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Drug Development & Delivery

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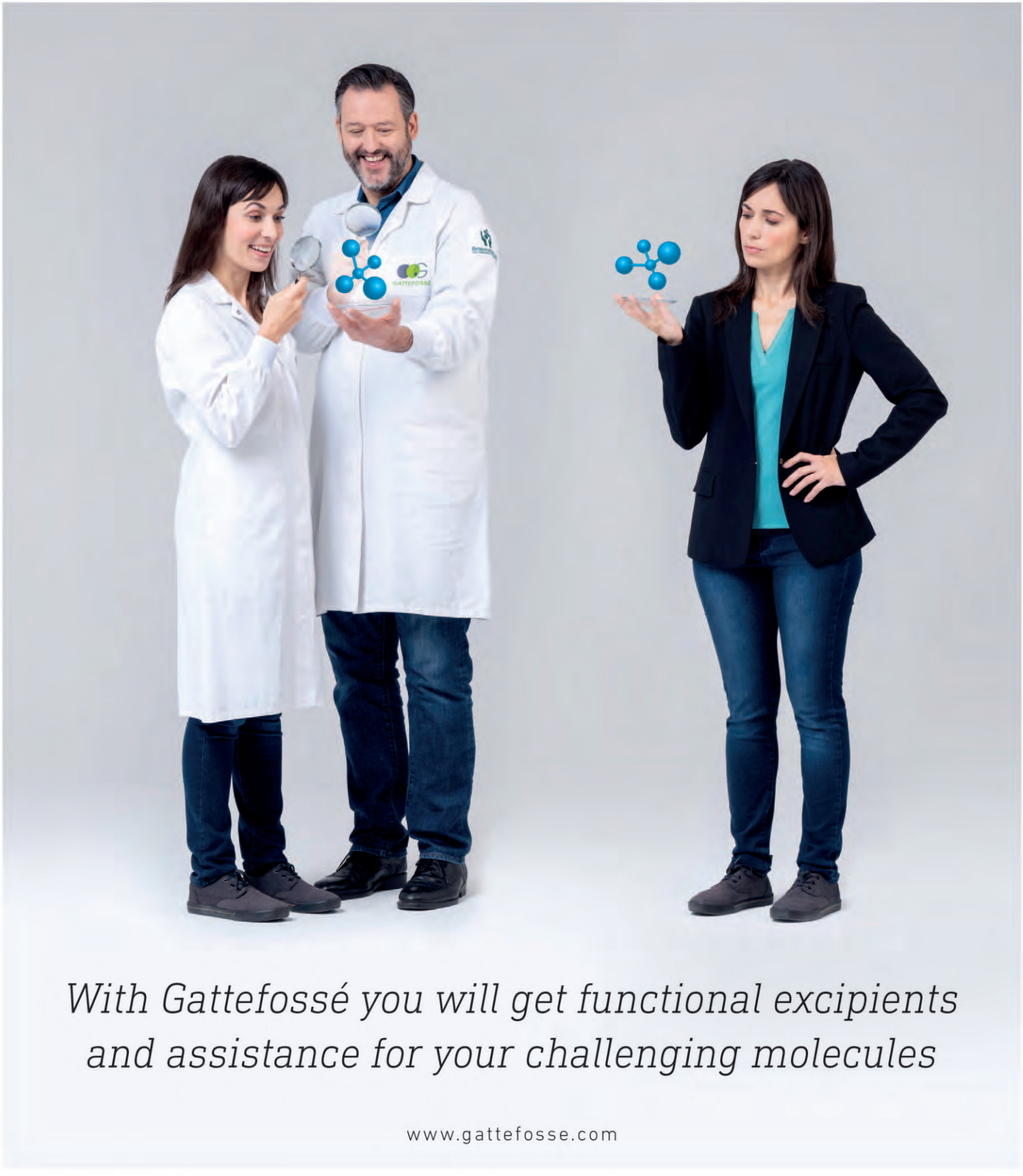

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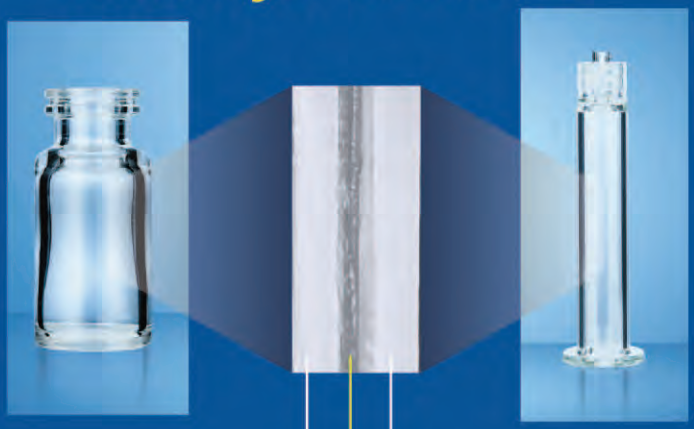
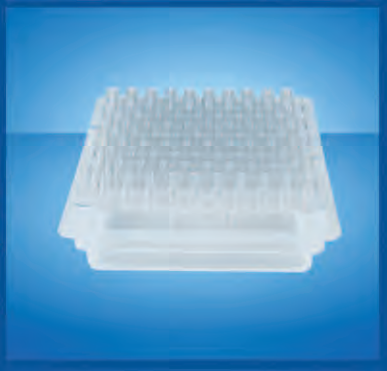


Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)



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Drug Development & Delivery

April 2021 Vol 21 No 3

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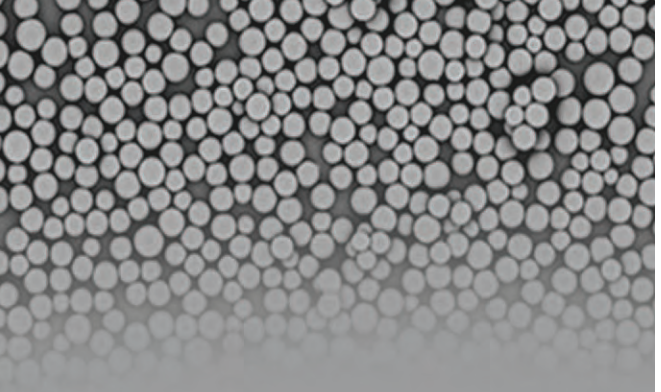

Microspheres for Sustained Release

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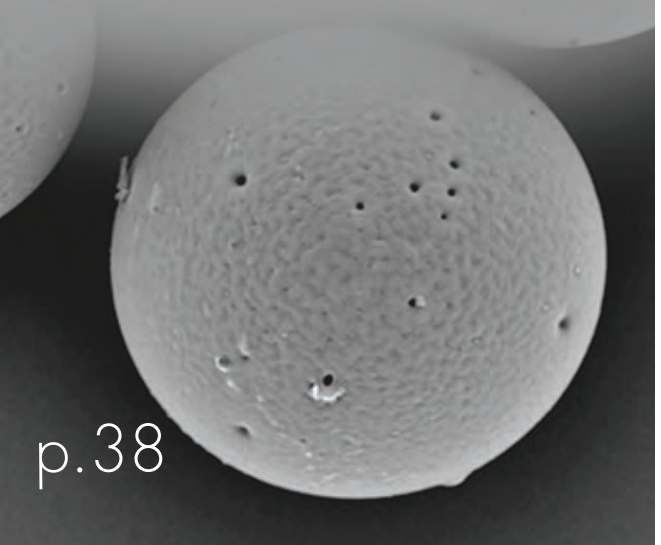

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THE DIFFERENCE OF ONE DRUG DELIVERED

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Owen Mumford Introduces 16-G Safety Lancet Into Unistik Touch Range for High-Volume Capillary Blood Sampling

Owen Mumford recently announced it has introduced a 16-gauge (16 G) safety lancet for high-volume capillary blood sampling into its leading Unistik product range. The new Unistik Touch 16 G has one-touch activation and Comfort Zone Technology that minimizes the pain of finger sampling.

The new safety lancet has been designed for healthcare professionals (HCPs) and test kit manufacturers. For HCPs who need to perform higher volume blood sampling on patients for a wide range of tests, including blood gas, electrolytes, blood coagulation, total bilirubin, and cardiac markers, it can be used in a variety of clinical settings and offers the benefit of fewer punctures for higher blood volumes.

It is also ideally suited for at-home and point of care testing (POCT) kits, making it a convenient choice for test kit inclusion by kit manufacturers who require reduced packaging, bulk order quantities, and can benefit from its small form and simple user features.

The Unistik Touch 16 G one-touch activation feature requires the user to simply press the device against the sample site. Activated automatically, the needle then retracts into the body of the device, minimizing the risk of re-use, pre-analytical errors for multiplex tests, cross infection, and needlestick injuries.

"The Unistik Touch range was developed in-house to make sampling more comfortable for patients and easier for HCPs to successfully obtain the right amount of blood first-time," said Jesper Jonsson, Director of Medical Devices at Owen Mumford. "Our proven pain-minimizing technology and simple one-touch activation makes it a very attractive option and the 16 G lancet has been developed and priced competitively to ensure the same benefits in patient comfort can be offered within the growing at-home testing and POCT markets. This new solution for high volume blood sampling perfectly complements our portfolio so we can offer the market an even wider choice of safety lancet."

The Unistik Touch 16 G is available in a range of packaging configurations including 100 ct, 200 ct, and bulk volumes. Further educational material has been created in collaboration with HCPs and key opinion leaders to support everyone in achieving reliable test results.

Owen Mumford is a leader in the design, manufacture and advancement of medical technology, commercializing medical products in its own brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. It has pioneered the evolution of medical devices for almost 70 years with solutions for the ease and comfort of administering life-saving medication, safe and comfortable blood sampling and testing, and rapid professional and self-diagnostic testing kits. With many patents existing and more pending, Owen Mumford continually evolves the leading-edge technology that empowers it to make a world of difference to the comfort, safety and dignity of patients, healthcare professionals and caregivers across the world. The company has a global presence across the UK, USA, Europe and Asia, employing over 800 associates and is a trusted partner to many of the world's biggest diagnostic and pharmaceutical companies. For more information, visit www.owenmumford.com.

Timber Pharmaceuticals Announces 50% Enrollment in Phase 2b CONTROL Study

Timber Pharmaceuticals, Inc. recently announced 50% of patients in the Phase 2b CONTROL study evaluating TMB-001 (topical isotretinoin) in patients with moderate-to-severe congenital ichthyosis (CI) have now been randomized. The company also announced it has been awarded the final tranche of a $1.5-million grant from the US FDA Office of Orphan Products Development (OOPD) Orphan Products Clinical Trials Grants Program based on clinical milestones in the development of TMB-001.

"There are many rare dermatologic diseases that do not have any approved therapies, and we are committed to advancing research focused on novel topical treatments that may enable targeted delivery to the epidermis and dermis while minimizing systemic absorption," said Alan Mendelsohn, MD, Chief Medical Officer of Timber. "People living with CI face many significant challenges in everyday life, not just physically but also with psychological well-being and self-esteem. Our success with enrolling the CONTROL study is a testament to the tremendous need for new treatment options. We are grateful to the patients who are participating and organizations like the Foundation for Ichthyosis & Related Skin Types (FIRST) that are helping raise awareness of this study amidst all the difficulties of the COVID-19 pandemic."

CI is a group of rare genetic keratinization disorders that leads to dry, thickened, and scaling skin. People living with CI may have limited range of motion, chronic itching, an inability to sweat normally, high risk of secondary infections, and impaired eyesight or hearing. Moderate-to-severe subtypes of CI, including X-linked ichthyosis and lamellar ichthyosis, affect about 80,000 people in the US and more than 1.5 million globally.

