throughout the past 5 or 6 years, a lot of the excitement, especially for investors, has been around cancer therapies. That work has largely been on bloodborne cancers, but there are now approaches being applied to solid tumor therapies. There is likely to be a continued focus on LV and it being used in other CAR-T and Natural Killer cell therapies both for bloodborne cancers as well as solid tumors.

As previously noted, most LV vectors currently use the VSVG envelope, and one area of innovation will involve developing other envelopes to see if there are ways to use LV vectors *in vivo* and targeting specific organs or used in combination with some immune suppression to reduce the immune response to the virus.

Other platforms will likely develop over time. There has been interest in foamy viruses – a RV belonging to the Spumavirus genus – but they proved extremely difficult to make. Recently, there has been a great deal of interest in using bocavirus as a vector platform, it shows promise in systemic applications like an AAV, but with the added benefit of being capable of carrying a transgene almost as large as that of an LV vector. However, innovation in the space must be facilitated through investment and addressing several challenges that are currently hamstringing progress.

CHALLENGES AROUND CAPACITY, TECHNICAL CAPABILITIES & EXPERTISE

Physical capacity to produce gene and cell therapy products continues to be a bottleneck. Even as more capacity is added, the industry seems to be growing even faster. Some of the expansion is being hampered by the lack of availability of materials - the supply of items, such as plasmids, media, and the numerous disposables from pipettes to bioreactors, has continued to be tight.

The solution will, in part, come from increasing the production of these materials. There also has to be a greater focus on learning how to better utilize the supply so more product can be manufactured with the same amount of material.

The ability to scale up the manufacture of therapies in a cost-effective manner is also essential. The industry must find systems that can be run as a "small" version for the preclinical and early trial work but then be scaled up into larger equipment for commercial use, rather than simply scaling volumes by duplicating small systems that inherently uses more resources and physical space within facilities.

The availability of a workforce with appropriate skills is also going to continue to be a challenge. Currently, the industry is largely clustered in a few locations - in the US, there are a few key metropolitan areas on the east and west coasts that have very high concentrations of C&GT companies. As a result, the companies in these locations are running into problems finding the workers they need. This competition for the limited number of workers is driving up wages and that is anathema to the idea of reducing costs. It also means projects are delayed because the expertise and workers needed to do the work are not available. There may be several approaches to solving this. The industry may expand into locations other than the east and west coasts; a longer-term solution however would involve federal, state, and local governments supporting and funding dedicated life science workforces. The cities, states, and countries that invest in educating and training a workforce will attract the companies and the jobs and tax dollars they bring. Any country that wants to stay in the forefront of this industry must be able to supply the workers, otherwise they will see the industry and jobs move elsewhere.

REGULATORY APPROACHES

A decade ago, the new treatments in the G&CT space advancing to the clinic sparked excitement about the eventual path to commercialization. This spurred regulatory agencies to work with researchers and companies to move these treatments forward, but given the uncharted waters, even the questions to be asked were evolving. Now, some of these treatments have been approved, and parties on both sides of the regulatory equation have learned how to evaluate the development phase and the important regulatory factors and questions. For example, progress in regulatory perspectives has led to a preference for a single producer cell line clone for use through all development phases.

Regulators, such as the FDA and the European Medicines Agency (EMA), have published formal and informal guidelines to help viral vector companies produce products. Due to the evolving nature of the C&GT industry, regulations surrounding these products are updated to keep up with the rapidly growing field and its development – for example, the FDA has provided or updated nine guidance documents within the last 2 years.[4]

This will continue to evolve, and each new type of therapy will bring its own learning curve to the regulatory process. Moreover, it will continue to be important for gene therapy developers and manufacturers to work hand in hand with regulatory agencies as more open discussions around issues, challenges, and best practice will put the industry in a better position to collaborate on any future regulations and guidance.

DRIVING THE INDUSTRY FORWARD

If the industry wants to keep moving up the steep growth curve, then capacity and raw materials must be readily available. The innovations in therapies, platforms, and processes will all come with time, money and increasing availability of resources.

Investment into basic research at the university level and into small start-ups coming from venture capital, private equity, industry, and the capital markets will be essential - university labs and small start-ups are well-positioned for the needed innovation. Invariably, these companies start out with a small team that is willing to take risks and then grow into larger companies or go through a series of acquisitions that bring those innovations into larger biotechs and big pharma. These larger entities can use their resources and expertise to commercialize the product and get it to market.

Outsourcing to niche CDMOs with the smaller scale capabilities and expertise required to develop scalable processes at this stage will be essential to expediting a C&GT's path to market. ◆

BIOGRAPHY

Bill Vincent, following 25 years in the pharma sector, set out to bring academia and pharma closer together by founding Genezen in 2014. Initially focusing on contract manufacturing, Genezen quickly expanded to include cell manufacturing and testing services. Today, as Executive Chairman, he focuses on business strategy, whether that is evaluating new opportunities and technologies, or facilitating activities for Genezen's clients and employees. Prior to Genezen, he was Founder and President at Rimedion (acquired by Ossium Health in 2017).

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SYNER-G BioPharma Group

Syner-G BioPharma: A Track Record of CMC Excellence

"It's our belief that Syner-G offers the most comprehensive and the best CMC services to our clients," says Prabu Nambiar, PhD, Founder and CEO of Syner-G BioPharma Group. Syner-G provides expert CMC consulting services to small molecule, biologics, cell and gene therapy, and drug-device combination product innovators through a unique approach to Chemistry, Manufacturing, and Controls. The company's CMC 360™ is a holistic approach that emphasizes three key elements: Technical Development, Regulatory Services, and Quality/GxP Compliance. Each of these verticals is supported by an experienced leader, but they also collaborate to ensure that drug development progresses expeditiously and seamlessly in conformance and compliance with regulatory requirements.

Dr. Nambiar founded Syner-G Pharma CMC Consulting in 2007 to meet the growing need for expert CMC consulting in the outsourced drug development paradigm. Syner-G refocused on evolving as a boutique CMC consulting firm in 2012 when Binesh Prabhakar, MS, MBA, Senior Vice President, Quality Assurance and Compliance, joined the company as the cofounder. Since then, they built the founder-owned-and-operated company with clear definitions of the services – led by an experienced leadership team – and continued growth to meet increasing demand. In 2020, Syner-G received an equity investment from Riverside Partners and subsequently, the company rebranded in 2021 as Syner-G BioPharma Group to reflect an expanded growth strategy toward becoming a broader spectrum pharmaceutical development consulting firm across multiple areas. And 2022 began with the acquisition of Impact Pharmaceutical Services to expand Syner-G's capabilities in the areas of regulatory and medical writing.

Vertical team leaders at Syner-G Biopharma Group (from left to right): Ray Forslund, Drew Barlow, Prabu Nambiar, and Binesh Prabhakar.

Drug Development & Delivery recently spoke with the two founders, as well as Drew Barlow, MPH, Senior Vice President, Head of Regulatory Affairs; Ray Forslund, PhD, MBA, Senior Vice President, Head of CMC Development & Project Management; and Frank Sorce, MBA, Senior Director, Business Development, about the company's evolution, its approach to CMC, and the future of the organization.

Q: As the company has evolved, how do you now define Syner-G's business model, and how does this model suit your clients?

Dr. Nambiar: Our technical, regulatory, and quality teams (verticals) are led by practice heads who are charged with managing their talent on a daily basis to ensure the highest levels of support, commitment, and advice for our valued clients. This model ensures that each vertical continues to stay abreast of the ever-changing regulatory environment and feeds off each other to best serve our clients and solve sophisticated drug development and regulatory challenges.

The scope of our client projects is defined by the characteristics of their compound and the nature of support they may require. For example, we may be approached by someone developing a biologic compound, and they self-identify as deficient in their quality management systems. This client will be best served by the biologics group within our technical vertical, with a prominent assist from our quality vertical. Truly understanding the therapeutic modality, phase of development, dosage form, and the clients' needs is essential to designing the most cost-efficient and phase-appropriate approach.

Q: Describe the company's approach to CMC and what makes it unique in the contract space?

Dr. Forslund: With pharma/biotech's increased focus on rare diseases and the need for expedited development of life-saving drugs, CMC tends to become a bottleneck for commercial readiness. Syner-G's experience in strategizing risk- and science-based approaches for CMC development, using a Quality by Design paradigm, has helped multiple clients to successfully seek approval via a breakthrough development pathway. Syner-G's strategic approach to CMC stands on our guiding principles: patient safety, science-based, risk-based, and phase-appropriate with regulatory compliance. We consistently follow these guiding principles across our three verticals (Technical, Regulatory, and Quality) for each and every client engagement we undertake. Based on the hundreds of regulatory submissions we have participated in, and clients we've served over the years, we know these are the principles regulators want to see and they produce the results our clients are seeking. We

also feel we have an unparalleled dedication to CMC, while becoming embedded in our client's culture.

In addition to the three key verticals, Syner-G appreciates the importance of Project Management in successful and timely execution as well as achievement of milestones. Our team believes that in an outsourced model, it is not "outsource and forget," but "you get what you manage." To fill this need, Syner-G has added Technical/CMC Project Management solutions as part of our service offering. So, if you are working with a CDMO, a Syner-G-assigned project manager will oversee day-to-day activities for an optimal outcome. You outsource it and we manage it.

What makes us unique is the way we work. From our client's perspective, it's like flipping a switch. Just bring Syner-G on board and watch us make CMC happen. We know what needs to be accomplished, how to do it, and how to communicate it to the regulators both in the US and globally. The three functions are structured at Syner-G similar to those in a pharma company, so services can be introduced in a plug-and-play model by clients interested in any one of the areas or a combination of them.

Finally, our firm is comprised of experienced and dedicated professionals – with a passion for science and aspirations to bring lifesaving drugs to patients – led by an exceptionally strong leadership team. These folks work collectively to bring great value to the organization and our clients. All these elements have created a curious, entrepreneurial, and efficient corporate culture that is eager to learn and serve.

Q: What is the benefit of dividing the company into these verticals? How do they collaborate to benefit the client?

Mr. Barlow: The three verticals, what we call CMC-360™, are the key moving parts of CMC drug development. We've learned over time that each client has specific and unique needs; sometimes this is localized to a regulatory need and other times it's related to a technical drug development need. To best ensure the organization can meet these needs efficiently, Syner-G feels it is important to have laser-focused, cross functional teams of experienced professionals learning and feeding off each other to take a rigorous approach to problem solving within their field of expertise and be led as a group. When it's necessary to discuss a client's situation, each of our consultants are empowered to engage a colleague in another vertical or the practice head to work towards the best solution possible for their client. Our vertical configuration and intra-vertical communication ensure we align with our mission of helping our clients bring lifesaving therapies to patients around the world.

