Drug Development & Delivery

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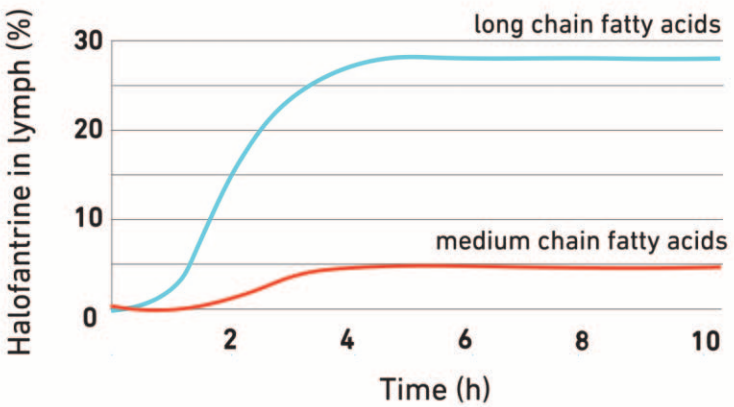

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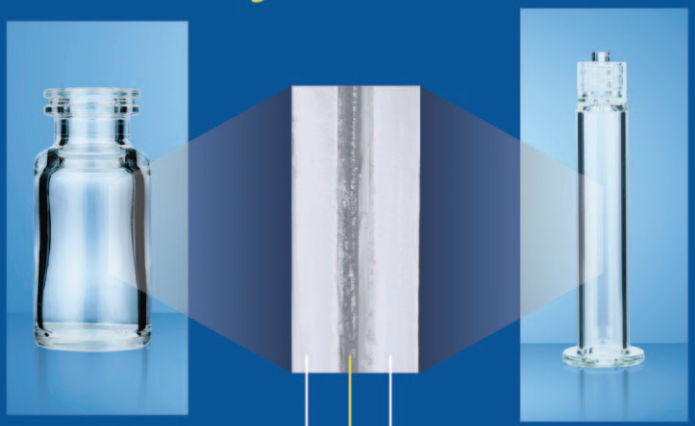

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Next-Generation Wearable Drug Delivery

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Stevanato Group & Corning Incorporated Sign Licensing Agreement to Offer Corning Valor Glass Vials in Presterilized SG EZ-fill Packaging Configuration

Stevanato Group recently announced a licensing agreement with Corning Incorporated to offer a combined solution that will provide biopharmaceutical companies with improved levels of protection for injectable drugs while enabling smoother manufacturing operations.

A new product, Corning Valor RTU Vials with SG EZ-fill Technology, offers the industry the unique combination of Corning Valor Glass vial attributes with SG EZ-fill integration and packaging advantages, including the following.

Stevanato Group's EZ-fill secondary packaging solution eliminates a step in drug manufacturing and production by allowing pharmaceutical and biotech companies to use the SG EZ-fill presterilized containers without having to go through additional wash and sterilization processes. The SG EZ-fill solution provides a fully integrated, ready-to-use (RTU) option for aseptic fill-finish operations. Available in formats ranging from 2R to 30R and in both Nest & Tub and Tray configurations, the secondary packaging stores vials and cartridges safely, allowing more efficient, flexible, and streamlined production operations and shortening time to market.

Valor Glass is a purpose-built pharmaceutical package designed to address the challenges of today's manufacturing operations. Valor Glass is chemically durable with uniform surface chemistry. It resists damage and breakage, eliminates delamination, and reduces glass particulate generation. Valor Glass is the result of Corning's extensive expertise in glass science, optical physics, vapor deposition, precision forming, and extrusion. Valor Glass enhances the storage and delivery of drugs, provides more reliable access to medicines essential to public health, and optimizes manufacturing efficiency.

"Corning is thrilled to expand our packaging portfolio by offering Corning Valor RTU Vials with SG EZ-fill Technology. This agreement marks an exciting step forward as we build a full suite of pharmaceutical glass packaging solutions," said Brendan Mosher, Vice President and General Manager, Corning Pharmaceutical Technologies. "The combination of Corning's purpose-built Valor Glass and Stevanato Group's RTU technology is a win-win for the industry; our expanded offering increases speed-to-market while improving primary packaging quality and performance."

Stevanato Group, a leading global provider of drug containment, drug delivery, and diagnostic solutions, designed its SG EZ-fill secondary packaging to store glass containers safely in a tray or Nest & Tub configuration for efficient filling, while minimizing glass-to-glass contact. The platform – launched in 2010 – is the ideal solution from lab-scale filling to the industrial filling process.

"The agreement with Corning represents another milestone for the SG EZ-fill presterilized platform," said Andrea Zambon, Corporate Business Development Director at Stevanato Group. "The partnership reinforces our technology leadership and market position in secondary packaging for aseptic manufacturing. By choosing our cost-efficient, scalable solution, Corning has opted for an industry-verified platform that has a proven track record of success with over 30 fill-finish machine manufacturers on more than 250 filling lines."

Evonik Markets New Enteric-Protected Ready-to-Fill Capsules for Fast, High-Performance Drug Development

Evonik recently launched the EUDRACAP platform of easy-to-handle capsules to help the pharmaceutical industry accelerate speed to market for complex oral drug products in early development stages. EUDRACAP enteric is the first product of the platform to become commercially available. This enteric coated pre-locked capsule gives pharmaceutical companies access to a capsule that can optimize gastric resistance, boost intestinal absorption, and enhance bioavailability.

EUDRACAP is Evonik's latest system solution built on the company's unique technology platform for advanced drug delivery. "With the help of EUDRACAP, we expect strong growth within our innovation growth field Healthcare Solutions," said Paul Spencer, Head of Product Line Drug Delivery & Medical Device Solutions at Evonik's Health Care business line. "EUDRACAP will foster our position as a fully integrated CDMO along the entire pharmaceutical value chain."

The new EUDRACAP platform leverages Evonik's established EUDRAGIT functional coatings to optimize the release profile of oral drug products. The coated HPMC (hydroxypropyl methyl cellulose) capsules are particularly suited to protect sensitive active pharmaceutical ingredients from moisture and gastric acid.

Oral drugs are being developed rapidly and there is new emphasis on those using mRNA or targeting the microbiome. This has created a great demand in the pharmaceutical industry for ways to increase the number of sensitive molecules in drug product portfolios.

"EUDRACAP is our answer to many of the challenges innovators in the pharmaceutical industry are facing when pioneering oral drug products," says Dr. Axel Schröder, Head of Global Business Segment Oral Drug Delivery Solutions at Evonik Health Care.

In addition to EUDRACAP enteric, the EUDRACAP Select line provides tailor-made CDMO (Contract Development and Manufacturing Organization) services for customer requirements, including a range of sizes, colors, and customized release profiles.

"We can help reduce risk and get the finished dosage form in the hands of our customers for clinical and commercial use as fast as possible," said Dr. Bettina Hölzer, Senior Project Manager Strategic Marketing Oral Drug Delivery Solutions at Evonik Health Care. With EUDRACAP, customers can tap into Evonik's expertise across application areas such as colonic delivery, microbiome delivery, personalized dosage forms and bioavailability enhancement.

EUDRACAP is the latest in a portfolio of product innovations launched by Evonik's Health Care business over the past few years. In 2020, Evonik began marketing EUDRATEC Fasteric, an advanced oral drug delivery technology that provides enteric protection followed by rapid, homogeneous release for effective targeting of the upper small intestine.

Evonik Health Care, which is part of the Nutrition & Care division of Evonik, is one of the world's leading CDMOs for complex oral and parenteral drug products that require advanced drug delivery solutions. It is also one of the world's largest suppliers of active pharmaceutical ingredients (APIs), amino acids, cell culture ingredients, medical device excipients, and leading global CMO (Contract Manufacturing Organization) for APIs and intermediates.

Ginkgo Bioworks & Biogen Announce Collaboration & License Agreement to Develop Novel Gene Therapy Manufacturing Platform

Ginkgo Bioworks and Biogen recently announced a gene therapy collaboration in which the companies aim to redefine the industry standard for manufacturing recombinant adeno-associated virus (AAV)-based vectors.

Recombinant AAV-based vectors are widely used to develop innovative gene therapies and have the potential to treat certain neurological and neuromuscular diseases as well as other conditions across multiple therapeutic areas. Currently, manufacturing is time-consuming and expensive making it difficult to develop therapies for diseases with high dose needs and with large patient populations. Ginkgo seeks to solve these challenges by applying its mammalian cell programming platform, with the aim to improve the efficiency of AAV-producing plasmid vectors and cell lines, which could accelerate Biogen's development of novel gene therapies.

"We believe that Ginkgo's unique combination of cell programming expertise, proprietary tools and knowledge of biological systems make them an ideal collaboration partner to explore a large number of design ideas with the goal of optimizing constructs," said Alphonse Galdes, PhD, Head of Pharmaceutical Operations and Technology at Biogen. "They share our goal of ensuring approved therapies are not delayed by manufacturing constraints and are available to patients worldwide."

"We are excited to collaborate with Biogen as they aim to develop treatments that may potentially slow, halt or cure neurological and neurodegenerative diseases and seek to enhance the industry standard for AAV manufacturing," said Jason Kelly, CEO of Ginkgo Bioworks. "Synthetic biology is leveraging the power of living cells to develop the next generation of therapeutics, everything from CAR-T, to CRISPR and gene therapies, which we believe will have a material impact on the lives of many."

Under the terms of the agreement, Biogen will receive access to Ginkgo's proprietary cell programming platform and capabilities. Ginkgo will utilize its bioengineering facilities and resources with the aim of enhancing the AAV production titers of Biogen's gene therapy manufacturing processes. Ginkgo will receive an upfront payment of $5 million and is eligible for milestone payments up to an additional $115 million should the collaboration programs achieve certain research, developmental and commercial milestones.

At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp.

Ginkgo is building a platform to program cells as easily as we can program computers. The company's platform is enabling the growth of biotechnology across diverse markets, from food and agriculture to industrial chemicals to pharmaceuticals. Ginkgo is also actively supporting a number of COVID-19 response efforts, including community testing, epidemiological tracing, vaccine development and therapeutics discovery.

Biogen & Envisagenics Announce Collaboration to Advance RNA Splicing Research

Biogen Inc. and Envisagenics recently announced a new collaboration to advance ribonucleic acid (RNA) splicing research within central nervous system (CNS) diseases. As part of the collaboration, Biogen will leverage Envisagenics' proprietary artificial intelligence (AI)-driven RNA splicing platform, SpliceCore, to define and understand the regulation of different RNA isoforms in CNS cell types.

Genetic information encoded in the human chromosome is converted into RNA molecules which is then used as the template to make proteins. RNA splicing is the process that trims out extra information embedded in the intermediate RNA molecules, and this trimmed RNA is what is then used to produce functional proteins.

"Since Biogen's earliest days, RNA splicing has been an integral part of our history and mission dating back to co-founder Phillip Sharp's discovery of the process in 1977," said Alfred Sandrock, Jr, MD, PhD, Head of Research and Development at Biogen. "By combining Envisagenics' SpliceCore platform with our deep expertise in this scientific approach, we believe that Biogen will be able to advance our understanding of RNA splicing and potentially identify new drug targets for CNS diseases."

"Envisagenics is thrilled to work with Biogen because we share a commitment to identifying potential treatments for CNS diseases through innovative AI technology like the SpliceCore platform. Envisagenics and Biogen recognize the power of RNA splicing to aid in the discovery of potential therapeutics," said Maria Luisa Pineda, PhD, Chief Executive Officer of Envisagenics. Envisagenics' Chief Technology Officer, Martin Akerman, PhD, added, "scientists have only recently been able to uncover disease-causing novel isoforms at scale, thanks to improvements in the speed and sensitivity of bioinformatics software like SpliceCore."

Traditionally, the process of detecting, cataloging and interpreting RNA splicing errors has been laborious, slow and costly. However, by tapping into Envisagenics' machine learning algorithms and high-performance computing, Biogen may now be able to identify, test and validate splicing errors at scale. Through this collaboration, Biogen will gain access to SpliceCore's database of approximately seven million potential RNA splicing errors, which is the largest database of splicing errors in the world. This will provide Biogen with a broader lens to evaluate splicing events that may be targeted for therapeutic gain. In addition, collaboration aligns to Biogen's broader objective of identifying and validating genetic targets of disease to increase the probability of success in CNS drug discovery.

Envisagenics is an Artificial Intelligence-driven biotechnology company that focuses on the discovery of novel RNA splicing variants that cause cancer and other genetic diseases. Its principal technology is the SpliceCore discovery platform. The platform re-envisions the human genome with a validated exon-centric approach, combined with machine learning algorithms and high-performance computing. It is up to 250 times more likely to discover novel targets than gene-centric discovery tools.

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Calithera Biosciences & Antengene Enter Worldwide License Agreement for Development & Commercialization of CB-708

Calithera Biosciences, Inc. and Antengene Corporation, Ltd. recently announced an exclusive, worldwide license agreement for the development and commercialization of CB-708, Calithera's small molecule inhibitor of CD73.

"This agreement validates the capabilities of our drug discovery engine and represents a significant milestone for our CD73 program," said Susan Molineaux, PhD, President and Chief Executive Officer of Calithera. "Antengene brings significant enthusiasm and proven global capabilities to the development and future commercialization of CB-708, a potential best-in-class oral small molecule CD73 inhibitor. This licensing agreement enables the continued advancement of this promising program, while allowing Calithera to focus our resources on our more advanced clinical programs evaluating telaglenastat in non-small cell lung cancer and CB-280 in cystic fibrosis."

CB-708 is a highly potent, selective, orally bioavailable small molecule inhibitor of CD73. Preclinical data presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting and the 2019 Society for Immunotherapy of Cancer (SITC) Annual Meeting demonstrated that CB-708 has immune-mediated, single agent activity in syngeneic mouse tumor models. In preclinical studies, CB-708 was well-tolerated and showed enhanced anti-tumor activity when combined with either an anti-PD-L1 immunotherapy or with chemotherapeutic agents, such as oxaliplatin or doxorubicin. CB-708 has completed GLP toxicology studies and is poised to advance into clinical development.

"We are excited to continue the advancement of CB-708 through our deep experience in global clinical development and extensive track record in commercialization in major markets around the world," said Dr. Jay Mei, Founder and Chief Executive Officer of Antengene. "CB-708 is a highly differentiated oral small molecule CD73 inhibitor with best-in-class potential. Antengene will continue to complete the GMP manufacturing of CB-708 and advance it into clinical trials for the treatment of multiple cancers including solid tumors and hematologic malignancies. This agreement brings a great addition to our synergistic portfolio of 12 assets with combinatory potential, is a testament to our abilities in accelerating global development, and represents another step in realizing our mission of treating patients beyond borders."

Under the terms of the license agreement, Calithera will receive an upfront payment and potential development, regulatory, and sales milestones of up to $255 million. Additionally, Calithera is eligible to receive tiered royalties on sales of the licensed product up to low double-digits. Antengene Investment Ltd, a wholly owned subsidiary of Antengene Corporation, will receive exclusive, worldwide rights to develop and commercialize CB-708.

Calithera Biosciences is a clinical-stage biopharmaceutical company pioneering the discovery and development of targeted therapies that disrupt cellular metabolic pathways to preferentially starve tumor cells and enhance immune-cell activity.

Antengene Corporation Limited is a leading clinical-stage R&D driven biopharmaceutical company focused on innovative medicines for oncology and other life-threatening diseases. Antengene aims to provide the most advanced anti-cancer drugs to patients in the Asia Pacific Region and around the world.

2020 Global Drug Delivery & Formulation REPORT

Part Four of a Four-Part Series

Part 1: A Review of 2020 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2020

Part 3: Notable Drug Delivery & Formulation Transactions and Technologies of 2020

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, Vice President Operations, and Selda Candan, Vice President Data Analytics, PharmaCircle LLC

Introduction

The pharmaceutical pipeline in 2020 developed in two ways that would have been surprising the year before. The first of these was the introduction of thousands of products into development for the treatment of Infectious Disease to treat COVID-19. There are currently more than 2,500 identified products in development for COVID-19. This includes products newly designed and developed for either prevention or treatment, products found in the pipeline cupboard and dusted off in hopes of success, and products approved for a variety of non-COVID-19 indications that offer important adjunctive benefits. One of the most critical adjunctive products, one that surprisingly requires FDA approval, is Oxygen. Its shortage in many parts of the world is leading to many avoidable deaths. A summary of the current COVID-19 pipeline is presented later in this report.

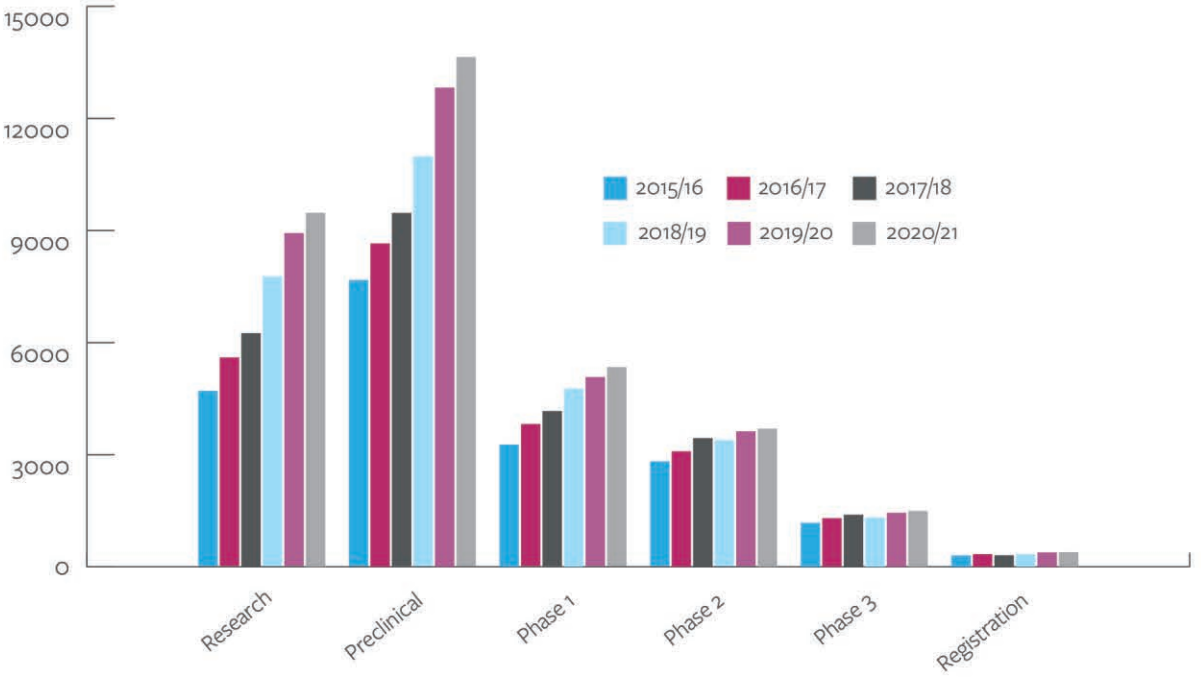
A second surprise is the large number of Cell Therapy products that have entered Phase 1 development. There are more than 2,000 cell therapies approved or at some stage of development, including more than 550 in Phase 1 development and some 1,275 products at a Research or Preclinical stage of development. A significant number of the Phase 1 products are being developed by companies based in China.

Beyond these two outliers, the development pipeline continued to show strong growth as more and more investment money rushes in to capture the financial potential of the new ideas bubbling up from emerging companies hoping to treat disease with new molecular and therapeutic strategies.

Once again, this year's Drug Delivery and Formulation Pipeline analysis leans on PharmaCircle's Pipeline Dynamics companion module to the Pipeline & Products Intelligence module and covers 6 years of the pharmaceutical pipeline history. By capturing detailed records annually of what products were at what stage of development from 2014/15 through to 2020/21, it is now possible to visualize the dynamic history of pharmaceutical product development. The following pages include pipeline snapshots and comparisons for a number of parameters that are of most interest to drug delivery and formulation professionals – Disease Area, Molecule Type, and Delivery Route.

The Research and Preclinical Pipeline Continues to Outpace Clinical Stage Products in Terms of Growth

Pharma Pipeline Product Development, 2015/16 to 2020/21 (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2020/21 pipeline data covers the 12 months ending March 2021.

The constant influx of funding for new companies has fueled a boom in new product development from Research and Preclinical through to all stages of Clinical development. The impact of early stage investments over the past few years is seen in the number of early stage clinical products. This has not yet led to a significant increase in later-stage clinical products. This may be a result of less selective criteria for products to enter early stage clinical development or possibly the simple economics of late-stage development that limit development to only the very best candidates.

The relative ratio of Research and Preclinical products to Clinical Stage products in 2020/21 is 2 to 1, compared with a 1.6 to 1 ratio in 2015/16.

A Surprise in 2020/21 was the Sharp Increase in Clinical Stage Cell Therapy Products

Molecule Type as a Share of All Clinical Stage Products, 2020/21

	Phase 1	Phase 2	Phase 3	Registration	Share of All Clinical Products (2020/21)	Share of All Clinical Products (2015/16)
Small Molecule	51%	61%	66%	73%	57%	62%
Antibody	12%	10%	11%	10%	11%	9%
Protein	6%	8%	7%	7%	7%	10%
Peptide	5%	6%	5%	4%	5%	7%
Cell & Gene Therapy	17%	7%	4%	2%	11%	8%
Oligonucleotide & RNA	2%	1%	1%	0%	2%	2%
Stem Cell	4%	2%	2%	1%	3%	0%
Carbohydrate	1%	1%	2%	1%	1%	1%
All Other	1%	2%	3%	3%	3%	0%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2020/21 pipeline data covers the 12 months ending March 2021.

The increasing lean toward Biologics seen over the past few years continued in 2020/21. For the 12 months ending April 2021, the share of clinical-stage products accounted for by Small Molecules dropped to 57% as compared with 62% in 2014/15. This represented a relatively large drop when compared with the year earlier when Small Molecule products held a 60% share.

A very notable shift was seen in the number of Cell Therapy products identified as in Phase 1, a total of 543 products. Combined with Gene Therapy products, the two accounted for 17% of the Phase 1 product pipeline, significantly exceeding the Antibody product share of 12%. The Gene and Cell Therapy share drops in Phases 2 and 3. It remains to be seen if this large Phase 1 cohort will translate into more later-stage products in the years to come.

Stem Cell products also seem to be in favor as evidenced by a reasonably large bump in Phase 1 products in development. This contrasts with no negligible share for Stem Cell products in 2015/16.

The share of Antibody products in clinical development are up by a third over 2015/16. Clinical-stage Peptide and Protein products are down sharply in terms of share.

RNA and Oligonucleotide products still represent a very small share of the clinical development pipeline, with perhaps some evidence of future increases based on the growth of the Phase 1 product pipeline.

Infectious Disease Products, Unexpectedly Showed the Greatest Increase in Clinical Stage Products

Active Clinical Stage Programs by Disease Area, 2014/15 to 2020/21

	2014/15	2020/21	Change
Cancer	1,642	3,140	91%
Infectious Disease	886	2,073	134%
CNS	686	1,024	49%
Endocrine/Metabolism	519	629	21%
Inflammation/Immune	461	611	33%
Skin Disorders	295	437	48%
Cardiovascular Diseases	306	375	23%
Pain Management	263	317	21%
Respiratory	257	280	9%
Eye Diseases	164	332	102%
All Other	1,103	1,027	-7%
Total	6,582	10,915	66%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2020/21 pipeline data covers the 12 months ending March 2021. (The figures here represent programs rather than products.)