The Phase 2b CONTROL study is a randomized, parallel, double-blind, vehicle-controlled study to assess the efficacy and safety of two concentrations of TMB-001 for the treatment of moderate-to-severe subtypes of CI. The study is targeting enrollment of 45 patients aged nine years old and older.

"We hope that by formulating isotretinoin into a proprietary topical we might be able to allow for chronic use on up to 90 percent of body surface area without eliciting the side effect profile of systemic isotretinoin preparations," added Dr. Mendelsohn.

Timber Pharmaceuticals, Inc. is a biopharmaceutical company focused on the development and commercialization of treatments for rare and orphan dermatologic diseases. The company's investigational therapies have proven mechanisms-of-action backed by decades of clinical experience and well-established CMC (chemistry, manufacturing and control) and safety profiles. The company is initially focused on developing non-systemic treatments for rare dermatologic diseases including congenital ichthyosis (CI), facial angiofibromas (FAs) in tuberous sclerosis complex (TSC), and scleroderma. For more information, visit www.timberpharma.com. For more information about the Phase 2b CONTROL study, visit https://ichthyosistrial.com/.

Axol Bioscience & Censo Biotechnologies Announce Merger

Axol Bioscience Ltd and CENSO Biotechnologies recently announced that the two companies have signed a merger agreement. The new entity will become a leading provider of product and service solutions in the iPSC-based neuroscience, immune cell, and cardiac modeling for drug discovery and screening markets. It will offer customers validated ready-to-use cell lines and a suite of services with broader expertise, robust functional data, and customization capabilities, all with shorter lead times.

Axol Bioscience's investors include Dr Jonathan Milner and award-winning EIS fund manager, Calculus Capital. CENSO Biotechnologies' major investor is leading Edinburgh-based EIS fund manager, Par Equity. The transaction is accompanied by a fundraising round in excess £3.8m, led by Calculus Capital and Par Equity. The investment will be used to enable growth of the business and acquisition of talent to meet customer demand.

Under the terms of the agreement, Axol Bioscience CEO, Liam Taylor, and the Axol senior leadership team will take over the management of the combined entity, with the intent to migrate the brand to Axol Bioscience. The agreement sees CENSO's interim CEO, Dr Tom Stratford, appointed non-executive director of the combined board, on behalf of Par Equity.

Liam Taylor, CEO Axol, said "Axol has experienced a rapid increase in demand for their iPSC-based products and services over the last three years. Merging with CENSO immediately and significantly grows our scientific team and breadth of expertise. That, and the addition of two sites for iPSC-derived cell line manufacturing and custom service work, will increase our production capacity and future-proof our organization to ensure demand can continue to be met with the short lead times and quality that our customers depend on."

Dr. Tom Stratford, CENSO interim CEO and non-executive director of the combined board, on behalf of Par Equity, added "CENSO's strength is our scientific team, as trusted partners in designing, executing, and managing custom project work. The combined entity will now be able to leverage Axol's strength in iPSC-derived cells as well as complementary services such as electrophysiology to further our ability and efficiency to serve customers. We bring to bear capabilities, bandwidth, and expertise to scale the manufacturing of those tools in a way that benefits both customer bases and the wider market."

Dr Jonathan Milner, Founder, and former CEO of Abcam and Chairman of the Axol Bioscience board, said "Consolidating these two players in the iPSC space that have complementary expertise and offerings is the most direct and low risk path to gaining a more competitive market position and moving both organizations from thriving start-ups to a more polished commercial entity that is able to meet aggressive demand increases."

Micropore Appoints Technology Distributor for Japanese Market

Award-winning UK-based particle engineering specialist Micropore Technologies has just announced the appointment of the Mutual Corporation as the representative for sales of its patented membrane technology in the Japanese market.

Established for over 70 years, headquartered in Osaka, and with offices/production and research facilities in Fukuoka, Shizuoka, Tokyo, Toyama, and Yachimata, the Mutual Corporation designs, manufactures, imports, and exports manufacturing equipment with a strong focus on the pharmaceutical and cosmetic sectors.

Micropore's patented scalable emulsification and encapsulation technology offers manufacturing capacities from 10 grams/hour up to 1500 kg/hour of products with precisely controlled particle sizes. It also offers lipid nanoparticle and liposome manufacturing technologies for vaccines and gene therapies.

Micropore's GMP-compliant technology utilizes tubular membranes with no moving parts. The very low shear forces involved protect sensitive ingredients from processing damage – significantly reducing production wastage (which can be up to 50% using traditional homogenization and encapsulation techniques); and reduces processing energy by around a 70% – again contributing a positive impact on the end cost of products.

Mutual Corporation is very well connected throughout Micropore's target market sectors. Throughout the history of the company, Mutual aims to contribute to the development of society by applying the motto "coexistence and mutual prosperity." Based on the spirit of mutuality, Mutual endeavours to strive for a prosperous future together with its business partners, shareholders and employees. Together Mutual Corporation and Micropore will serve the parentral drug, vaccine and gene therapy markets as well as the personal care and other demanding market sectors.

Dai Hayward, CEO of Micropore, said "We are delighted that Mutual Corporation will help us enter the challenging Japanese market. They bring a wealth of expertise and knowledge and I look forward to our partnership developing positively."

Mutual offers comprehensive support for production systems and solutions installed in facilities such as pharmaceuticals, cosmetics, foods and so on through expertise in four market sectors – engineering, manufacturing, trading, maintenance.

Micropore's has won multiple international awards for its innovative membrane-based technology, most recently an Excellence in Pharma Award for Membrane Crystallisation of APIs at the 2020 CPhI Pharma Awards.

Micropore's patented encapsulation technology originated in the department of chemical engineering at Loughborough University. Dr Marijana Dragosavac Senior Lecturer and Undergraduate Admissions Tutor at Chemical Engineering department at Loughborough and Micropore's Chief Scientific Officer has published many papers in the field. Micropore Technologies Limited was established over ten years ago as a high-technology spin-out of Loughborough University and is a solutions provider commercialising products and technology based on its patented encapsulation and emulsification processes. For more information, visit www.microporetech.com.

Catalent Expands Partnership With Johnson & Johnson to Significantly Increase Capacity for Sterile Manufacturing & Packaging of COVID-19 Vaccine in Italy

Catalent recently announced an expanded partnership with Janssen Pharmaceutica NV and Janssen Pharmaceuticals, Inc., two of the Janssen Pharmaceutical Companies of Johnson & Johnson, whereby Catalent Biologics will significantly increase the manufacturing capacity for large-scale commercial supply of Janssen's COVID-19 vaccine at Catalent's manufacturing facility in Anagni, Italy, including vial-filling, inspection, labeling, and packaging services.

Catalent and Janssen had previously agreed to dedicate an existing vial-filling line at the Anagni facility. As part of this expanded agreement, Catalent will accelerate the qualification and scale-up of an additional high-speed vial-filling line that is expected to be operational in the fourth quarter of 2021, to support the production of the Janssen vaccine through late 2022.

"We are pleased to expand our partnership with Janssen to support demand of its COVID-19 vaccine in Europe," said Mario Gargiulo, President, Catalent Biologics, Europe. "Our global network of state-of-the-art biologics facilities, combined with our deep expertise in manufacturing scale-up and commercial launch, is well-suited to help provide a solution to this public health crisis."

Catalent's 28,000-sq-m facility in Anagni has a demonstrated track record in technical transfers and successful commercial product launches and offers extensive capabilities in aseptic liquid filling for biologics and sterile products across multiple vial sizes, and comprehensive primary and secondary packaging solutions, including serialization, to support product launches for oral solids, sterile, and biologics products. Catalent's Switzerland affiliate serves as the principal for this contract, while Anagni will perform the manufacturing and packaging services. Similarly, Catalent's Bloomington, Indiana, facility currently provides manufacturing and packaging services for Janssen's COVID-19 vaccine supply chain in the United States.

Catalent Biologics is a global leader in development, manufacturing and analytical services for new biological entities, cell and gene therapies, biosimilars, sterile injectables, and antibody-drug conjugates. With over 20 years of proven expertise, Catalent Biologics has worked with 600+ mAbs and 80+ proteins, produced 13 biopharmaceutical drugs using GPEx cell line development technology, and manufactured 35+ commercially approved products. Catalent Cell & Gene Therapy, a unit of Catalent Biologics, is a full-service partner for adeno-associated virus (AAV) vectors, lentiviral vectors and CAR-T immunotherapies, with deep experience in viral vector scale-up and production. When Catalent acquired MaSTherCell, it added expertise in autologous and allogeneic cell therapy development and manufacturing. Catalent Cell & Gene Therapy has worked with worked with industry-leading partners across 70+ clinical and commercial programs. For more information, visit biologics.catalent.com.

Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, cell and gene therapies, and consumer health products. With over 85 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable global clinical and commercial product supply.

2020 Global Drug Delivery & Formulation REPORT

Part Two 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: Josef Bossart, Ph.D., Executive Editor, PharmaCircle LLC

Introduction

Drug Delivery and Formulation is increasingly becoming as much an opportunity to creatively apply available technology to existing therapeutic challenges as it is to develop novel technology. This past year presented examples of both.

The most notable new products of 2020 were the first two COVID-19 vaccines to be introduced for clinical use, Pfizer/BioNTech's Comirnaty and the Moderna COVID-19 Vaccine. These products depended on a novel mechanistic approach, the use of mRNA to express antigen proteins, and novel technologies to deliver these therapeutics in sufficient quantities to the nucleus of cells.

Also notable was the approval of two antibody-based products, Janssen Biotech's Darzalex FasPro and Roche's Phesgo. Both products used Halozyme's well-validated Enhanze formulation technology to turn hours-long infusions into much more patient-friendly subcutaneous injections. The applications may have been obvious to some, but the development work was done remarkably quickly, with both products taking about 4.5 years from first clinicals to approval.

Mycapssa from Chiasma joined a very short list of approved oral peptides. A combination of oral absorption enhancer and enteric liquid-filled capsule technologies were necessary to provide the quantities of octreotide required to provide a therapeutic benefit for the treatment of acromegaly. Following on last year's approval of Rybelsus, Mycapssa provides additional validation for the oral administration of peptides.

The notability of Jazz's Xywav, an oral liquid formulation of calcium, magnesium, potassium, and sodium oxybates, revolves more around concept than formulation. By eliminating a problematic sodium issue with their blockbuster Xyrem product but retaining the same dosage form and instructions, Jazz Pharmaceuticals has provided an important patient benefit and given the company an extended commercial runway. It doesn't necessarily take sophisticated technology breakthroughs to meaningfully address real-world patient needs.

A shout out goes to two products that used relatively pedestrian technologies to address real-world patient needs. The first, Hanmi Pharmaceuticals' Amosartan XQ Oral Tablets, combines four multisource cardiovascular agents into a single oral tablet for the treatment of hypertension and hyperlipidemia, making it much easier for patients to be compliant. Mallinckrodt's Gimoti Nasal Spray for diabetic gastroparesis provides metoclopramide in a delivery form that doesn't depend on reliable enteral absorption without the need for an injection.

A common theme over the past few years has been the realization that innovation in the drug delivery and formulation space is as dependent on creative ideas using existing technology than it is waiting for the next big technology breakthrough. In next month's report, we will take a look at exactly what is new and exciting in the area of drug delivery technologies.

Comirnaty & Moderna COVID-19 Vaccines

Comirnaty (Pfizer Inc, BioNTech, Inc.)

Active: BNT162b2
Molecule Type: mRNA
Indication: Active Immunization to Prevent COVID-19
Delivery Route: Injection - Intramuscular
Dosage Form: Injection Suspension, Multidose Vial
DD Category: NP Solid Lipid, NP Lipid Cationic
Dosing: Two doses, 21 Days Apart
First Approval: Temporary Authorisation 2020-12-02 (UK)
Delivery Technology: Acuitas LNP Technology
Delivery Technology Owner: Acuitas Therapeutics

Moderna COVID-19 Vaccine (Moderna, Inc.)