With various therapeutic modalities, the CMC requirements vary depending on factors such as complexity of the active ingredient, formulation, indication, patient population, and stage of development. With patient safety and regulatory compliance as guiding principles and primary objectives, Syner-G helps design and implement science- and risked-based, phase-appropriate CMC solutions to expeditiously advance a drug during development and/or sustain the commercial supply chain post-approval. Our CMC business units operate in an integrated fashion to ensure the solutions we provide fully conform to the scientific standards and regulatory requirements from a global perspective.

Q: What does the name rebrand say about the future direction of the company?

Dr. Forslund: About five years ago, Syner-G introduced the biologics CMC group to the marketplace. Since then, it's been growing in size and in the number of clients we support annually. With this important addition to the organization from a service offering standpoint, it only made sense to add "Bio" to our moniker. And because we had been supporting pharma since our inception, the "biopharma" part of our name truly described the type of clients we have and can support. We look to continue to grow this portion of our service platform and consistently add talent where needed. In addition, with increasing requests from our clients for medical writing, clinical regulatory, regulatory submission, and other scientific consulting services, such as toxicology and DMPK, Syner-G intends to expand our service platforms to serve our clients on a broader and deeper scope. This would give the client a "one-stop-shop" model for maximum scientific consulting for drug development. With this growth plan in mind, we named the new organization Syner-G BioPharma Group. Towards this end, Syner-G has recently announced the acquisition of Impact Pharmaceutical Services located in the heart of the southeast, Research Triangle Park, NC.

Q: Regarding that acquisition, what advantage does this bring to Syner-G and the clients of both organizations? How do the two companies complement one another?

Dr. Nambiar: The acquisition of Impact Pharmaceutical Services is truly complementary in every sense. Their capabilities in the areas of medical writing, clinical regulatory affairs and strategy, regulatory publishing/submission, and project and program management have no real overlap with the capabilities offered historically by Syner-G. Bringing these capabilities under Syner-G's roof allows us to fully support all components (Modules 3, 4, and 5) of the common technical document (CTD) when it comes to regulatory submissions for clients, and brings in a highly educated and experienced group of professionals to the Syner-G family. Just as important are our cultures, which could not be more aligned. Like us, Impact is curious, entrepreneurial, eager to learn, and efficient in what they do. And, like us, they are founder owned and built. The integration is going smoothly, and we very much look forward to building the enterprise on a wider and sturdy foundation, while holistically helping our clients move forward with regulatory submissions and drug development throughout the life cycle.

Q: How has the equity investment from Riverside contributed to Syner-G's evolution?

Mr. Prabhakar: As stated earlier, forming and introducing the biologics group was a major milestone for Syner-G and has proven to be a very wise and profitable endeavor, which we strive to expand over time. When Syner-G decided to bring on a financial partner, we sought an investment firm with significant pharmaceutical and biotech service expertise, deep experience in working with founder-owned companies, and a strong cultural fit with our organization. The partnership with Riverside will ensure that we continue to deliver on our vision of providing the highest quality science and risk-based CMC technical, regulatory, and compliance consulting service and strategic advice to our clients. They have also assisted Syner-G in creating a brand that best communicates what we do and are capable of doing, and further rounding out the executive management team with formal human resource, finance, and business development functions. Riverside also has broad experience in helping pharma service providers with a strong healthcare advisory board who lend broad perspectives, network, and strategy to Syner-G. All of these elements will allow Syner-G to scale and sustain our business over time.

Q: With 80-plus clients and 80-plus more expected as a result of the Impact acquisition, and at least a couple hundred successful regulatory filings under your belt, what is next for Syner-G? Where do you see the company in the next three to five years?

Dr. Nambiar: As Syner-G finalizes its integration with Impact and bolsters its service capabilities into medical writing, regulatory publishing, and submissions, as well as overall better support of the drug development process, we'll continue to look for ways to better meet the needs of the pharma and biotech industries. Obviously, we'll have to continue to attract and retain the tremendous talent we have, but we'll also have to grow our company as we add clients via our expanding capabilities platform. Syner-G has strong employee retention that is driven by a culture of teamwork and professional collaboration. They are all exposed to a full opportunity to learn, grow, and advance their careers while making an impact in the development and production of lifesaving and life-changing drugs. Given the continued growth of the outsourced and virtual drug development model, the demand for Syner-G's services is continuously growing. To meet this demand, we will continue to grow the team organically, but we wouldn't rule out future acquisitions and partnerships while maintaining our culture and continue to live by our operating philosophies. We strongly believe the future is bright for Syner-G and look forward to the challenges and opportunities this ever-evolving industry has to offer.

Mr. Sorce: We are not limited by the therapeutic modality, dosage form, geography, or the size and scale of the work. Our expertise will serve us well across all these landscapes while continuing to bring folks on board to grow the organization. This will result in tangible and sizeable benefits for Syner-G. ◆

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PLATFORM TECHNOLOGY

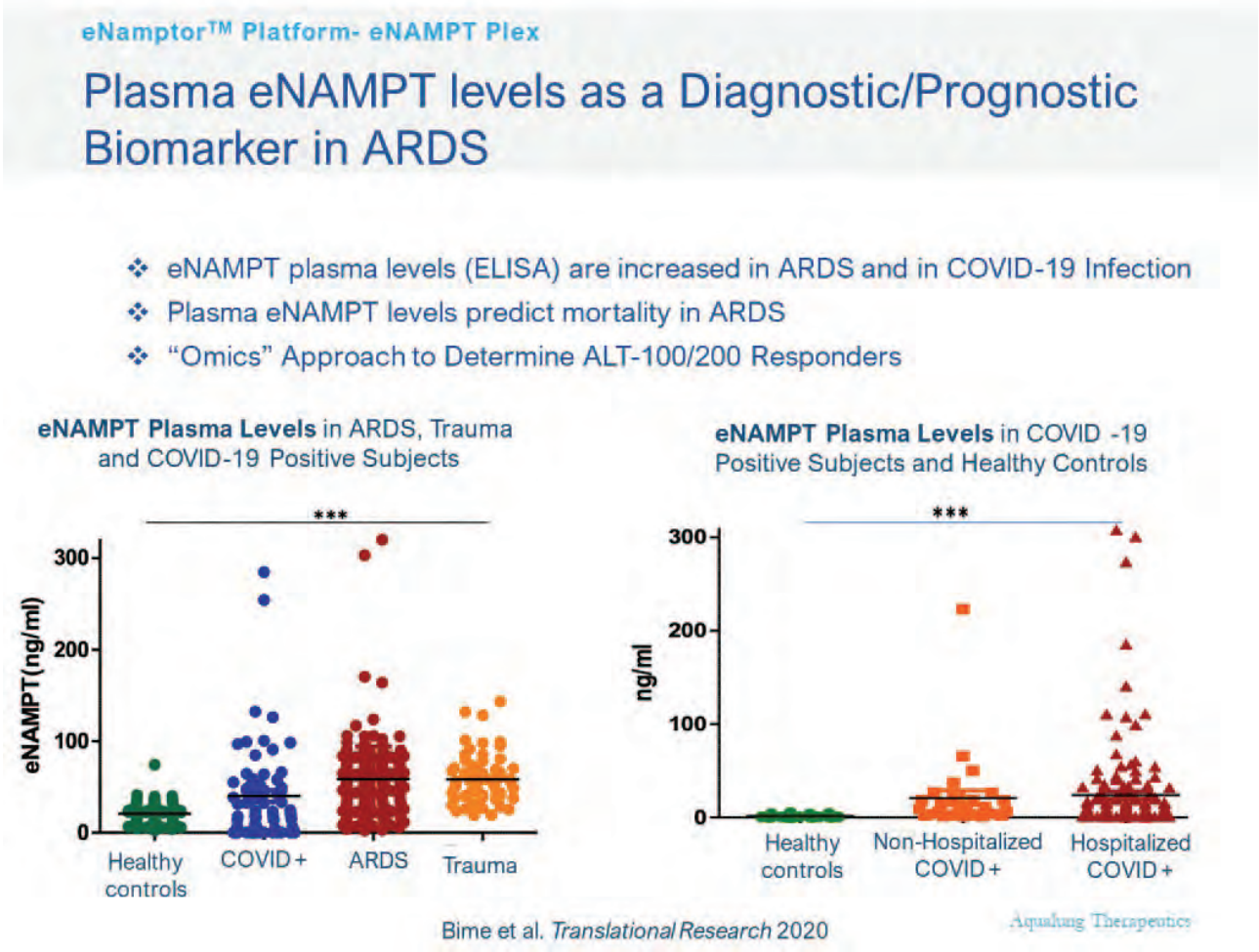
Predictive Medicine, Biomarkers & the Multiple Unmet Needs in Acute Respiratory Distress Syndrome

By: Joe G.N. Garcia, MD, and Stan Miele

INTRODUCTION

Precision Medicine is typically used to describe therapeutic strategies to benefit a particular group of patients that are optimized by using genetic, biochemical, or molecular profiling. It has often been simply stated as the "delivery of the right drug to the right patient at the right time." From a translational research perspective, biomarkers are an important part of the precision medicine approach not only clinical trial design, but also a relevant part of drug utilization upon FDA approval. As an example, HER2+ breast cancer tissues express high levels of a protein called human epidermal growth factor receptor 2 (HER2), which accelerates cancer cell growth