The sharp rise in the Infectious Disease pipeline was unexpected but is not surprising given the attention paid to therapeutics and vaccines for the treatment of COVID-19. Every company it seems dug into their product cupboard to see what might be useful for the treatment of COVID-19. The urgency to develop life-saving therapeutics allowed many companies to enter the clinic with more hope than supporting data. Both prophylactic and therapeutic approaches received considerable attention and investment.

Cancer and Eye Disease programs continued to be a major area of clinical trial activity and investment. The Cancer pipeline increase was largely a result of new molecular strategies being identified and the development of novel molecular motifs to take advantage of these insights.

The increase in the Eye Disease pipeline is a result of increasing needs with an aging population and a relatively attractive reimbursement environment. This is a market that has largely focused on small molecule therapeutics but has now come to embrace the potential of biologics. Non-small products now constitute almost 50% of the Eye Disease clinical pipeline.

Injectables Continue to Take Share from All Other Delivery Routes

Delivery Route Products as a Share of All Clinical Stage Products, 2020/21

	2014/15	2020/21
Injection	46%	51%
Oral	40%	38%
Topical	5%	4%
Ophthalmic	2%	2%
Inhalation	3%	2%
Nasal	2%	2%
Transdermal	2%	1%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). The 2020/21 pipeline data covers the 12 months ending April 2021. (Early-stage clinical programs, notably Phase 1, products often do not provide information regarding Delivery Route. These products are not included in the analysis.)

The continuing adoption of Injection-based products reflects the previously noted shift of the pharmaceutical product development pipeline to Cancer and Infectious Disease products that require more precise dosing and are generally administered in the in-patient setting. The development of patient-friendly injection devices has further extended the use of injectables to more chronic out-patient indications, such as rheumatoid arthritis and multiple sclerosis.

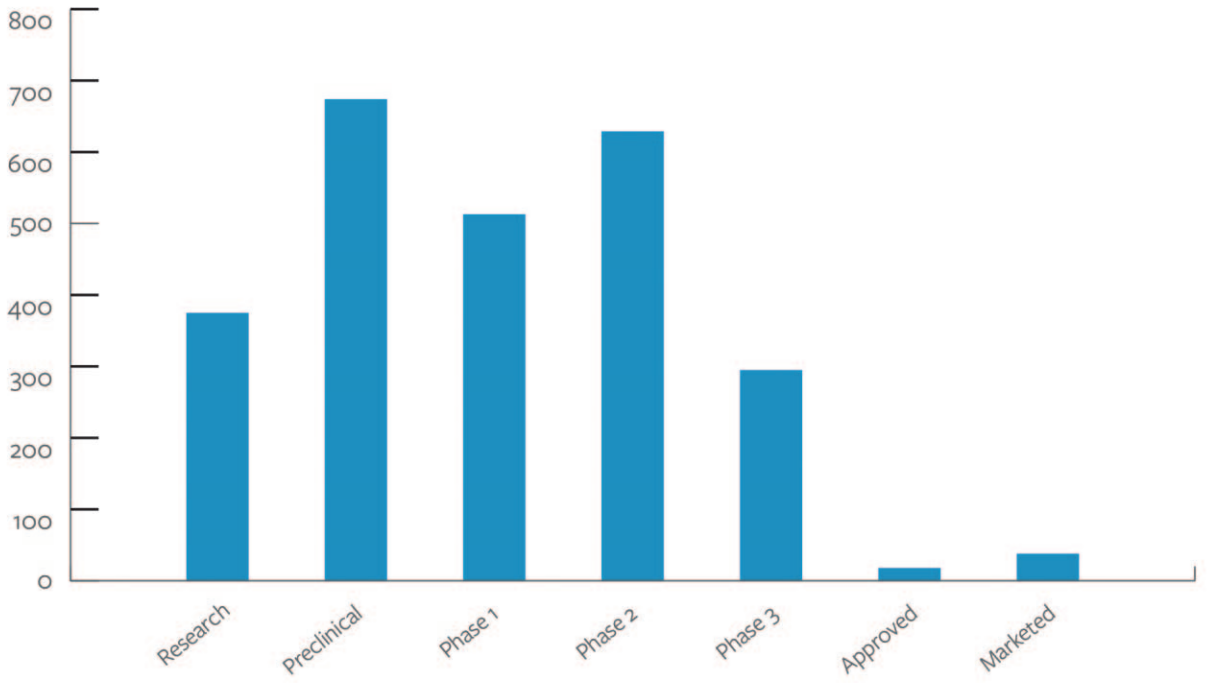
Inhalation has become a less popular route for new product delivery as the number of respiratory product opportunities has decreased. This is partly a result of newer products targeting more severe respiratory conditions with Biologics. The historically important Respiratory indications of Asthma and Chronic Obstructive Pulmonary Disease are now largely managed with inhaled generic products, creating a huge challenge in terms of cost effectiveness for any new inhaled products hoping to address these conditions.

Nasal and Transdermal delivered products face a similar challenge. Generics have captured the previously important therapeutic opportunities suitable for Nasal and Transdermal delivery, and the newer Biologics are not suited for delivery by either route. Historically, these routes have been an important option for the more convenient dosing of small molecules not suitable for Oral dosing.

Oral delivery remains the patient preferred route of delivery. The increasing number of biologics, generally not suitable for oral delivery, is contributing to the decreasing share of oral products in the development pipeline. This trend is likely to continue until some sort of oral enabling or enhancing technology making some of the smaller Biologics reasonable candidates for oral delivery.

COVID-19 Vaccines and Therapeutics - A Robust Clinical Pipeline

COVID-19 Products in Development by Most Advanced Phase



Source: PharmaCircle Pipeline & Products Intelligence Module as of mid-April 2021.

COVID-19 Products in Development by Delivery Route

	Research	Preclinical	Phase 1	Phase 2	Phase 3	Approved	Marketed
Oral	30	83	132	275	153	1	18
Nasal	10	53	26	17	4	1	1
Injection	177	346	277	271	112	16	17
Inhalation	12	40	34	40	13	0	0
Buccal or	0	9	5	4	1	0	1
All Other	5	10	6	1	0	0	1

Source: PharmaCircle Pipeline & Products Intelligence Module as of mid-April 2021. Note: Research and Preclinical stage products may not have disclosed delivery routes.

The COVID-19 development pipeline includes a variety of novel vaccines and therapeutics as well as a number of previously approved products that are being applied to provide supportive treatment. A good example are steroids like dexamethasone that are used with seriously ill COVID-19 patients to manage overactive immune responses.

Unsurprisingly, Injection medications are the most common given that treatment is usually administered in a critical care setting. Both Nasal and Inhalation delivery are being explored as more convenient and efficacious routes to address COVID-19 symptoms at earlier prehospitalization stages of infection.

An overview of the COVID-19 pipeline is available at www.PharmaCircle.com. This includes a detailed summary of therapeutics and vaccines in development as well as ongoing clinical trials along with the latest epidemiology statistics.

Final Thoughts

Beyond the surprises noted earlier with respect to COVID-19 and Cell Therapy products, the pipeline in 2020 developed much as it had for the past decade. Increased investments in emerging companies and novel therapeutic concepts have created a larger research and preclinical pipeline with some spillover seen in the larger Phase 1 product cohort. These investments have not yet impacted the Phase 3 pipeline. All of this is reasonable as approvals and pipelines reflect events and efforts of the past. In this sense, the 2020 pipeline is the result of work and investments in 2019 and before. With the restrictions and refocusing demanded by COVID-19, it is not clear what the future pipeline will look like. Will 2020 be a "dip" a "recession" or a "depression" to use economic terms? Did 2020 provide companies the opportunity to rethink their strategies going forward and reconfigure operations to also meet non-pandemic challenges? Next year's pipeline analysis will provide a sense of how COVID-19 has impacted drug development, but it will still take 3 years or more to properly understand the full impact.

Some additional trends not properly captured in the charts and tables presented in these four articles include:

1. A continued shift to Injectables as a consequence of the focus on Biologics.
2. An expansion of the investment in next-generation Biologics, particularly variations on nucleic acid chemistry and function.
3. CDMO/CMO/CRO further validated their importance to the development of innovator products. Companies small and large are not just contracting out work, they are contracting out responsibility and decision-making to these expert suppliers.
4. Diagnostics are less and less an afterthought or nice to have. Diagnostics are critical to identifying responding patient subpopulations during clinical trials and supporting the mega dollar prices for orphan drug products. As we saw in 2020, the rapid development and deployment of COVID-19 diagnostics was a critical part of the strategy for fighting the pandemic.
5. There is considerable interest and investment in Artificial Intelligence and Machine Learning. The fruits of this investment are yet to be realized. As with many technologies, it can take a decade or more for the benefits of technology to be seen.

An early indicator of the impact of COVID-19 on the pharmaceutical product pipeline will be FDA approvals for 2021. A quick look at FDA approval numbers for "innovative" products (Type1, Type 1,4 and Type 4) at the FDA through mid-May 2021 finds 19 approvals. This compares with 22 approvals the year earlier. These numbers are the tip of the iceberg and too close to draw any conclusions in terms of where the pharmaceutical pipeline might be headed as a result of COVID-19.

We will be back next year with 2021 approval and pipeline information that may help us understand if we experienced a COVID-19 dip, recession, depression, or just business as usual.

About the Authors

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Kurt Sedo earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery. Mr. Sedo's responsibilities with PharmaCircle include oversight of data integrity, product development, project management and customer service. In addition to authoring articles, Mr. Sedo regularly presents overviews of the state of drug delivery and formulation at industry conferences.

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Formulation Forum

Nanosuspension Dosage Forms: Product Development & Scale Up

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

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INTRODUCTION

Nano-formulation of poorly water-soluble drugs has been proven in commercial products to 1) enhance drug dissolution and oral bioavailability, and 2) increase drug loading and release duration for parenteral drug delivery. Preparation of drug nanosuspensions can be top-down, bottom-up, or a combination of both techniques. This month's forum will focus on nanosuspensions prepared via the top-down process, ie, wet milling process.

During the nanosuspension formulation development process, efforts should first focus on screening to identify the lead formulation that generates stable nanosuspensions that achieve the desired drug efficacy and pharmacokinetic properties in animals and humans. Thereafter, the nano-milling process should be optimized to determine the critical process parameters with the aid of factorial design during scale up. Finally, consideration should be made in how the nanosuspensions can be incorporated in the final market image dosage form per the desired pharmaceutical product profiles based on the need of patients and available technologies.

QUALITY TARGET PRODUCT PROFILE OF NANOSUSPENSIONS (QTPPS)

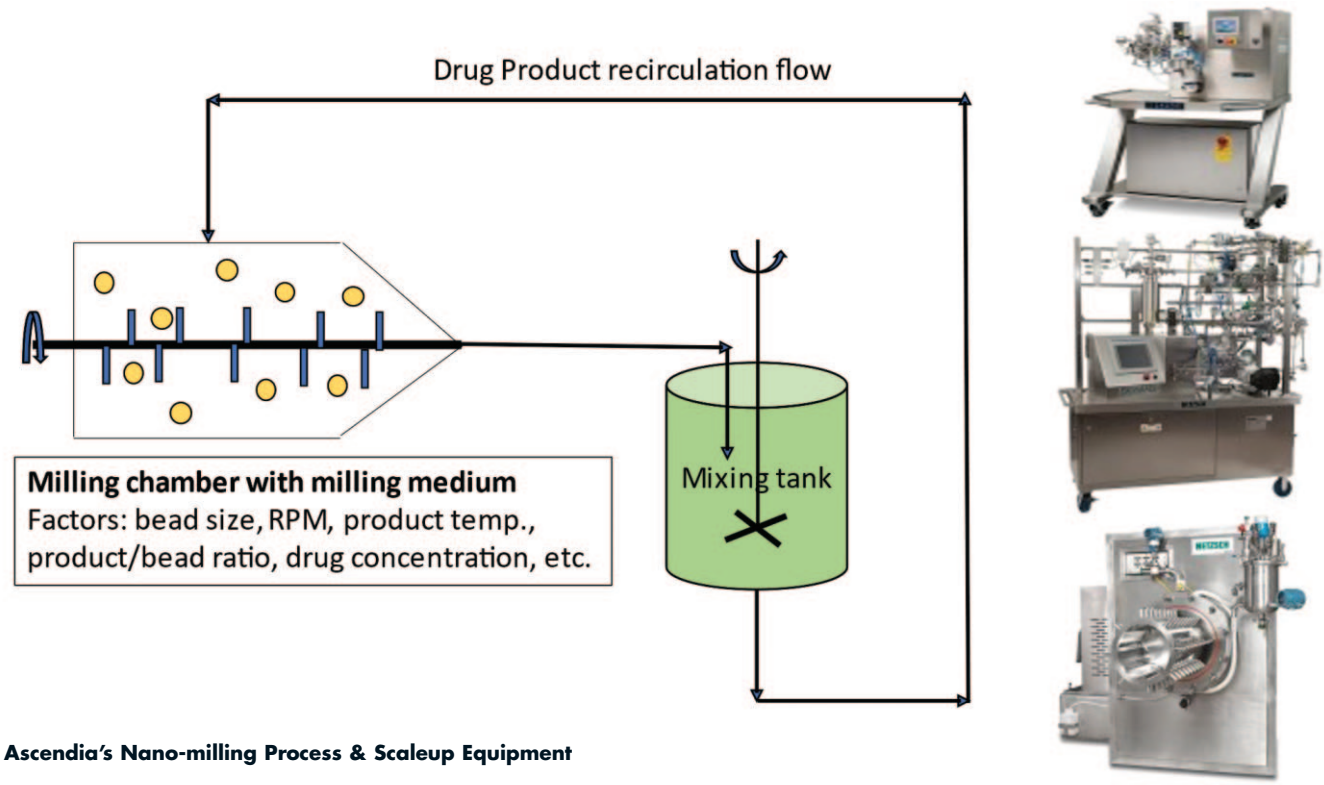
A Target Product Profile (TPP) is a planning tool for therapeutic candidates based on FDA guidelines. Based on the relationship between

TABLE 1

QTPPs	Target	CQAs
Target Patient Population	<16 years old by IM route	Product excipients selection and administration method should be suitable for pediatric application
Product PK Profile	4 weeks long-acting injection	Target dose, Pharmacokinetic parameters (T_{max}, C_{max}, C_{min}, AUC); drug absorption rate
Dosage Form	Sterile suspension	Assay, impurity level, CU, ID, and others required by USP <1> injection: Injections and Implanted Drug Products (Parenteral) — Product Quality Tests
Microbial Attributes	Sterile and low endotoxin level	Product sterility and endotoxin level, container/closure integrity, and initial bioburden and endotoxin level for API and excipients
Product Properties	Robust formulation and manufacturing process	In process for assay, CU, and particle size distribution; finished product release testing for drug assay/related substance, CU, particle size distribution/zeta potential, osmolality, re-suspendability, viscosity; particulate matter, drug solid form, in vitro drug release, sterility, endotoxin, and appearance
Stability	Stable at least 18 months at target storage conditions and at least 6 months at accelerated storage conditions	Assay/related, sterility, container/closure integrity, drug particle size distribution/zeta potential, viscosity, re-suspendability, particulate matter, drug solid form, in vitro drug release, sterility, endotoxin, and appearance

Nanosuspension Quality Target Product Profiles

FIGURE 1



Ascendia's Nano-milling Process & Scaleup Equipment

product quality attributes and product safety and efficacy profiles, a Quality Target Product Profile (QTPP) should be determined to define the desired profiles of the finished product and Critical Quality Attributes (CQAs). Below is an example of QTPPs and CQAs for a sterile nanosuspension dosage form.

FORMULATION DESIGN OF NANOSUSPENSIONS

Successful nanosuspension formulation development depends on careful evaluation of compound physical chemical and biopharmaceutical properties, such as solubility, pKa, solid surface properties, permeability, meting point, and crystal lattice structure. A good candidate for nanosuspension has the characteristics of BCS Class II compounds: low solubility, high melting point, high permeability, and a strong tendency of food effects. A formulation screening study is usually conducted under a small scale to find the suitable stabilizer(s), ie, a polymer, a surfactant, or a combination of polymer/surfactant for the nanosuspension. Different surface properties of API, such as surface charge, hydrophobicity, functional groups responsible for ionic, hydrogen bond, and Van der Waal interactions, may demand different types and levels of stabilizers. The performance of nanosuspensions should be confirmed by *in vitro* studies, such as stability, re-dispersibility, and *in vivo* performance in animal models.

Selection of stabilizer(s) is crucial for nanosuspension formation and stability, which should be the first step in the development of the nanosuspension product. The stabilizer can help prevent drug particles aggregation during milling and storage, and to stabilize the freshly created surfaces during the milling process. Factors such as stabilizer(s), milling speed and time, temperature, drug loading, bead size, and ratio of drug suspension to the milling medium, etc, play a significant role in the particle size distribution of the milled suspension. Stabilizers can stabilize drug suspension by a mixture of a polymer, ie, steric stabilizer (Poloxamer, PVP, HPC, PVPVA, PEG, etc), and an ionic/nonionic surfactant, ie, electrostatic stabilizer (Tween, SDS, sodium deoxycholate, Pluronic, etc).

QBD DESIGN IN PROCESS DEVELOPMENT

Figure 1 show a typical nano-milling process and scale up equipment utilized by Ascendia. The transfer of laboratory results for nano-milling from labs to production scale requires understanding of the critical process parameters, such as the specific energy input, stress energy of the grinding media, stress coefficient and residence time distribution. The product of stress number and stress energy is proportional to the specific energy input. When

scaling up is performed, formulation variables and process parameters, which may have a significant impact on the nanosuspension production, are drug loading, stabilizer level, milling speed, time, temperature, grinding media size and density, suspending vehicle viscosity, ratio of the volume of formulation to grinding media, percentage fill of milling chamber, etc.

Preliminary formulation screening studies are often conducted in a lab milling system that has a different design from that of the scale up, which could result in different milling efficiency. Studies indicate the size of the grinding media, the peripheral speed of the agitator, and the density of the grinding media has a major impact on wet-milling in an agitator bead mill (literature information from NETZSCH-Feinmahltechnik GmbH). Kwade defined the stress energy of the grinding media as a function of grinding media density (ρ_{GM}), grinding media diameter d_{GM}, and agitator peripheral speed (Vt). (A. Kwade Autogenzerkleinerung von Kalkstein in Rührwerkmühlen. Dissertation, TU Braunschweig, 1996, ISBN 3-8265-2082-3).

$$E_{kin} \propto SE_{GM} = d_{GM}^3 \cdot \rho_{GM} \cdot v_t^2$$

Kwade showed that with a constant specific energy input, there is an optimum stress energy in which the smallest product median particle size is achieved (Figure 2, adapted from Kwade's paper).

SUMMARY

For drug nanosuspensions, parameters like stabilizer concentration, drug loading, milling speed, milling time, bead diameter/density, temperature, amount of beads versus drug product, etc, are important formulation and process variables. Critical process parameters (CPPs) that impact nanosuspensions' critical quality attributes should be identified by means of a DOE design. The ranking of CPPs impact on CQAs may change as a result of a change in milling design during the scale-up process. It is important that a design space of the CPPs be defined during the scale-up process in order to achieve a robust formulation and manufacturing process. ◆

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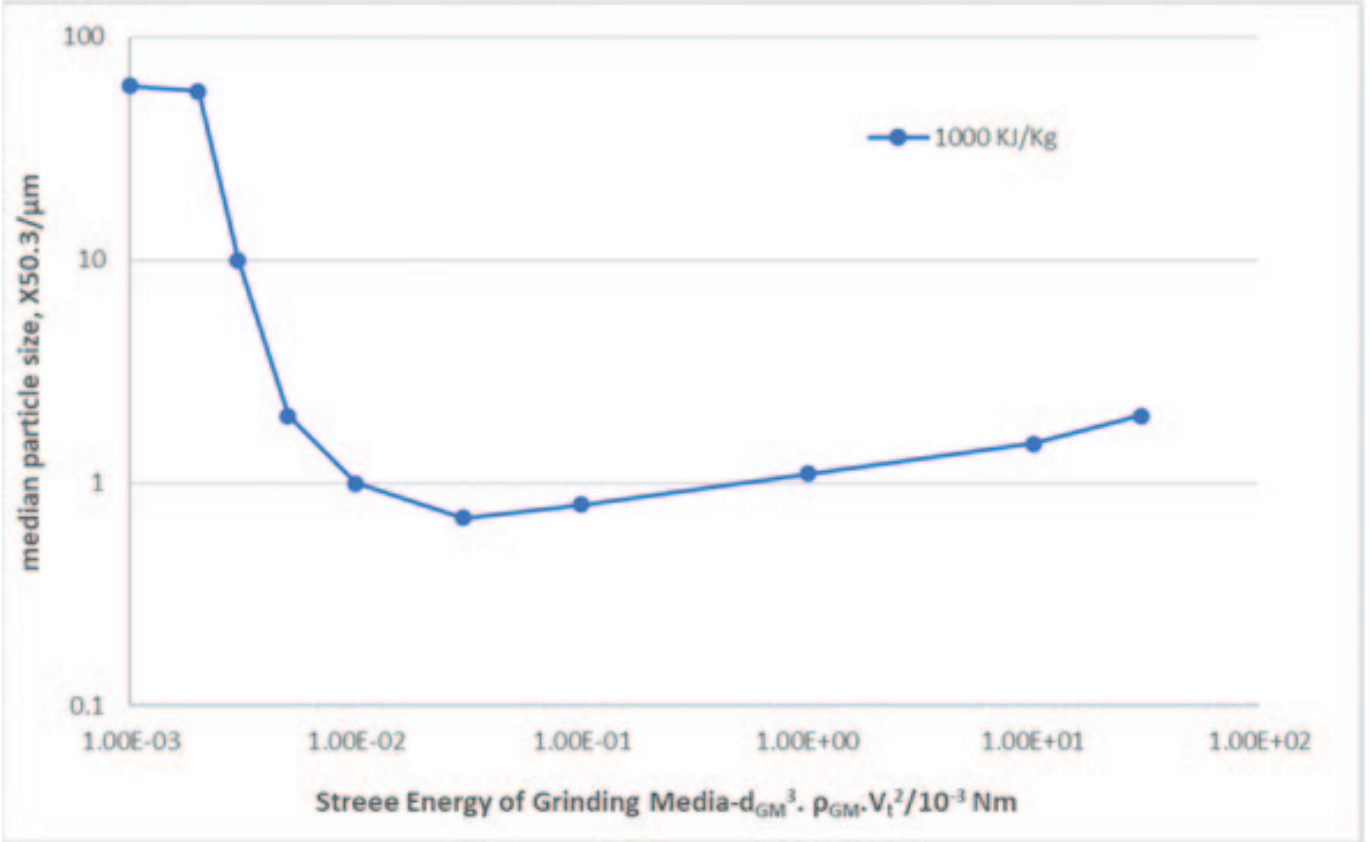
FIGURE 2



Under a constant specific energy input, median particle size as a function of the stress energy of the grinding media.

OPEN INNOVATION PLATFORM

Beyond the Rule of Five: Scouting for Novel Formulation Approaches to Enable the Subcutaneous Application of Molecules With Poor Drug-Like Properties in Preclinical Research – Facilitated Through opnMe.com

By: Ines Truebenbach, PhD; Menorca Chaturvedi, PhD; Markus Koester, PhD; and Achim Grube, PhD

INTRODUCTION

bRo5 (beyond Lipinski's rule of 5) compounds, like PROTACs, offer novel opportunities for drug discovery to address difficult or previously undruggable targets. Nevertheless, these molecules often have poor drug-like properties, such as low permeability, low aqueous solubility, and are therefore difficult to access via oral administration. Other routes of administration have been explored in preclinical drug discovery to enable the evaluation of a molecule's PK, efficacy, and safety profile without optimization of the compounds' properties. The subcutaneous administration route is often chosen as an alternative. Even though the subcutaneous application route has immense potential in the preclinical context, there are only a few well-described formulation options or excipients available.