Active: mRNA-1273
Molecule Type: mRNA
Indication: Active Immunization to Prevent COVID-19
Delivery Route: Injection - Intramuscular
Dosage Form: Injection Suspension, Multidose Vial
DD Category: NP Solid Lipid, NP Lipid Cationic
Dosing: Two doses, 28 Days Apart
First Approval: Emergency Use Approval 2020-12-19 (US)
Delivery Technology: Moderna LNP Technology
Delivery Technology Owner: Moderna, Inc.

Development Summary

Both products began development in the first quarter of 2020 following the disclosure of the COVID-19 virus structure.

Comirnaty's first in human trials began in April followed by Phase 2/3 trials in July. The first approval, a Temporary Authorisation in the UK, was granted in December, followed later in the month by similar approvals in the US, EU, and other countries.

Trials for the Moderna COVID-19 Vaccine were initiated in February 2020, followed by Phase 2 in May, Phase 3 in July, and a rolling submission in Canada in October. First approval, Emergency Use Authorization, was received in the US in December. This was followed by an approval in the EU and other countries in early January 2021.

Although labelled as Temporary and Conditional, these are for all practical purposes full approvals with potentially hundreds of millions of doses being administered by the end of 2021.

Platform/Technology Summary

Both products rely on the use of mRNA for the expression of the COVID-19 spike antigens. The mRNA is delivered to the nucleus of cells with the use of lipid nanoparticles. In the case of Comirnaty, the delivery technology, Acuitas LNP Technology, is provided by Acuitas Therapeutics, a small Vancouver Canada-based company. A related Acuitas delivery technology has been previously used for the delivery of RNAi therapeutics, notably Alnylam's Onpattro.

The Moderna COVID-19 Vaccine uses a similar delivery approach albeit with its own proprietary nanoparticle lipid technology, Moderna LNP Technology.

Formulation Summaries

Comirnaty is provided as a 0.45-ml frozen multidose vial suspension requiring thawing and dilution. It is formulated with proprietary lipid nanoparticles.

Moderna COVID-19 Vaccine is provided as 5-ml frozen multidose vial suspensions requiring thawing. It is formulated with proprietary lipid nanoparticles.

Reflections

The development of these two products from "scratch" in less than a year is remarkable. It was built on years of work and investment in understanding the potential of mRNA, the development of the supporting delivery technology to direct and express the antigens, and experienced clinical trial design and execution.

Reflections

The development of these two products from "scratch" in less than a year is remarkable. It was built on years of work and investment in understanding the potential of mRNA, the development of the supporting delivery technology to direct and express the antigens, and experienced clinical trial design and execution.

The Moderna COVID-19 Vaccine may be the more impressive of the two products from a corporate perspective. This was the first Moderna product to be taken through development to approval. The company currently has 20 products in clinical development, 3 in Phase 2, and 17 in Phase 1 for a variety of indications, including COVID-19, CMV, RSV, Influenza, and a variety of cancers.

In the case of Comirnaty, it was fortuitous that BioNTech, who provided the mRNA technology and know-how, had previously established a partnership with Pfizer for the development of mRNA influenza vaccines. BioNTech also had a previous relationship with Acuitas, the delivery technology provider. Only with the contribution of Pfizer's expertise in all aspects of drug development, GMP processes, and distribution was it possible to bring Comirnaty to patients so quickly.

Make no mistake, mRNA technology and the supporting delivery technologies will provide important future therapeutics. A quick look at PharmaCircle's Pipeline & Products Intelligence module finds 52 mRNA products are currently in clinical development with another 163 at the preclinical or research stage.

Darzalex FasPro (Janssen Biotech)

Active: daratumumab
Molecule Type: Antibody
Indication: Cancer, Multiple Myeloma
Delivery Route: Injection - Subcutaneous
Dosage Form: Solution, Single-Dose Vial
DD Category: Injection Site Absorption Enhancers
Dosing: Injection, 3-5 Minutes, Every 1 to 8 Weeks
First Approval: 2020-05-01 (US)
Delivery Technology: Enhanze
Delivery Technology Owner: Halozyme Therapeutics, Inc.

Phesgo (Genentech, Inc.)

Actives: trastuzumab, pertuzumab
Molecule Type: Antibody (both)
Indication: Cancer, Breast
Delivery Route: Injection - Subcutaneous
Dosage Form: Solution, Single-Dose Vial
DD Category: Injection Site Absorption Enhancers
Dosing: Injection, 5-8 Minutes, Every 3 Weeks
First Approval: 2020-06-29 (US)
Delivery Technology: Enhanze
Delivery Technology Owner: Halozyme Therapeutics, Inc.

Development Summary

Both of these products from Janssen and Roche followed very similar timelines, taking about 54 months from first patient dosing to FDA approval. Both products are new formulations of products previously approved for administration by infusion. In the case of Darzalex FasPro, the first approved formulation of daratumumab, Darzalex, was approved in 2015 with a complex administration plan requiring up to a 7-hour infusion.

Phesgo is a subcutaneous combination formulation of Perjeta and Herceptin, which were approved in 2012 and 1998, respectively. The administration of these products involved sequential infusions that took 60 minutes for Perjeta and 90 minutes for Herceptin.

The development of both Darzalex FasPro and Phesgo as follow-on formulations followed what has become a well-understood playbook for the application of Halozyme's Enhanze to antibody therapeutics wishing to transition from infusion to subcutaneous administration.

Platform/Technology Summary

ENHANZE is based on the high-dose recombinant human hyaluronidase PH20 enzyme (rHuPH20). The enzyme depolymerizes hyaluronic acid (HA) and transiently modifies the local injection area, which increases dispersion and absorption of co-administered therapeutics by temporarily opening flow channels under the skin/or into tumors that accumulate HA, making large-volume subcutaneous injections practical.

Formulation Summaries

Darzalex FasPro is provided as a 15-ml refrigerated injection solution in vials. There is very little to the formulation beyond the inclusion of Halozyme's proprietary hyaluronidase. The additional excipients include three amino acids, Polysorbate 20, sorbitol, and water for injection. Phesgo is provided as a 10-ml and 15-ml refrigerated injection solution in vials. The formulation is remarkably similar to Darzalex FasPro but with the substitution of trehalose and sucrose for sorbitol. Both products incorporate 2,000 units per ml of hyaluronidase.

Reflections

Halozyme's Enhanze has become the industry standard technology to improve patient convenience when larger volume injectables, often biologics, require extended intravenous injection times. Both Darzalex FasPro and Phesgo embody the industry's focus on creating competitive advantage with an improved patient experience and reduced administration complexity. In the case of Darzalex FasPro, a 6-hour or longer administration period is reduced to 5 minutes. For Phesgo, administration is reduced to 5 minutes instead of sequential administrations requiring 2.5 hours. Both products will certainly benefit from extended market exclusivity. Any biogeneric product will need to not only address the issues related to the intellectual property (IP) protecting the individual molecules, but also the IP associated with the Enhanze technology and any new IP associated with the reformulated products.

Mycapssa (Chiasma Inc.)

Active: octreotide (1019 Da)
Molecule Type: Peptide
Indication: Acromegaly
Delivery Route: Oral
Dosage Form: Capsule
Dosing (Duration): Single Infusion (One Hour)
DD Category: Oral Peptide / Macromolecule, Tight Junction Modifiers, Oral Enteric/ Delayed Release
First Approval: 2020-06-26 (US)
Technology: Transient Permeability Enhancement (TPE) Technology
Technology Owner: Chiasma Inc.

Development Summary

The development of Mycapssa from first clinical trials to approval has taken about 10 years with Phase 1 safety and pharmacokinetic results announced in June 2010. Phase 3 trials were initiated in 2012, and a New Drug Application was filed in 2015. This was followed by a 2016 Complete Response Letter from the FDA that required the company to conduct an additional double-blind efficacy trial. Positive results were announced in 2019, followed by a resubmission the same year and FDA approval a year later.

Platform/Technology Summary

The Transient Permeability Enhancement Technology as applied to Mycapssa consists of an enteric-coated liquid-filled capsule containing an oily suspension of the drug and sodium caprylate in hydrophilic microparticles that are mixed with castor oil or a medium-chain glyceride and/or caprylic acid. Sodium caprylate is claimed to provide a transient opening of the tight junctions, providing enhanced paracellular peptide absorption.

Formulation Summary

Mycapssa is provided as 20-mg liquid-filled capsules requiring refrigeration. The formulation has a dozen and a half listed excipients, including sodium caprylate, glyceryl monocaprylocaprate, and tricaprylin.

Reflections

Mycapssa provides octreotide, a well-validated treatment for acromegaly, as an oral formulation that previously required injection either two to three times daily (Sandostatin and generics) or monthly (Sandostatin LAR). Octreotide is a smaller peptide with a molecular weight of 1,109 Daltons. The Mycapssa formulation has a bioavailability of about 0.5%. This compares with Novo Nordisk's Rybelsus, which has a bioavailability of about 0.4%-1%, although Rybelsus is a much larger peptide with a molecular weight of 4,114 Daltons.

The Chiasma TPE Technology, like Novo Nordisk's Eligen Technology, is based on the use of sodium salts of caprylic acid. While the Eligen technology uses a variety of proprietary caprylic acid analogs, including sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNC), the TPE technology uses sodium caprylate in combination with other glycerides. Importantly, Mycapssa is delivered in a liquid-filled enteric capsule, Capsugel's Liquid-Filled Hard Capsule.

Mycapssa, following on the approval of Rybelsus the previous year, validates the opportunity for the oral delivery of smaller relatively sensitive biologicals. It will take a big step to deliver even larger peptides, such as insulin, 5,808 Daltons, and a veritable leap to address the challenge of cytokines where molecular weights approach 20,000 Daltons. In the meantime, outpatient administration of these larger molecules is being made much easier with the continuing development of new injection technologies and devices.

Xywav (Jazz Pharmaceuticals)

Actives: sodium oxybate, calcium oxybate magnesium oxybate, potassium oxybate (126 to 246 Da as salts)

Molecule Type: Small Molecule

Indication: Cataplexy, Excessive Daytime Sleepiness

Delivery Route: Oral

Dosage Form: Solution

DD Category: Oral

Dosing: Twice Daily

First Approval: 2020-07-21 (U.S.)

Delivery Technology: Not Applicable

Delivery Technology Owner: Not Applicable

Development Summary

The first evidence of clinical development for Xywav, also known as JZP-258, was the initiation of a multicenter Phase 3 trial in March 2017 for the treatment of cataplexy or excessive daytime sleepiness, an Orphan indication that became the approved indication. A subsequent trial in idiopathic insomnia was initiated in November 2018. A New Drug Application was filed in March 2020, and approval received in July 2020, in total a little more than 3 years after first clinical trials. Xywav's remarkably short regulatory approval time of 4 months was due in part to its receiving Priority Review Status.

Platform/Technology Summary

There is nothing notable regarding the formulation technology, a simple aqueous- based solution with sweetener.

Formulation Summary

Xywav is provided as an aqueous solution with sucralose, an artificial sweetener in room-temperature stable bottles of 180 ml. Dosing is similar to previously approved Xyrem.

Reflections

Sometimes important new products don't require breakthrough technology, just breakthrough thinking. Improved formulations of approved pharmaceuticals have a checkered reputation, often perceived as developed solely for the purpose of extending market exclusivity. While this may be a major reason for the development of Xywav, the formulation provides an important benefit for patients that is easy to overlook.