FIGURE 1



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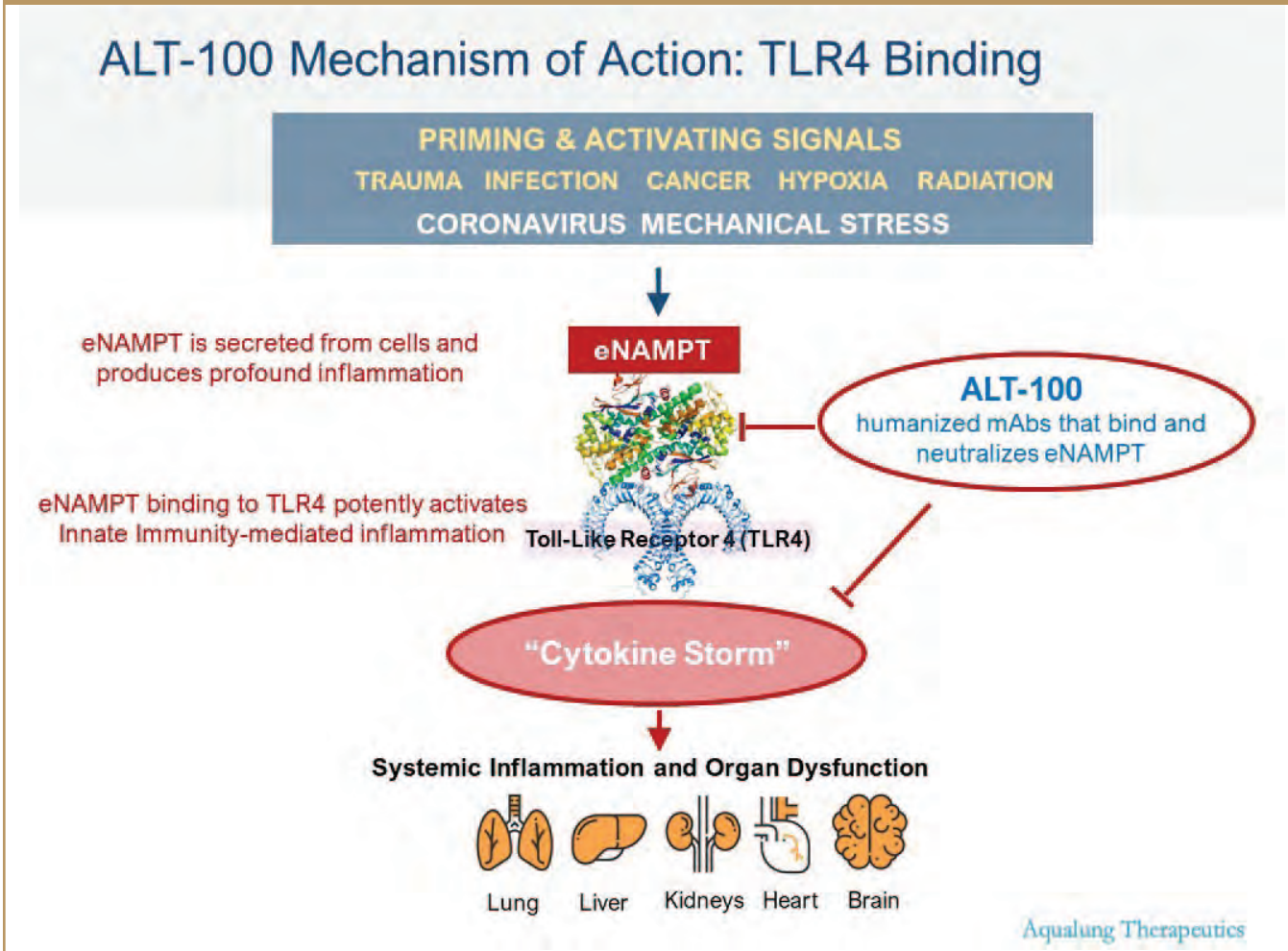


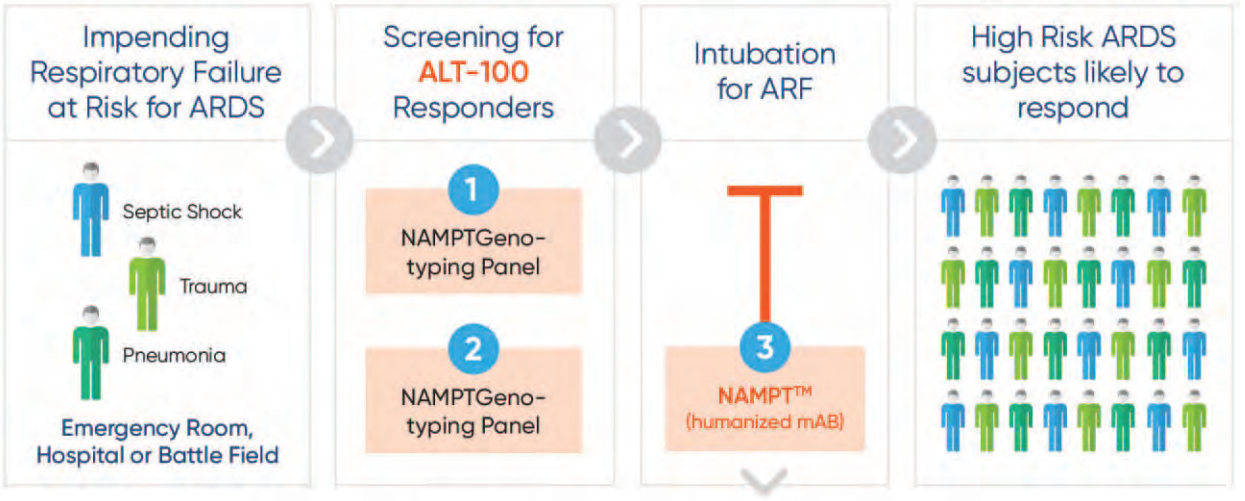
and is the underpinning for the observed aggressive behavior of HER2+ breast cancer. Women with breast cancer are tested for this specific subtype as there are HER2+-specific medications that address this aggressive cancer. The use of this genetic assay is a type of biomarker certainly more common in oncology that enhances the likelihood of a response to a specific therapy. This identification of HER positivity in expression frames the notion of "personalized" or "predictive" medicine for highly specific cancer therapies. Unfortunately, the application of personalized or predictive medicine approaches have yet to be adopted as part of the drug development paradigm for active drug utilization and patient stratification for the vexing and often lethal inflammatory condition known as Acute Respiratory Distress Syndrome (ARDS).

ARDS & THE MULTITUDE OF UNMET NEEDS: CRIPPLING GAPS BETWEEN CLINICAL DISCOVERY & UTILITY

Prior to the COVID-19 world-wide pandemic, caused by the species-jumping novel coronavirus SARS-CoV-2, more than 700,00 individuals (at press time) in the US and 2 million cases globally (at press time), annually developed ARDS from trauma, sepsis, bacterial, and viral infections, exhibiting a cumulative mortality of 40%. The root cause of ARDS mortality is unchecked inflammation with exposure to mechanical ventilation, which is nearly universally required in ARDS patients, significantly contributing to the inflammatory burden of ARDS and ARDS mortality, a complication known as ventilator-induced lung injury (VILI). The COVID-19 pandemic has highlighted multiple unmet needs in ARDS. These include the absence of effective FDA-approved pharmacotherapies as neither SARS-CoV-2 vaccines or anti-SARS-CoV-2 drugs address the unchecked inflammation that drives multi-organ dysfunction and ARDS mortality.

Despite recent innovations in translational research and an exponential increase in the discovery of novel biomarkers, precision medicine approaches have yet to be applied to ARDS, and validated ARDS biomarkers remain

FIGURE 3



absent. This critical unmet need in ARDS exposes a critical gap between the fast pace of biomarker discovery and the successful translation to clinical use, and highlights the need of biomarkers to impact a more streamlined drug approval process. The lack of reliable and validated ARDS biomarkers is a contributor to the myriad reasons for the failure of clinical trials in ARDS. ARDS heterogeneity contributes to the requirement for large numbers of enrolled subjects to demonstrate clinically significant benefit. A major value for precision medicine approaches is the reduction in subjects required to demonstrate clinical benefit. Stratification of ARDS patients with reliable biomarkers that are predictive of mortality would optimize participant selection for clinical trial enrollment by focusing on those subjects most likely to benefit from novel clinical interventions. More than 45 promising candidate biomarkers in ARDS have been described in the medical literature; however, to date, no biomarker has been successfully developed as an accepted point of care surrogate marker of disease.

COVID-19 INDUCED ARDS & PRO INFLAMMATORY CYTOKINES

These unmet needs that exist in ARDS are particularly highlighted by the unprecedented numbers of COVID-19-induced ARDS cases, which has strained healthcare systems across the world and exposed the need for biomarkers that would accelerate drug development and successful phenotyping of COVID-19-infected patients at risk for development of ARDS and ARDS mortality. Only 5% of COVID-19-infected patients develop ARDS, require mechanical ventilation, and are at high risk for multiorgan failure and death. Insights into promising stratification-enhancing, biomarker-based strategies in COVID-19 and non-COVID ARDS may enable the design of successful clinical trials of promising therapies. IL-1b, TNF-a, IL-6, IL-1, and IL-18 have been associated with increased mortality from ARDS. However, none of these pro-inflammatory biomarkers have sufficient specificity to serve as a stand-alone prognostic biomarker. Higher plasma levels of IL-6, IL-8, IL-1RA, measured as part of a panel of 6 biomarkers were associated with increased risk of mortality. Unfortunately, no single biomarker has been shown to reliably provide information about the patient's overall disease outcome, and thus stratify patients for enrollment in clinical trials. However, recent efforts to combine biomarkers demonstrate that prognostic ability can be greatly enhanced. Sadly to date, there have been more failures in clinical trials of therapeutic drugs to treat hospitalized COVID-19-induced ARDS patients.

Several high-profile efforts targeting IL-6 and IL-6 receptor antagonism (Tocilizumab-Roche/ Sanofi, Sarilumab-Regeneron/Sanofi), in COVID ARDS failed to improve COVID-19 ARDS mortality in Phase 2/3 clinical trials of COVID-19 patients with severe disease With runaway inflammation being an inherent problem associated with COVID-19 -induced ARDS patients, many of the proposed therapeutic drugs have focused on an individual cytokine (IL-6) or pathway that can play an integral role in addressing unchecked inflammation. While a reduction in one individual cytokine (biomarker) can play an important role, all too often it may not be enough to address some of the other ele-

ments of unchecked inflammation, and therefore can lead to a failed clinical trial and unmeaningful benefits to patient outcomes.

The absence of successful ARDS clinical trials that target inflammatory pathway components poses a vexing problem that potentially implicates several issues, including: (1) poor target selection, that is, targeting cytokines downstream in the inflammatory cascade, and (2) delayed administration of the anti-inflammatory therapeutic, that is, at a point where the capacity to influence the severity of inflammatory cascade activation is minimal.