Based on the success of a recently completed open innovation challenge in drug delivery,[1] we have decided to use Boehringer Ingelheim's portal, opnMe.com, once again: We invite scientists from around the world to submit their innovative and even unconventional ideas to tackle this fundamental challenge.

We are looking for proposals that would provide innovative formulation approaches to facilitate the subcutaneous application of bRo5 molecules in a preclinical setting.[2] As an incentive to submit proposals, we provide all selected applicants with access to an unprecedented selection of novel bRo5 compounds. Additionally, successful applicants will have the opportunity to directly interact with scientific experts to establish successful collaborations.

Here, we provide a short overview of the bRo5 compound class from a formulation developer's perspective. Further, it will provide insights into the opnMe call and how we plan to incentivize innovative drug delivery solutions.

BACKGROUND

Developed in the 1990s, Lipinski's rule of five (Ro5) was an attempt to rationalize compound design in preclinical research. The set of rules concerning a molecule's physicochemical properties state that poor oral absorption or permeability are more likely when a molecule exhibits the following characteristics: >5 hydrogen bond donors, a molecular mass > 500, calculated logP is > 5, and a sum of nitrogen and oxygen atoms greater than ten.[3] Today, there is an increasing focus on less druggable targets, such as the disruption of protein-protein interactions (PPI), that offer high potential for the development of new therapeutic agents and may require beyond rule of 5 (bRo5) chemical matter.[4] In 2020, 31% of all approved NCEs failed to meet Lipinski's criteria.[5]

"Recently, we have reported on the successful completion of an open innovation challenge in the context of drug delivery.[1] The overall success has surpassed our internal expectations and therefore, we decided to launch the next project."

There is great therapeutic potential in the bRo5 chemical space. PROtelolysis Targeting Chimeras (PROTACS) have attracted great attention both from academia and industry. PROTACs regulate protein function by degrading target proteins instead of inhibiting them, providing more sensitivity to drug-resistant targets and a greater chance to affect the non-enzymatic functions. PROTACs have been proven to show better selectivity compared to classic inhibitors.[6] A challenge for preventing PROTACs from realizing their therapeutic potential is their lack of compliance to the Ro5. *In vivo* studies reported with PROTACs in peer-reviewed literature have typically been performed through parenteral delivery rather than oral administration.[7]

bRo5 compounds typically have poor physicochemical, drug metabolism, and pharmacokinetic properties, such as high lipophilicity, low solubility, low permeability, and high metabolic clearance. For these molecules, it is a challenge to achieve the desired exposure via the p.o. administration route.[8] Other routes of administration have been explored in preclinical drug discovery to enable the evaluation of a molecule's PK, efficacy, and safety profile. The subcutaneous administration route is often chosen as an alternative as it offers several advantages. Absorption upon subcutaneous administration is normally rapid because the subcutaneous space is richly proliferated with blood vessels. The area is easily accessible, and many sites of injections are available.[9,10]

The subcutaneous route is amenable to different formulation principles, e.g., suspension and solution formulations, minipumps, or extended-release formulations like PLGA-microparticles.[11] The choice of formulation type can play a major role when evaluating the *in vivo* profile of a compound during drug discovery. Reaching a constant and/or maximum exposure is critical when assessing the pharmacokinetic, pharmacodynamic, and safety profile of a molecule. While subcutaneously applied suspension formulations typically yield an extended-release profile, solution formulations target high compound exposures. The subcutaneous delivery of bRo5 molecules comes with a set of challenges. Due to their lipophilic nature, the development of a solution formulation is difficult. For all preclinical *in vivo* models, there are tolerability constraints in terms of maximally tolerated amounts of excipients, like co-solvents or complexation agents.

opnMe PLATFORM TO INCENTIVIZE INNOVATION

The prospect of open innovation is to gather out-of-the-box ideas beyond existing networks. The Molecules for Collaboration program on opnMe.com offers the opportunity to initiate joint research projects. One successful example for a recently completed project was launched in October 2020. By the submission deadline on December 17, 2020, 73 scientists worldwide submitted proposals on novel strategies to tackle a major problem in pharmaceutical research, namely poor solubility. Eventually, 20 high-quality projects were selected to obtain access to our unique molecules.[1]

In our upcoming call, we are looking for suitable subcutaneous formulation approaches that could potentially enable the early phases of drug discovery for bRo5 molecules. We invite researchers and technology developers to submit proposals that would provide innovative formulation approaches for the subcutaneous administration route in a preclinical setting, to enable subcutaneous formulations of bRo5 molecules for preclinical PK, PD, and safety studies.

As an incentive to submit proposals, we provide all selected applicants with access to an unprecedented selection of novel bRo5 compounds, covering a diversity of structural classes (e.g., PROTAC) and potential therapeutic mechanisms. We expect that this collection will provide high value to test your formulation technologies with the most recent and innovative molecules. These structurally diverse molecules also come with additional internal data (Table 1) characterizing the molecules' physicochemical properties, like lipophilic-

TABLE 1

Drug Target	ACB1 PROTAC	LFA1	MDM2::p53	HCV Protease	HCV Protease
Comment	weak base	weak base	acid	zwitterion	weak base
Mol weight [g/mol]	936.1	646.5	593.4	815.8	843.0
# H Acceptors	11	6	6	10	11
# H Donors	5	2	2	4	3
$logP/D_{pH7.4}$	6.4	3.8	6.3	5.6	3.7
SOL in aqueous buffer pH 2.2 [mg/mL]	>1	0.06	< 0.001	0.03	0.003
SOL in aqueous buffer pH 4.5 [mg/mL]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
SOL in aqueous buffer pH 7.4 [mg/mL]	< 0.001	< 0.001	0.04	0.03	< 0.001
SOL in EtOH [mg/mL]	> 10	3.7	> 10	8.3	9.8
SOL in Acetone [mg/mL]	8.1	0.5	> 10	2.8	> 10
SOL in ACN [mg/mL]	> 10	0.4	> 10	9.4	9.2
SOL in DMSO [mg/mL]	9.5	9.2	> 10	0.4	8.6
SOL in DCM [mg/mL]	> 10	4.2	> 10	> 10	> 10

EtOH: Ethanol, ACN: Acetonitrile, DMSO: Dimethyl Sulfoxide, DCM: Dichloromethane

ity (log P/D7.4) and solubility over a wide pH range. Additionally, all criteria are listed that assign a compound to the bRo5 chemical space (number of H-bond donors and acceptors, molecular weight). Each compound exhibits at least one violation to Ro5. Solubility in organic media is often a prerequisite for application of formulation technologies and therefore, is vital information to formulation developers.

All compounds were designed for recent, disease-relevant targets, some of which are highlighted in more detail below:

- ACBI1 causes degradation of the BAF chromatin remodeling complex proteins SMARCA2 and SMARCA4, as well to a lesser degree PBRM1. The compound is a PROTAC (proteolysis-targeting chimera) that induces degradation of its targets via inducing the formation of a triple complex of the target, the PROTAC, and the E3 ligase VHL, resulting in target ubiquitylation and proteasomal degradation.

- HCV NS3 protease is a 180-amino acid chymotrypsin-like serine protease. It is an essential component of HCV replication and infectivity. The NS3 protein contains two functional domains: a serine protease and a helicase domain. Both HCV compounds which are offered as part of this call bind to the active site of NS3 that is located in the shallow and broad protein-protein interaction surface of the protease and the helicase domain of the enzyme and are nanomolar to picomolar inhibitors of protease activity and of viral replication for various HCV genotypes and for resistant mutants D168V and R155K. Boehringer Ingelheim was the first company to establish proof-of-concept in humans for an HCV NS3 protease inhibitor as a treatment of HCV infection.

PROPOSAL SUBMISSION & TERMS FOR COLLABORATION

As part of this latest call for research proposals in the field of formulation research, we are open to all applications if they arrive by July 29, 2021, 11:59 PM PST. Our internal review process will commence in August 2021 and will be finalized until end of September 2021. The winners will then be notified, and collaboration work will commence in Q4 2021 or Q1 2022. Please refer to opnMe.com for more information, including detailed information on the call for proposals and the success criteria.[2]

As an incentive, selected project teams will be provided with suitable amounts of the molecules to facilitate their research and/or to validate your new proposed technology. We expect to provide quantities, which are typical for early drug discovery phases (up to 200 mg initially) of each drug substance completely free-of-charge. With the provided compounds, we aim to create a new way to help scientists validate their formulation approaches and to publish their data to advance scientific knowledge. Furthermore, we are transparent about the rights and obligations of the researchers who approach the portal to submit their innovative ideas, especially with regard to intellectual property, which will remain with the scientist.

Successful applicants will have the opportunity to directly interact with scientific experts and leaders in drug delivery at Boehringer Ingelheim to share information and to discuss additional guidance or resources needed to maximize the potential of the work. Additional support could include provision of additional molecules, *in vitro* and *in vivo* assessments, access to state-of-the-art analytical methods, as well as the possibility of site visits to the Boehringer Ingelheim facility in Biberach, Germany.

SUMMARY

bRo5 compounds have a tremendous impact on the treatment of diseases with high unmet medical needs such as cancer. Thus, there has been increased interest in the discovery and development of bRo5 drugs in the pharmaceutical industry. Due to their poor physicochemical properties, such as low solubility and high lipophilicity and their poor permeability, the investigation of bRo5 chemical matter is fraught with risk and uncertainties.[4]

Already in the early stages of drug discovery, the successful formulation of bRo5 compounds for preclinical studies, such as PK, PD, and safety investigations, is challenging.

Boehringer Ingelheim's opnMe.com platform incentivizes fundamental research and advances the translation of important new concepts into practical approaches. The current opnMe.com call for proposals is an opportunity for researchers in the field of formulation development to test their innovative ideas and approaches for subcutaneous drug formulation on a unique set of structurally diverse bRo5 structures from current research projects, e.g., a PROTAC.[2] Additionally, we hope that this call will facilitate active collaboration and the pragmatic implementation of innovative drug delivery solutions.

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BIOGRAPHIES

Dr. Ines Truebenbach is a Head of Laboratory in the Drug Discovery Sciences (DDS) CMC group in Research at Boehringer Ingelheim. She is currently responsible for the delivery of high-quality and innovative formulations for preclinical PK and PD studies, which enable tailor-made exposure studies for various applications. Her areas of expertise include formulation development for new molecular entities (NMEs), like peptides, oligonucleotides, or bRo5 molecules (PROTACs). She joined Boehringer Ingelheim in 2019 after earning her PhD in Pharmaceutical Biotechnology.

Dr. Menorca Chaturvedi is a Senior Scientific and Digital Manager at Boehringer Ingelheim. She is currently responsible for the scientific alliance management activities for opnMe.com. opnMe collaborates with Boehringer Ingelheim scientists across different therapeutic areas and countries, to present innovative scientific challenges via the opn2EXPERTS and Molecules for Collaboration programs. Prior to joining Boehringer Ingelheim in 2021, she worked on different research and digital projects across academic and non-profit organizations.

Dr. Markus Koester is a Director of Discovery Research Coordination Germany at Boehringer Ingelheim. He leads the global digital communication and portal activity of Boehringer Ingelheim's open innovation platform, opnMe.com. opnMe was launched in 2017 with a Molecules to Order initiative. It now offers 57 molecules to order and received more than 1,000 orders from 60 countries around the world. In addition, with its two collaboration programs, Boehringer Ingelheim has received more than 1,000 research proposals by now. Prior to joining the company, he worked for Merck KGaA and two biotech start-ups. Overall, he gained more than 20 years of pharma experience in roles ranging from R&D to commercial.

Dr. Achim Grube is a Director of Drug Discovery Sciences (DDS) at Boehringer Ingelheim and leads the DDS-CMC group. The core mission of the group is the physicochemical characterization, solid form finding, and preclinical formulation development and manufacturing of new chemical entities from the early research phase to start of development. He has worked at Boehringer Ingelheim for more than 10 years with experience managing analytical and product development, drug delivery, and preformulation. He has diverse experience with a broad range of delivery systems and various routes of delivery.

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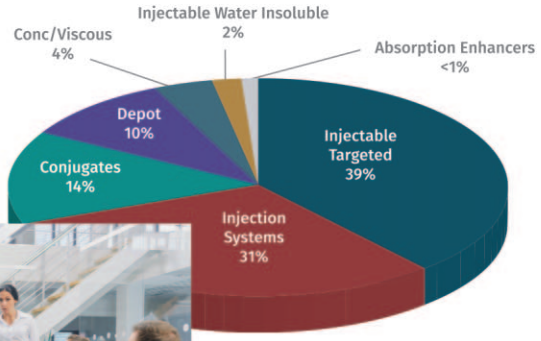
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
SODIUM STEARYL FUMARATE **(Core/Content)**	29.29 mg
COLLOIDAL SILICON DIOXIDE **(Core/Content)**	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



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

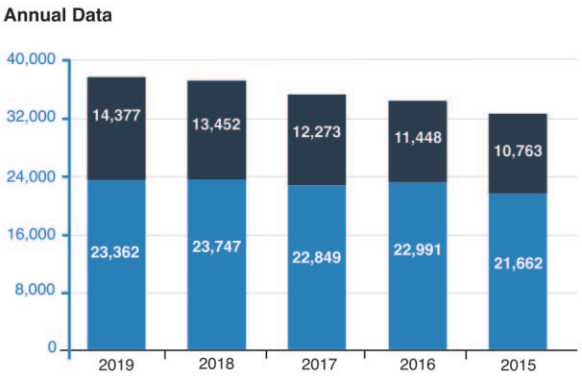
Select Companies

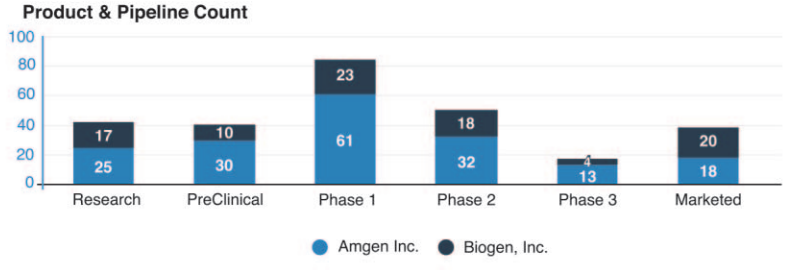
Amgen Inc. x

Biogen, Inc. x

Attribute Type

- Gross Profit
- Net Income
- Number of Employees
- Operating Income
- Research and Development Expenses
- Sales, General and Admin. Expenses
- Total Assets
- Total Current Assets
- Total Current Liabilities
- Total Equity
- Total Liabilities
- Total Revenue





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WEARABLE PLATFORM

Next-Generation Wearable Drug Delivery: Prefilled Devices Provide a Truly Patient-Centric Solution

By: Mindy Katz

A SHIFTING HEALTH LANDSCAPE

Recent technological and biotech developments are changing how we take medications, as well as the types of drugs we take. This has been particularly noticeable with the increasing introduction of new biologic and biosimilar medications, designed to better manage chronic and high-burden diseases. Composed of larger volumes and higher viscosities than small-molecule injectable drugs, these new medications require alternative methods of delivery.

Concurrently, the continued move toward value-based care is placing increasing emphasis on the patient experience, while mounting healthcare costs are encouraging pharmaceutical companies to develop solutions that better address the needs of both patients and healthcare providers. Meanwhile, the general trend toward home care and self-administration as a more effective

FIGURE 1

"Eitan Medical - Sorrel recognized that the first challenge to overcome would be the development of a reliable, controlled, and accurate delivery system. Due to the vast range of injectable medications already available – some requiring a controlled, variable, and accurate dosing regimen, while others rely on a fast bolus injection – it was imperative for Eitan Medical - Sorrel to ensure its technology could accommodate the wide array of current and emerging medications."

way for patients living with chronic diseases to manage their conditions has highlighted the need for patient-centric solutions to encourage adherence to treatment routines.

Finally, the ongoing COVID-19 pandemic – which has led to many routine treatments being postponed, particularly for immunocompromised patients – has highlighted the need for patient-centric solutions that enable patients to self-administer medication safely and efficiently at home. In many ways, COVID-19 has served as a catalyst for innovation in healthcare, accelerating the introduction of new technologies that will long outlive the pandemic.

THE MARKET AT A GLANCE

The wearable injectors market is expected to increase at a compound annual growth rate of over 25% over the next decade, with a number of key factors driving this growth, including the following:

1. An increase of chronic diseases – approximately 50% of all adults in the US are currently living with long-term clinical conditions, placing higher burdens on health systems and providers.
2. The rising costs of healthcare – and growing recognition of how home care and patient self-administration can result in significant savings by reducing the number of hospital admissions and improving patient recovery times.
3. The need to improve medication adherence – and how intuitive and easy to use home-based administration devices, with connectivity features that enable real-time patient engagement, can improve therapy adherence and treatment outcomes.

The changes that these driving factors bring to the healthcare market set Sorrel on the path to develop a true solution for wearable drug delivery devices.

ADDRESSING THE MARKET'S NEEDS

Sorrel is a medical device product line owned by Eitan Medical. Based in Israel, the epicenter of healthcare innovation, Eitan Medical's track record includes the development and commercialization of the Sapphire infusion system, an infusion pump platform poised for both the hospital and homecare markets, distributed in over 25 countries.

While researching the wearable drug delivery market, Eitan Medical - Sorrel found the broad experience and multidisciplinary expertise accumulated across its R&D, regulatory, quality, and manufacturing teams to be an excellent fit to address the particular needs and challenges of the wearable drug delivery market.

Reliable, Controlled & Accurate Delivery

Eitan Medical - Sorrel recognized that the first challenge to overcome would be the development of a reliable, controlled, and accurate delivery system. Due to the vast range of injectable medications already available – some requiring a controlled, variable, and accurate dosing regimen, while others rely on a fast bolus injection – it was imperative for Eitan Medical - Sorrel to ensure its technology could accommodate the wide array of current and emerging medications.

To that end, an electromechanical pumping mechanism was designed that allows a wide range of flow rates and ±5% accuracy, giving the platform inherent accuracy and the crucial adaptability required for medications requiring lower rates and accurate deliveries, as well as those requiring bolus injections. By selecting only established and trustworthy com-

FIGURE 2

ponents for its pumping mechanism, Eitan Medical - Sorrel was able to secure the reliability that it targeted.

Primary Container Agnostic for a True Platform Solution

A variety of parameters affect the choice of volume, material, and manufacturer of a primary container for a specific medication, which is generally the choice of the pharmaceutical company. Formulation, chemical interactions, business partnerships, and cost are all part of the equation when it comes to selecting a container closure system.

Eitan Medical - Sorrel's goal was to allow pharmaceutical partners the freedom to utilize a variety of drug reservoirs, whether vials or cartridges, with a technology specifically designed with the flexibility to allow its partners to incorporate the primary container of their choice. Being able to accommodate a wide range of volumes, ranging from 1 mL to 25 mL, the device platform can be easily customized to fit multiple products in a pharma company's pipeline.

This required decoupling the pumping mechanism from the primary container to provide the necessary flexibility. The platform can therefore be customized to suit the different dimensions of any primary container, with only minor design changes.

HARNESSING TECHNOLOGY FOR PATIENT CENTRICITY

It is imperative to create the best possible user experience for self-administering patients. A simple user interface allows for a positive experience that lowers the occurrence of use errors and promotes greater adherence to treatment. Eitan Medical - Sorrel therefore designed a device platform that is intuitive and easy to use, requiring as few steps as possible from the patient. As a combination product, patients can receive the drug-device system as a single unit, prefilled and preloaded with medication. The user only needs to remove the device from its packaging, peel the adhesive liner, adhere to the body, and initiate treatment.

UV-LED for Disinfection at Point-of-Care

A fundamental challenge in the development of prefilled and pre-loaded devices involves the process of integrating the primary container (filled via an aseptic drug filling process) and the drug delivery device (assembled and then sterilized) in a way that guarantees a disinfected fluid path from medication to patient. The requirements for addressing such a challenge would be to ensure a cost-effective solution without the need for user intervention, all while causing minimal disruption to established pharma processes. Current standard practice of manually swabbing the primary container septum with ethanol prior to loading it into the device does not allow for the desired pre-loaded and easy-to-use wearable solution. Meanwhile, creating a microorganism-free fluid path for a pre-loaded solution can require making significant changes to established pharma processes to accommodate proprietary primary containers that contain the entire fluid path, or the loading of a primary container into the device under aseptic conditions.

Seeking a solution that allows prefilled primary containers to be assembled into devices either at the pharma company, a contract manufacturer, or in Eitan Medical - Sorrel's own facilities, led to the development of a UV-C LED technology for disinfection at point-of-care, enabling a prefilled and pre-loaded device configuration through the use of standard containers without interference to existing drug filling lines. This method results in automatic, verified, and controlled local disinfection at the point-of-care. As with all components within the system, the UV LED is widely available, time- and scale-tested, and cost-effective for a disposable device. This enables Eitan Medical - Sorrel to deliver optimized product configurations for

the end-user while also adapting to pharma practices.

Smart Sensing

As a result of the growing trend toward home care and self-administration, patients are increasingly dependent on their devices, while physical interaction with healthcare professionals is diminishing. It is therefore vital that devices enhance the user experience – notifying, prompting, and providing the confidence necessary for successful self-administration. To that end, all Eitan Medical - Sorrel devices incorporate a blend of integrated smart sensors – combined with visual, audio, and tactile indicators – to clearly communicate the device status to the user and guarantee a successful administration.

Sensors detect air and occlusion, delivering alerts according to pre-defined parameters. A dedicated sensor ensures that the delivery will not begin until the device has been firmly adhered to the skin, while additional internal sensors detect needle positioning and device temperature. A series of internal system checks ensure the device is functioning correctly prior to initiating the treatment. This is achieved through integrating sensors with smart algorithms, when necessary using one sensor for multiple purposes.

Connectivity

Recent years have seen greater emphasis being placed on digital health, and connectivity of medical devices has subsequently become a key focus. The power of connectivity can be harnessed in a variety of ways, largely to promote patient engagement and adherence to therapy. The recent COVID-19 pandemic has highlighted the need to keep individuals who do not require hospitalization out of hospitals, mitigating infection rates, and avoiding health systems being overwhelmed with patients. This dynamic has added greater urgency for effective solutions that enable patients to remain home while ensuring they still receive optimal care and attention.

The Eitan Medical - Sorrel devices are designed with full connectivity in mind, with both Bluetooth and near field communication (NFC) capabilities built-in, enabling connectivity via two widely accepted and secure routes of communication. Patients will thus be able to share their treatment data with caregivers, healthcare providers, and other stakeholders. Care teams can also monitor patients discreetly outside of hospital settings to ensure they are keeping to their therapy routines without disrupting their daily lives. For use in clinical trials, Eitan Medical - Sorrel developed a dedicated smartphone application that enables easy sharing of treatment reports during investigational use.

MOVING FORWARD

With increasingly positive expectations for the wearable device market to provide an intuitive and user-friendly drug delivery experience to patient populations, Eitan Medical - Sorrel continues to optimize its wearable platform solution, investigating new technologies and processes to improve the offerings for both patients and providers. In July 2020, the company opened new manufacturing and cleanroom facilities to increase efficiencies and manufacturing capacity. The state-of-the-art facility is enabling Eitan Medical - Sorrel's transition from initial design and development, with low-volume manufacturing, to scalable high-quality production of wearable drug delivery devices to meet the needs of numerous global pharmaceutical partner programs. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Mindy Katz is Vice President, Marketing and Alliance Management at Eitan Medical where she heads the company's alliance management, marketing, and product management activities for the Pharmaceutical Solutions business unit. Mindy's involvement in the company's early days influenced Eitan Medical's decision to pursue the wearable drug delivery market, resulting in the development of the Sorrel™ wearable drug delivery platform.