Xywav, a mixture of calcium, magnesium, potassium, and sodium oxybate salts, reduces the sodium daily dose by more than 90% compared to Xyrem. The recommended doses of Xywav deliver only 4%-6% of the RDA of sodium. This means one less thing for patients and physicians to worry about and that can only improve compliance, which leads to more sales. The formulation was carefully designed to keep the dosing instructions for Xywav exactly the same as for Xyrem. A dosage of 3 g of Xyrem, 6 ml, is exactly the same for Xywav, 3 g and 6 ml, making the transition seamless. Combination of oxybate salts were balanced to keep exactly the same recommended doses. There is a slight difference in formulations with a sweetener added to the Zywav formulation.

Formulation Forum

Understanding of Amorphous Solid Dispersions & Their Downstream Development

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

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INTRODUCTION

Amorphous solid dispersion (ASDs), in which drug is amorphously dispersed within polymer(s), would significantly increase drug dissolution rate by a simultaneous increase in local aqueous solubility as a result of amorphous formation and excipient solubilization effects, and in dissolution surface area by a reduction in particle size to the minimum level. Amorphous solid dispersions have experienced an exponential growth since the late 1990s. This phenomenon is partially attributed to the current need to address the high percentage of poorly water-soluble compounds in drug pipelines and the availability of new large-scale manufacturing technologies, eg, spray dried, liquid (melt)-filled capsules and hot-melt extrusion. A few new ASD products manufactured by various technologies have gained marketing approval since 2000. However, due to the lack of full understanding of solid dispersion properties and reliable prediction of product scale up, stability, and in-vivo performance, ASDs are still not fully utilized in drug delivery of drug candidates in clinical and commercial stages.

MECHANISM IN IMPROVING ABSORPTION

Drug absorption process of oral administrated solid dosage forms into the systemic circulation involves dosage form disintegration, drug dissolution, and drug permeation across intestinal cell membranes into the systemic circulation.

The slowest step described earlier determines the rate of drug absorption process.

Drug in dosage form (^{k}dissolution) → Drug in solution (^{k}a, absorption) → Systemic circulation]

For many poorly water-soluble drugs, especially the BCS II compounds, the drug absorptions process is often limited by the drug dissolution rate from the dosage forms (kd<<ka). As a result, not only the maximum drug plasma concentration (C_{max}) and time to reach the C_{max} for this type of poorly water-soluble drug will be dictated by the dissolution rate of drug from the dosage form, the fraction of drug absorbed will also be affected by the drug dissolution rate if the time required for complete dissolution is longer than the transit time of the dosage form at the drug absorptive sites.

The effective dissolution surface area can be increased by particle size reduction to the micron or the nanometer size range or by increasing wettability of the hydrophobic drug, whereas improvement in the solubility can be made possible by polymorph/salt form selection, complexation, solubilization, pro-drug, micro-emulsion, amorphous formation, and solid dispersion. Because the apparent solubility could be potentially increased more than 1000-fold as a result of amorphous formation, ASDs could potentially improve the bioavailability of BCS II and IV compounds to an acceptable level without redesign of the molecular structure according to the maximum absorbed dose (MAD) model (Equation 1).

$$MAD = \text{Solubility} \times K_a \times Vol_{int} \times T_{transit}$$

INTRINSIC INSTABILITY OF AMORPHOUS MATERIALS

One of the major hurdles with commercialization of ASDs are their physico-chemical stability and difficulty in their prediction. Due to the inherent high free energy state of amorphous materials compared to their crystalline counterpart, they bring the advantage of a high degree of supersaturation and therefore a high apparent solubility that result in high dissolution rate.

However, due to the same reason, the thermodynamic driving force for recrystallization to a lower energy physical form is high, which compromise stability and dissolution rate. The heterogeneity of ASDs make the predictability of physico-chemical properties of solid dispersion, such as solid state structure, dissolution mechanism, stability on storage, and the *in-vitro/in-vivo* correlation, difficult. ASDs have high entropy, enthalpy, and thermodynamic free energy compared to their crystalline form. Because the stability of the dosage form will be mainly determined by the amorphous API drug itself, good physical chemical characterization and accurate prediction of stability of the amorphous drug are the keys to the success of ASDs. Furthermore, because most low-molecular-weight pharmaceutical drugs having a Tg of <75°C recrystallize out readily during stability or in-vivo dissolution, it is often necessary to add excipients, particularly polymers, to form a multiple-component amorphous system (ie, ASD) in order to stabilize and inhibit the amorphous drug from crystallization at its solid or aqueous states. The introduction of stabilizing agents into the multiple-component amorphous system would not only optimize the stability of the amorphous drugs, but also improve the functionality and handling of the amorphous dosage form, eg, a reduction in stickiness, powder flow properties, moisture scavenging and protection requirement in storage conditions, and packaging, etc.

THERMODYNAMICS OF AMORPHOUS SOLID DISPERSIONS

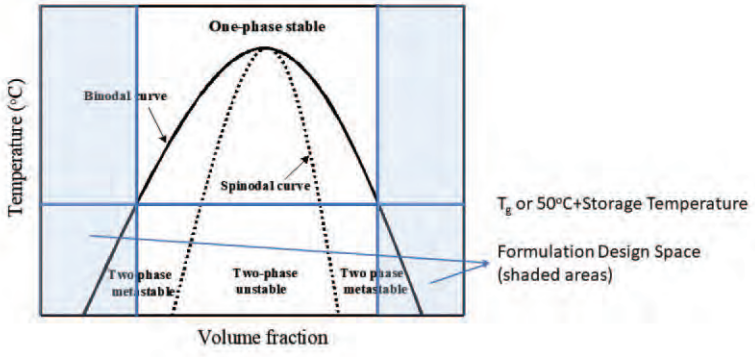
To take advantage of the higher solubility of amorphous solids and to mitigate risks associated with physical instability, an understanding of molecular structure of solid dispersions and their relationship with the physical-chemical properties is essential for development of stable ASDs. Two of the physical properties that are of especially important to physical stability of ASDs are the drug-polymer miscibility and the solid solubility of the crystalline drug in polymeric matrices. Miscibility refers to capability of mixing two liquids in any ratio without separation of two phases, whereas solubility is defined as "the spontaneous interaction of two or more substances to form a homogenous molecular dispersion." An understanding of these two properties will help in selecting an appropriate polymer and determining an optimal amorphous drug-loading level for rational design of a stable ASD formulation.

According to thermodynamic theories, a typical phase diagram of a two-component solution system exhibiting a miscibility gap is illustrated in Figure 1. The phase diagram is divided into regions showing one-phase stable, and two-phase metastable and unstable phases. The binodal curve separates the stable homogenous phase from the two-phase regions, whereas the spinodal curve divides the two-phase region into a metastable and unstable phase. Phase separation may be induced by a temperature jump or a concentration fluctuation that causes the system to transition from the one-phase stable phase into the unstable regions. Depending on the location of the region, phase separation may follow two distinct mechanisms called nucleation and growth, and spinodal decomposition. Nucleation and growth happen when phase separation occurs inside the two-phase metastable region near the binodal line where the free energy change for phase separation is low. Because nucleation involves creation of a new surface, there is an activation energy barrier required for nucleation and growth. For a dispersion with a composition located within the spinodal region, the system that is unstable against any fluctuations in concentration will undergo phase separation via spinodal decomposition. Even though there is no thermodynamic energy barrier for spinodal decomposition, phase separation can be stopped or become extremely slow when the temperature is below the glass transition of the system.

If treating the ASD as a solution system, the drug and polymer forming an ASD should be miscible (located in the stable one-phase region) in order to form a stable, homogeneous, molecular mixture of drug and polymer, ie, amorphous solid solution. At the

FIGURE 1

Phase Diagram of a Two-Component Solution system with a Miscibility Gap



Phase diagram of a two-component solution system with a miscibility gap.

"One of the major hurdles with commercialization of ASDs are their physico-chemical stability and difficulty in their prediction. Due to the inherent high free energy state of amorphous materials compared to their crystalline counterpart, they bring the advantage of a high degree of supersaturation and therefore a high apparent solubility that result in high dissolution rate. However, due to the same reason, the thermodynamic driving force for recrystallization to a lower energy physical form is high, which compromise stability and dissolution rate."

very least, drug and polymer should be miscible in their liquid/molten state. Otherwise, metastable drug-rich amorphous phases as well as polymer-rich phases will be present in the solid dispersion formed upon solidification, and any subsequent perturbation, such as fluctuations in temperature or concentration, will further cause recrystallization of the metastable amorphous drug present in the system. In general, it is believed the formation of a single phase as an amorphous solid solution is essential for the stability of amorphous drug present in the solid dispersion system. According to nucleation theories, the re-crystallization of an amorphous drug within a solid dispersion can be significantly inhibited or reduced by an increase in the glass transition temperature, a decrease in drug molecular mobility, drug-polymer interactions, an increase in critical crystallization energy barrier by a reduction in the thermodynamic driving force, or by interference with the molecular recognition process for recrystallization. All of the aforementioned stabilization mechanisms require drug-polymer mixing and interactions at the molecular level. When phase separation happens for a drug-polymer amorphous system, the polymer would have limited impact on the stability of the amorphous drug present in the drug-rich phase due to lack of the intimate interactions between the drug and polymer required for stabilization.

Based upon the same thermodynamic phase separation theories, an ASD should also be prepared preferably at a drug concentration below the solid solubility of its crystalline form, so that the dispersion system will fall within the one-phase stable region, and drug is homogeneously distributed within the solid matrix at a molecular level. Otherwise, when the amorphous drug loading is above its solid solubility for practical reasons, the system may become supersaturated and fall within the metastable two-phase regions. As a result, a fraction of drug might be present in the metastable amorphous form.

FORMULATION DEVELOPMENT AND SCALE UP

The process flow of ASD formulation development consists of the following steps:

1. Formulation screening (miscibility, stability, and dissolution)
2. Selection of polymer based on results from first step
3. Stability testing and prediction of long-term stability
4. Bio-pharmaceuticals evaluation *in-vitro* and *in-vivo*
5. Selection of manufacturing method for ASDs (spray dry, HME, liquid fill capsule, fluid bed process, co-precipitate, solvent evaporation, etc)
6. Process development and scale up for final dosage form
7. Characterization of the dosage forms
8. IVIVC

Different dosage forms of ASDs may be chosen depending on the stage of development. Early stage formulation prefers aqueous suspension or drug-in- bottle approaches that can be easily prepared by a Tox lab or by Clinical Pharmacology Unit from the ASD powder. From Phase 2 and onward, a market formulation present as a capsule or a tablet form is desired in order to avoid a costly PK bridging study before transition into a Phase 3 pivotal human study (Table 1).