ENTER EXTRACELLULARLY SECRETED NICOTINAMIDE PHOSPHORIBOSYL-TRANSFERASE (ENAMPT) AS A NOVEL COVID-19 ARDS TARGET

We have previously utilized genomic intensive approaches and cellular and preclinical studies of bacterial pneumonia and excessive mechanical stress/ventilator-induced lung injury (VILI) to identify eNAMPT as a novel damage-associated molecular pattern protein (DAMP), a clsss of immune-related proteins that serve as sentinels for bacteria or viral infection. Circulating eNAMPT is an essential participant in ARDS/VILI pathobiology and functions as a master activator of evolutionarily conserved inflammatory cascades. eNAMPT is an ARDS biomarker, as high eNAMPT levels at the time of admission to the intensive care unit correlate with disease severity and may predict mortality in patients with sepsis and ARDS. Furthermore, genetic variants in the NAMPT gene, known as single nucleotide polymorphisms or SNPS, are associated with an increased risk of developing sepsis/trauma-induced ARDS/VILI and increased ARDS mortality. eNAMPT, a highly druggable target and a humanized eNAMPT-neutralizing mAb (ALT-100), has been developed that has been proven to be efficacious in preclinical ARDS/ VILI models. Thus, an eNamptorTM precision medicine platform comprised of a plasma biomarker test, a genetic test, and a specific monoclonal antibody, has the potential to serve in clinical trial design that applies precision medicine strategies in ARDS, perhaps ending the drought for effective FDA-approved drugs in ARDS.

SUMMARY

In ARDS, the unmet need is to identify reliable, validated ARDS biomarkers that minimize ARDS heterogeneity and allow for stratification of subject selection for enrollment in clinical trials of tailored therapies. Combined with a more streamlined drug-approval process, biomarker- and genotype-based treatment of specific ARDS endotypes has never been as within reach as it is today. ◆

BIOGRAPHIES

Dr. Joe "Skip" G.N. Garcia is the Founder & Chief Executive Officer of Aqualung Therapeutics. He is a University of Arizona Endowed Merlin K. DuVal MD Professor of Medicine and an elected member of the National Academy of Medicine. Dr. Garcia is an internationally recognized physician-scientist with over 30 years of research experience in pulmonary disease and has led multi-billion-dollar academic organizations. He is a leading authority on the genetic basis of inflammatory lung disease with emphasis on health disparities, particularly of the underserved minorities. He has over 500 peer-reviewed publications to his credit, has an expansive portfolio of NIH-sponsored research, and continues to direct large federally funded programs. He is a passionate advocate for the training of physician-scientists and is an active supporter of minority medical and science students. Dr. Garcia is internationally recognized for his development of novel therapies for critically ill patients with acute inflammatory lung disease holding over patents.

Stan Miele is President of Aqualung Therapeutics. He is a recognized global executive with success in sales, marketing, and P&L leadership in the pharmaceutical/medical device and biotech industries. He was formally the Chief Commercial Officer at bioLytical Laboratories and Sucampo Pharmaceuticals Inc. He was also President of Sucampo Pharma Americas for 6 years. He was instrumental on some key licensing agreements for Sucampo, inclusive of the agreement with Abbott Japan, and also Takeda Pharmaceuticals (now Shire). He is actively part of the team ensuring proper execution of clinical development, manufacturing, licensing, capital funding, alliances, and ensuring Aqualung meets all critical milestones. He will be helping the company move toward accelerating the pipeline/platform technology and moving the eNamptorTM platform toward commercialization.

BATCH RELEASE

The Business Case for Reinventing Batch Release

By: Aparna Seksaria

A digital blueprint for unlocking efficiencies that can turn batch release from a cumbersome profit drag to an agile profit center — without compromising safety or quality.

INTRODUCTION

The headlines have been hard to miss: Regulators stepping in to force a manufacturer and its production partner to suspend operations at a troubled Covid-19 vaccine production plant for several months and discard several million vaccine doses that would have contributed to fighting the pandemic, all due to a contamination issue; and, in a separate instance, another manufacturer and its production and distribution partners having to discard hundreds of thousands of Covid-19 vaccine doses, also due to batch contamination.

While these two cases occurred months apart on separate continents and involved different biopharmaceutical companies and completely different production and distribution partners, both raise serious questions about the ongoing viability of the traditional batch release processes, practices, and systems the pharmaceutical industry has long relied on throughout the stages of commercializing a product, whether that product is being fast-tracked during a crisis, as has been the case during the pandemic, or if it is being developed under a more conventional timeline.

From manufacturing issues, chemical contamination, the presence of impurities, and cGMP deviations to failed content uniformities, lack of appropriate approvals and beyond, the potential health hazards to patients that can prompt a batch recall are myriad. The sheer number of product recalls (more than 60 logged by the FDA for 2021 as of mid-October), the astronomical cost these recalls exact on companies and their brand reputations, and the hard-to-quantify but sometimes tragic toll that a flawed batch can take on a human or animal life, can be irrevocable and unforgiving.

Digital batch handling can turn batch release from a cost center to a profit center for a manufacturer.

TODAY'S REALITIES SHAPE A VISION FOR THE FUTURE

To safeguard lives, ensure the final drug product adheres to predefined objectives, and ensure product and process control, pharma companies have long followed scientific risk-based holistic and proactive approaches like quality-by-design.

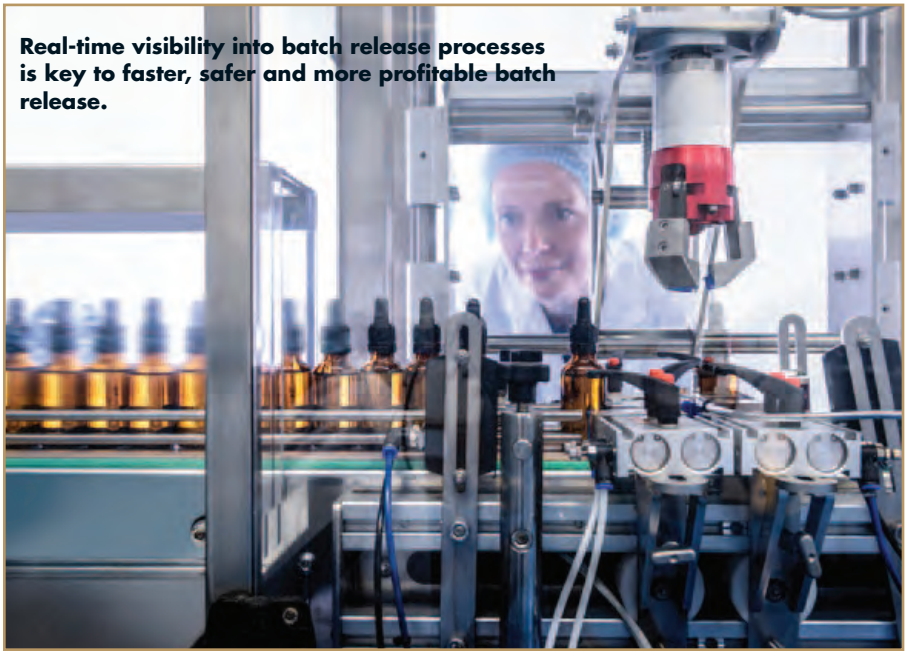
From early stage manufacturing through the commercial release, numerous critical quality parameters are identified and tested to ensure safety and efficacy of the drug product. Batch release is one of those processes. It deserves not only closer scrutiny, but an end-to-end re-engineering to do away with the cumbersome, inefficient manual processes, siloed information, and lack of standardization involved in the pooling of information from satellite systems.

For pharmaceutical companies — and pharma supply

chains — to bring safe, commercial-ready products to market quickly and profitably, and for them to meet growing demand for highly personalized, batch-size-one types of products, it's critical that they take steps to de-risk and speed up processes like batch release, and do so without compromising quality, safety or the bottom line.

Realizing the vision for a smoother, efficient, and less costly batch release is predicated on companies embracing certain Industry 4.0 digital capabilities, many of which are already proven or have begun to find their way to the pharmaceutical manufacturing business. In that vision, batch release would be:

- Agile, with a single "cockpit" to view and manage the entire quality release process.
- Faster, incorporating a review-by-exception (RBE) approach so quality managers (QMs) and qualified persons (QPs)can quickly pinpoint the root causes of exceptions without the process grinding to a halt, leading to shorter batch review cycle times.
- Less error-prone as data siloes and manual data entry processes are banished, which produces a substantially better right-the-first-time rate.
- Transparent, with all stakeholders working from the same set of data and common, accepted quality standards/parameters.
- Compliant, with the ability to readily adapt to changing regulatory requirements as well as reporting requirements that differ from country to country.
- Heavily automated, with intelligent digital tools to quickly comb through and draw insight from huge amounts of data, evaluate exceptions, then make automated decisions accordingly.
- Reproducible, a result of greater automation and less reliance on changeable human factors.
- Readily scalable, due to standardized processes across internal operations and supplier operations.
- Harmonized across the operation and the supply chain.
- Ready to support the "batch size of one" associated with emerging cell and gene therapies.
- Profitable, by contributing to the bottom line instead of sapping costs from it.



Real-time visibility into batch release processes is key to faster, safer and more profitable batch release.

RELEASE & REWARD

Batch release as a profit center rather than a cost center? As farfetched as that might sound, based on calculations from SAP's work with its pharma customers, companies that put this vision for a harmonized, automated batch release into practice stand to reap a range of benefits in the following areas:

Speed: Digital batch handling can significantly reduce the order preparation time and can bring down the overall batch review time by more than half, thereby increasing the number of batches that can be reviewed, in a particular timeframe, by manifold. The operational efficiency resulting from accelerating the quality batch release business processes can be quite impactful and will significantly contribute to the productivity of the manufacturing process, in turn increasing the out-of-the-door shipments.

Cost Savings: The massive efficiency boost that results from the reduction of time spent by QM reviewing batches by exception can significantly reduce operating expenses, thereby improving the cost of quality. Even a mere 20% reduction in the cost of quality for a firm whose operating expenses per therapeutic area in the range of 80-100 million can translate into an average cost saving of $20 million per study.

Compliance: Adopting a single monitor for the Identification of an erroneous batch and tracking the source of error will help close CAPAs (Corrective and Preventive Action) at a quicker rate, thereby reducing the number of non-conformities open at a single time, leading to higher quality compliance. Assignment, review, resolution, justification, approvals, and documentation of CAPA, all tracked through one instance, can help hasten quality reviews and aid in preventing their recurrence.

Non-Linear Growth: This level of batch release efficiency means that companies can add products without necessarily adding people, an important consideration given today's tight labor market, and growing demand for batch-of-one products for cell and gene therapy (CGT) and other applications.

Freeing People for Higher-Value Work: Relieved of the time-consuming manual and redundant data-collection, review and management processes that are part of batch release, QMs, and QPs can focus on other work that adds value to the enterprise, like innovations that improve the overall quality process.

Custodianship: In addition to having fragmented solutions, the traditional batch release process often requires hand-holding by the quality analysis, quality control, and manufacturing teams. Because reviews, identification of discrepancies and deficiencies, investigations, and comments often are conducted offline over company-specific collaboration tools and emails, they can be difficult to retrieve. Having a central monitor to record and report decisions and tie them to the source of truth will ensure tighter custody over batch specific information, overall QA release process, conditional transfers, and recalls.