To date Ms. Katz held a number of positions within the group, including serving as VP Marketing and Director of Product at Sorrel Medical, and prior to that as Program Manager at Q Core Medical, where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. She holds a BSc in Biomedical Engineering from the Technion – Israel Institute of Technology.

Drug Development
EXECUTIVE

Paul Shields, PhD

Chief Operating Officer

Enteris BioPharma

Enteris BioPharma: How to Build a Preferred CDMO Partner

Since its founding in 2013, Enteris BioPharma, a clinical-stage biopharmaceutical company based in Boonton, NJ, has grown into an important player in the drug development and delivery market by utilizing its proprietary drug delivery technologies, Peptelligence® and ProPerma™, to develop and produce oral formulations of BCS class III and IV compounds, including peptides, peptidomimetics, and small molecules. These pioneering platforms hold the potential to radically alter treatment paradigms. Many of these drugs can only be administered parenterally due to poor oral bioavailability, which can limit market opportunities for the drug maker and reduce patient compliance with treatment regimens. In addition to its proprietary technology, Enteris is also investing heavily in its contract development and manufacturing capabilities, which have evolved into a key pillar of the company's business strategy.

Recently, Enteris completed a major expansion project at its 32,000-sq-ft manufacturing facility, providing the company with the wherewithal to take clients from the laboratory bench through commercial launch. The unveiling of its new and improved CDMO operations marks a major milestone for Enteris and is no small accomplishment given that the company completed the construction despite the disruptions brought on by COVID-19. *Drug Development & Delivery* recently interviewed Dr. Paul Shields, Chief Operating Officer of Enteris BioPharma, to discuss the changing face of the CDMO industry and how Enteris plans to leverage its newly expanded CDMO operations to take advantage of a variety of growth opportunities to build deeper partnerships.

Q: What role does contract development and manufacturing play in Enteris' business strategy?

A: I cannot overstate the importance of our CDMO operations to the future of Enteris. The backbone of our business has been partnering with pharmaceutical companies to use our core Peptelligence and ProPerma drug delivery technologies to design and advance oral tablet formulations of peptide or BCS class II, III, and IV small molecule products, and this has not changed. Yet the specific expertise needed to successfully develop and manufacture these oral formulations is every bit as valuable as the technology itself.

Contract manufacturing has been a key source of revenue for Enteris, yet we are only now about to begin to realize its full potential. Enteris recently announced the expansion of its Boonton, NJ, manufacturing facility and the launch of its CDMO business segment, providing custom solutions to the formulation, development, and manufacturing of solid oral doses for difficult-to-formulate BCS III and IV compounds, including peptides and highly potent compounds. Enteris now provides bench-to-market development services, including the development, manufacture, testing, and release of Phase 1 to Phase 3 clinical trial supplies, as well as commercial production. We believe this will bolster our strength as a development partner and play a key role in our ongoing business development efforts. To be sure, near- and medium-term licenses involving Peptelligence and ProPerma are expected to bring lucrative upfront, milestone and royalty payments. These partner programs, however, also have the potential to generate development and manufacturing revenue that will fuel future growth and enhance our value as a company.

Q: How does Enteris' CDMO capabilities add to the company's strength as a development partner?

A: The formulation, development, and manufacturing of oral, peptide-, and small molecule-based drugs is a tricky business and requires specific skills and expertise. Enteris provides total integrated CMC service support, including preformulation, formulation, analytical research and development, quality assurance, and clinical and commercial manufacturing of solid, oral dosage formulations while keeping our partners' product vision the highest priority. As such, we are uniquely positioned within this niche with the capabilities and expertise to meet an array of development and manufacturing needs under a single roof, which can save our clients time and money.

The idea of a CDMO as a one-stop-shop has been a growing trend in the industry, and for good reason. When pharmaceutical companies work with multiple contract services organizations during the drug development and manufacturing process, it can cost them in terms of money, time, and risk. Projects can become difficult to manage, whereas if the majority of the work is handled in one place, information flow improves, and it alleviates concerns about time and risk mitigation. This can be especially important when transferring between late-stage clinical to commercial production. While some CDMOs have the capability to manufacture clinical trial materials up through Phase 1 or Phase 2, transferring a complex formulation to another CDMO can prove costly and time consuming. With our expanded CDMO capabilities, Enteris can remain a trusted and reliable manufacturer as client programs progress through each stage of drug development.

Q: What expertise do you bring to the table that differentiates Enteris from other CDMOs?

A: On the manufacturing side, we have considerable expertise in technologies to improve solubility and permeability, and we specialize in applying aqueous film coats at scale. We value and emphasize analytical development and validation. Our quality assurance and control systems are fully compliant with the FDA, EMA, and ICH. It is important to note that regardless of whether we are working with a solid oral dose developed using our Peptelligence or ProPerma technologies, or another formulation technology, Enteris can ensure optimal manufacturing of a client's clinical and commercial supplies.

But CDMO is about more than manufacturing. We have an unparalleled team of industry-leading scientific subject matter experts in the areas of formulation, analytical research and development, quality control, quality assurance, and manufacturing. We apply a risk-based, phase-appropriate approach to cGMP analytical activities, such as specification setting, analytical method development, and analytical validation. What's more, we have thorough experience with high-potency active pharmaceutical ingredients (HPAPIs), industry-leading expertise in enteric coatings, and extensive

experience working at small batch sizes, sometimes fewer than 100 units, in instances where API supplies are limited due to cost, scarcity, or other factors.

Q: Why was it important for Enteris to invest in the expansion of its Boonton, NJ, manufacturing facilities?

A: Enteris is a growing company with a number of value-creating opportunities on the horizon. Following the acquisition of Enteris in 2019 by SWK Holdings Corporation (Nasdaq: SWKH), we initiated an aggressive business development and marketing program designed to identify and secure potential licensing opportunities with pharmaceutical companies seeking to develop orally delivered versions of their peptide and small molecule products. The expansion of our manufacturing capabilities goes hand in hand with those efforts, allowing us to pursue deeper manufacturing relationships with developmental clients.

Q: What capabilities do you have now that you did not have before?

A: Enteris now has the ability to provide bench-to-market development services, including the development, manufacture, testing, and release of Phase 1 to Phase 3 CTM. We also have the ability to handle production for commercial launch.

The renovated 32,000-sq-ft manufacturing facility includes 6,000 sq ft of cleanroom space with approximately 2,500 sq ft dedicated to the containment and processing of HPAPI. The facility also includes 1,700 sq ft of flexible suite space that can be adapted to a partner's development and manufacturing needs.

Q: Enteris completed the expansion projects amid a global pandemic. What challenges did you have to overcome?

A: Delivering on a construction timetable amid the COVID-19 pandemic was no easy feat, and the team at Enteris is to be congratulated for meeting the challenge. There were hurdles along the way that we needed to work around, such as renovating one part of the facility while maintaining production capacity in another. Throughout the project, our team found creative solutions to address the specific challenge, which reflected the same ingenuity we bring to the production of pharmaceuticals.

Interestingly, there were some advantages to conducting a large-scale construction project during the lockdown in that with most of our employees working from home, there was little disruption to their activities as a result of the construction. The build-out could occur during the normal workday rather than scheduling heavy construction for off-hours or weekends.

Q: Speaking of COVID-19, the pandemic shined a light on the shortcomings of the global supply chain. How do you see it changing the CDMO industry?

A: The disruption caused by COVID-19 caused significant challenges with drug shortages and increased production costs. It made clear the need to reduce our industry's reliance on overseas markets for key materials, as well as the actual manufacturing of medications prescribed to millions of Americans. Given this dynamic, we see more demand for US-based CDMOs with the ability to handle complex manufacturing needs for specialty pharmaceutical and biotechnology companies.

Q: What should a drug developer look for from a CDMO?

A: Obviously, much depends on the specifics of a project and the drug developer's needs. Topping the list of criteria should be a proven track record with a history of quality focus and regulatory compliance, the company's core competencies, and the breadth of the services it provides to clients. Does the CDMO provide bench-to-market development services, including the development, manufacture, testing, and release of all stages of CTM and commercial production? For complex drug products, drug makers should look for a partner skilled in highly specialized formulation, manufacturing, and process technology areas. And if your API is expensive, potent, or challenging to

source, it will be important to find a CDMO with a proven ability to manufacture small scale batches.

Another issue to consider is the size of the CDMO and how your company might be prioritized. Understandably, companies that cater to larger drug makers often allocate more resources to those clients. It's smart business. However, this can result in smaller drug makers and their projects falling through the cracks. We recognize there is a growing trend in the market in which small organizations and small and mid-size biotechnology companies are developing their assets to commercial launch. As a nimble and highly specialized CDMO, Enteris is very cognizant of their needs, and has the experience and abilities to ensure these companies receive our dedicated and bespoke service.

Q: Looking ahead, what do you see as the key opportunities for Enteris' contract manufacturing operations over the next 12 months?

A: We see considerable opportunities in 2021, subject to any COVID-19 constraints, to leverage our newly enhanced manufacturing capabilities.

Under our CEO Rajiv Khosla, Enteris has increased the business development pipeline for the Peptelligence and ProPerma technologies. In addition, we will actively pursue new high-value relationships with companies seeking CDMO capabilities in the US, such as manufacture of CTM, formulation development, and analytical method development, including for HPAPIs, regardless of whether the product is a solid oral formulation using our proprietary oral formulation technologies or other tablet technology. ◆

PRODUCT DEVELOPMENT STRATEGY

ESCP, Estimating Product Performance Part 4 – Building Playgrounds & Fences

By: Josef Bossart, PhD

INTRODUCTION

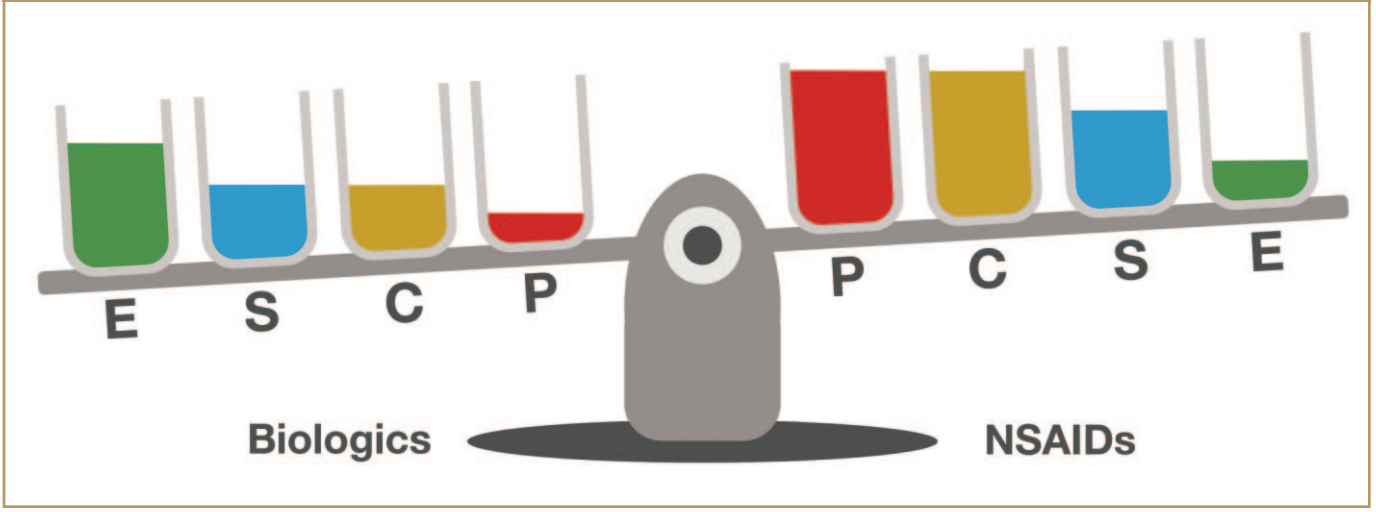
Fences not only make for good neighbors; they also make for better playgrounds. And, if you aren't competitive on an existing seesaw or in an existing playground, the answer may be to build one tailored to your skills.

The pharmaceutical market saw a major business shift in the 1990s. It started with an appreciation that biologics could address important therapeutic needs beyond those treatable by small molecules. This was accompanied by the realization that many of the large-volume disease opportunities research-based companies depended on were figuratively disappearing. While still important, these markets were becoming unattractive in the face of dose-optimized generics. It was nearly impossible to develop a product that could tip any of these seesaws, even with heavy "lubrication."[1]

For example, the H2-blockers that revolutionized the treatment of peptic ulcers were challenged by generics as well as proton pump inhibitors. The hypertension market saw a succession of new therapeutic products being introduced. Beta blockers were replaced by ACE inhibitors and dose-optimized calcium antagonists, which in turn were replaced by angiotensin receptor antagonists, all of which were facing pressure from generics. The same was true for the cash cow markets of anxiolytics and antidepressants. There was some opportunity in the area of antipsychotics in terms of alternate dosage forms, but this was soon challenged by me-too products and generics.

Safety and **Efficacy** were "good enough," **Convenience** was more than acceptable with typical once-a-day oral dosing. All that was left unoptimized was **Pricing**, and generics were prepared to meet that market need.

EFFICACY ALWAYS TIPS THE BALANCE



BUILDING NEW SEESAWS

The response by the industry was to move from these large indications and explore smaller opportunities that were far from satisfied in terms of Efficacy and Safety. Patients with cancer, autoimmune, and neurological conditions were desperate for new treatments. They not only wanted disease-treating medications; they also wanted disease-modifying options.

Biologics proved to be an important platform to meet these needs. It was in the 2000s that the first truly effective treatments with disease-modifying properties using biologics were introduced for conditions such as Multiple Sclerosis, Hepatitis C, Rheumatoid Arthritis, and Psoriasis.

These new products effectively created new seesaws and new playgrounds. Comparing a product like Enbrel (etanercept) to a simple anti-inflammatory like Voltaren (diclofenac) for Rheumatoid Arthritis made no sense. Had they been on the same seesaw, a product like Enbrel or Humira would have overwhelmed any NSAID despite the latter's Convenience and Pricing advantage. Meaningful competition in the future would be on these new seesaws. There would still be competition among NSAID products like Voltaren, Naprosyn, and Motrin, but this competition would largely move to an OTC playground.

PRICING BECOMES FLUID

The initial target of many of these next-generation products were relatively large indications, such as Rheumatoid Arthritis; 2 million patients, Hepatitis C; 3 million patients; and Multiple Sclerosis, 400,000 patients, just in the US. These indications though were dwarfed by earlier disease areas, such as Hypertension with more than 100 million patients, Major Depression with 16 million patients, and Peptic Ulcer with 25 million patients.

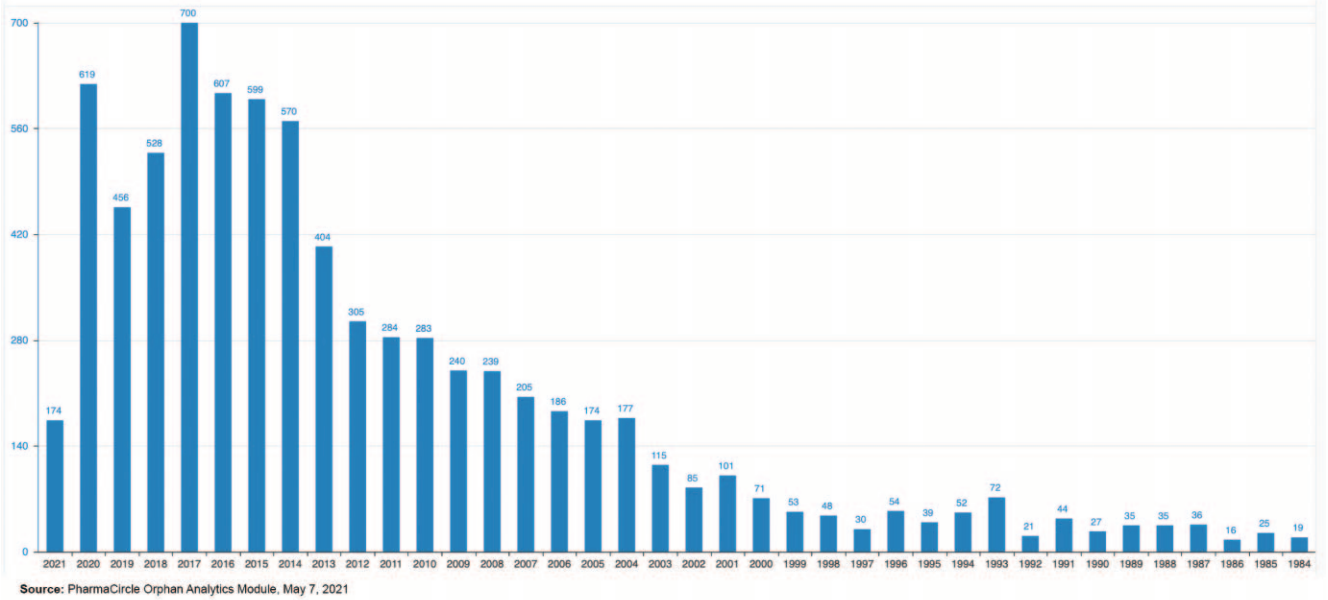
This new generation of pharmaceuticals provided so much benefit in terms of Efficacy, often disease-modifying efficacy, that they were able to command a significant Pricing premium. Starting cautiously, companies quickly realized that prices in the range of $25,000 to $100,000 annually were acceptable.

While there were complaints about Pricing from patients, physicians, payors, and government health plans, the benefits were sufficient to drive demand and sales, even when there were compromises in terms of Safety and Convenience. The importance of Efficacy as the driver of acceptance was clearly validated, especially for these serious chronic medical conditions.

THE EMERGENCE OF ORPHAN PLAYGROUNDS

With the passage of Orphan Drug legislation in the US (1983), Japan (1993), and the European Union (2000), a whole new series of playgrounds became commercially attractive. The US Act applied to medical conditions for which there was a very small population, less than 200,000 patients, and provided certain tax benefits along with a period of exclusivity for applicable products, even when composition of matter patents on these molecules had expired. In some cases, the orphan indications represented tens, hundreds, or

ORPHAN DRUG DESIGNATIONS BY YEAR US, EU & JAPAN (1984-MAY 2021)



Source: PharmaCircle Orphan Analytics Module, May 7, 2021

thousands of patients. In other cases, the numbers bumped against the upper limit of the act that required a careful parsing of a disease condition definition to qualify as an Orphan Product.

The Orphan Act spawned two distinct business strategies. The first was the traditional Pharma approach of identifying undertreated conditions and finding or discovering molecules and treatment strategies that could positively impact these conditions. This was not unlike the strategy used historically for the development of new treatments but with the commercial incentives of the Orphan Drug Acts.

A second strategy involved finding molecules in use for Orphan indications but not formally approved for these indications. This approach carried little risk given the historical experience and, in many cases, required very little clinical investment. Often, the majority of expenses and effort was related to collating the published information, arranging GMP manufacture, and drafting the filings. Many products required very limited clinical trials or just the promise to conduct trials post approval. This led to abuse by a number of companies. The more egregious examples included KV Pharma and Makena (hydroxyprogesterone caproate) for preterm birth, Turing Pharmaceuticals and Daraprim (pyrimethamine) for toxoplasmosis, and Catalyst Pharmaceuticals and Firdapse (amifampridine) for Lambert-Eaton Myasthenic Syndrome. In these cases, product prices were increased by hundreds and thousands of percent with little obvious benefit or product investment.

PRICING BECOMES EVEN MORE FLEXIBLE

The real attraction of developing products for orphan indications lay in the pricing flexibility it offered. Treating patients for a couple of thousand dollars per year was attractive for conditions like hyperlipidemia and depression in which treatment was often chronic and there were millions of potential patients. When the populations decreased for more specialty indications like multiple sclerosis, a product with an annual price of $50,000 could still hit the blockbuster mark with only 20,000 treated patients.

With Orphan Products, the available populations dropped by a factor of a hundred or even a thousand. The solution was to raise prices even further. Annual prices for these therapies quickly rose to $100,000, $500,000, and more. With no alternatives, the various payors, in the face of patient advocacy group pressure and with some reluctance, accepted the bargain rationalizing that these premium prices were offset to a large extent by the savings realized with the generics used for the large-volume indications.

FENCING PLAYGROUNDS

The concept of building fences has been a core strategy for pharmaceutical product development. The industry's investment in biologics is not only a reflection of their therapeutic potential but also the significant regulatory exclusivity they provide, the regulatory hurdles to interchangeability, and the myriad of process patents involved in their production. This has provided some multibillion-dollar biologics with exclusivity that exceeds 20 years, a period of exclusivity that small molecule products developers rarely, if ever, enjoyed.

Layer on the benefits of Orphan Drug legislation, and it is easy to understand why the industry has embraced biologics and orphan drugs. This partly explains the investment in gene and cell therapy products, which provide even more potential layers of patent protection and often the benefit of Orphan Drug incentives. But these new markets and products are still candidates for seesaw analysis, albeit on new seesaws and playgrounds.

SEESAWS, PLAYGROUNDS & FENCES

The fundamental ESCP process, Efficacy, Safety, Convenience, and Pricing, outlined in this, and the previous three articles, provides an intuitive approach to estimating pharmaceutical product opportunity.[1,2,3] Applying these concepts can be summarized in the following four steps:

Step 1 - Identify the playground your product will be competing in. Put your buckets on the seesaw and see how they stack up against the competition. Identify your strengths and weaknesses and decide if they can be improved. If you aren't competitive, consider moving to the next step.

Step 2 - Identify other playgrounds where you might be more competitive. Is there a therapeutic opportunity that needs its own playground? Can you build it?

Step 3 - Repeat Steps 1 and 2 on a regular schedule as you get more information about your product and the market. Things change.

Step 4 - When you find your playground and seesaw, start building fences. Strong fences are keys to successful products.

For most companies and products, the challenge will be to design and develop a product that can compete effectively on an existing seesaw. Creating new playgrounds or seesaws is challenging, expensive, and risky, but can offer the greatest opportunity.

One final note about the ESCP process. It is not a substitute for a rigorous assessment of the therapeutic and market opportunity. The ESCP process can help guide companies at the earlier stages of product development, especially smaller companies that have limited resources and expertise. Too many companies do the hard work of bringing a product through to approval only to find the market isn't interested. Ready-Aim-Fire fire provides consistently better results than Ready-Fire-Aim.

Going forward, *Drug Development & Delivery* will be hosting a series of articles on its homepage and newsletters that applies these concepts to past, current, and pipeline products - a Playground Faceoff. ◆

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Special Feature

Outsourcing Formulation Development & Manufacturing: Meeting Demand for Biologics & Specialty Drugs

By: Cindy H. Dubin, Contributor

Increasing patent expirations of major drugs, the growing burden of chronic diseases, and elevated global awareness of vaccines are leading to a surge in outsourcing formulation development services. Industry experts say these trends put a value on the global pharmaceutical CDMO Market at $160.12 billion in 2020, and could reach $236.61 billion by 2026,[1] while the North American CDMO market is expected to reach $101.1 billion by 2030.[2] As more pharma/biopharma companies opt to partner with CDMOs, much of this activity is occurring in the early phase of development with the goal of overcoming risk, along with saving time and money as a drug passes through the development pipeline.