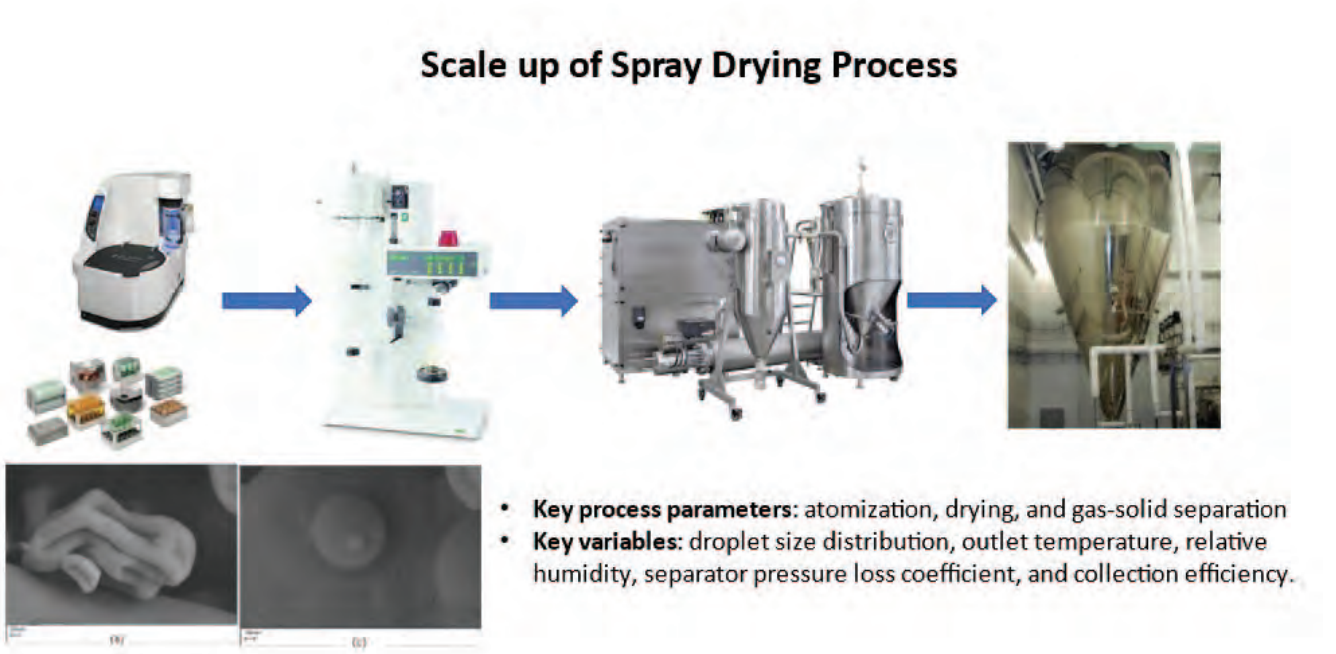
It is critical to select a robust stable formulation and to consider the scale-up effects at the early development stage. Spray-drying is a well-established and widely used process for

TABLE 1

Development Stage	Dosage Options
Preclinical	Suspension, Drug-in-Bottle
Phase 1	Suspension, Liquid-Melt in Capsules, Drug-in-Bottle
Phase 2 & 3	Capsule, Tablet

ASD Dosage Selection at Different Stages

FIGURE 2



Scale up of ASDs via the spray-drying process.

transforming formulation in liquid into dry powdered forms. In addition to hot-melt extrusion technology, liquid-melt filling technologies for encapsulation of melt solid dispersions into hard capsules are another alternative technology for solid dispersions. The manufacturing of this SD dosage form involves the dissolving of drugs in melted carriers and the filling of the solutions into hard gelatin capsules. Due to simplicity in the manufacturing processes and potential in significant improvement of bioavailability of poorly water-soluble drugs, solid dispersion systems by liquid-filled technology is an attractive option for development of insoluble drugs.

A spray-drying manufacturing process consists of five steps (Figure 2):

1. solution preparation containing the drug and excipients dissolved in solvent
2. atomization of the spray solution
3. primary drying of the atomized droplets in the spray chamber
4. collection of the ASD via cyclone
5. secondary drying to reduce the residual solvent to acceptable limits

In the spray-drying process, not only can the micrometrics properties of spray-dried solid dispersion powder be controlled by controlling the temperature and evaporation rate at the inlet and outlet of the spray dryer, but also phase separation of drug and polymer could be prevented by rapid removal of solvent from the droplets of the spray solution and thereby rapid solidification of the droplets.

Three critical process parameters are the focus areas during scale-up: atomization, drying, and separation. DOE design can be explored to understand key spray-drying process parameters and their relationship to the critical-quality attributes (CQAs). Nozzle design and pressure may have significant impact on the atomization of droplets that result in different ASD particle size distribution. Because pressure nozzle commonly used in large-scale spray dryers generates broader particle size distribution, the sensitivity of drug dissolution and bioavailability as related to ASD particle size distribution should be evaluated early to ensure the formulation and process robustness. Higher inlet temperature and lower outlet temperature tends to result in faster evaporation rates and smoother surface of ASD particles.

SUMMARY

Understanding the properties of ASDs and their relationship to the downstream product scale up, stability, and *in-vivo* performance is critical to successfully utilize them for drug delivery of insoluble drugs in early development and commercialization of human drugs in a timely and cost-effective manner. ◆

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INHALATION DELIVERY

Inhaled Drug Development: Optimizing Delivery

By: Sandy Munro, PhD, Nikki Willis, and Geraldine Venthoye, PhD

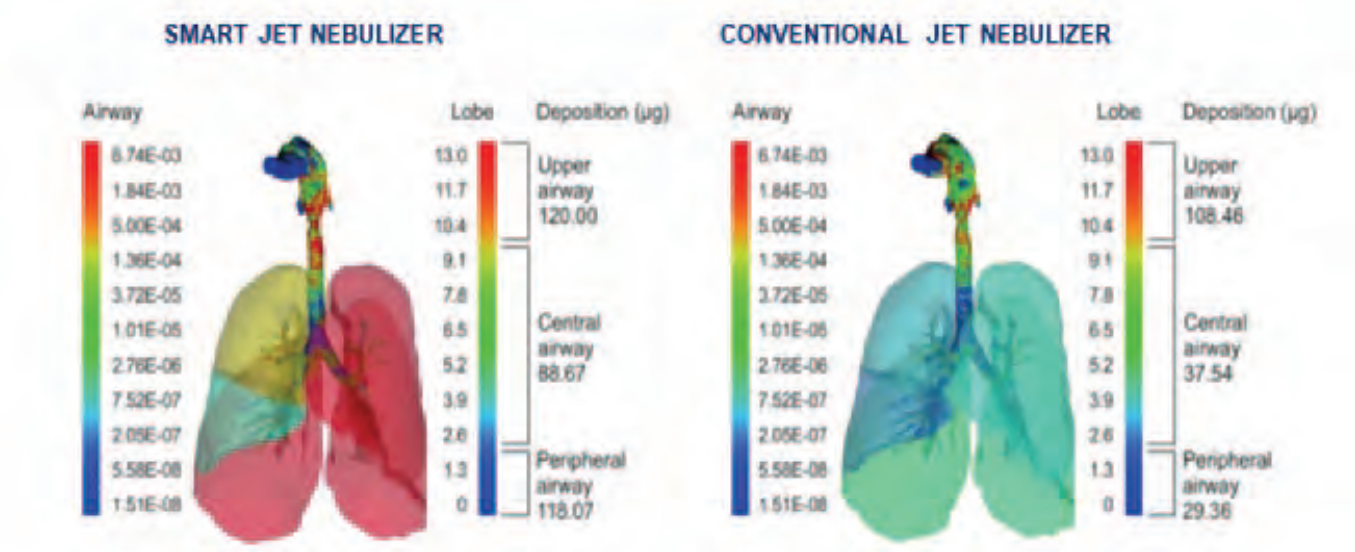
INTRODUCTION

When developing a drug to be administered through an inhaled route, there are many factors to take into account, some or all of which may change as the development program moves toward commercialization. No two development programs for inhaled drug products will be driven by the same factors; any new product concept, therefore, needs to be approached with a fresh mindset and without preconceptions or bias ideally in terms of the delivery technology or device. There also needs to be a recognition that as the program progresses, there may be a requirement to adapt the strategy as each new phase is reached in the journey from early phase development through scale-up to commercialization. Although retaining the same delivery platform throughout the entire process might be the preferred option, it may be necessary to switch from the one used in the earlier stages of development, even up to proof-of-concept, to the one that ultimately might be commercialized.

One of the first major considerations in choosing a delivery technology will be the physical properties of the active pharmaceutical ingredient (API): whether it is a small molecule API or a biologic; whether it is readily solubilized; and the likely dose range. Cost is also a significant factor in the early development stage – not only the cost and availability of the API, but also the cost of any device and the likely volumes involved.

Additionally, there are strategic issues that need to be borne in mind, including the development strategy being employed, and the nature of the client or development partner and their need for early value inflexion on clinical proof-of-concept. A new chemical entity (NCE) typically has an uncertain future, putting the empha-

FIGURE 1



***In-silico* lung deposition modeling for a smart jet nebulizer (left) versus a conventional jet nebulizer (right).**

sis on successful proof-of-concept studies and the need for dosing flexibility, speed, and cost management.

As one method of delivery, using a smart nebulizer can be a very effective way of developing a product to the early clinical stage. This technology platform can quickly maximize lung deposition consistently from patient to patient with a simple and straightforward formulation development process, consuming minimal drug material to get the best probability of success.

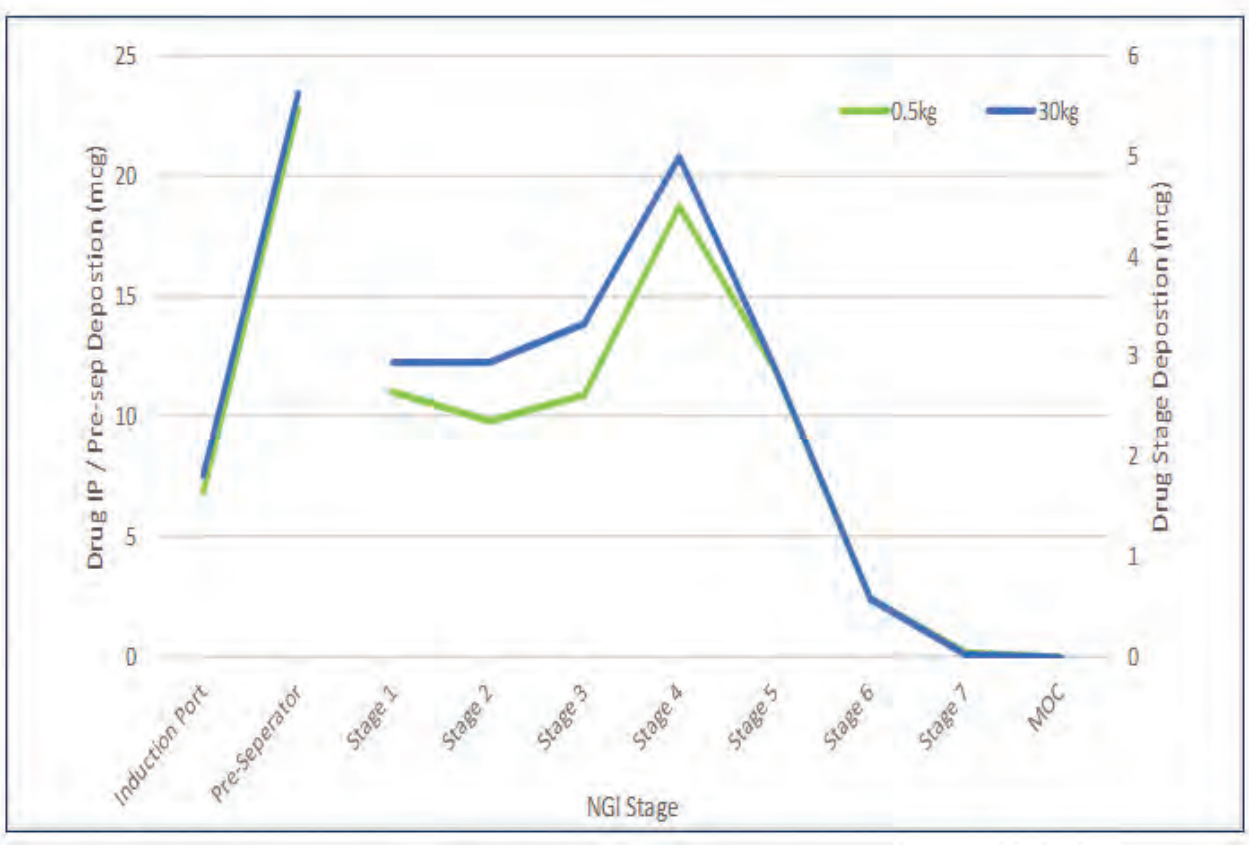
DEVELOPMENTAL CONSTRAINTS

In one project, for example, an innovator company was developing a highly water-soluble small molecule to target deep and very high lung deposition. The molecule was in the higher dose range, making it potentially less amenable to being formulated as a dry powder inhaler (DPI), although a capsule format might also have been suitable. Aimed at treating a niche disease, it required consistent dosing from patient to patient with a simple formulation development process. The more drug that could be dosed to the lungs and the more reproducibility that was achieved, the better the chances of a positive outcome.