Automating certain batch release processes frees QMs and QPs for higher-value work.

THREE KEYS TO REINVENTION

Each new recall, each FDA intervention, and each news headline about a suspect batch release practice or negative outcome is a reminder that the gap between this ideal vision for batch release and where many companies stand today remains substantial. Closing it is a matter of focusing on, and dedicating resources to, three key areas.

The first is Operational Efficiency. Too many pharmaceutical companies lean heavily on disparate systems, software, spreadsheets, and manual, paper-based processes to maintain their batch records. The result: cumbersome data-management, inaccurate and/or missing information, wasted resources, delayed releases, and at times, unfavorable outcomes that may or may not grab the attention of regulators and the public.

The answer? A single, integrated "control tower" or "cockpit" that provides visibility into and control over the huge volume of data involved in batch release, internally from a manufacturer's own operations as well as externally from raw material suppliers to CMOs, CROs, and so on. It gives QMs in-the-moment access to all the data they need to rapidly analyze exceptions and make decisions about flagging and quarantining a batch for a potential contamination issue, moving a batch from one phase of development to the next, etc. Meanwhile, batch record data and updates, and other documentation, flow between quality teams in real time as processes and tasks are completed.

For this "eye in the sky" construct to be viable, companies will need to adopt Internet of Things-enabled Industry 4.0 practices in their own factories, with the ability to analyze data to identify bottlenecks, quality issues, and problems with factory assets in real time. It also requires a willingness for supply chain partners to use a common digital platform and share their data. In the end, this sharing of data

fosters collaboration and trust among partners, and aligns their interests.

Standardization is the second key to better batch release. The goal: implement and adhere to a set of common practices, processes, systems, and functions that reinforce thresholds, parameters, workflows, etc, throughout the entire batch release. A lack of standardization inside and across quality teams and departments, and along the supply chain (with CMOs and the like) is one of the biggest bottlenecks and risk factors in batch release today.

Perhaps the most important step toward reducing risk and eliminating bottlenecks is moving from a review-by-default to a review-by-exception approach during the production review process, whereby quality teams, enabled by digital tools, focus on identifying and analyzing process deviations as they occur, then making decisions about next steps based on what the data (and analytics) suggest.

Using RBE opens the door to greater automation of processes, including automatic collection and reconciliation of data, automatic release of batches that are deemed ready for market, and the ability to use automated, intelligent tools to identify then address root causes and process trends that may impact the quality and safety of a product. While it's impossible to say if an RBE approach could have prevented the Covid-19 vaccination recalls, what is clear is that it can enable companies to expedite the safe auto-release of a significant share of batches and shrink the timeline on batch release from a month or more, to perhaps 6 or 8 hours.

The third key to reinventing batch release is Intelligent Technology. With the ability to apply predictive analytics and other artificial intelligence- or machine learning-driven tools to batch release data (and RBE in particular), and to entire batch management and manufacturing processes, companies gain speed, accuracy, and optimization, not only in their batch releases, but also on the factory floor.

In the quality departments, where workflows still heavily rely on manual and paper-based processes, adoption of RPA (robotic process automation) can be a game-changer by eliminating routine data-entry tasks and improving the agility of the process.

With manufactures and regulatory bodies advocating the adoption of sensors and PAT (process analytical technology), the pharma industry is bound to see a huge increase in data points. Applying automation to chartered decisions can help speed the time-to-market of new batches.

Adoption of AI (artificial intelligence) and ML (machine learning) technologies can aid in understanding the critical quality parameters of the "golden batch", starting from the quality and quantity of raw material used, ingredients added at various stages, the calibration of the equipment used throughout the process, the temperature variability and sensitivity of the atmosphere and can help replicate the perfect process resulting in consistent high yielding quality batches.

Intelligent digital technology, we know, is essential to unlocking the operational efficiency and standardization that are so important to faster, more flexible and ultimately safer batch release. But the true catalyst to all this is a mindset shift, whereby a pharma company's decision-makers choose to abandon outmoded, risk-laden manual batch release approaches and shift to digital, data-driven and exception-based approaches, realizing that doing so can have a profoundly positive impact on the company's ability to compete in a business where speed to market and product safety are paramount, during a pandemic and otherwise. ◆

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BIOGRAPHY

Aparna Seksaria is Industry Solutions Manager for SAP's life sciences business group, where she leads customer co-innovation solutions and acts as a trusted advisor, providing clear guidance, roadmaps, and industry best practices that enable companies to transform into intelligent enterprises.

Drug Development
EXECUTIVE

Fabio Gratton
CEO
inVibe

inVibe: Changing the Research Game with Voice

Fabio Gratton began his career as a Hollywood scriptwriter. There, he learned that storytelling is difficult, but can be made easier by listening to people to discover their innermost needs and desires. And when he co-founded his first healthcare marketing company about 15 years ago, he quickly realized that pharma had an enormous unmet need — listening to patients and their impassioned stories about illness, treatment, and recovery.

Fast forward to inVibe, a voice research company founded in 2013 (and as of January 2022 has become a division of THREAD), where Gratton, as CEO, has applied this same empathy to market research. Somewhere between traditional quantitative (e.g., online surveys) and qualitative (e.g., focus groups and in-depth interviews) research was a gap where patients were not being sufficiently heard. He realized that innovative uses of digital technology could be adapted to collect, analyze, and deliver these stories back to clients.

Drug Development & Delivery recently spoke with Gratton about patient-focused drug development (PFDD), inVibe's language model, and the value this technology brings to a patient's treatment journey.

Q: What progress has been made in patient-focused drug development and what are the continued challenges?

A: The good news is that numerous governmental and industry-based initiatives have spawned a new era in patient-focused drug development. Although just getting started, PFDD has documented approaches to data collection, identified best practices and benefits/risk tradeoffs, and analyzed input on patient communications

preferences.

These efforts tap into the reality that patients are willing and oftentimes enthusiastic to share their feelings about the disease burden and their treatment journey with experts, and actively assist with the generation of evidence and actionable data. Unfortunately, company culture, limited cross-functional collaboration, and leadership hesitancy can create barriers for organizations. But even if those challenges are circumvented, the listening process itself is difficult and demands a new approach.

Human communication is messy. At inVibe, we realized early on that even after we got patients to share their deepest thoughts and feelings, we had another problem: How to extract key insights we could then report back to clients in a way that offers a chance to ask more questions, and provide actionable recommendations.

Q: What is GPT-3 technology and how is it extracting those key insights?

A: Our solution is a combination of human expertise and next-gen technology. Trained linguists sort through the data and help organize it; and the latest machine learning algorithms, such as Generative Pre-trained Transformer 3 (GPT-3) enable unprecedented semantic analysis and search capabilities. Our clients benefit from a more thorough analysis and dynamic reporting, fulfilling our mission for clients to actually hear from patients and listen to them, rather than merely process and regurgitate data.

GPT-3 technology was created by OpenAI and is the most expansive machine learning model of its kind. Without exaggeration, the tech literally scans nearly the entire Internet to contextualize and extract meaning from our voice data inputs. The richness of qualitative data is also what can make organizing and processing that data such a challenge. With GPT-3, we are able to design algorithms for specific tasks that reduce busy work and allow analysts to quickly get to meaningful insights.

Q: How is inVibe using GPT-3 technology?

A: By integrating GPT-3 technology, we have developed an algorithm to identify and extract patient concerns from open-ended questions that lead to increasingly specific and nuanced answers — often revealing concerns never before considered. With our machine learning capabilities and human-powered linguistic analysis, the industry has an unprecedented opportunity to listen to and extract key insights from patients throughout the drug development process. This mitigates potential downstream setbacks, and proactively enables study designers to focus on the needs and concerns of patients before drugs even hit the market.

To cite a specific use case, we recently applied the firepower of GPT-3 to the lupus clinical trial landscape, seeking to reveal patients' preferences for study design and endpoints, and comprehension of patient-facing study materials. By offloading these tasks to a powerful language model, we were able to reveal rich qualitative insights in a much more streamlined fashion. Our technology worked like this: Patients were recruited and screened directly from their own smartphones; they viewed stimuli; listened to automated open-ended questions; responded by simply speaking; then their voice responses were analyzed using a combination of sophisticated software and human expertise. The results were shared with the client through dynamic dashboards that revealed key insights, and suggested actionable recommendations for the brand team.

Q: How are pharma and patients responding to this drug development approach?

A: Clients have embraced the concept, and inVibe quickly demonstrated value across disease states ranging from diabetes to oncology. By empowering patients to record their candid feelings directly into smartphones and then analyzing it with a hybrid of human linguistic expertise and advanced machine learning technology, we have changed the game in research.

With proven success across the post-launch life cycle of pharma brands, we also soon realized the importance of applying this novel approach to the drug development process. Our hunch that providing a platform where patients could share their perspectives without friction was correct — and so was our belief that regulators would see it the same way, eventually proven by the FDA Patient Focused Drug Development (PFDD) guidance, and Congress recently passing the Cares Act that created new guidance to ensure patient voices are heard early in clinical trials.

Not only are the government and advocacy groups standing behind technology and linguistic integration into the drug development process, but patients appreciate their voices finally being heard. The end result is empowered healthcare stakeholders — and improved therapeutics. Because key

decisions at the development phase have a cascading effect throughout the life cycle of a drug, companies can save considerable money and time — and provide better treatments — by accurately understanding the needs and expectations of their end users: the patients.

That excitement and rationale have also been instrumental in our decision to become a division of THREAD, a technology platform helping to decentralize clinical trials. Together, we're best positioned to infuse the drug development phase with the power of the patient voice.

Q: What will this mean for the future of patient-focused drug development and personalized medicine?

A: I have a Pollyanna outlook on life that permeates all the work that I do in healthcare. Despite the ongoing challenges to listening and understanding patients, I'm confident that the industry will evolve, and along with it so too will our capacity to improve the patient experience to the point where we're not simply better at managing disease, but preventing it.

The key to accomplishing that goal is to embrace technology so that we empower our humanity. Researchers too often consider what they do, and how they do it, a pure numbers game, mistaking map with territory. In contrast, everything we do is ultimately designed to improve and extend human life. Technology is a means to that noble end. That's why at inVibe we always start with the problems to be solved on our way to better listening to, and understanding, patients. As we tackle obstacles to data collection, analysis, and reporting, we also keep our minds and hearts on the vision of what an idealized future could and should be like for a healthy society. The future of patient-focused drug development is inspirational.