This annual *Drug Development & Delivery* report highlights the formulation development and manufacturing offerings from some of the leading CDMOs to address a myriad of challenges – from complex compounds to poor solubility to dual-release profiles.

Samsung Biologics' CLD Lab.

Adare Pharma Solutions: Formulating Child-Friendly, Broad-Range Dosing

A European-based pharmaceutical company wanted to improve its pancreatic enzyme product (PEP) delivery to patients who have difficulty swallowing several capsules a day, especially children with cystic fibrosis (CF) and other conditions. Providing a broad dosage range for optimal symptom control and precise dosing was also a requirement.

Adare Pharma Solutions scientists paired the API with Adare's MMTS™ Minitabs technology as it can be sprinkled onto soft foods (<5pH). Adare was also able to expand the dosage range to 40,000 USP units.

"This method has been proven effective, safe, and well-tolerated in treating pediatric CF patients (ages 1-6 years old) in a Phase 3 pediatric study, and a broad dosage range from 3,000 to 25,000 USP units was also proven," says Luigi Boltri, Senior Director Pharmaceutical Sciences, Business Support & New Technologies, Adare.

In another situation, a particularly bitter pediatric macrolide in powder form was brought to Adare for needs beyond just taste masking. The API also needed fast release due to a narrow absorption window, a smooth syrup mouthfeel acceptable to children and infants, more than 7 days of taste masking after suspension, and drug loading suitable for its high dose.

Adare scientists paired the API with its Microcaps® taste-masking technology platform and coated with a pH-dependent polymer.

"Rapid release was demonstrated *in vitro* and *in vivo*, achieving the targeted bioequivalence," says Mr. Boltri. "The API's particle size distribution (in the range of 100-200µ) remained virtually the same minimizing any possibility of a gritty mouthfeel while also achieving over 10 days of taste masking in extemporary suspension. A high drug load of up to 70% was also achieved."

Alcami: QbD Addresses API Supply in Orphan Drug Formulation

According to the Food and Drug Administration and the Orphan Drug Designation program, orphan status applies to drugs and biologics defined as "those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 people, but are not expected to recover the costs of developing and marketing a treatment drug." Due to the high costs and low demands of the drug product, it is important to efficiently use API supply during the formulation process.

Dr. Elsie Melsopp, Head of Solids Formulations for Alcami, says the company successfully helped a client overcome an API supply shortage using Quality by Design (QbD) studies to successfully formulate an orphan drug product. The client needed full development and product readiness with an extremely short supply of the API. In addition, the scale-up batch was small because of the low volume of product demands of their orphan drug.

Considering that small batches present a challenge in proving robustness of the processing equipment, the Alcami project team, in collaboration with client team members, prepared a failure mode, effects, and criticality analysis (FMECA) of the formulation and process. As a result, the team identified and prioritized studies that would provide the necessary product and process understanding needed to develop a control strategy, ensure the reproducibility of the product, and meet its intended safety, efficacy, stability, and performance profile regardless of the manufacturing scale.

The QbD studies were designed concisely to minimize the use of the API and evaluate the critical product parameters that could affect the product quality attributes of the drug product, per FDA's QbD guidance.

"Alcami supported this product with supply constraints and successfully developed a capsule formulation for two dosage strengths," she explains. "The formulations group performed studies at a micro-laboratory scale using a scientifically-based approach to identify a lead prototype. The results provided a formulation amenable to two dosage strengths by applying a proportional dosing weight method." The product is currently in late-stage development with the New Drug Application filing expected late 2021.

Ascendia's technology makes the insoluble soluble.

Ascendia Pharmaceuticals: Versatile Technologies Deliver Most Compounds

Increased complexity in dosage form design has led many to work with a specialty CDMO to resolve compound issues, accelerate the product development timeline, and reduce cost in development and manufacturing.

As a CDMO, Ascendia has invested heavily in drug delivery technologies, such as EmulSol, NanoSol, and AmorSol, which are versatile for use in delivery of small molecules, biologicals, and large molecules. "Our technologies can cover almost all new compounds with different challenging properties (BCS II, III, IV and biologicals); we have generated 6 patents using our technologies in house or for our clients," says Jim Huang, PhD, CEO, Ascendia Pharmaceuticals.

He explains how one client was in search of a specialty CDMO for complex sterile injectable nanosuspension for an unstable compound. "Using NanoSol technology, we were able to develop a stable sterile suspension by controlling the impurity generation during manufacturing process, resulting in a transition to a proof-of-concept study in a timely matter."

Ascendia is also expanding its GMP capacity for discovery to later stage development of sterile and non-sterile dosage forms.

August Bioservices: Late-Stage Trial Services

According to Marty Henehan, Vice President of Commercial Development for August Bioservices, a US-based CDMO with formulation and manufacturing expertise, the benefits for pharma companies partnering with CDMOs for clinical and commercial-stage manufacturing are several-fold. "First and foremost, it is important to remember that late-stage clinical trial products are being used to treat real people – to confirm the drug is safe and effective, to assess any potential side effects, and to compare the drug being evaluated to current treatments. Therefore, the stakes can't be any higher from a human care perspective." Mr. Henehan adds that pharma companies who have reached the later phases of the clinical trial process have painstakingly managed their development processes over several years and want to avoid making a preventable mistake so late in the game.

August Bioservices formulates, manufactures, and tests drug products in aseptic or terminally sterilized vials, prefilled syringes or cartridges, and fills IV bags from 25mL up to 5 liters.

As product pipelines are expanding industry-wide to include generics, biosimilars and biologics, new technologies and capabilities are being required of CDMOs to support the unique formulation and manufacturing specifications of these molecules. "August has experience formulating, manufacturing, and launching products in the finished dose pharmaceutical industry – both branded and generic – with a strong focus on injectables across a multitude of presentations (prefilled syringes, vials, IV bags)," he says.

He adds that August has state-of-the-art instrumentation and more will be added in a 2021 expansion project and a 2023 new facility build. "We currently have a high-speed vial line and we are adding a prefilled syringe line, an IV bag line, lyophilization, and terminal sterilization capabilities this year. On the analytical side, we also have an Extractables and Leachables testing program, in addition to formulation and analytical services."

Greg Sacha, Senior Research Scientist at Baxter's Bloomington, Indiana Facility Preparing Samples for Thermal Analysis.

Baxter BioPharma Solutions: Solving Vial Fogging Issue in Lyo Formulation

As an experienced provider of fill-finish services, Baxter BioPharma Solutions' laboratory is well-equipped to evaluate formulations containing a biologic, evaluate the physical behavior of lyophilized formulations, and to isolate and identify particles. One of the instruments utilized for studying lyophilization is the tunable diode laser absorption spectroscopy (TDLAS) for analyzing the flow of water vapor from the product chamber to the condenser. The data from TDLAS is used to develop a primary drying design space. The instrument is also available for use at full-scale. Three of the lyophilizers are capable of controlling ice nucleation for studying the effect of freezing conditions on drying time and product quality.

Wendy Saffell-Clemmer, Lead Scientist/Research and Development, Senior Director at Baxter BioPharma Solutions shares an example of a successful resolution of a problem that occurred during manufacturing a lyophilized product that exhibited severe vial fogging. "Lyophilized formulations can exhibit dried solution above the surface of the dried cake and the dried solution can appear in the area of the vial where the stopper seals in the neck," she says. "This not only affects appearance, but can be a risk to quality assurance."

The reason for vial fogging is not entirely clear and can be random, she adds. Some risk factors are the presence of a surfactant and the variability in vial surfaces. A product manufactured for one client often appeared with low levels of vial fogging. However, one batch exhibited more than 90% of vials with severe fogging that reached into the neck of a vial. The Baxter Research and Development laboratory studied the effect of different vial types on the extent of fogging and helped the client identify a vial that worked well with their product. The product returned to full-scale manufacturing using the new vial that has a hydrophobic surface and no fogging occurred on any of the vials.

CycloLab: Cyclodextrin-Based Formulations

CycloLab Cyclodextrin Research & Development Laboratory Ltd. develops improved formulations of low water solubility and poor bioavailability by applying various cyclodextrins. As a result of cyclodextrin complexation, the pharmacokinetic parameters of these "guest" compounds may become significantly more favorable, says Dr. Istvan Puskas, Research Chemist at CycloLab. "Compared to traditional drug formulations, wherein

a surfactant and/or a co-solvent is applied for the same purpose, using cyclodextrins is still regarded as an inventive approach."

When an innovator applies to get approval for a new cyclodextrin-based composition of a known drug compound, the question of bioequivalence is raised by the pharmaceutical authorities even for injectables, he explains. The innovator must demonstrate bioequivalence of a classically solubilized composition to a complex, cyclodextrin-based formulation. Traditional animal studies to justify bioequivalence are demanding in terms of cost, duration of test, and documentation, including sensitive ethical issues. To bypass this difficulty, biowaiver data such as *in vitro* permeation studies are often found just as convincing as *in vivo* results in the approval process, says Dr. Puskas.

CycloLab conducts comparative simple and reliable *in vitro* tests using a reference marketed product and an innovative cyclodextrin-based formulation regardless if the new composition is developed by CycloLab or previously elaborated by the study sponsor. By conducting *in vitro* permeation studies, the customer may get insight into the physical state of the dissolved drug in simulated biological fluids or in human plasma. By analyzing the permeation rates of the drug from the reference marketed product and from the cyclodextrin-based complex through different semi permeable membranes, the justification of bioequivalence might be established. The method is based on the discrimination of free and cyclodextrin or protein bound portion of the drug substance.

To further illustrate the nature of drug-cyclodextrin interactions, computer modeling on the noncovalent association, aggregation studies in different dilution states may be performed. In addition, competitive cyclodextrin binding studies are provided in human serum albumin as well as in whole plasma. CycloLab's study report on the experimental data is issued ready for submission to relevant authorities to support the approval process.

Emergent BioSolutions: Developing & Manufacturing Viral Vector-Based Therapies

In 2020, Emergent announced a $75 million investment into its Canton, Massachusetts drug substance facility to increase the campus footprint and expand its manufacturing capabilities into viral vector-based gene therapy. The investment includes a state-of-the-art, multi-suite operation up to 1000L in scale. The expansion will bolster Emergent's integrated CDMO service offering for development and manufacturing of viral vector-based gene therapies.

"Emergent's extensive experience in viral vectors and vaccine development provides a solid background in the capabilities and know-how needed for the scale-up and production, in addition to the processing and purification of cells and viruses for advanced therapies," says Catherine Hanley, Vice President & Interim CDMO Business Unit Head, Emergent BioSolutions.

A new Groninger® FlexPro 50 filling suite located at the Emergent Camden Drug Product facility in Baltimore enhances capabilities for aseptic fill/finish processing. The FlexPro 50 utilizes isolator-based technology for aseptic processing of pre-sterilized syringes, cartridges, and vials, and can support liquid or lyophilized products, says Ms. Hanley.

Additionally, a viral drug product facility in Rockville, Maryland is currently undergoing a 58,000 sq. ft. expansion that will include a state-of-the-art high speed fill/finish line with fully integrated isolator technology and an automated inspection, labeling and packaging line, enhancing capabilities in large-scale fill/finish manufacturing of viral biotherapeutics

Emergent's new state-of-the-art Groninger FlexPro 50 isolator system located at the Camden Drug Product facility in Baltimore.

and vaccines.

Finally, the Winnipeg, Manitoba, Canada development and manufacturing site houses a state-of-the-art Vanrx® SA25 Aseptic Filling Workcell. "This provides our clients with a high level of sterility assurance through an automated handling, filling, and closing process, designed to minimize line losses."

LLS Health's commercial manufacturing facility is designed for flexible batch sizes and equipped for aseptic filling of 2-30mL vials.

Lubrizol Life Science Health: Development & Manufacturing Solutions for Poorly Water-Soluble APIs

Lubrizol Life Science Health (LLS Health) recognizes a growing need for aseptic manufacturing capacity that can bridge the gap from clinical to commercial scale and accommodate complex processing steps. To this end, the company has continued to invest in its proprietary SteriMill™ technology, which enables aseptic nanomilling for nanoparticulate suspensions suitable for parenteral administration (such as intravenous injection), long-acting injectables, and ophthalmic formulations. The SteriMill platform is one of several solubility and bioavailability enhancement techniques that Lubrizol deploys.

LLS Health has also invested over $10 million in its commercial manufacturing facility, building upon its decades as a clinical GMP manufacturer and allowing Lubrizol to partner with clients as they go to market. The commercial facility opened in 2019 and features 6,000 sq. ft. of purpose-built processing space to scale-up products that employ nanomilling or other formulation steps prior to filling. LLS Health's ISO 5 filling line is equipped for 2-30mL fills in vials, and the company is also bringing its clinical experience with ophthalmic bottles to the commercial space. The first pre-approval inspection of the site will take place in the second half of this year, positioning LLS Health to support existing clients and new projects in need of commercial production, says Robert Lee, PhD, President, CDMO Division of LLS Health.

A client reached out to LLS Health looking for technology to improve oral delivery of a poorly water-soluble API and provide intellectual property protection of their asset. After brainstorming with the client, Dr. Lee says LLS Health applied its patented LyoCell® technology to develop a formulation with high drug loading, taste masking, and a manufacturing process that could be scaled for use in an oral liquid formulation.

"LyoCells are lipid-based particles that possess powerful drug-solubilizing properties and are compatible with a variety of APIs, whether small molecule or biopharmaceutical," he says.

LLS Health is currently scaling the LyoCell manufacturing process to thousands of liters of concentrate that will be incorporated into the client's final product. The scaled manufacturing process will be transferred back to the client for future production.

Metrics Contract Services: Mitigating Time, Cost, & Risk

To enhance services at Metrics, the company has continued to invest in the single campus model where a dosage form can go from initial concept to global commercial supply under a single FDA registration. Technology transfer will always add cost and take more time. "To mitigate cost, time and risk, we believe in offering scale-up solutions in like-equipment and the benefit of team continuity under a common quality system as a sponsor's product navigates the clinical pathway to commercialization," says John Ross, President, Metrics Contract Services.

A client came to Metrics needing to convert a drug-in-capsule to a formulated capsule for a Phase 2a clini-

Metrics Contract Services' clinical, analytical, development, and commercial services are located on one site, under a single FDA registration, in Greenville, NC.

cal study. The drug was highly potent and moisture sensitive, requiring %RH of less than 30% at all times during handling and manufacture, explains Brad Gold, PhD, Vice President, Pharmaceutical Development, Metrics Contract Services.

Given the high potent banding, development and manufacture had to occur behind hard-wall isolation. Use of HEPA-filtered inlet and outlet air would be required. The idea of combining clean/dry compressed air, with ultra-low moisture contribution as 'make-up' for some inlet air, was presented and engineered, as a solution.

Dr. Gold says Metrics demonstrated, through several dry runs, that this approach was a good solution to controlling humidity levels inside a containment isolator. "Formulation prototypes and clinical trial material were manufactured successfully, with state-of-the-art control for operator exposure. Moreover, the critical quality attribute of humidity level during manufacturing was addressed, as Metrics was able to effectively operate its high potent containment isolators with acceptable differential pressure, while simultaneously controlling %RH to under 30%."

Quotient Sciences: Combining Development Activities Saves Time

For the past decade, Quotient Sciences has created a delivery platform that integrates drug product and clinical testing activities to achieve program acceleration. To support this further, Quotient recently acquired Arcinova, the UK-based CDMO, because of its expertise and capability in early-stage drug substance and bioanalysis work.

"We see a great opportunity for investing in and integrating drug substance services into our existing drug product and clinical testing platform," says Sarah Stevens, Vice President Drug Development Sciences, Quotient Sciences.

Drug substance manufacturing often sits on the critical path in early development with drug product manufacturing and clinical trial initiation routinely suffering from late API supply, she says. As one of the major causes of project delays, it is important for biotech companies to work closely with API manufacturers early in the development process to ensure the drug substance is not only supplied on time, but that potential formulation or downstream challenges have also been identified or flagged up front.

"The investment in this capability will enable the integration of drug substance, drug product, and clinical testing capabilities – all under one organization with a single Project Management function," she says.

In this environment, chemists work hand-in-hand with formulators and biopharmaceutics experts, sharing information about the properties of the molecule and troubleshooting formulation strategies. Drug product manufacturing scientists work alongside clinical teams, ensuring that the needs of the clinical trial and patient groups are met.

She says: "This will cut through more industry silos by combining a range of drug development capabilities, creating additional timeline savings for our clients and ultimately helping to get new drug molecules to patients, faster."

Recipharm: Changing Delivery Method for Repurposed Drug

Recipharm is continuously looking to improve its aseptic fill-finish capabilities for sterile liquids, and lyophilized products, says Torkel Gren, Science & Technology Officer. "This will be important for a lot of biologics and biosimilars because the two important characteristics of most biomolecules are that they have none or very low bioavailability and their stability is limited. This means that they have to be administered by injection and, in many cases, lyophilization is needed to get a product with acceptable shelf life."

Recipharm is also working to in-

crease its dedicated manufacturing capability for small batches of GMP drug substances in addition to large batches for commercial.

"We are committed to providing the infrastructure and capacity to support customers through the drug substance and drug product development process to bring these innovative small-molecule treatments to clinical trial," he says. "With our investment, we will continue to support customers in both areas as a single, integrated supplier, minimizing delays from tech transfers between partners."

One customer recently approached Recipharm for help repurposing some registered drug substances as fixed-dose combination for a new indication. To achieve the right effect, one of the ingredients had to be delivered through modified release. "We proposed delivering one of the API in minitablets and the other in coated pellets; the minitablets and pellet were then filled into capsules," Mr. Gren explains. "This approach avoided incompatibilities between the substances and provided both immediate and modified release. Moreover, the proposed technology allowed the drug-containing components to be adjusted independently of each other, minimizing development timeframes."

Recro: Investing in Oral Solid Dose Development

Recro continues to strategically invest in new capabilities to serve the needs of the oral solid dose pharma industry. Supply chain disruption risks and the re-onshoring movement have prompted many companies to look for US-based CDMOs and CMOs for either primary or second source development and manufacturing. To serve this growing need, in the past year Recro added various capabilities and service offerings.

"One of our clients came to us with a risk mitigation and supply chain security plan for one of its commercial products," explains Richard Sidwell, Vice President and Chief Scientific Officer. "They preferred a US manufacturer mainly to have a secondary source, but it was also crucial to have improved distribution in their critical market. We saw this as an opportunity to install larger-scale equipment and expand our high shear granulation and fluid bed capabilities."

In 2020, Recro completed the construction of two new processing rooms and installed a Freund-Vector VFC-120MX Flo-Coater fluid bed as well as a Freund-Vector GMXB-400 high shear granulator. Both of these installations are now fully qualified and in use for client projects.

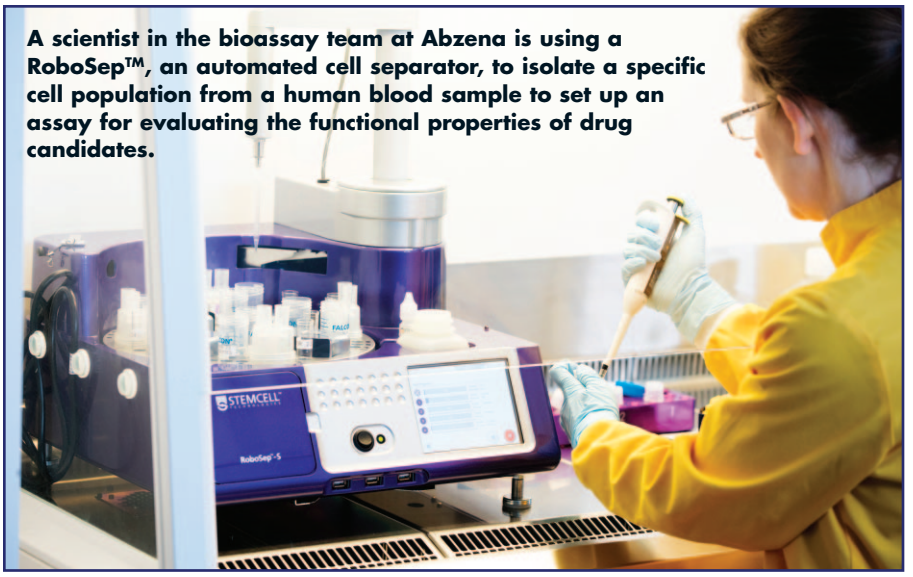
Another client had a need for a multiparticulate capsule with a high drug load. The challenge was that the API appeared to exhibit unusual physical behavior in the drug layering suspension formulation, explains Dr. Sidwell. "We suggested performing a series of small-scale suspension preparations and film casting to identify a formulation that would enable a path forward for the drug-layering process. After several quick experiments, we confirmed the behavior we were seeing was related to a physical drug-excipient interaction that happened in the presence of water. By careful selection of excipients and process solvents for the spray suspension, we were able to resolve the issue and successfully produced the desired drug-loaded pellets."

Abzena: Expediting Timelines in Formulation & Manufacturing

When one of its partners required a formulation to support long-term storage for early-phase clinical studies and had no manufacturing capabilities or formulation experience, they turned to Abzena. An additional challenge was very low drug substance available. "To overcome the challenges, we suggested a large formulation screen and a pre-formulation study to accelerate and refine the candidate selection," describes Campbell Bunce, PhD, Chief Scientific Officer of Abzena. "A 50% improvement in stability was seen in the lead and backup formulations when compared to our partner's control."

These results led to the partner discontinuing their preferred excipient and adopting the new formulations. As both lead and backup were similar, the client decided to combine the technologies used in both formulations and utilized this in development of their product. The formulation was also patented, helping to secure the IP and commercial rights of this lead candidate.

In addition to formulation studies, Abzena has invested in optimizing analytical workflows that support selection of the best, de-risked lead drug candidate to progress to development



A scientist in the bioassay team at Abzena is using a RoboSep™, an automated cell separator, to isolate a specific cell population from a human blood sample to set up an assay for evaluating the functional properties of drug candidates.

and manufacture, says Dr. Bunce. This extends into development of a new cell line expression platform that allows material to be produced very early to truncate development timelines. The expedited timelines are achieved using the material for analytical method, formulation, and downstream development.

"It is important to invest in breadth and depth of skill sets around a diverse range of mammalian expression systems that align with the older cell lines used for out-of-patent-biologics, as well as modern systems with improved productivity," he says. "This allows versatility around supporting biosimilar and novel biologics manufacture and it is critical to respond to the global demand, across a range of therapeutic areas. This not only extends manufacturing capacity, but ensures flexibility around scale of manufacture and constant innovation around processes to shorten timelines."

Aurigene Pharmaceutical Services: Pellet-Filled Capsule for Dual-Release Formulations

Early clinical phase formulations are often simple powders, granules, drug-filled capsules, or injectables. It can become challenging when a modified-release product needs to be developed for preclinical and first-in-human studies. Limited availability of the drug substance, the requirement of flexibility in dosing, and tight timelines are major challenges for such projects. Aurigene Pharmaceutical Services (formerly Dr. Reddy's CPS) has had quite a few of these experiences. One is a highly water-soluble, high-dose drug that needed a modified-release profile with two components: immediate release and slow release.

"The small biotech that approached us had worked with another CDMO for early development and developed polymer-coated tablets," explains Rashmi Nair, Director, ROW Business at Aurigene Pharmaceutical Services. "However, for dose-ranging studies, they were planning to evaluate six doses in clinical Phase 1 trials. Making six tablet strengths and optimizing each of them was a herculean task and neither cost nor time-efficient. When we took up the project, we decided to work backward from the therapeutic rationale of the product, the competitive landscape of marketed or other clinical programs, and a formulation that could be closer to a commercial formulation."