A hand-held mesh nebulizer was chosen as it allowed all of the pre-Phase 1 clinical study pharmaceutical development work to be completed with only a small quantity of material (100 g). This was sufficient to conduct all of the formulation development work and analytical method development, as well as phase-appropriate validation, stability testing, and product performance characterization studies. Only as much drug was dissolved as was required for the immediate testing, meaning that expensive and scarce API was not wasted during early development.

In-silico lung deposition modeling studies showed that smart jet nebulizers were more effective than conventional jet nebulizers in terms of lung deposition, and also significantly better than a high-performing DPI (Figure 1). The figure shows that twice as much drug was deposited in the central airways compared with the conventional system, and almost four times as much in the smaller airways. A smart nebulizer approach also offered the potential for more consistent delivery because the patient was guided to take every breath in the same way by the device. In the mesh nebulizer system, the dose sat on top of the mesh and typically more than 90% percent of the dose was delivered to

FIGURE 2



Comparison of the particle size distribution of the emitted dose at two different scales measured by inertial impaction.

the patient. A further advantage of smart nebulization is its ability to deliver a variety of different clinical doses through only two solution strengths by dispensing different volumes into the nebulizer. In this case, the development program resulted in a clinic-ready product in only 18 months.

MANUFACTURING CONSIDERATIONS

In early development phases of any project, there is an inevitable trade-off between the scale of manufacture and the number of batches that can be produced to build scientific understanding. However, one of the keys to successful development is an assurance of the ability to scale-up the manufacturing processes. Drug product development in the respiratory field, where reliable scale-up can be difficult to achieve, presents the challenge of deciding what constitutes an appropriate scale at each stage of development.

Minimizing the risks associated with the scale-up of manufacturing processes is vital to developing successful products, and so the choice of equipment is important to be able to move seamlessly from laboratory scale to commercially representative scale during the development and, ultimately, commercial-scale filling equipment.

SCALE UP VALIDATION

In a project to develop a generic DPI treatment for asthma and chronic obstructive pulmonary disease (COPD), a blend scale-up model was validated to demonstrate that it was possible to achieve comparable drug product performance from batches made at 500-g laboratory blend scale and batches made at 30-kg commercial blend scale (Figures 2 & 3). Figure 2 gives a comparison of the particle size distribution of the emitted dose for the two different scales, and Figure 3 gives a comparison of the emitted dose at the two different scales.

This model enabled a significant amount of the development work to be conducted in the laboratory at development scale, minimizing material costs and enabling faster execution of experiments, but also gave confidence in the ability to move to the larger scale at a later date. This assurance also meant that capital investment at the commercial manufacturing site could be made at a later development stage, based on a risk-based approach for this project.

PATIENT NEEDS

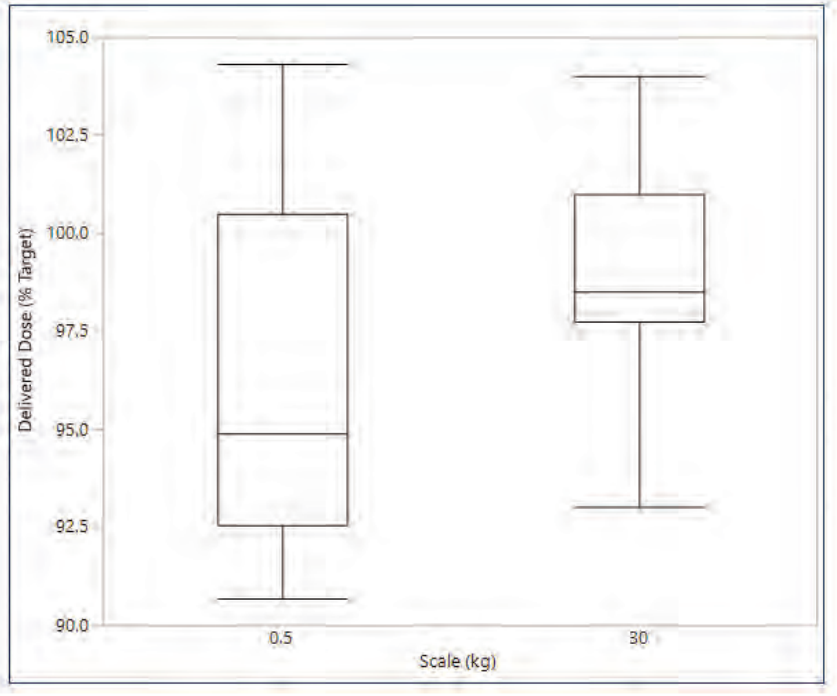
Whatever delivery platform is chosen for the final product, it must be suitable not only from the point of view of design and manufacturing, but also from the perspective of the needs of the target patient population, taking into account age range, any dexterity or cognitive issues that could affect usability and compliance, lifestyle, and patient expectations based on other available devices.

Other considerations should include the nature of the disease, whether the therapy will be delivered at home or in hospital, whether delivery needs to be to the deep lung or the central airways, and the number of doses per day.

PHASE-APPROPRIATE DEVELOPMENT

The initial choice of a platform may not necessarily be appropriate for every stage of a development program. Ideally, a development project would yield a well-

FIGURE 3



Comparison of the emitted dose at the two scales.

characterized, commercially ready device, and a process and formulation at the pivotal clinical stages of development. However, in reality, it is not until a commercial process has been established, and many batches manufactured and tens or hundreds of thousands of devices delivered into the hands of patients, that a fuller understanding of the product is achieved. It is therefore important to approach defining the target delivery technology in a "device agnostic" manner, without being influenced by previous programs or a technology bias towards a particular platform.

ENSURING SUCCESS

Success of a program at the commercial stage is defined by a range of elements. Clearly, maximizing volumes and increasing access to patients requires being in a position to roll out a product in as many geographies in which it can be approved. It is vital for commercial success to maximize volumes and capacity, yields, process capability, efficiencies through synergies and economies of scale, and to have the greatest supply chain flexibility while minimizing risk, obsolescence, cycle times, downtime, costs, and working capital. It is also essential to eliminate redundancy, waste, and excess inventory over time. Maximizing volumes can also provide opportunities to reduce costs and help maintain a positive margin position even in adverse or competitive pricing environments.

A global supply chain and procurement function is therefore key within any development company, giving it the ability to manage the forecasting, logistics, cost management, contractual, and business continuity elements. It must also ensure effective management of inventory, including safety stock, and distribution to its clients and ultimately to patients. This discipline and experience brings great value when managing situations that threaten to disrupt supply of critical medicines.

Ongoing assessment and evaluation in the commercial phase will enable the product to evolve, grow, and maximize its potential through focused continuous improvement. Feeding the know-how and experience acquired in this phase back to development teams will aid industrialization, minimize cost-of-goods, and build robustness into future products.

Significant experience in all stages of the development life cycle, and applying the best technology solutions at each stage, can help organizations to successfully take an inhaled development program from feasibility through development and on to commercialization.

Selecting the delivery device or technology platform on the basis not only of the needs of the patient and the nature of the disease, but also on opportunities for accelerating the proof-of-concept or early clinical stages by using fast-to-clinic approaches can help to accelerate the project through later-stage development by combining the approach with seamless scalability, designing in manufacturability, and choosing an appropriate manufacturing strategy. ◆

BIOGRAPHIES

Dr. Sandy Munro is Vice President – Pharmaceutical Development at Vectura. He has been with Vectura since 2008 and is responsible for the company's new technology development and also for product development programs utilizing Vectura's smart nebulizer devices.

Nikki Willis is Vice President – Pharmaceutical Development at Vectura. She has worked in inhaled product development for over 30 years, and leads Vectura's pharmaceutical development department, responsible for dry powder inhaler (DPI) product development programs.

Dr. Geraldine Venthoye is Executive Vice President – Product Development at Vectura, where she leads Vectura's Pharmaceutical Development and Medical Device Development departments, and is responsible for the strategic and technical advancement of the company's products, development services and technology platforms.

BIOSIMILAR DEVELOPMENT

Guidance on Biosimilar Interchangeability: The Debate Over Drug Delivery Devices

By: Darren Mansell

INTRODUCTION

In 2019, the US FDA issued its final guidance document titled *Considerations in Demonstrating Interchangeability with a Reference Product*.[1] The guidance document details the pathway for how biosimilar products may be deemed "interchangeable" and substituted for the reference biologic without the intervention of a clinical prescriber.

As early experience in following this guidance has matured over the past year or two, a number of issues have arisen that may impede best available outcomes for patients, one of which is the question of whether "interchangeability" guidance may stifle innovation (and therefore improved patient experience) in drug delivery devices.

Before looking at the US situation, it is interesting to note some differences when compared with Europe. EU guidance on interchangeability separates the drug from the delivery device, specifically making way for device innovation: "Some differences may be allowed if they have no effect on safety and efficacy - for example differences in the formulation of the medicine, presentation and administration device."[2] This is significant, because delivery device usability and comfort for therapies that require frequent administration can offer competitive advantage, either to biosimilar producers trying to gain market share, or original biologics companies seeking to retain their market position. Evidence for this assertion may be seen in a number of pharma companies that have for some years been making moves to seek exclusive arrangements with device manufacturers to gain competitive edge in the switching/retention process.[3] Certainly, in Europe, with its regime that separates drug from delivery device, the EU has approved more biosimilars for each reference biologic than the US – almost across the board.[4]

Whatever the significance of such comparisons, however, this short article plays out the situation and seeks to stimulate discussion and feedback from readers.

REGULATORY GUIDING PRINCIPLES

One of the FDA's guiding principles is to enable the availability of best therapies and facilitate the best patient outcomes. While the larger part of the FDA guidance focuses on matters of medical therapeutic science, "human factors" have in recent years become an equally important consideration – including a focus on drug delivery devices that ease discomfort, avoid pain, and facilitate dosage accuracy.

The enhanced importance of these aspects ("human factors") is exemplified in the FDA's guidance that recommends involving patients as early as possible in the clinical evaluation of new products – precisely to embrace human factors (ease of use, pain avoidance, etc) and the total patient experience.[5] One would therefore hope that guidance on the interchangeability of biological drugs and biosimilars would encourage the use of alternatives to the original ("reference") biologic that are at least the same, if not better. Moreover, the room for improvement may be applied equally to the delivery device as the drug itself.

DRUG DELIVERY SPECIFICS

What, then, does the FDA guidance on interchangeability say, especially with respect to drug delivery devices? The guidance document states that, "FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use."[6] This clearly focuses on the clinical outcomes – after all, in scientific terms, a biosimilar is not the same drug, but it does offer the same therapeutic benefit.

The purpose of interchangeability is to allow a biosimilar to be substituted for a reference (original) biologic by a pharmacist, without reference to the prescribing clinician. According to the Biologics Price Competition and Innovation Act (BPCIA) in the US, a biosimilar can be designated as "interchangeable," whereby it may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.[7] However, the rules vary from jurisdiction to jurisdiction, and international harmonization of interchangeability policies has some way to go.

Further to the demonstration of interchangeability from the perspective of biosimilarity, there are additional considerations for demonstrating interchangeability for a combination product that includes a device constituent part (eg, a container closure system such as a safety syringe or an autoinjector) to deliver the biological product. This is pertinent for manufacturers of combination products and contract manufacturers of medical devices that produce integrated drug delivery devices on behalf of clients (pharmaceutical companies) who incorporate them into a final combination product.