By better understanding end-users through patient-reported outcomes measures, researchers are already able to integrate these critical insights directly into their processes, methodologies, and even their study designs. The end result is to create more patient-centric trials with increased participation and retention, better study designs, and clinical results that precipitate more effective and safer treatments for all. By combining their dedication to patients and embracing the next-gen in market research capabilities, pharma is poised to catch up to the tech firms paving the way for the ideal consumer experience.

Drug development is only one of many opportunities for personalized medicine to come into its own. The patient experience must be integrated across every touchpoint and milestone in the patient journey. Thanks to this already proven combination of innovative technology and human-powered analytical expertise, those voices are not only being heard, but listened to, allowing for better understanding. Identifying differences between patients and heightening sensitivity to their needs, we are able to create a more personalized experience that improves the entire healthcare system.

Given how healthcare is often a matter of life and death, no initiative is more significant than improving public health. Patients are speaking, and pharma is, with the help of innovative market research, listening more. ◆

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- **Donna Boyce,** Senior Vice President, Head of Global Regulatory Affairs, *Pfizer*
- **Benjamin Borgo, PhD, MBA,** Head of Portfolio Management, Genome Engineering and Modulation, *MilliporeSigma*
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- **Kelvin H. Lee, PhD,** Director, *NIIMBL,* and Gore Professor, Chemical and Biomolecular Engineering, *University of Delaware*
- **John J. Lewin, III, PharmD, MBA, BCCP, FASHP, FCCM, FNCS,** Chief Medical Officer, *On Demand Pharmaceuticals*

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PERMEABILITY STUDIES

Onion Epithelial Membrane as a Model for Predicting Intestinal Absorption of Drugs

By: Antoine Al-Achi, PhD, Mounika Nangineedi, MS, Chaitali Koli, MS, Asmita Chikhale, MS, Sujay Gurav, MS, Aman Parashar, MS, Prithvijeet Singh Kharnal, MS, Harsh Gajjar, MS, and Samarth Makwana, MS

INTRODUCTION

The oral route of drug administration remains the widely preferred administration route for most new chemical entities.[1] The oral route is preferred by virtue of its convenience, low costs, and high patient compliance compared to alternate routes.[1]

Most of the drugs administered through an oral route tend to absorb in the small intestine.[2] Different factors that decide the extent of drug absorption are the rate of dissolution, solubility, and permeability.[3] A drug should have acceptable aqueous solubility and good intestinal permeability to achieve a therapeutic concentration in the body.[1] Although the stomach and upper intestine are the preferential drug absorption sites, the low-aqueous solubility of a drug remains the reason for variable absorption.[4] *In-vitro* methods are primarily used to determine the permeability of drug molecules.[1] *In-vitro* methods are either animal tissue based or cell based.[1]

To study drug permeability, the Caco-2 cell line (Cancer coli-2) is widely used because the Caco-2 cell monolayer has functional and morphological similarities to the human enterocytes.[5,6] The Caco-2 (Cancer coli-2) cell line is derived from human colorectal adenocarcinoma, and it was found that it resembled the characteristics of enterocytes upon differentiation. For example, the Caco-2 cell layer possesses a typical brush border and shows the enzymatic activities of typical enterocytes.[5] Therefore, a drug's intestinal permeability can be studied using this cell line because of its resemblance to the enterocytes. However, there are several drawbacks of using this line in research. The Caco-2 cell monolayer is expensive to run due to the requirement to maintain sterility throughout the process, is time-consuming as it typically requires between 14-21 days to exhibit functions and characteristics of those of the enterocytes, and requires skilled personnel for handling.[1]

In a paper by Ansari et al, permeation studies of three drugs with different molecular weight and lipophilicity characteristics were performed using natural membranes as a barrier.[7] The researchers studied the diffusion of metronidazole, diclofenac sodium, and erythromycin through the outer membrane of *Prunus persica* (peach), the outer membrane of *Lycopersicon esculentum* (tomato), the inner layer of egg, and the middle epithelial layer of *Allium cepa* (onion).

In this study, 19 drugs with varying partition coefficient, water solubility, and molecular weight values were chosen to compare their diffusion through the middle epithelial membrane of onion with that of their Caco-2 cell line. These values are shown in Table 1. This research examined the feasibility of replacing the Caco-2 cell monolayer with the onion membrane for permeation study.

MATERIALS & METHODS

Materials

Humulin R-U100 (Serial # 207420367192 and 085322276966) was purchased from the North Carolina Mutual Wholesale Drug Company. Acacia (lot # SLBL3988V and BCBJ3460V), dirithromycin (≥ 95%) (lot # MKBV2310V), glyburide (lot # SLBZ3091), metformin hydrochloride (lot # LRAB3694), nadolol (lot # BCBZ85680), phosphate buffered saline (10x con-

centrate, Bio performance certified, suitable for cell culture) (lot # SLBP3595V), potassium phosphate monobasic (lot # SLBR0890V), roxithromycin (≥90% HPLC) (lot # 036M4124V), and tragacanth (lot # SLBF0511V and 1576K) were from Sigma Aldrich. Chemicals from Spectrum Chemicals were furosemide (lot # 1IK0405), mannitol (lot # X50002), and terbutaline (lot # 4HK0017). The following chemicals were obtained from Thermo Fisher Scientific: Methanol (lot # 163830) and sodium phosphate dibasic (lot # 91796). Acetonitrile (lot # 60192), ethyl alcohol (lot # 201021524), hydrochloric acid (0.1 N HCl) (lot # 1635C443), phosphate buffer saline (lot # 20B0456252), and sodium trimetaphosphate (STMP) (lot # 61500383) were from OmniSolv, EMD, Amresco, VWR, and Alfa Aesar, respectively.

TABLE 1

Drug (Molecular Weight g/mole)	Log Partition Coefficient	Permeability Coefficient (P_{app}) Through Caco-2 Cells ($x10^{-6}$ cm/sec)[a]	Water Solubility (g/L)	Apparent Permeability Coefficient (P_{onion}) Through Onion Epithelial Membrane ($x\ 10^{-6}$ cm/sec) Mean (Standard Deviation) (Number of Replicates)	Reference
Amlodipine Besylate (567.05)	3.00	7.57	0.0753	0.162 (0.025) (7)	8
Ciprofloxacin (331.34)	0.28	2.55	30.0	0.0465 (0.069) (7)	9
Diltiazem HCl (450.98)	2.80	29.8	0.465	0.158 (0.041) (7)	10
Dirithromycin (835.086)	1.60	4.0	0.002	0 (0) (6)	11
Furosemide (330.74)	2.20	13.59	0.0731	0 (0) (6)	12
Gatifloxacin (375.4)	2.60	5.29	60.0	0.069 (0.13) (7)	9
Glyburide (494.003)	4.70	21.6	0.004	0 (0) (7)	13
Human Insulin (5807.63)	-13.10	0.65	0.2	0 (0) (7)	14
Ibuprofen (206.285)	3.97	30.1	0.021	0 (0) (6)	15
Indomethacin (357.79)	4.27	22.7	0.00093	0 (0) (6)	15
Levofloxacin (361.37)	2.10	28.36	100.0	0.064 (0.084) (7)	16
Metformin HCl (165.625)	-1.37	5.5	100.0	0 (0) (7)	17
Metoprolol Tartrate (684.82)	1.88	36.86	16.9	0.33 (1.49) (7)	18
Nadolol (309.4)	-1.12	0.56	8.33	0 (0) (6)	18
Norfloxacin (319.33)	-1.03	4.92	178.0	0.038 (0.027) (7)	19
Oxprenolol HCl (265.35)	2.10	65.5	2.5	8.16 (11.55) (13)	20
Propranolol (295.8)	-0.45	6.03	0.0444	0.704 (0.24) (7)	12
Roxithromycin (837.05)	1.70	5.2	0.0000189	8.86 (3.74) (7)	21
Terbutaline (225.28)	-1.34	0.417	213.0	0 (0) (6)	22

Physical properties and the apparent permeability coefficient (cm/sec) through the onion epithelial membrane of the various drugs included in this study.

FIGURE 1

Gel Formulation: Gum acacia 1 g, Gum tragacanth 5 g, and DI water 100 g (see Methods).

Methods

Preparation of the Colloidal Drug Dispersion - Gum acacia and gum tragacanth were weighed in a ratio of 1:5 (1 gm and 5 gm). The weighed items were transferred to a porcelain mortar, and 70 g of DI water was added. The mixture was triturated for 2-3 minutes and kept aside for hydration for 24 hours. After 24 hours, 30-g DI water was added, and the mixture was triturated until a gel-like consistency was achieved. The gel containing drug was prepared by adding 12.56 mg of the drug to 8 g of the formulated gel (1.57 mg of the drug/g of gel) (Figure 1).

Drug Analysis - Drug concentration in the receiver compartment was evaluated by high-performance liquid chromatography (HPLC) or spectrophotometrically (UV/Vis). The followings were specifications for the HPLC systems (mobile phase; isocratic (I) or gradient (G); column; wavelength, and flow rate):

Waters 717 Plus:

- Amlodipine Besylate and Diltiazem HCl (acetonitrile: potassium dihydrogen phosphate buffer (60:40). pH-3 adjusted with 0.03M HC; (I); Zorbax SB-C18 (4.6*150mm); 240 nm; 1mL/min).

- Human Insulin (solution A: methanol, solution B: aqueous (0.1% trifluoroacetic acid) mobile phase: A:B (50:50); (I); Inertsil ODS-3, 5 µ, lot # TQ5-2053; length 250 mm; ID 4.6 mm; 220 nm; 1 mL/min).

- Ibuprofen (acetonitrile and aqueous buffer (60:40 v/v), aqueous buffer (USP water; trimethylamine, O-phosphoric acid in 1000 mL 1:0.5 ratio); (I); Waters C-18; 5 µ; 3.9x150 mm; serial # W41001J; 220 nm; 1 mL/min).

- Indomethacin (acetonitrile and USP water (1 mL of acetic acid, USP in 1-L solution) (50:50 v/v); (I); Waters C-18; 5 µ; 3.9x150 mm; serial # W41001J; 264 nm;1 mL/min).

Agilent 1100 series:

- Furosemide (100% Acetonitrile and 20-mM phosphate buffer at pH 4.5; (G) at 15% organic phase to 75% organic phase in 20 minutes; Inertsil ODS-2 (serial # 4HI10128) (150 mm x 4.6 mm, 5 µ) at 40°C; 220 nm; 1 mL/min).