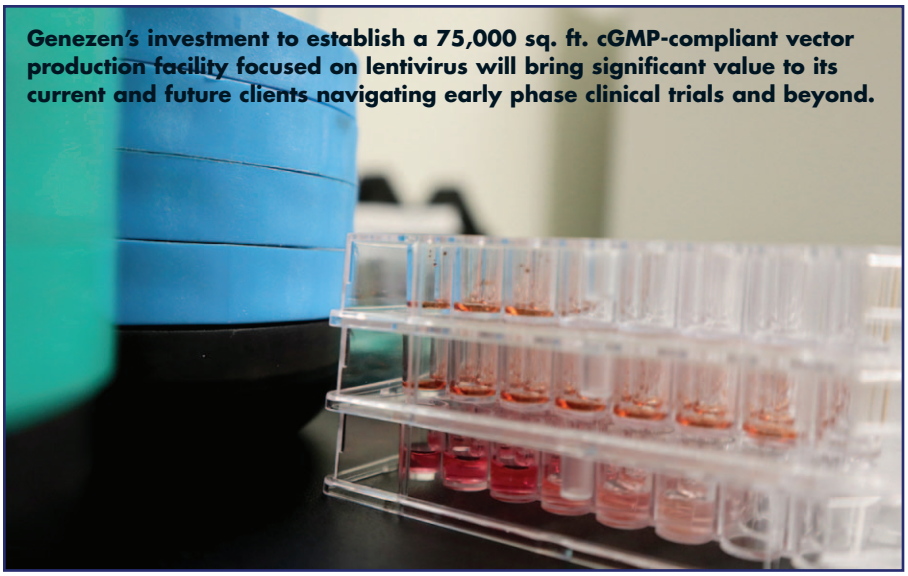
Aurigene designed a pellet-filled capsule formulation. Immediate-release pellets and slow-release pellets were manufactured separately through the Wurster coating process, which is easily scalable, says Ms. Nair. A rotary filling machine filled these pellets into capsules. "By varying pellet fill, we created different doses from 20mg to 200mg. The beauty of this formulation was that we could use the same formulation for the clinical Phase 1 and 3 studies."

For commercial manufacturing, the formulation was the same, the process was modified with high-speed guns for Wurster coating, and to prevent static charge and agglomeration, a pure steam generation step was introduced during polymer coating.

Today, this is a commercial product. A life cycle extension product was created by utilizing the same slow-release formulation and adding another drug as immediate-release granules.

Genezen: Single-Campus Approach De-Risks Development

Genezen is a CDMO entirely focused on cell and gene therapies, with specific expertise in lentiviral vectors. The company has recently received a growth equity investment from Amper-



Genezen's investment to establish a 75,000 sq. ft. cGMP-compliant vector production facility focused on lentivirus will bring significant value to its current and future clients navigating early phase clinical trials and beyond.

sand Capital Partners. The funding is being used to build an initial 25,000-sq. ft. cGMP-compliant lentiviral vector production facility as part of a multi-phase master plan for the development of a 75,000-sq. ft. site. The site will offer multiple cGMP production suites, including capabilities for host cell expansion, host cell banking, and viral vector production via transient transfection and producer cell lines.

Genezen will also deliver a full suite of process development capabilities to support cGMP and commercial readiness, upstream and downstream process improvements, research grade and preclinical vector production, and analytical assay development and validation from the site. "Capabilities to develop producer cell lines will help reduce dependence on GMP-grade plasmids, an investment in state-of-the-art closed systems will ensure safety of the product and reduce risks of human error, and in-house QC assays will speed release testing," says Pratima Cherukuri, Chief Scientific Officer at Genezen. "This single-campus approach is increasingly appealing for pharma companies as it de-risks development and scale up."

She adds that the new site offers fixed-bed bioreactor technology, enabling Genezen to offer a closed lentiviral vector production platform culminating in aseptic fill-finish of vector products into sterile bags for use in cell therapy. The site will also build on existing adherent platforms (cell stacks and fixed-bed bioreactors) and refine existing suspension platforms to offer improved scaling for larger production volumes. Analytical testing services, including unique Recombinant Competent Lentivirus assays (extended culture and PCR methods) for end-of-production release and patient sample testing are also available.

Idifarma: A Focus on Complex & High-Value Drugs

Idifarma has implemented several technologies to provide a comprehensive service for the development and manufacture of Dried Powder Inhalers (DPIs), including spray drying and encapsulation, and has agreements with various relevant entities for the use of the latest technologies for the characterization of DPIs, says Alfredo Gomez, Head of Site at Idifarma.

"We continue to invest in spray drying technology for highly potent drugs," he says. "Our focus on complex and high-value drugs has recently led us to invest in a software tool for a continuous control system of the process to analyze as many pa-

Spray drying process with a potent drug at Idifarma.

rameters as possible, for a complete guarantee of compliance with specifications as well as for rapid process optimizations."

Samsung Biologics: Expanding Capacity for End-to-End Support

Samsung Biologics assist clients with developing and manufacturing product pipelines in an expedited timeline. The CDMO has been maximizing operational efficiency and expanding capabilities for end-to-end outsourcing support, and its latest efforts include the construction of a fourth plant, which, upon completion, will give Samsung Biologics a 620KL of total capacity.

Samsung Biologics also continues to upgrade its capabilities to accommodate clients by investing in single-use technology and additional aseptic filling capacity. In addition, the opening of a new R&D Center in San Francisco expands the company's global presence, says James Choi, Senior Vice President and Chief Information and Marketing Officer, and Head of Investor and Global Public Relations, at Samsung.

To enhance its development services, the company has launched a proprietary cell-line, S-CHOice, which facilitates high performance to enable rapid advancement to IND approval. Samsung Biologics continues to support traditional fed-batch manufacturing by implementing N-1 perfusion technology at the cell culture stage to accommodate rising demand in the latest technology that enhances cell density.

Stelis Biosource: New Manufacturing Technology for Lyophilization & Viral Vectors

Stelis Biosource has expertise in biosimilars as well as vaccines and other biotherapeutics. The company is focused on growing its capacity, capabilities, and knowledge to scale up in the cell and gene therapy space. According to Dr. Anand Khedkar, Sr. Vice President, R&D, Stelis Biosource, the company is investing in various manufacturing platforms for both drug substances and drug products.

"We already have microbial and mammalian platforms and are about to commission a viral vector manufacturing platform," he says. "We are also in the process of researching and integrating other platforms to help bring new kinds of therapeutic products to the market. On the drug product side, we have invested in high-speed vial lines, a high viscosity prefilled syringe filling line as well as a cartridge filling line. We have created dedicated facilities for viral vaccines, high viscosity products, monoclonal antibodies and other products. We also have the capability to manufacture lyophilized vials."

Vibalogics: Manufacturing Viral Vector Vaccines & Gene Therapy

Global demand for CDMO services is at an all-time high, fueled by broadening biologics pipelines. Vibalogics is investing in global infrastructure expansions in both the existing clinical cGMP facility in Germany and the establishment of a new US facility in Massachusetts. Driven by a $150 million investment and a 110,000 sq. ft. facility, Vibalogics will enable the market with further contribution to the overall global supply of manufacturing services for oncolytic viruses, viral vector vaccines, and viral vector gene therapy products, says Joe Sinclair, VP of Business Development & Corporate Strategy for Vibalogics. "We are preparing for the future expansion of this space with a complete suite of virotherapy services and end-to-end service solutions.," he says

Investment in both novel and widely-utilized production and analytical platforms has enabled Vibalogics fit-for-service across a broad class of products and range of customers' needs in viral production, he continues. Modular design and multi-product considerations within the facilities

Stelis Biosource is an end-to-end CDMO for biologics and vaccines.

Vibalogics' $150 million late-phase clinical and commercial virotherapy manufacturing facility located near Boston.

enable a variety of products and processes. Emerging trends in utilizing suspension cultured cell substrates and a need for larger capacity has driven Vibalogics to invest in state-of-the-art technology, such as 2,000L scale bioreactors, with ongoing evaluation of platforms at 4,000L and higher.

Vibalogics is also heavily focused on plant design considerations and process capabilities to allow for aseptic production routinely required for viruses of larger size that cannot be sterile filtered. ◆

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GENE EDITING TECHNOLOGY

Expanding the CRISPR Toolbox for Genome Editing

By: Ashley Jacobi

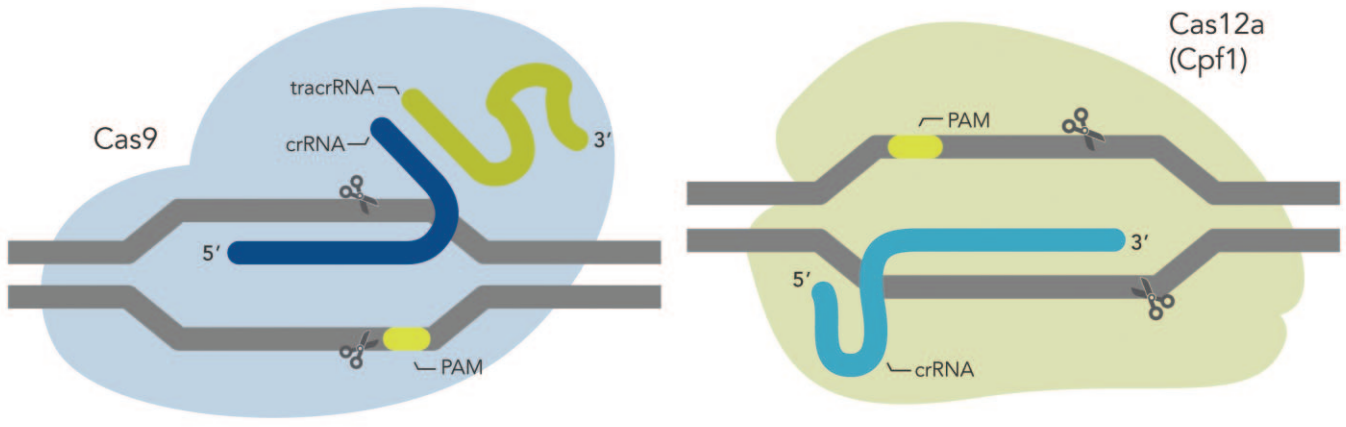
Genome editing technologies have existed since the 1990s but have recently made a surge, largely due to the discovery of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology in 2012.[1] CRISPR genome editing is being investigated by researchers to make precise and permanent changes to DNA in animals and plants. Current applications include efforts to increase crop resilience and yield, to help contribute to feeding the growing world population. With two billion more people to feed by 2050, solutions are needed to increase food production without overwhelming the planet and genome editing is one practical option. In addition, it offers patients suffering from untreatable diseases hope that one day there will be a one-time cure available to them.

AN OVERVIEW OF THE TECHNOLOGY

CRISPR technology comprises two components: a nuclease, e.g., Cas9, which acts like a pair of scissors and is responsible for cleavage of double-stranded DNA, and a single guide RNA (sgRNA), which forms a complex with the nuclease and guides it to the target site. The technology is groundbreaking because it can be designed to make a break at a specific target sequence in the DNA within a living cell, allowing researchers to modify practically almost any locus in the genome of any organism.[2] It is also more cost effective, precise and faster than previously available editing methods like zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs).

As the most commonly used nuclease in CRISPR gene editing, Cas9 can be applied to target specific stretches of genetic code and edit DNA at precise locations, which may make it possible to correct the DNA mutations underlying diseases like sickle cell

FIGURE 1



disease (SCD), Huntington's disease and cystic fibrosis. However, DNA cleavage and editing may occur at additional sites in the genome that have a similar DNA sequence from that of the intended site. Such events are called "off-target effects" (OTEs). Use of wild type (WT) Cas9 to target certain gene locations has been shown to lead to more than 50 percent of the edits being unspecific.

While CRISPR/Cas9 gene editing offers unparalleled genome editing efficiency, and can function in various cell types and species, challenges remain due to low target site specificity and on-target efficiency. Many researchers have tried modifying the guide RNA and mutant Cas9 proteins to improve target specificity, but these alterations often also reduce on-target editing performance.

REFINING THE CAS9 ENZYME AND INTRODUCING CAS12A

At Integrated DNA Technologies (IDT), we have successfully engineered a high-fidelity Cas9 that has greater targeting specificity than the WT Cas9, while retaining nuclease activity that is comparable with WT Cas9. In fact, our HiFi Cas9 is the most active and specific high-fidelity Cas9 enzyme available, when delivered as an RNP complex, which provides optimal targeting specificity.

Although Cas9 is the most commonly used CRISPR nuclease, others do exist. Cas12a (formerly known as Cpf1) has recently emerged as an alternative to Cas9 in the toolbox of CRISPR-based genome editing tools.[3] There are several unique features of Cas12a that distinguish it from Cas9; most notable is the fact that Cas12a targets AT-rich regions of the genome, compared with Cas9, which targets GC sequences. However, wild type Cas12a suffers from lower nuclease activity than Cas9.

At IDT, we recently developed the Alt-R CRISPR-Cas12a (Cpf1) Ultra system. The new variant, Cas12a Ultra, has enhanced editing activity and can be used across a broader temperature range than the WT Cas12a enzyme, making it useful for genome editing in a variety of organisms, including plants and mammals. Given the unique characteristics demonstrated, Cas12a has several potential uses for gene editing, which differ from Cas9.

APPLICATIONS FOR CAS12A & BEYOND

In AgBio applications, gene editing using Cas12a could be used to make crops more resilient, increase yields and boost nutritional value. Mushrooms with longer shelf lives, potatoes low in the possible carcinogen acrylamide, and soy beans that produce healthier oil are already being developed and tested, to name just a few.[4] The technology can also be applied to livestock and research is underway to better understand how gene editing might be used to help farmers in Africa breed more productive chickens and cows.[5]

Interestingly, research is being conducted to analyze the impact of using gene editing to prevent malaria-type disease transmission. Although current efforts and tools to prevent transmission must remain in effect, full eradication will require technological advances. And gene editing is a tool being investigated. One way to do so that has been demonstrated to work is targeting female mosquitoes that are able to transmit malaria and using gene drives – making inheritable edits to their genes – to render them sterile or skew them towards mostly producing male offspring, unable to transmit the disease. However, eradicating a disease is one thing, practically eradicating a vector species (e.g. through an all-male population) is another. Along with the widespread potential impacts and other unknowns of these efforts, ethical, legal, social and regulatory implications need to be carefully considered.

These considerations also need to encompass the rapidly growing list of new Cas enzymes being developed, other than Cas9 and Cas12a, and the applications that are being developed for them. These other enzymes can work alongside Cas9 or serve different functions. For example,

FIGURE 2

Cas13 is a unique enzyme in that it targets RNA not DNA. Once it is activated by a single strand RNA (ssRNA) sequence that matches its CRISPR RNA (crRNA) spacer, it unleashes a non-specific ribonuclease activity and destroys all RNA regardless of sequence. This characteristic has been harnessed in vitro for precision diagnostics.[6] Mammoth Biosciences are developing a CRISPR diagnostic platform, which may include Cas12a, Cas13a, and Cas14. The use of multiple Cas nucleases means that a larger range of sequences can be recognized, thus allowing the panel to provide diagnostic information on a broader range of diseases, conditions, and pathogens. The Cas13 crRNA spacers can be designed to DNA orthologs and generated through a transcription reaction in vitro. However, increased CRISPR performance has been observed with RNA synthesized by providers such as IDT.[7]

WHERE DO WE GO FROM HERE?

While there are many ever-improving tools available to scientists performing ground-breaking research, and the potential of CRISPR genome editing appears limitless, there remain challenges that need to be overcome to realize the technology's full potential. Most importantly is the off-target editing that can occur. However, there are other technical questions that remain less known. These include the potential that more than half of humans may have pre-existing humoral and cell-mediated adaptive immune responses to CRISPR/Cas9 proteins, which are mostly derived from S. aureus and S. pyogenes – known bacteria that cause infectious disease in humans at high frequency. Another challenge to overcome relates to the delivery of these tools into cells and organisms. With time and continued research, these challenges could be overcome, opening up the possibility to realize the technology's full potential. ◆

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BIOGRAPHY

Ashley Jacobi is a Senior Staff Scientist in the Molecular Genetics Research and Development group at Integrated DNA Technologies (IDT). Ashley has been with IDT for 14 years, and during that time, she has been an author on 18 manuscripts published in peer-reviewed journals, contributed to numerous patent applications, and has presented at a wide variety of international biomedical research conferences. She has been conducting research in RNAi and antisense oligo technologies, but more recently has been focusing on the development of novel CRISPR RNA sequences and modification patterns that allow for more efficient and specific cleavage by the S.p. Cas9 and A.s. Cas12a CRISPR nucleases.

ORAL THIN FILMS

The Quest for a Magic Pill May Not Be a Pill at All

By: Robert Davidson

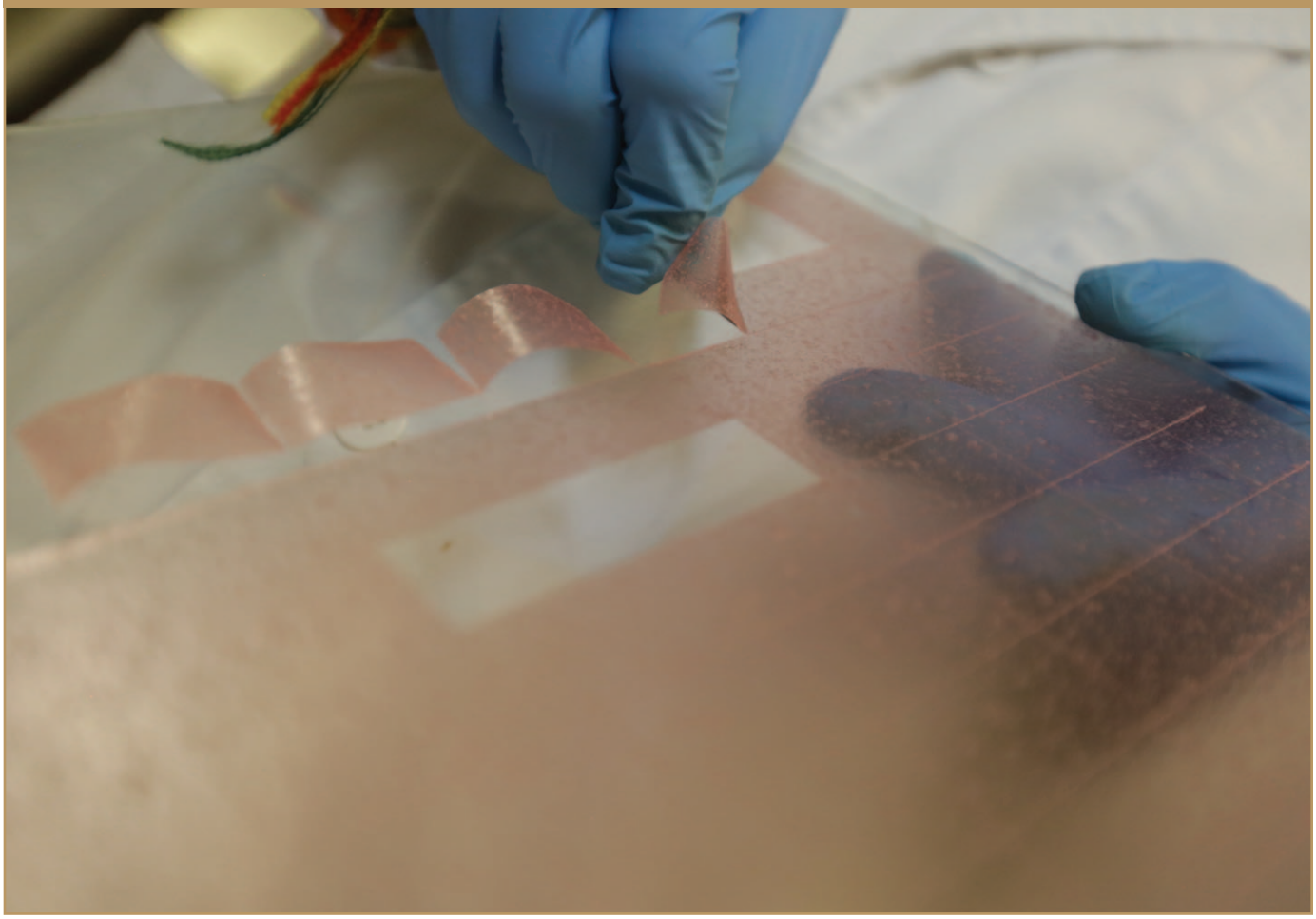
INTRODUCTION

In an article published in the October 2018 issue of *Drug Development & Delivery* titled *Better Drug Release & Patient Experience With Buccal Films*, we discussed how using buccal films in drug delivery would have beneficial outcomes for patients by not only improving prescription adherence, but improved biological activity with minimum side effects. Since then, there has been significant advances in clinical development of this novel drug delivery system, and the technology is rapidly moving from just a theory to practical real-world application.

HISTORY

Over the decades, the quest for a "magic pill" has eluded researchers. But perhaps it is not the drug or compound, but the method by which we deliver the drug that ultimately decides a drug's efficacy. Delivery methods can vary. Whether a drug is administered orally, intravenously, intramuscularly, intrathecally, subcutaneously, sublingually, buccally, rectally, vaginally, ocular, nasally, inhalation, cutaneous, or even via transdermal patch, the many different pathways into the body can be beneficial, but some are often met with restrictions.

FIGURE 1



In the case of oral administration of drugs, clinical developers know that oral drugs are generally the safest and least expensive pathway into the body, but not the most efficacious due to the first-pass effect, which degrades the drugs extensively.

In short, the widely published phenomenon is caused when a drug is metabolized through the digestive tract while en route to a target in the body, resulting in a reduced concentration of drug being delivered.

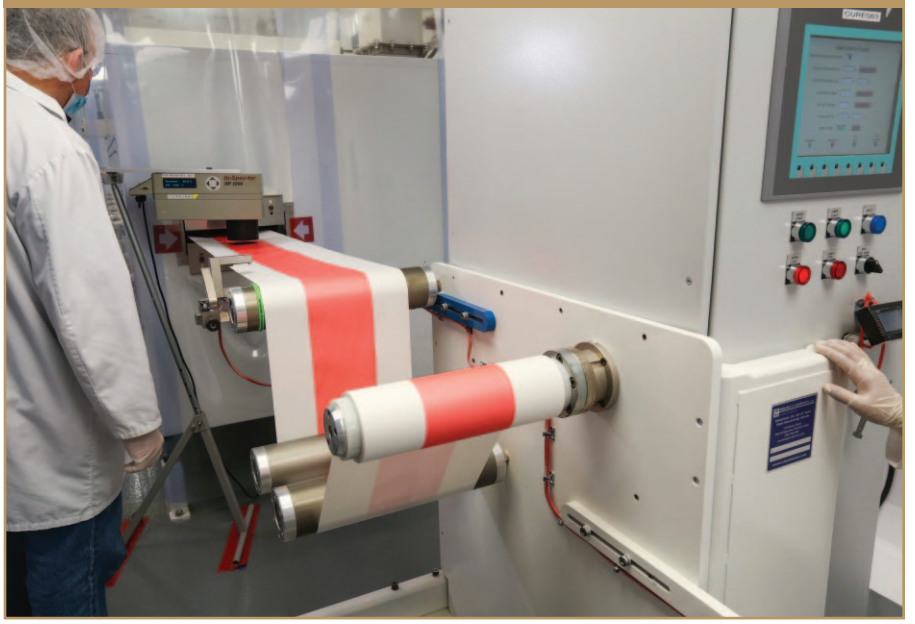
While usually associated with the liver, first-pass effect can occur in other body tissues, such as those found in the lungs, vascular, and gastrointestinal tract. Because first pass can vary among patients, appropriate dosing needs to be considered, and in those patients in which it is exceptionally prominent, an alternative administration of drugs may be required to bypass the digestive system.