ANOMALIES IN PRACTICE

The guidance document includes a section on considerations for the container closure system or any device constituent. While not proscriptive, it contains enough pointers to identify inputs, such as performance testing, stability studies, shelf-life testing, useability, and risk management, for sponsors to prepare an approach that can be discussed and agreed with the FDA at the beginning of the design phases.

Here is where we encounter a little confusion and potential conflict with patient best interests. The guidance first of all seems to limit device improvement potential when it states that "A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed. For example, if the reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product for a different presentation, such as an auto-injector."[8]

However, this is immediately followed by apparent encouragement to potentially seek delivery device enhancements or improvements (which could benefit the patient and provide commercial competitive edge). This guidance reads: "However, if a sponsor is considering the development of a presentation for which the reference product is not licensed, this should be discussed with the FDA. In such cases, the FDA will evaluate whether the proposed presentation could support a demonstration of interchangeability." Early interaction is clearly essential, as the guidance notes: "Sponsors are encouraged to contact the FDA early during product development to discuss the proposed presentation [delivery device] and specific considerations related to licensure of the proposed product as an interchangeable under section 351(k) of the PHS Act."[9]

PIONEERS VERSUS FOLLOWERS

So where does this leave the issue? Because of the multitude of different products and presentations, what is not clear - and will be the challenge for sponsors - is the line between "similar and not-similar." As the guidance advises, the solution to this is to engage with the FDA early in development and agree a route forward.

The probable result, until the market's experience proves otherwise, is that sponsors (pharma companies) will split into "pioneers" and "followers." At Owen Mumford, we know that pioneers exist, because we're already working with some of them on enhanced device "presentations" for biosimilar drugs to propose to the FDA. These biosimilar companies clearly recognize that device enhancements can offer patient experience benefits and, at the same time, provide an element of competitive edge to encourage switching. There is certainly a discussion emerging in the wider biologics industry over whether biosimilars and device improvements can more easily be introduced for naïve patients.[10]

Nevertheless, the issue remains over whether current guidance may suppress device innovation – innovation that is to the patient's benefit. Particularly with combination products that incorporate a device-constituent, we can see a scenario of sponsors "playing it safe" and adhering very closely to the design of the reference product. This, of course, would stifle a body of innovation: why introduce features into the proposed product that are not present in the reference product, when it may increase the risk around gaining approval and require more work to demonstrate that the proposed product is interchangeable? However, if those features are shown to be improvements over the reference product or have been introduced to address on-market issues, then this should be seen as a "positive difference" that adds benefit and ought to be encouraged by the FDA.

SUMMARY

In short, then, clarity around the issue is likely to develop rapidly over the next couple of years as the biosimilars "pioneers" bring device developments in front of the FDA for approval. A positive outcome from those consultations and applications is important to fulfil the FDA's objective of increasing patients' access to therapies with the greatest "safety, efficacy, and security" available.[11] As an industry, we should encourage this discussion to make sure that developmental debate is completed with the minimum of delay. ◆

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BIOGRAPHY

Darren Mansell is a Regulatory Affairs Manager with Owen Mumford Pharmaceutical Services, where he has worked for over 14 years and is integral in ensuring products meet regulatory requirements to facilitate compliance and sales in worldwide markets. He works in a cross-functional team with colleagues from Operations, R&D, and sales teams to deliver new and existing drug delivery and diagnostic products to customers. As well as securing regulatory approval for OMPS products, he also provides expert compliance advice and support to customers.

OPEN INNOVATION PLATFORM

Incentivizing Drug Delivery Research Using an Open Sharing Platform

By: Keith R. Horspool, PhD, Shirlynn Chen, PhD, and Markus Koester, PhD

INTRODUCTION

Toward the end of 2020, Boehringer Ingelheim launched a drug delivery initiative using Boehringer Ingelheim's open innovation platform, opnMe.com. The objective was to stimulate scientific understanding, and development of potential new technologies, for delivery of compounds with challenging solubility by offering a set of more contemporary poorly soluble drugs free-of-charge for independent research activities. Success with this pioneering approach was regarded as a potential catalyst for further initiatives on this platform as well as a vehicle to generally encourage similar efforts in pharma/biotech and enhanced interactions in areas where improved knowledge and capabilities will accelerate drug product development. The following provides a summary of the initial reaction to this unique offering, including demographics of institutions submitting proposals for consideration. It provides insights on the possibilities of such endeavors and how these could facilitate future research using integrated foundational learnings coupled to pragmatic implementation to rapidly translate scientific concepts into drug delivery technologies to overcome challenges posed by new therapies and lead to more patient-centered products.

BACKGROUND

A novel approach was launched to provide the external drug delivery community with open access to a cohort of novel chemical entities designed to engage with contemporary therapeutic targets. The collaboration platform opnMe.com was employed to post a call for scientific proposals addressing the ubiquitous challenge of drug insolubility.

Boehringer Ingelheim launched the opnMe.com open innovation portal in 2017 with the release of about 20 molecules Molecules to Order (M2O) that could be requested free of charge with "no IP strings attached." These were projects fresh from the drug discovery bench, and the intention was to encourage research scientists to come forward with novel hypotheses for the molecules presented. Since its launch, more than 30 additional molecules to order have been added, and other opnMe.com formats have been initiated, including a Molecule for Collaboration (M4C) program, which was used as the basis for launching a specific call to address a common drug delivery challenge for the pharma industry – poor solubility.

The aim was to create a new way to help scientists to validate their scientific hypotheses and to publish their data to advance scientific knowledge. The launch phase of the drug delivery challenge on opnMe.com was reported previously in this publication (online) in December 2020.[1] For the call a simple question was posed: "Presented with a set of novel, late-stage molecules, how would you propose to improve their solubility to generate insights into future drug delivery?" The submission process required a simple two- to three-page summary briefly describing the scope and benefits of the proposal.

This launch phase is now complete, and this latest article describes our experience with creating the concept and a summary of the overall response to the call. Note that for the next stage of the process, successful participants will be provided significant

TABLE 1

Drug Target	CCR1	CCR1	LFA-1	HCV NS3	RORc
Mpt °C	207	192/206	173	271	182
Log $P/D_{7.4}$	2.6	1.4	4.0	4.2	3.4
pKa	2.5	2.4	2.4	2.9, 6.4	2.1
Sol pH 2.2 mcg/ml	77	32	<0.1-2	3.6 (pH 1.1)	7
pH 4.5 mcg/ml	19 (pH 4)	9	0.6	<0.05 (pH 4.2)	6
pH 6.8 mcg/ml	20	8	0.4	0.6 (pH 5.5)	3
pH 7.4 mcg/ml	20	8	0.4	1.2 (pH 7)	4
Fa/FeSSIF* mcg/ml	40/75	19/50	9.8/80	14/-	12/57
Papp** (10^{-6}cm/sec)	10	2.9	ND	8	63.2

* Fasted (Fa) and Fed (Fe) State simulated intestinal fluid
** Apparent permeability coefficient (Caco-2 data)

Poorly soluble and pharmaceutical relevant molecules with diverse physicochemical properties.

quantities of each drug substance free-of-charge with the possibility to receive additional preclinical data, and/or direct discussion with Boehringer Ingelheim scientists, depending on the scope and potential of the proposal. Importantly, there is transparency about the rights and obligations of those who approach the portal to submit their exclusive ideas, in particular with regard to intellectual property, which remains with the participant. Participants in the program will also be encouraged to publish results of their work in peer-reviewed journals.

RESULTS

Application of the opnMe.com platform was viewed as the most expeditious way to implement this initiative, although there were some potential risks associated with the strategy given the platform was designed to serve Research and not Development collaborations. Years of experience in drug delivery development, and the challenges therein, led us to believe that an unprecedented offer to supply a set/group of proprietary molecules for study would be of great value to the scientific community. Typically, single molecules are supplied for Research applications of opnMe.com that typically are designed to explore target identification opportunities, etc. In comparison, to maximize evaluation of drug delivery concepts/technologies, a set of compounds was considered essential for success.

Furthermore, the data set had to be curated to achieve sufficient physicochemical and therapeutic diversity (Table 1) with compounds that were no longer in development and yet still available in sufficient amounts to supply funded proposals. The quantity of compounds supplied also had to be negotiated as Research calls generally require only milligram quantities of material for collaborations supported by opnMe.com. Such quantities were considered inadequate for meaningful drug delivery research, especially comparative assessment of exciting new drug delivery concepts, so drug substance quantities were increased to gram quantities, with an initial supply of up to 20 g of each compound.

Socializing the opnMe.com call also required a change in approach to enable diverse communication to appropriate communities active in drug delivery. The call was distinguished on opnMe.com by creating an alternative virtual vial presentation that represents a container for each of the compounds. This aided in differentiation from Research initiatives available on opnMe.com and will likely be the vial image used for further drug delivery/drug development opportunities posted on the platform. Additional communication channels included advertising in key scientific journals, articles in other commercial drug delivery publications, social media (such as LinkedIn, Twitter,) and personal communications. An indication of the interest generated was reflected in the initial article written for Drug Development & Delivery that received more than 864 views.[2]

The opnMe.com call was open for

"The opnMe.com call was open for several months as is usual for any M4C initiative on the platform. Proposals were submitted throughout this period with many responses coming close to the deadline. At the last count, 74 proposals were received, which reflects a very positive and robust response with high interest in the initiative. The response rate is at the top end of proposal numbers generated by previous M4C opnMe.com initiatives and is regarded as a highly successful call."

several months as is usual for any M4C initiative on the platform. Proposals were submitted throughout this period with many responses coming close to the deadline. At the last count, 74 proposals were received, which reflects a very positive and robust response with high interest in the initiative. The response rate is at the top end of proposal numbers generated by previous M4C opnMe.com initiatives and is regarded as a highly successful call. Interestingly, the demographics of the proposals showed more worldwide interest was stimulated by this drug delivery call than is typically the case. The 74 proposals were received from 29 countries, which reflects coverage that is some of the most comprehensive to date. Top countries were the US (10), Germany (6), France (5), Japan (5), UK (5), Australia (4), and Italy (4). At the next level were Iran, Pakistan, Poland, and Spain with three proposals each. Two proposals came from China, Finland, Greece, Hungary, and Israel; 13 other countries provided one proposal.

The majority of proposals (61, 82%) were from academic groups, with the rest (13, 18%) coming from drug delivery companies. This ratio of academic to commercial respondents is also viewed as highly favorable given this is the first time that a drug delivery initiative has been attempted and there are still certain aspects that need to be refined. For instance, in terms of how handling of materials will be addressed by various parties and how initial interactions might lead to additional future collaborations beyond mere supply of substances in the current approach. At the time of writing this article, the internal review of all proposals was still ongoing according to the predefined time plan. Based on preliminary feedback, Boehringer's scientific panel has been impressed with the novelty and quality of submitted proposals. Next steps will be initiated with selected proposals over the course of the next several months.

CONCLUSION

Drug delivery has a vitally important role to play in converting important new therapies into breakthrough, patient-centered products for the future. The diversity and complexity of these exciting opportunities will require intensified scientific endeavors that transcend the traditional academic-industry divide. Companies need to be enlightened in their approaches to incentivize fundamental research that can then be jointly developed to translate important new concepts into practical realities. Advancing new delivery technologies deserves special consideration to ensure that new approaches can be made commercially viable in a fraction of the time taken in years past. Collaborative innovation platforms, such as the drug delivery call on opnMe.com, represent valuable new mechanisms for fostering such forward-looking strategies beyond typical consortia approaches that generally only support participation by a limited population, involve a relatively narrow scope, and have significant associated costs.