- Glyburide (0.05% trifluoroacetic acid (TFA) (Fisher biotech, lot # 005866) in water and 0.05% TFA in acetonitrile; (G) at 30% organic phase to 60% organic phase in 12 minutes; Phenomenex Luna C18 (2) column (150 X 4.6 mm and 5 µ) (serial # 210357); 215 nm; 1.5 mL/min).

- Metformin HCl (0.05% TFA in water and 0.05% TFA in acetonitrile; (G) at 2% organic phase to 90% organic phase with the run time of 10 minutes; Phenomenex Synergi Hydro column (150 X 4.6 mm and 5 µ) (serial # 177045-1); 220 nm; 1.5 mL/min).

- Nadolol (mobile phase A: 20-mM phosphate buffer of pH 4.5 and mobile phase B: 100% acetonitrile; (G) at 15%-40% B in 10 minutes; Inertsil ODS–2 (4.5 x 150 mm, 5 µ, serial # 4HI10128); 220 nm; 1 mL/min).

- Terbutaline (Phosphate buffer pH 4.5 (Acros Organics, lot # A0359848) and 100% Acetonitrile (OmniSolv, lot # 60192); (G) at 15%-75% organic phase in 20 minutes; Inertsil ODS–2 (4.5 x 150 mm, 5 µ, serial # 4HI10128); 220 nm; 1 mL/min).

The spectrophotometry systems (drug and wavelength) were:

UV-Vis Genesys 10S (serial # 2L6R357214) (Thermo Fisher Scientific):

- Ciprofloxacin (271 nm)
- Dirithromycin (209 nm)
- Gatifloxacin (293 nm)
- Levofloxacin (287 nm)
- Norfloxacin (271 nm)
- Roxithromycin (203 nm)

UV/Vis Spectrophotometer (serial # B084260512; Jasco):

- Metoprolol Tartrate (274 nm)
- Oxprenolol HCl (274 nm)
- Propranolol HCl (290 nm)

The linearity of the methods was assessed by calculating the coefficient of determination (R^2).

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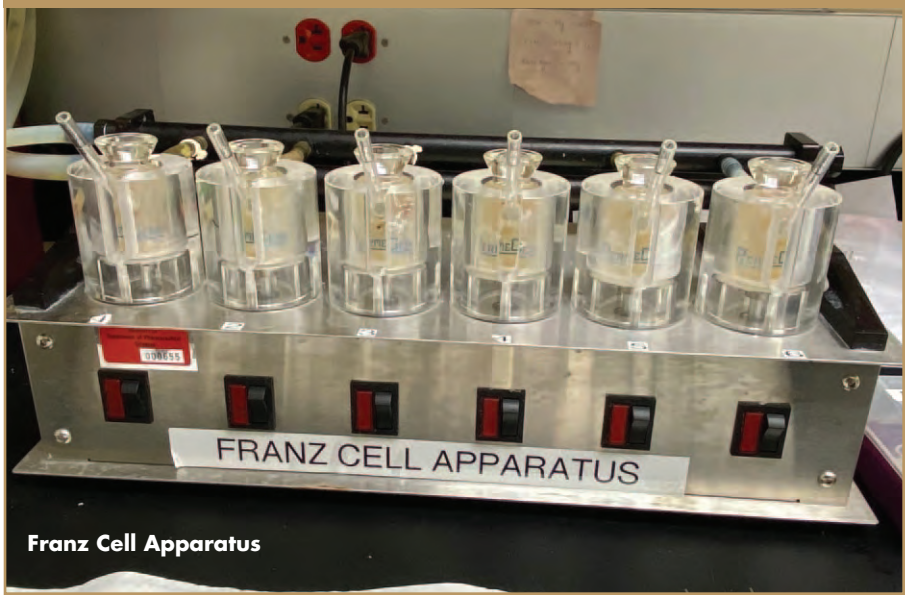
Determination of Thickness of Onion Membrane - The inter-lamellar layer of the onion was peeled, and the thickness of the onion membrane was measured before placing the membrane over Franz diffusion cells. The thickness was measured from the edges to maintain the integrity of the membrane. The thickness of the onion membrane was measure using a micrometer gauge (Westward).

Permeation Study Through Onion Epithelial Membrane - Franz diffusion cell (10 mL; area of diffusion 0.64 cm^2; 6-13 replicates per drug) (PermeGear, Hellertown, PA) was used for the diffusion study of drugs at 37°C (Figure 2). Phosphate buffer saline (PBS, 1x) was added to the receiver compartment, and a stir bar was dropped in it. The inter-lamellar layer of onion was peeled out, and thickness was measured. After measuring the thickness, the onion membrane was placed over the receiver compartment, and an O-ring was placed over it (Figure 3). The donor compartment was placed over the receiver compartment, and the assembly was clamped carefully. The volume of 1x PBS was adjusted by adding some of it through the sampling port until the level reached the 10-mL mark on the sampling port. Then, 1 g of the gel formulation with (1.57 mg of the drug/g of gel) or without drug was introduced into the donor compartment with the help of a spatula. Samples also contained 2 U/mL insulin (this was used to ensure the physical integrity of the onion membrane as insulin was shown in the preliminary studies that it did not diffuse through the onion epithelial membrane; thus, its presence in the receiver samples indicated that the membrane was damaged). Samples at respective time points were collected and analyzed using HPLC or spectrophotometrically. The first 0.3 mL of fresh 1x PBS was added to the compartment during the sampling process, and then 0.3 mL of sample was pulled out. The addition of the 0.3 mL of buffer prior to taking the sample was done to prevent the formation of air packets underneath the epithelial membrane. The time points for taking the samples were 0, 0.083, 0.5, 1, 3, 5, 7, and 25 hours.

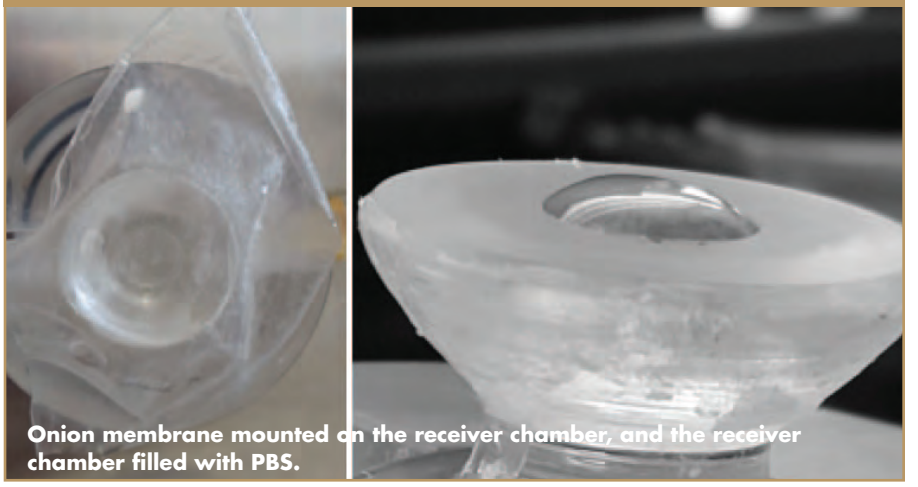
Statistical Analysis - Data are presented as mean and standard deviation unless indicated otherwise. A multivariate, standard least squares method was used to calculate the parameter estimates of log K, the molecular weight, and P_{onion} on their effects on the apparent permeability coefficient value through the Caco-2 membrane. In addition, the Wilcoxon Sign Rank test was used to compare the median P_{app} value of drugs through the Caco-2 cell monolayer system versus that obtained from the onion epithelial membrane. A p-value of less than 5% is considered significant. JMP® Statistical Discovery Software (version 14.0; SAS Institute, Cary, North Carolina) was used for the statistical analysis.

FIGURE 2



Franz Cell Apparatus

FIGURE 3



Onion membrane mounted on the receiver chamber, and the receiver chamber filled with PBS.

RESULTS & DISCUSSION

The HPLC and spectrophotometric methods showed good overall linearity (R^2 = 0.9839 ± 0.035; n = 19) for the drug analysis. Drugs showed different degrees of passage through the onion epithelial membrane (thickness = 0.14 mm ± 0.04 mm; n = 72). The apparent permeability coefficients (P_{onion}) of the drugs were computed from the Franz cell diffusion experiments (Table 1). From the first-order diffusion process, P_{onion} was estimated using the following equations:

$$\ln C_d = \ln C_0 - kt$$

$$k = P_{onion} S / V_d$$

Where C_d is the concentration of the drug remaining in the donor compartment at time t, C_0 is the initial concentration of the drug in the donor compartment at time t = 0, S is the surface area for diffusion (0.64 cm^2), and V_d is the volume of the donor compartment (10 mL). A plot between the log K values of the drugs and *the ratio* of the permeability coefficient through the onion membrane and Caco-2 is shown in Figure 4. This graph shows an optimum zone where the onion membrane may be used to replace the Caco-2 monolayer model for diffusion. According to Figure 4, this optimum area lies in the region where the log K values are greater than 0 but less than 2. The empirically obtained peak point for this optimum region for diffusion corresponded approximately to a value for log K of 1.7. This indicates that the onion membrane may be a suitable model to be used in place of the Caco-2 cell layer model when the drug solubility in lipid is about 50 times that of its solubility in water.