To compensate, higher doses of a drug is generally necessary, but this also raises the possibility of generating unwanted side effects. Therefore, researchers often need to conduct extensive…and expensive…clinical studies to determine the proper dose needed to achieve a specific clinical outcome.

CHALLENGES & OPPORTUNITIES

In the history of drug development, buccal administration is gaining interest not only for rapid and controlled release of drug compounds, but given the highly likelihood of degradation, the optimum method that is needed to bypass the gut and liver. Eliminating or reducing degradation is a major step in improving bioavailability and can potentially allow a lower dose of drug to be administer, which could reduce potential side effects in some patients.

FIGURE 2



Moreover, given the large area for drug application, the mouth provides an excellent platform for drug administration than other entries into the body. But does it really work?

In a recent study, CURE Pharmaceutical sought to answer that question by utilizing its oral thin film technology CUREFilm®, CURE's proprietary emulsion oral thin film dose form, or OTF, to administer a 25-mg dose of CBD in healthy patients.[1]

It is worth noting that CBD is a phytocannabinoid compound that is fat soluble and has limited bioavailability. Not only is it difficult for the body to absorb via traditional oral ingestion, but it also suffers extensive degradation via the first- pass metabolism, much like other compounds that are administered orally.

This open-label, randomized, single-dose, crossover study of 14 healthy adults compared the pharmacokinetics of a commercially available soft gel formulation (liquid encapsulated within a shell) of 25-mg CBD to 25 mg of CBD delivered via CUREfilm. CUREfilm OTF resulted in a significantly higher maximum serum concentration (~3x increase in C_{max}) and a faster onset/absorption (~3x decrease in T_{max}), compared to the reference product. No safety concerns were reported. In both arms of the study, the product was administered orally (PO) and, hence, ingested.

The study also included a subjective survey comprising of eight questions to aid in the understanding of CUREfilm OTF as an acceptable dosage form. Results showed that none of the participants experienced discomfort, pain, numbness, or irritation during administration. Additionally, 80% indicated "great" palatability, with 90% rating CUREfilm OTF experience as very pleasant or neutral.

The study results indicate that using this proprietary delivery platform not only improved the bioavailability of CBD in healthy patients, but that it is uniquely designed to overcome digestive obstacles and deliver drugs more effectively.

The data also showed that improved bioavailability resulted in higher serum concentrations and provided a significantly faster absorption into the body versus

commercially available 25-mg CBD soft gels.

Thus, while this delivery method improved cannabinoid bioavailability, it stands to reason that the technology could be applied to other molecules that have similar challenges and could potentially achieve multiple patient benefits, such as allow for lower dosing of active ingredients, resulting in less side effects and better patient compliance. This is just the tip of the iceberg as the marketing potential for other drugs show promising result.

As a result, CURE Pharmaceuticals announced earlier this year that the US FDA acceptance of an Investigative New Drug (IND) application to administer sildenafil citrate, the key ingredient in Viagra™ to treat Erectile Dysfunction (ED) utilizing our technology. At this writing, we expected to initiate our Phase 1 clinical trials in the first half of 2021. Since both sildenafil citrate and CUREFilm have been previously reviewed by the FDA, we filed our application via the 505(b)(2) pathway, which should expedite the US clearance process.

According to a report from QVR Research, the global ED drug market is projected to reach $66 billion by 2025, and according to the most recent market reports, only 10 pharmaceutical products are available on the market that utilize the novel drug delivery system.[2] However, due to the many benefits associated with the oral thins, such as improved patient compliance, safety profile, and potential lack of side effects of higher drug dose needed when taking a tablet, demand is rising.

In addition to CURE Pharmaceuticals, there are several other companies in the space, such as ZIM Labs, Indivior plc., Aquestive Therapeutics, Suminomo, Dainippon Pharma, and IntelGenx Corp. However, there are several of the larger, legacy pharma companies in the space, such as Pfizer, Novartis, Allergan, NAL Pharma, and Solvay to name a few. Given the amount of interest in the delivery method and the current roster of players, the potential pipeline has seemingly unlimited possibilities.

SUMMARY

With the positive outcomes that we have experienced in our own clinical development, the potential to meet a larger consumer base and find solutions for unmet medical needs is compelling. There is no doubt that the demand for oral thin films is among an emerging market worldwide, and North America, with its high number of pharma companies and deep pockets for clinical research, is leading the way. But while discovering drugs that treat a myriad of diseases or conditions is paramount and at the heart of what life science companies do, these compounds are of little use if they cannot get to the source of problem and treat a condition without causing additional undo harm to the patient. The cure cannot be worse than the disease. So, while we set our sights to finding the best therapeutics, we must also keep a focus on how we get the therapeutics where it needs to go. Effective drug delivery is almost as important as the drug itself. ◆

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BIOGRAPHY

Robert Davidson is the CEO of CURE Pharmaceutical. Prior to his role at CURE Pharmaceutical, he served as President and CEO of InnoZen Inc., CEO of Gel Tech LLC, CEO of Bio Delivery Technologies Inc., and has served on multiple corporate boards. He was responsible for the development of several drug delivery technologies and commercial brand extensions, including popular zinc product Zicam. He has worked with brands, such as Chloraseptic™, Suppress™, as well as Pediastrip™, a private label electrolyte oral thin film sold in major drug store chains. He earned his BS with a concentration in Biological Life Sciences. He also earned his Masters Certificate in Applied Project Management from Villanova University, Masters of Public Health from American Military University, Virginia; Masters in Health and Wellness from Liberty University, Virginia, and Masters in Sustainability leadership and Post Graduate Studies at the University of Cambridge with letter of commendation.

CLINICAL TRIALS

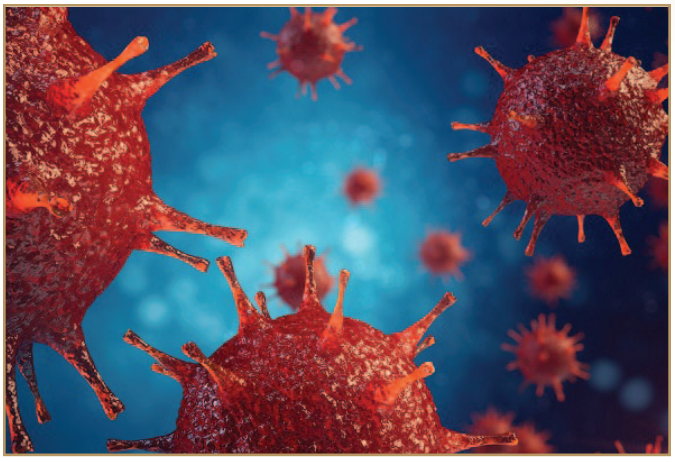
Statistical Challenges in Preserving Integrity of Ongoing Clinical Trials During the COVID-19 Pandemic

By: Karen Ooms, Msc

INTRODUCTION

The pharmaceutical industry is a patient-centric industry and is being impacted by the COVID-19 pandemic in ways not seen before. Implications range from a marked slow in recruitment rates due to enforced social distancing policies worldwide to a complete halt in drug development programs as pharmaceutical companies rationalize their investments in these uncertain times. It is unfeasible and often impossible to keep a trial running "as usual" for a variety of reasons, eg, site visits being replaced by remote ones. However, the consequences of this pandemic on ongoing clinical trials can be objectively assessed, and with the correct mitigation strategies put in place, study integrity can be preserved, optimizing use of the available resources for both patients and sponsors.

The following discusses some of the challenges posed to clinical trials from a statistical perspective, offering potential solutions to overcome them with the aim of maintaining scientific accuracy and regulatory compliance. The need for flexibility and how this can be achieved without affecting patients' safety and study validity will be a key consideration explored. It is worth mentioning that the discussion needs to be tailored to the specific therapeutic area as the challenges faced and the solutions required will be different for each. For instance, studies for life-threatening diseases (eg, oncology) most likely can't pause for both ethical and practical reasons, whereas studies on less serious illnesses might not suffer this problem.



SAMPLE SIZE: ARE WE GOOD OR NOT?

Getting the sample size right is the foundation that ensures a successful study whilst minimizing the number of patients undergoing potentially invasive study procedures and curtailing costs for the sponsor. In an ideal world, we might think of continuing as planned until normality is restored and procedures restart as before. However, shareholders and investors might disagree: the costs of running a study that doesn't deliver study results in the originally agreed timelines can be overwhelming for major pharma companies and simply a killer for smaller biotech companies.

One potential solution is to investigate the impact on study power if recruitment was stopped and only patients currently recruited were allowed to continue and complete the study. Such an exercise is similar to what is often done while planning the

study, to evaluate the impact of different assumptions (eg, comparator arm response level, variability, etc), with the difference that some new information obtained from external sources might have arisen that allow a more precise characterization of assumptions. If a new study, in which unblinded results had only been made available after the present study protocol was finalized, suggested that the response in the comparator arm was in fact different from what was originally assumed, the current sample size might still allow sufficient power to detect a clinically relevant effect. Whilst this situation is not a very common one, re-evaluating study power in a large number of scenarios (either via closed formulas or simulations) will provide the study team with a better understanding of what actions need to be put in place. However, if the only scenario to allow a sufficient power to be achieved requires a treatment effect twice as large as originally planned, it might be worth considering if the study can continue with the same characteristics prior to the pandemic.

This last example brings up an important item; the extent to which study design itself can be altered to respond to the currently evolving scenario. Let us assume that a study was planned to enrol 200 patients to demonstrate a difference in a continuous outcome between treatments ≥ 3. We further assume that the mean response was 10 in the treatment arm and 5 in the comparator arm with an 80% power (standard deviation = 5 and a one-sided test at a 2.5% level, drop-out rate assumed to be 0% for simplicity). If no further information on the potential treatment effect has arisen from external sources, it is clear that if, eg, only 150 patients have currently been recruited, it is not possible to halt recruitment now because this would leave us with only 68% power and increase the chances of the study being a failure.

In this situation, a viable option is to amend the study protocol to include an unblinded (and previously unplanned) interim analysis with the main purpose of estimating the current treatment effect and deriving measures of future study success (ie, conditional power or predictive power, depending on whether you root for frequentist or Bayesian statistics) given the current data. Using this information (yet considering all available patient-level data), the Data Monitoring Committee can make a better decision as to whether the study is still likely to succeed or not. The advantage of this approach is that only studies that are reasonably likely to deliver positive results, and for which no safety concerns arise, will continue, freeing up resources for other projects and minimizing unnecessary efforts on all sides.

It is relevant to point out that going down this route has implications on study design. If an unblinded interim is added, preservation of type I error rate needs to be maintained via, eg, alpha-spending functions that ultimately imply an increase in the overall sample size. Whilst this might seem counter-productive, considering the difficulties in achieving the planned, and lower, sample size, this ensures the efforts of recruiting additional patients are only done for promising compounds.

ESTIMANDS & MISSING DATA: IS COVID-19 AN INTERCURRENT EVENT?

Intercurrent events should be outlined in the protocol and the estimands defined to outline the approach to each anticipated intercurrent event. During the pandemic, it is expected that protocol amendments will document changes to the design and conduct of studies in order to adapt to travel restrictions, limited access to sites, subjects, and site staff suffering from COVID-19, etc. It therefore seems reasonable to review and adapt study estimands as well.

Protocols may be adapted to allow for a pause in treatment, an alternative treatment, remote visits, larger visit windows, and so on. Subjects may miss visits due to logistical reasons or having the virus. Each of these situations can be treated as an intercurrent event and, for each, the most appropriate strategy selected. The most suitable approach will depend on the details of the trial, the study treatment, and the indication, and will need to be agreed by the whole study team. Consequently, adaptations may be required to the planned analyses to ensure consistency with the estimands defined in the protocol.

COVID 19-related intercurrent events may potentially cause an increase in missing data. Updates to the approach to dealing with missing data may be required to ensure it is done appropriately and is consistent with the estimands.

Where only minimal changes to the trial conduct have been implemented due to the pandemic, it might be reasonable and acceptable not to treat events related to COVID-19 as intercurrent events. The practical impact would simply be a larger than previously anticipated amount of missing data, and this can be tackled by amending the missing data approach outlined in the Statistical Analysis Plan, or by justifying the reasons for no changes.

Trials are ideally designed with the intention of minimizing missing data so adaptations will be required as a reaction to the pandemic. By making some changes at the procedural level, such as making use of local labs or switching to

standard-of-care or self-administration of the IP, data can be collected, whereas under the original protocol, these data would have been missing. These procedural changes will have some impact on the data collected, and analyses may need to be adjusted to take this into account. It is therefore critical that case report forms (CRFs) are amended to capture changes to trial procedures at each data collection, as well as reasons for treatment and/or study withdrawal. This information can then be considered in the statistical analyses so that it does not confound the treatment effect.

Let us consider the scenario in which there is an unacceptably large amount of missing data when determining the number of responders for the primary efficacy endpoint at the timepoint of interest. If the original analysis method was based on a generalized estimating equation (GEE), a weighted GEE could be considered instead, which would make use of the data from the preceding visits when computing estimates.

Sensitivity analyses may also be included to assess the impact of intercurrent events by utilizing techniques, such as multiple imputation under different outcome assignments.

IMPROVING DATA QUALITY THROUGH CENTRALIZED STATISTICAL MONITORING

It is likely that access to sites will be restricted for many months. This will necessitate the need for alternative mechanisms to provide monitoring and oversight activities. Therefore the need for centralized statistical monitoring is upon us, and this is highlighted by recent guidance from the FDA on conduct of trials during the pandemic: "If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites."

While clinical research associates (CRAs) are no longer travelling to site, centralized statistical monitoring will be required to check for the usual data patterns and anomalies noted here:

- identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations
- examine data trends, such as the range, consistency, and variability of data within and across sites
- evaluate systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems
- analyse site characteristics and performance metrics
- select sites and/or processes for targeted on-site monitoring

However, it is also important to examine areas not previously required, eg, traditional visits versus non-traditional visits, protocol defined endpoint data collection versus updated endpoint data collection. When analyzing at site or regional level, it may be more important to have some awareness or measure of how far the virus had progressed at time of reporting in that region, what measures were being taken, and how regional healthcare systems were coping. Patterns must be monitored as the trial progresses, but with an awareness that a full understanding of the situation, its impact, and what results may or may not be acceptable is still unfolding. Communication between departments is therefore key; signals must be raised on anomalies, and they must be opened up for multi-disciplined discussion across study teams.

One example of anomalous measures in sites that can be captured by centralized statistical monitoring is if a temperature measurement at a particular site differs from the others due to, eg, miscalibrated thermometers. Tools such as CluePoints and SAS JMP can pick up these differences by analyzing means and variances of temperature readings and comparing across sites. Without site visits, the need for this kind of analysis is increased as such differences are less likely to be picked up. And during these times, analyses should not only be carried out across different sites but by also comparing, for example, traditional patient visits to those that are carried out at a different time or place due to the pandemic.

DOCUMENTATION: TO AMEND OR NOT TO AMEND?

All of the aforementioned areas impacted by COVID-19 call for updates to existing study documentation. However,

these updates can be made in different ways, and should be thought through carefully. To a certain extent, the rapidly evolving situation differs across regions and countries. As such, protocol amendments or updates to the Analysis Plans will have to account for this and factor in a certain level of uncertainty.

In addition to the items discussed in previous sections, other study features that should be considered for updating include the following:

Protocol Deviation Plan - many more patients will miss crucial visits, or will have to suspend treatment, and this in turn has an impact not only on the study estimands, but also on the definition of study populations as well as the list of protocol deviations. These are a critical part of a Clinical Study Report as they allow the assessment of the quality of study conduct and largely impact on regulatory decisions. Being able to identify what, in these new circumstances, is a deviation and what is not is key to ensuring the relevant information is collected, displayed, and analyzed. Descriptive comparisons of patterns before, during, and after the pandemic could be considered, both to measure the impact of mitigation strategies as well as to potentially identify under-reporting, ie, cases in which deviations occur but are not reported.

Analysis of Safety Data - in most studies, estimands are defined for efficacy assessment, with safety data often analyzed descriptively by looking at adverse event (AE) frequencies, lab parameter summaries, and trends over time in line plots. The nature of this pandemic, though, is likely to affect the level of AE reporting, resulting in an increase of mild-to-moderate events, such as pyrexia, sore throat, and other upper pharyngeal trait illnesses that in normal times could be dismissed as nuisance by patients and not reported. On the other hand, patients with undiagnosed COVID-19 might have further comorbidities that might never be related to the virus itself and would be incorrectly evaluated. Allowing, for example, stratified analysis of AE patterns might help to identify any relevant trend. Patient narratives will be key to ensure any such case is captured and properly discussed.

Data Management Plan - some additional built-in checks might need to be added, and the general schedule of data flows could benefit from an assessment of what the current situation could entail. For instance, the eCRF could be updated to collect relevant data on COVID-19 symptoms within a respiratory trial, or specific causes for treatment discontinuation.

It is important to stress that no matter how careful the assessment of the potential COVID-19 impact is, it is unlikely that all relevant impacted features will be identified straight away. Continuous monitoring will be required to capture every change in the current situation.

SUMMARY

The COVID-19 pandemic is the biggest challenge the world has faced in decades; it is impacting every aspect of daily life, and clinical trials are not exempt. The integrity and feasibility of ongoing studies is threatened as the outbreak continues globally.

The biopharma industry's response to the COVID-19 crisis has been commendable, with new treatments and vaccines already in testing. This industry focus, however, along with the burden the pandemic is placing on hospitals and medical centres worldwide is highly disruptive to ongoing clinical trials. The impact over the coming months and years will be widespread and multifaceted, and although it is not possible yet to identify the full extent and severity, it is possible to examine core components of studies on an individual basis and identify the most affected areas. By putting mitigating strategies in place, it may be possible to salvage some of, if not all, a study's potential.

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BIOGRAPHY

Karen Ooms is Executive Vice President and Head of Statistics at Quanticate, responsible for overseeing the Statistics department at Quanticate. She is a Chartered Fellow of the Royal Statistical Society and has a background in biostatistics spanning more than 25 years. Prior to joining Quanticate in 1999 (Statwood), she was a Senior Statistician at Unilever. She earned her MSc in Biometry from the University of Reading.

PRECLINICAL TESTING

Expanding Opportunities in Implantable Medical Devices With Optimized Preclinical Studies

By: Jaleel Shujath

INTRODUCTION

Implantable medical devices (IMDs) are increasingly used in established and novel clinical applications. Given such devices' invasive nature, they are subject to some of the strictest regulations and rigorous pre- and post-market controls. *In vivo* preclinical models represent a crucial tool to study how these devices function in physiological settings and provide vital supporting evidence for regulatory approval processes. However, standard experimental design and primary endpoints for preclinical studies are often limited, reductionist, and may overlook common and essential clinical aspects of a patient's condition that could impact device safety and performance.

The following outlines the growing importance of implantable devices in clinical settings and our daily lives, highlighting the current state of preclinical testing and the regulatory barriers faced by device developers. But, as described here, innovative preclinical study design and testing in multiple disease contexts can provide a deeper understanding of device function, enabling more effective product development and more precise insight into clinical effectiveness.

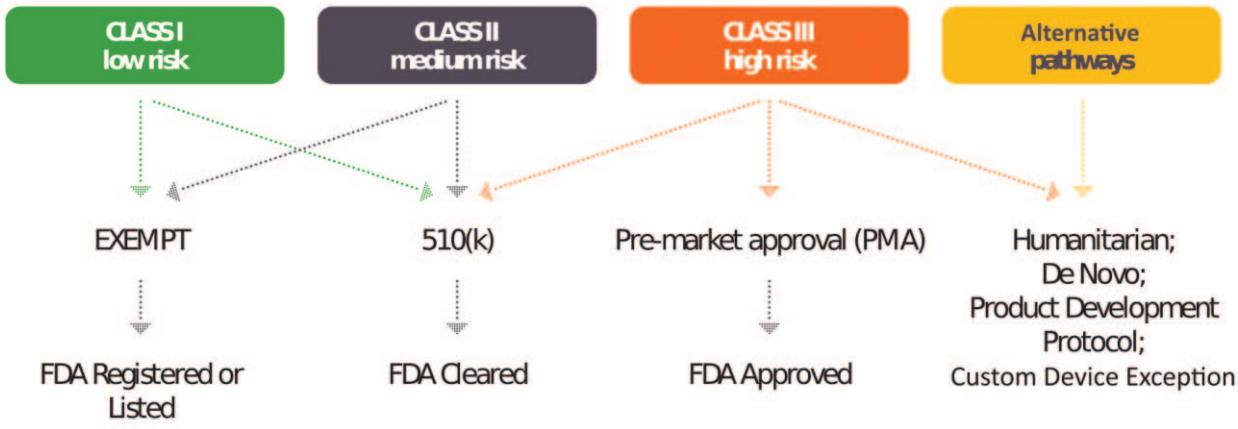
EXPANDING OPPORTUNITIES FOR DEVICES & PATIENTS

IMDs — a subset of medical devices — are used inside the body and include artificial hips, drug-eluting stents, insulin delivery devices, and pacemakers. The market for IMDs is increasing and is expected to reach a global value of $153.8 billion by 2026.[1] IMDs have been used for decades in surgical settings to provide life-saving therapies, primarily in orthopedics and cardiology. But more recently, significant interest in IMDs replacing or complementing existing pharmaceutical treatments has been growing in many clinical fields. There are also broader applications for IMDs in personalized medicine, health monitoring, and interfacing directly with physiological systems. Elon Musk's Neuralink technology, for example, is receiving significant media attention and highlights the scope of the future of IMDs.[2]

Several developments are facilitating the increased adoption of IMDs in all these contexts. One improvement comes from advances in materials with desirable functional properties that are also safe to use in sensitive locations in the body, such as blood vessels and heart muscle. Plus, the rapid development of wireless and Internet-of-Things technologies over the past decade is facilitating innovation of smaller, smarter implants, and secure wireless technologies and software developments, which expand the functionality of many existing monitoring technologies.

IMD technologies can alleviate patient burdens in many ways. As an example, diabetes, which is increasingly prevalent globally (especially in developed countries, like the US) often relies on patient-driven monitoring and treatment for effective disease management, creating a significant burden to the patient. Such problems could be resolved with effective monitoring and drug-delivering IMDs. Similar devices are set to become increasingly common in treating many conditions and replacing or complementing traditional pharmaceutical approaches.

FIGURE 1



The lowest-risk medical devices, Class I, are simple and usually require no pre-market submissions. Risk increases in Class II devices, in which pre-market notification is required. Class III devices are typically implanted, such as drug-eluting stents, and these devices require pre-market approval in the US.

REGULATORY CLASSIFICATION & CONSEQUENCES

The regulatory approval process reflects the different challenges involved in the development of IMDs versus pharmaceuticals. The key differences lie in how regulatory bodies classify IMDs and the resulting consequences for development pipelines. For example, the World Health Organization defines a medical device as: "any instrument, implant, software, or material intended to be used in human beings for a medical purpose, including diagnosis, prevention, monitoring, or treating a disease or injury and for support of the anatomy or of a physiological process."[3]

Major regulatory bodies develop classification systems for medical devices that stratify products by risk. The US FDA, for example, uses three categories: low risk (or Class I), which includes IMDs such as elastic bandages and nasal sprays; moderate-risk devices (or Class II), which includes glucose monitoring systems, pregnancy tests, and powered wheelchairs; and high risk (or Class III), which includes IMDs such as drug-eluting stents and pacemakers.[4] The regulatory controls required for these classes differ significantly (Figure 1). Implantable and invasive devices are typically higher risk due to invasive procedures, innate immune responses, and material toxicity.[5] Consequently, they require stringent pre-market approval (PMA) applications before entering the market. However, approval of these devices can be streamlined by showing equivalence with a marketed device not requiring PMA — termed predicate — via a 510(k).

In contrast to PMA applications, only 10% to 15% of 510(k) applications require clinical data and can rely heavily on preclinical studies to provide the data on the device's equivalence and performance compared to the predicate device.[4] As a result, 510(k) applications offer a quick route-to-market for iterations of existing products, analogous to an abbreviated new drug application (ANDA) for a pharmaceutical.

THE IMPORTANCE OF PRECLINICAL STUDIES

Preclinical studies are extremely valuable in IMD development, from trialing early devices to comprehensive evaluations of efficacy. A study's design depends on the stage of product development, with endpoints matched to the aims.

Feasibility studies allow initial *in vivo* tests of device implantation and removal in live animals (under anesthesia), as well as basic assessments of device function and safety. Extensive post-surgical histology is not typically required. Good laboratory practice (GLP) studies, on the other hand, are more involved, with more defined endpoints for safety or functionality. For example, a GLP study of a hemorrhage-control device might involve multiple applications of the device in a surgical setting. A battery of physiological recordings to assess the systemic animal state can be taken before post-surgical histology of the device location to evaluate local tissue damage.

Preclinical studies are used in both 510(k) and PMA applications for IMDs to assess safety and performance. These studies have several significant advantages over clinical trials. In particular, animal studies provide essential information about the physiological impacts of implanting a device important to assessing safety. For example, any implant results in a foreign body response (FBR) from surrounding tissue, which is crucial to understand from a safety and performance perspective (Figure 2).[6,7] An FBR is a physiological reaction of the body to foreign material in the tissue. It is a step-wise process of inflammation, wound healing, and potential end-stage fibrosis and scarring.[8] If not resolved, excessive fibrosis can result in fibrotic encapsulation of implanted devices, which can impair device integration, long-term functionality, and bioactivity.

Devices implanted in soft tissue or muscle typically create mild fibrosis surrounding the device, altering tissue mechanics and creating a stiffer tissue context for the device.[9] Additional local immune responses can cause inflammation, swelling, and bruising around the implantation site as well. These different aspects of FBR can impact device stability, safety, and function, which makes these responses crucial to model and understand. Moreover, the material composition, shape, and rigidity of an IMD can modulate the resulting FBR, which makes these studies part of a feedback loop for iterative design improvements to limit the unwanted response.[7,10]

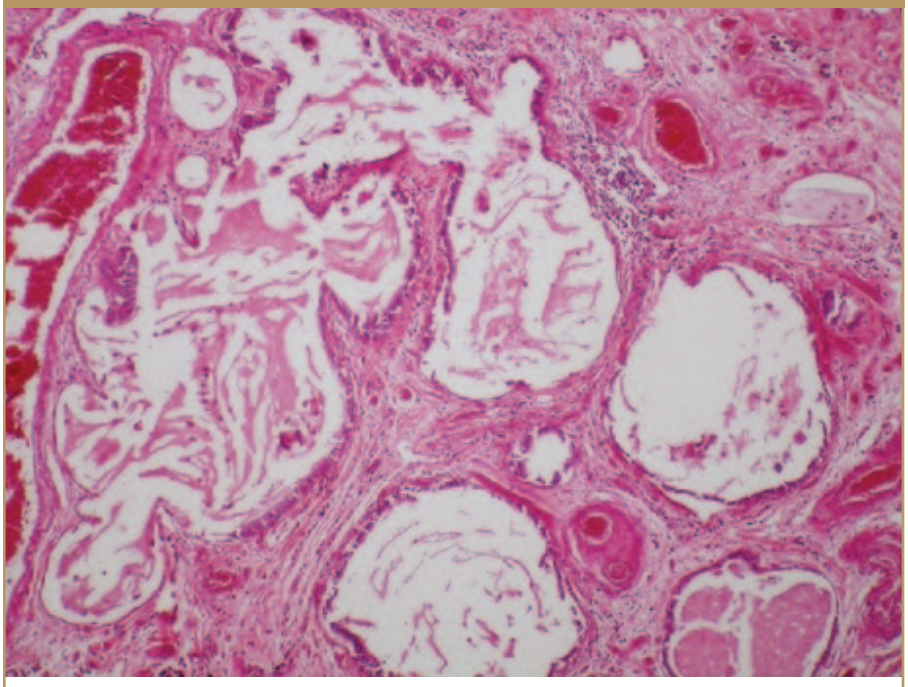
Predicting physiological responses to a particular implant in humans is challenging due to significant case-to-case variability based on the device's specific location in patients. In rats, for example, the microtissue anatomy of different subcutaneous implant sites can alter the FBR.[11] Although post-market risk evaluation is an integral part of any IMD development pipeline, there are limitations to the types of endpoints available in human subjects, such as tissue histology. As a result, animal models represent an essential tool for understanding the physiological response to an IMD.

Detailed histopathology from one or more time points after implantation can provide the most accurate assessment of inflammation and fibrosis at the site of implantation.[6] Additionally, systemic readouts, such as levels of inflammatory markers in blood or serum, can provide additional data on the inflammatory response, as well as useful functional endpoints for specific devices, such as implantable insulin pumps.

Aside from safety, preclinical studies are also crucial for assessing an IMD's performance. For instance, Phase 3 drug trials typically involve placebo-controlled studies to determine a drug's effectiveness versus a control. Equivalent clinical studies for IMDs are impossible due to ethical barriers to unnecessary surgery or implantation of sham devices. As a result, the assessment of a device's efficacy in controlled conditions or in comparison to other device designs relies entirely on preclinical studies.

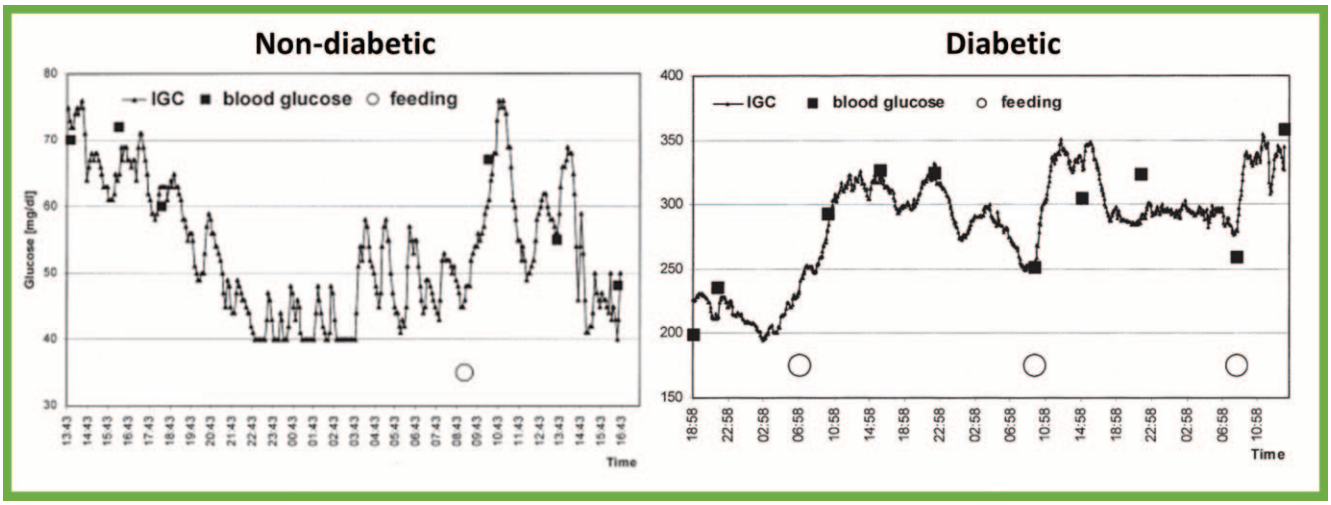
As shown, safety and performance studies focus on assessing device performance under routine conditions. For devices used in specific pathological states, preclinical studies tend to replicate this state as simply as possible. For example, vascular-seal devices can be implanted following acute arteriotomy in porcine models, and polymeric drug delivery systems can be implanted in the eye during the various stages of glaucoma in rabbit models. Although informative, these studies do not consider the impact of disease states or localized pathology — such as infection — on device function. This creates a critical knowledge gap in our understanding of how devices perform in realistic clinical

FIGURE 2



Histological stain showing fibrosis in scleroderma.

FIGURE 3



A continuous glucose monitoring (CGM) device tested in a porcine model of diabetes, which was induced with an injection of streptozotocin. Indocyanine green (IGC) provides information from the implanted device compared to recordings of blood glucose content (square boxes). In non-diabetic conditions (left), the CGM measures blood glucose more accurately than in diabetic animals (right).

settings. Nevertheless, preclinical animal studies can be extended to provide data to guide product development that *in vitro* or clinical follow-up studies cannot.

A SPOTLIGHT ON CONTINUOUS GLUCOSE MONITORS

Innovative study design and endpoints can help preclinical studies of continuous glucose monitors provide a more robust clinical performance assessment. In the US, approximately 10% of the population suffer from diagnosed or undiagnosed diabetes, a figure that has steadily increased over the past 20 years.[12] Standards of care, like finger prick tests and insulin injections, have several limitations, including reliance on patient adherence, regular invasive procedures, and patient-driven treatment. Continuous glucose monitoring (CGM) devices are small implants placed under the skin that regularly report blood glucose levels to the user via a software application. In 2018, Senseonics' Eversense became the first implantable CGM to gain FDA approval, coinciding with the approval of the interoperable Dexcom G6.[13,14] Given the regulatory barriers for breakthrough IMDs, these milestones will likely lead to more devices entering the market over the coming decade.

There are several well-established preclinical models for diabetes in the assessment of CGMs. Figure 3 illustrates the basic study design for testing the primary functional endpoint — blood glucose reading — in a chemically-induced model of diabetes in minipigs.[15] These studies allow a direct comparison of blood glucose with the estimated reading provided by the implant in diabetic and control animals, allowing an *in vivo* evaluation of a device's performance across a wide range of blood glucose values.

Experiments like these can be combined with follow-up histological assessments of the implant area. For example, a recent study in a rodent model of diabetes found a positive correlation between collagen content at the implant site (a readout of fibrosis) and delay in CGM readings.[16] That type of study provides a useful way to understand the underlying causes of the poor performance of CGMs *in vivo*.

Importantly though, diabetes is a metabolic disease often associated with other comorbidities, including obesity, lung disease, and liver disease. Indeed, smokers are 30% to 40% more likely to develop type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) increases the risk of type 2 diabetes by two- to three-fold.[17,18] These conditions are associated with broad systemic changes to metabolism and immune response and represent a common but distinct physiological context within which CGMs must function properly. Conditions such as NAFLD have established preclinical models, like the Amylin liver NASH (ALMN) diet, which leads to progressive accumulation of fat in the liver, fibrosis, and eventually cirrhosis. These models offer an ideal system for testing the performance of CGM devices under a secondary, clinically relevant disease context.

This type of data could lead to device designs that are more universally reliable or to stratify patients to offer specialized devices for those with relevant comorbidities.

THE ROUTE TO SAFER, MORE EFFECTIVE IMDS

Preclinical studies make up a vital stage in the development of IMDs. Established disease models and study designs enable effective assessments of safety and efficacy. However, these models can be further augmented to provide far greater insight into the function of these devices in real clinical settings, namely by combining disease models and correlating device performance with secondary endpoints. Given the growing importance of IMDs in the clinic, and our daily lives, the development of this preclinical approach is more critical than ever. ◆

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BIOGRAPHY

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Drug Development
EXECUTIVE

Mark Egerton, PhD
CEO
Quotient Sciences

Quotient Sciences

Molecule to cure. Fast.™

Quotient Sciences: Breaking Down the Silos Between Drug Substance & Drug Product

Pharma R&D is in its heyday, with funding at record levels. Additionally, the number of molecules in the industry pipeline seems to be increasing by about 10% per year on average.

As more companies get involved in drug development, the majority are small, virtual organizations that rely on outsourcing models. But outsource providers face technical challenges in finding molecules that work. Most development project teams are trying to "get to know/no quickly." The goal is to spend the minimum amount of money to have the greatest confidence that the molecule will be a success.

Moving from the edge of discovery research, or candidate selection, and into clinical proof of concept is where most attrition occurs in drug development. This is where Quotient Sciences has created a niche for itself over the past 15 years. Quotient has developed a novel platform called Translational Pharmaceutics®, which integrates drug product and clinical testing activities, breaking down the silos between Chemistry, Manufacturing and Controls (CMC) and clinical research to accelerate molecules through development. This helps biotech/pharma companies shorten timelines by at least 12 months, reducing spend, and reaching key milestones as quickly and efficiently as possible.

Quotient Sciences, a drug development and manufacturing accelerator, recently acquired Arcinova, a UK-based multiservice contract development and manufacturing organization. The acquisition expands Quotient's service portfolio and will enable the integration of drug substance, drug product, and clinical testing capabilities all under one umbrella.

Drug Development & Delivery recently spoke with Mark Egerton, PhD, CEO of Quotient Sciences, about how integrating these capabilities cuts through functional silos, simplifies drug development, and affirms Quotient's belief that molecules need to become cures, fast.

Q: Why was Arcinova attractive to Quotient?

A: The Arcinova acquisition gives us a new set of services and allows us to engage with a customer at the point of candidate selection. Now, we can support a molecule all the way from molecule selection to proof of concept and onwards to commercial product manufacture. The services that Arcinova offers are complementary to what Quotient provides to its customers. Arcinova manufactures drug substance – the active pharmaceutical ingredient – which Quotient doesn't and was eager to add to its service portfolio. When a customer comes out of discovery research and identifies the candidate they want to develop, the first thing they have to do is make larger volumes of drug substance to support the preclinical toxicology studies and initial clinical trials. That's what Arcinova does. To date, Quotient has specialized in understanding which formulation compositions to develop to maximize the delivery of an active drug substance at the right place, right time, and right concentration. We take those drug product compositions and manufacture them all the way to commercial manufacturing. So, with this acquisition, we are combining the active ingredient with the formulation capability. Our strategic goal is to integrate drug substance manufacturing into our Translational Pharmaceutics platform. We think the timeline acceleration that we can offer for a customer will increase from 12 months to 18 months.

Q: How will this acquisition break down the industry silos you see happening in pharma?

A: There is a lot of "siloing" in the industry. Many outsourcing companies have been formed along functional disciplines. It is quite rare to find companies that manufacture both drug product and drug substance, and in larger companies where both are offered, it's rare to have the functions integrated; very often they will be run as different business units. If you ask the marketplace whether drug substance has been successfully integrated into drug product, I think you will get a very mixed response.

Q: How will Quotient position itself to go up against other drug substance and drug product providers?

A: By being scientific-rich, engaging with the customer at point-of-candidate selection, and providing an integrated scientific perspective on how a molecule can be developed. For example, our drug substance scientists will be thinking ahead and asking questions such as: How will this drug substance be formulated? What is the intended clinical dosage form? How can we make the regulatory/CMC pathway as straightforward as possible? By operating in fully integrated teams, we will simplify hand-off points and knowledge transfer for the customer. We have seen initial signs of success from Arcinova's existing drug substance projects, of which 25% of molecules have already transitioned into simple drug products. When you combine Arcinova with Quotient's extensive drug product capabilities, we believe more customers will be compelled to integrate the activities and break down the traditional industry silos. Some of the big CDMOs in the industry market themselves on the basis that they have both drug substance and drug product capabilities, but they aren't actually integrated. We will drive true integration of these activities into a seamless program.

Q: How challenging was it to manage an acquisition during a pandemic? What lessons did you learn that you could apply to future acquisitions that may occur post-COVID?

A: Last March and April, like every business in the world, we were working extremely hard and adapting quickly to keep the business running smoothly. But, in May, we decided that we wanted to come out of this pandemic stronger than we went in, so we made a couple of key conscious decisions. The first was a complete review and overhaul of our modus operandi – with a much greater emphasis on flexible and adaptive working practices across all our facilities. This has led to an increase in productivity. The second decision was to continue to pursue the Arcinova acquisition and maintain our growth plan. The bulk of the due diligence and business planning was done from September to January and, despite the remote working, the process went well. Fortunately, I had built a relationship with the Arcinova founder in the summer of 2019 and, in hindsight, I think that gave me the confidence to undertake the acquisition as I had a good feeling for the Arcinova culture and values. Building trust in any business relationship is vital and, as a service business, everything we do is dependent upon people.

You've got to trust the people you will be working with and you can't beat face-to-face contact to go through that process. We did have a large video call upon signing the acquisition agreement, where everyone raised champagne in a virtual toast. And in the week following the deal's completion, I spent two days at the Arcinova site where a real celebration took place, face to face, in the same room – socially distanced of course.

Q: In what other areas would Quotient be interested in possibly acquiring companies to expand its service offerings and geographic locations?

A: The Arcinova deal opens up greater opportunities for us. Prior to Arcinova, Quotient had operating facilities in the UK and US so we offer mirrored services on both sides of the Atlantic. Arcinova is entirely UK-based so we are discussing if we should replicate the Arcinova offering in the US either by building organically or seeking an existing business to partner with us. Our core business focuses on small molecule early development as well as work on smaller scales of drug substance and drug product across all delivery routes, including oral solid, oral solution, inhaled, and injectables. As we move into larger scale manufacturing and commercial manufacturing, our capabilities are focused on solid oral dose forms (tablets and capsules). There is a strong desire to broaden our late-stage scale and capability set in other dosage forms like sterile injectables. That would be an interesting place for us to go.

Q: Describe your business plan and how acquisitions fit into that plan.

A: Quotient is anchored on a strong organic growth opportunity with the potential to double the size of the business in the next five years. This business plan is based on building our market share using our existing service portfolio. That being said, we will always look at acquisitions as a way of accelerating our growth plan and/or diversifying our service offering. We will remain highly selective about which acquisitions to make and they must be consistent with our manifesto: enhancing our ability to accelerate drug development timelines for our customers.

Q: How is private equity partner Permira guiding Quotient's growth plans?

A: We teamed up with Permira in the summer of 2019, and they are our fifth, and largest, private equity partner to date. I've been with Quotient for 16 years and we partnered with different private equity partners as we've transitioned through our growth plan. Permira was aligned and excited with our business plan and the vision that we are striving to achieve. They are focused on growth and supporting us to speed up that growth wherever possible. They are really helpful in terms of thinking through how to accelerate investments for organic growth and will provide us with support for getting the right acquisitions across the line, as demonstrated by the Arcinova deal.

Our chairman was introduced to us by Permira and he has extensive industry experience in pharmaceutical services. One of the first things we committed to when we teamed up with Permira was to build a new 85,000-sq. ft. facility in the Philadelphia area. This is in addition to our nearby 45,000-sq. ft. facility. We believe these two new facilities for drug product development and manufacturing – housing exploratory work through to commercial manufacturing – will accommodate our approximately 250 employees on site and will be a real showcase to potential customers.

Arcinova is the fifth acquisition that Quotient has made and the first since forming our partnership with Permira. Each of the other four acquisitions were underpinned with a specific strategic intent:

- Replication of our Translational Pharmaceutics platform in the US, and expanding our manufacturing capability from development through to commercial (SeaView and QS Pharma acquisitions in February 2017);
- Expanding our CDMO capability and capacity in the UK (Pii site acquisition in November 2017); and
- Accessing specialist formulation development skills for pediatric medicines (Co-Formulate acquisition in 2017).

We hope there will be further acquisitions, but we will continue to be highly selective and targeted to businesses that support our strategy. ◆

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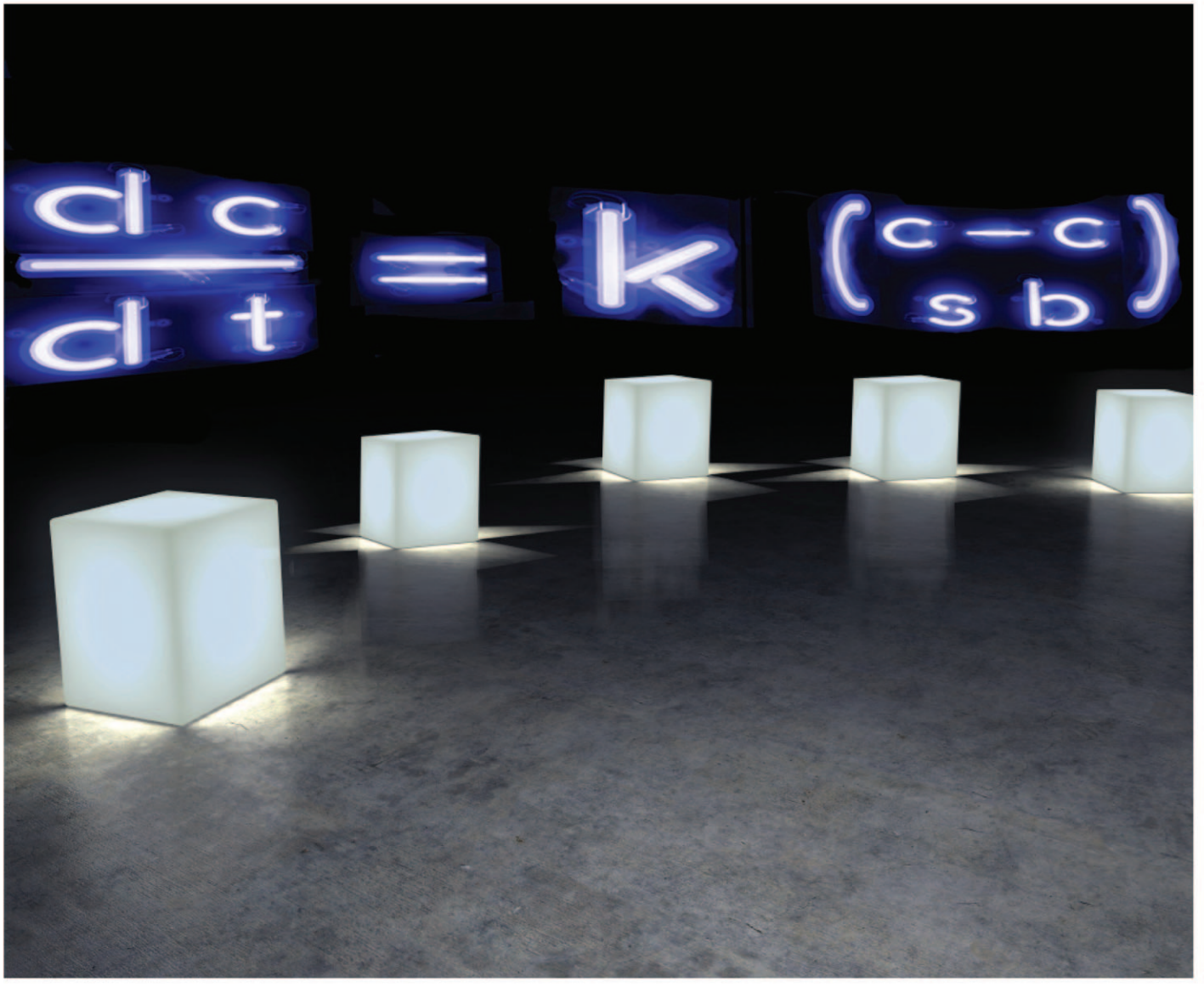

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