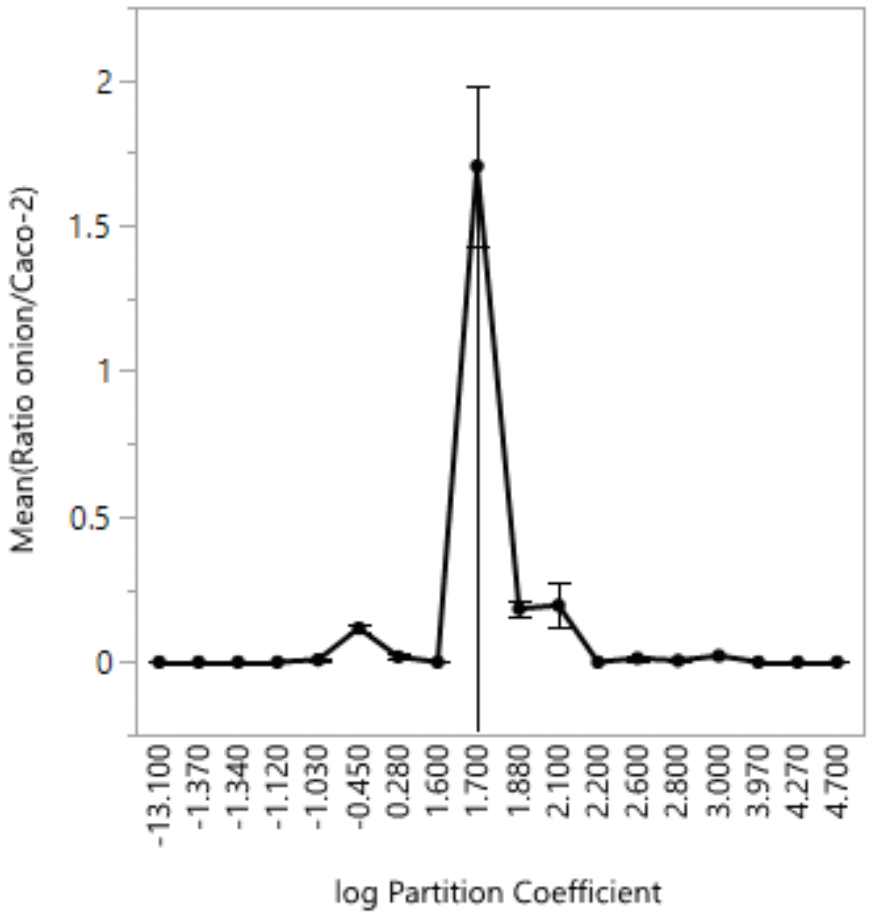
An empirical predictive equation for estimating the P_{app} through Caco-2 cells monolayer was developed and is shown in equation 3 ($p < 0.0001$):

$$P_{app} = 1.54\,x\,10^{-5} + (1.74\,x\,10^{-6})(\log K) + 1.40\,(P_{onion})$$

P_{onion} is the apparent permeability coefficient (cm/sec) of the drug through the onion epithelial membrane. Higher values for log K and P_{onion}, result in an increase in the predicted value of P_{app}. All terms in equation 3 were statistically significant (each at $p < 0.0001$). The molecular weight (within the range of values included in this research, from 165.625 g/mole to 5807.63 g/mole) of the drug was *not* statistically significant for predicting the P_{app} value.

Interestingly, a high percentage of the drugs tested in this study (9/19, 47%) failed to pass through the onion epithelial membrane. A similar observation was also noted with the Caco-2 cell monolayer model. Most drugs were typically found incapable of permeating the Caco-2 monolayer, having a median P_{app} reported value of 16 x 10^{-6} cm/sec.[23] The median value for P_{onion} in our drug sample was much smaller than that reported for the Caco-2 cell monolayer (0.038 x 10^{-6} cm/sec; *Wilcoxon Signed Rank test;* two-sided; $p < 0.0001$). Stated otherwise, on average, the rate of drug permeability through Caco-2 cells monolayer is over 400-fold higher than that expected through the onion epithelial membrane.

FIGURE 4



The plot represents the empirical relationship between the logarithm of the partition coefficient (log K) and the mean ratio of the apparent permeability coefficients (onion/Caco-2) (Table 1). The straight line projecting out from the peak point on the graph to the x-axis corresponds to a log K value of approximately 1.7. Each error bar is constructed using one standard error from the mean (n = 6-13 replicates/drug).

CONCLUSIONS

The epithelial membrane of onion may serve as a replacement to the Caco-2 cell line system provided that the drug has a log K value in the range of 0 to 2. The onion membrane diffusion model is best used when the log K is near the value of 1.7 as the ratio of the apparent permeability coefficients reached a maximum value. On average, the permeability rate of drugs through the onion membrane is many folds lower than that expected through the Caco-2 cell monolayer. ◆

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BIOGRAPHIES

Dr. Antoine Al-Achi is a Professor at Campbell University College of Pharmacy & Health Sciences. In that capacity, he teaches statistical methods and physical pharmacy to graduate students. He earned his PhD in Biomedical Sciences from Northeastern University, Boston, MA, in 1988. He has over 200 scholarly works, including poster presentations, review articles, research publications, books chapters, and books.

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Harsh Gajjar recently graduated from Campbell University with a Master's in Pharmaceutical Sciences - Industrial Pharmacy. He possesses knowledge of formulating nanoparticles using lyophilization and is experienced in performing diffusion study experiments. He is well-versed in JMP Software. He can handle various analytical instruments like HPLC, UV-Vis, Franz Diffusion Cell, Dissolution Apparatus, DSC, Malvern Mastersizer.

Samarth Makwana is an Associate Formulations Scientist at Eurofins Lancaster Laboratories PSS, LLC, Groton, Connecticut. He is involved in developing, preparing prototype formulations, and identifying potential stability and performance issues. He graduated with a Master's in Pharmaceutical Sciences (Industrial Pharmacy) and is a member of the Rho Chi Society. His research interests are novel drug delivery and diffusion studies.

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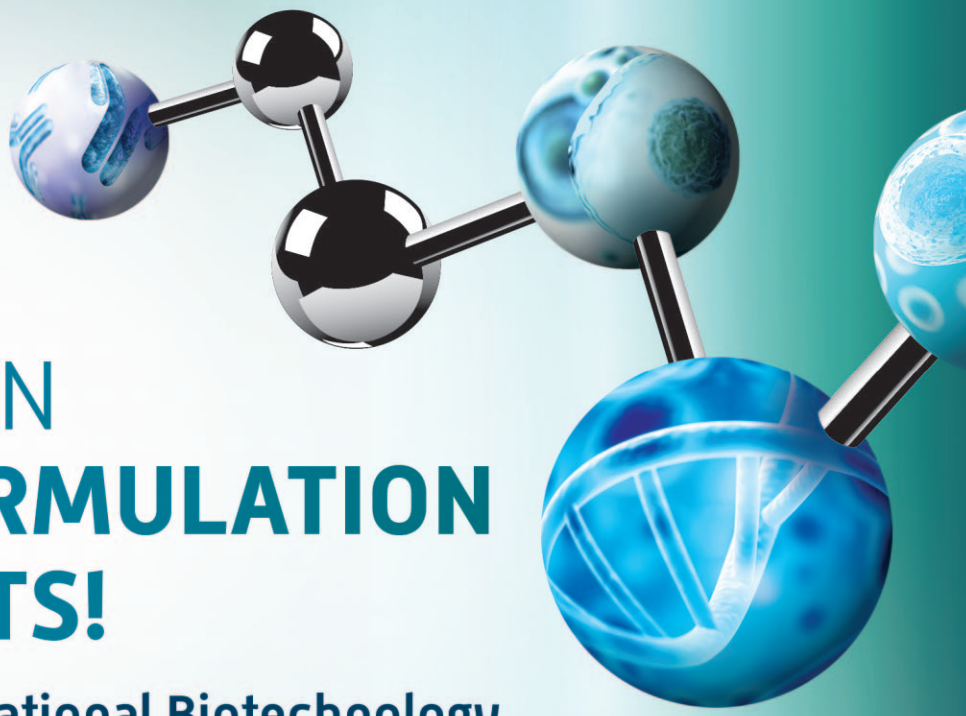

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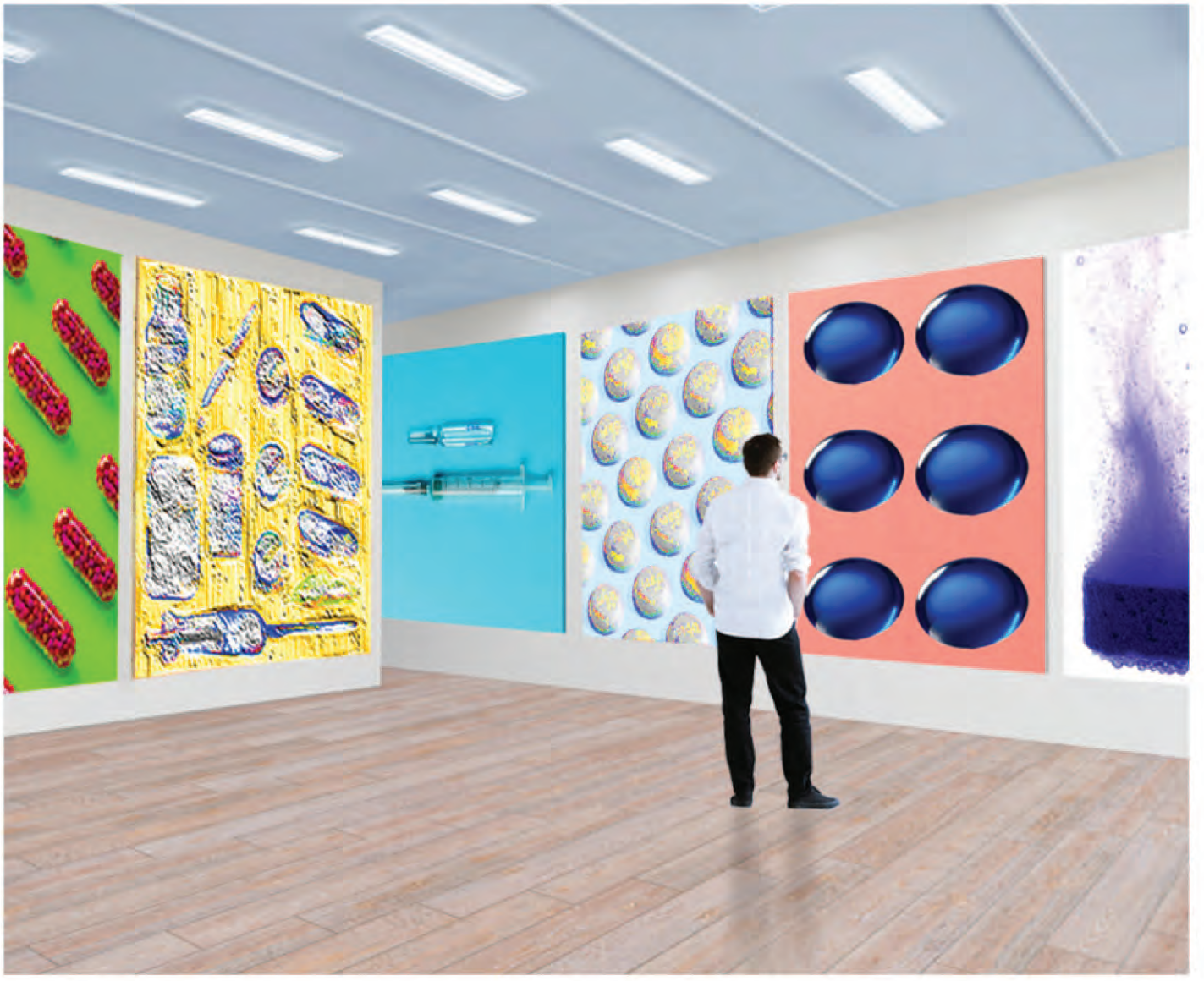

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