The current opnMe.com drug delivery call was a deliberate effort to persuade pharma, academic centers, and technology development companies to engage in alternative models to incentivize drug delivery research. The exercise is now entering the implementation phase and more will be learned from experiences running this new model. In the meantime, the initial signs are extremely encouraging in

terms of the interest and responses received from around the globe. They highlight vibrancy in the drug delivery community and keen interest to work on contemporary issues with contemporary substrate. Based on the positive reception to the concept so far, we are optimistic that mutual benefits will be realized and will serve to advance science in more integrated and accelerated ways in forthcoming years. We also anticipate extrapolation from this initial call to additional Development-led opnMe.com calls incorporating emerging therapeutic entities to build a more proactive scientific position for the future, with increased potential for earlier adoption and deployment of new drug delivery concepts and technologies. Proactively working together through shared materials and shared learnings/technologies will be key to addressing the delivery needs for important therapies and accelerating their translation into breakthrough products for patients.

ACKNOWLEDGEMENTS

The authors would like to express their sincere thanks and gratitude to: Thomas Trieselmann, Marc Grundl, Florian Montel (and all other persons supporting opnMe.com), Sven Schreder, Achim Grube, Dan Marino (and DD&D colleagues), Josef Bossart (and PharmaCircle colleagues), AAPS, and all others involved in supporting this initiative. ◆

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BIOGRAPHIES

Dr. Keith Horspool is the former Vice President of External Alternative CMC Development (EACD) at BI. EACD operates as a "biotech within pharma" using an integrated network of virtual resources to deliver all CMC requirements for projects, applying alternative development approaches for NCEs and NCE-like new modalities. Prior to joining BI, he worked at Pfizer and Astra Zeneca. He has worked in Pharma for more than 30 years with experience managing preformulation, product development, drug delivery, and materials science. He has diverse experience with a broad range of delivery systems and various routes of delivery, particularly oral, inhalation, and parenteral delivery.

Dr. Shirlynn Chen is a Director of External Alternative CMC Development (EACD) at BI. She has worked over 25 years at BI with broad experience in drug product development, including preformulation, formulation development and scale up, and regulatory CMC submission of various oral dosage forms. Her areas of expertise include physical pharmaceutics, preclinical, and clinical formulation design and development of complex oral dosage forms. She is currently responsible for drug product development in support of the global project portfolio, by applying alternative CMC project strategies for more effective NCE development and for advancement of NCE-like new modalities.

Dr. Markus Koester is a Director of Discovery Research Coordination Germany (DRCG) at BI. He leads the global digital communication and portal activity of BI's open innovation platform opnMe.com. As such, he was deeply involved in the concept development of the current CMC call. opnMe.com now covers 55 molecules to order and received more than 1,000 orders from 60 countries across the word. In addition, with its two collaboration programs, BI has received more than 1,000 research proposals by now. Prior to joining BI, 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.

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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)**	
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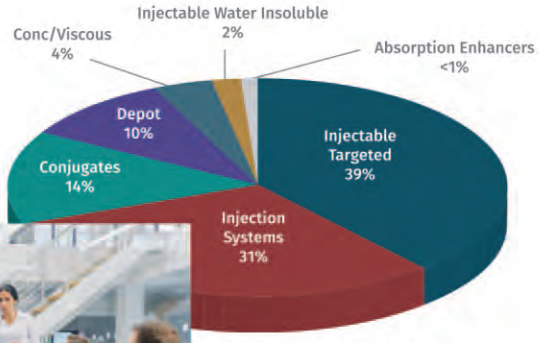
Evaluate New and Promising Technologies



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EMULSIFICATION TECHNOLOGY

Microspheres for Sustained Release

By: Alex Kerr, Sam Trotter, Poppy Maley

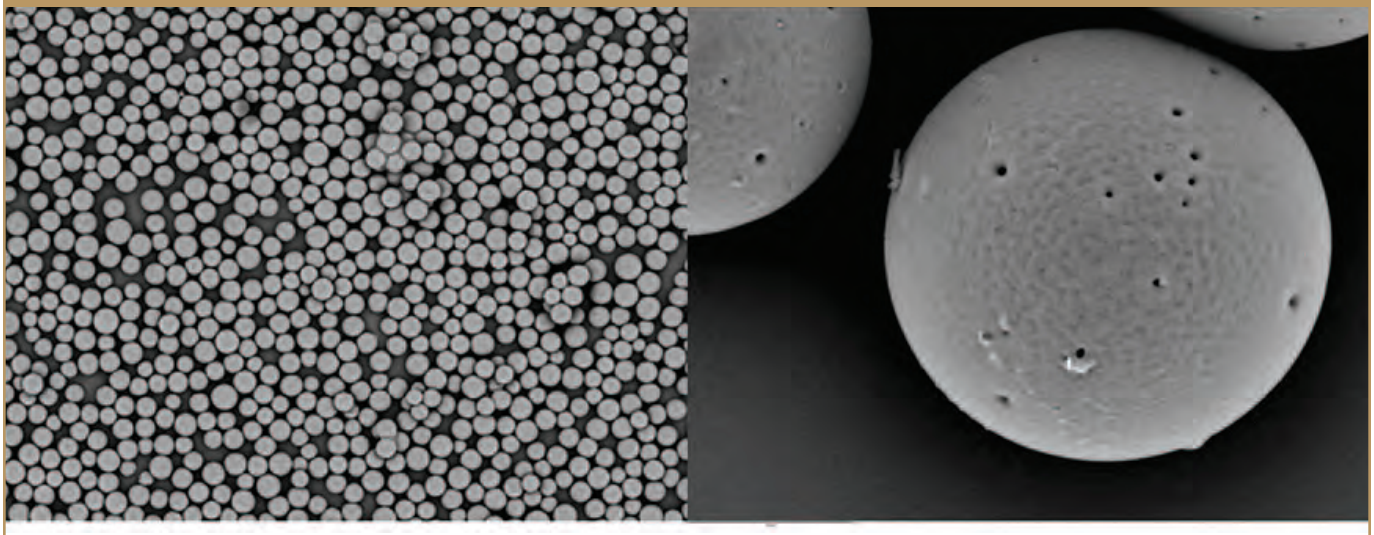
INTRODUCTION

Continued growth in interest in biodegradable polymers, stretching across the biomedical community for more than 50 years, has resulted in significant biotechnology advances in drug delivery, biomaterials, tissue engineering, and medical device development. Born out of interdisciplinary collaborations of individuals across the globe from fields as diverse as chemistry, engineering, biology, and physics, these researchers' shared interests in drug development have resulted in discoveries of more potent therapeutics in the form of peptides, proteins, nucleic acids, and other bioactive molecules. These therapies, more fragile than older approaches, require careful formulation of the drug delivery vehicle if they are to remain therapeutically intact with good economics until they perform their therapeutic purpose.

Popular drug delivery vehicles include lactide and glycolide homo- and copolymers because they can be fabricated into a variety of morphologies, including nano- and microspheres, thereby enabling highly tailored and versatile controlled and long-acting release to better control therapeutic outcomes. While not the preferred route of drug delivery, their main advantages are that they can deliver therapies directly to a target site and/or ensure better patient compliance over a prolonged time period.

Administration of drugs in the form of microspheres generally enhances the outcome through isolation of the given API at, or close to, the site of action and by extending drug release. Moreover, more delicate drugs, including peptides and proteins, can be protected against chemical and enzymatic degradation when entrapped in microspheres. Poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly-ε caprolactone(PCL) are

FIGURE 1



Monodisperse PLGA Microspheres (Micropore Technologies)

among the well-documented FDA-approved polymers used for the preparation of safe and effective vaccine, drug, and gene therapy delivery systems using well-described reproducible methods of fabrication.[1] Over recent years, InnoCore Pharmaceuticals of The Netherlands has developed copolymers, such as the SynBiosys range of multi-block polymeric materials, in an attempt to enhance control over physico-chemical and degradation characteristics.

It is noteworthy that biocompatibility is not only dependent on the polymer's intrinsic property, but also the particulate type and the biological environment. Hence, intensity and length of specific polymer-tissue interactions can be varied greatly in different organs, tissues, and species. The release of different drugs from PLA or PLGA matrices is the sum of surface and bulk diffusion as well as matrix erosion mechanisms, usually with a high initial burst rate.[2]

The advantages of long-acting formulations include enhanced patient compliance and convenience, and a lower dose of drug compared with a daily oral regimen. Despite these advantages, it is interesting to note that the limited number of different drug products placed on the market in the past 30+ years suggests that development of injectable, long-acting depot formulations is both demanding and challenging. What makes the development of long-acting PLGA formulations so challenging is down to several factors.

FORMULATION REQUIREMENTS

Formulating a sustained-release dosage form demands a clear understanding of the physicochemical and biological properties of the given polymer and the polymer's interaction with the API, with both married to an appropriate microsphere manufacturing technique. The design of a suitable morphology of porous microspheres of biopolymer to achieve the desired functionalities requires control over their physical properties, such as pore size, porosity, and microsphere size.

If required, templating methods can be used to create accurately sized porus structures. A variety of porogens, such as bovine serum albumin (BSA) and alginate microspheres, have been cited as suitable.[3] One important determinant of the porosity of the microstructure is the molar ratio between lactide and glycolide in PLGA. Also, higher molecular weight PLGAs are preferred for creating a more porous structure while low molecular weight PLGAs reduce microsphere size. As well as controlling for porosity and pore size, variations of these elements is one factor in determining the encapsulation efficiency of the chosen drug within the PLGA matrix, although higher encapsulation efficiency values are achieved by production using a double emulsion technique

A well-recognised issue with PLGA microspheres is their tendency to have a high initial burst release of drug. Typically 60% of drug loading is released in the first 24 hours. Generally undesirable, this effect has been known to produce toxic levels of API in plasma, with detrimental effects. This burst release is largely due to surface porosity and can be modified, for example, by the addition of buffer to achieve a plasticising "skin" on the PLGA or through storage at high humidity to "seal" the surface.[4] Another researcher has demonstrated the use of alginate coating to achieve the same effect.[5] The concentration of BSA has a significant influence on the pore size. During the formation of double emulsions, the osmotic pressure drives water penetration from the external water phase into internal water phase, leading to the formation of interconnected pores and finally, porous PLGA spheres after solvent evaporation. It is, therefore, reasonable to expect smaller pores to have a lower osmotic pressure, corresponding to a lower BSA concentration in the internal water phase.[6]

As described earlier, the final determinant of desired functionality is control over microsphere size during a robustly scalable manufacturing method. A good manufacturing technology will also allow the attributes of the chosen polymer system to deliver optimal encapsulation efficiency values while controlling burst release.

Sterilization carried out on the finished microspheres can lead to changes in the expected performance. For this reason, an aseptic process for microsphere production is desirable.

MICROSPHERE PRODUCTION

The customary production method, the solvent evaporation process, necessitates emulsification. There are two specific forms of emulsion processes: single emulsion and double emulsion. With the single emulsion process, an appropriate amount of PLGA is dissolved in an organic solvent, eg, dichloromethane, containing the API. The solution containing API and polymer is then subsequently emulsified by addition to aqueous solution containing surfactant or emulsifying agent to form an oil-in-water emulsion.

After formation of the stable emulsion, the organic solvent evaporates,

which can be accelerated by continuous stirring, dilution, adjustment of temperature or reduction of pressure. As it evaporates, the dissolved polymer precipitates to transform the droplets of polymer into solid microspheres. The microspheres thus developed are then sieved, washed, and lyophilized under sterile conditions, resulting in a final microsphere drug product suitable for fill-finish processing.

In the double emulsification process, water-soluble drugs are initially encapsulated by creating a primary emulsion of aqueous API solution in solvent+polymer solution. The resulting water-in-oil emulsion is then emulsified into aqueous buffer/surfactant solution to produce the secondary emulsion. The particle size and encapsulation efficiency of the system is controlled by solvent and stirring rate, among other factors.

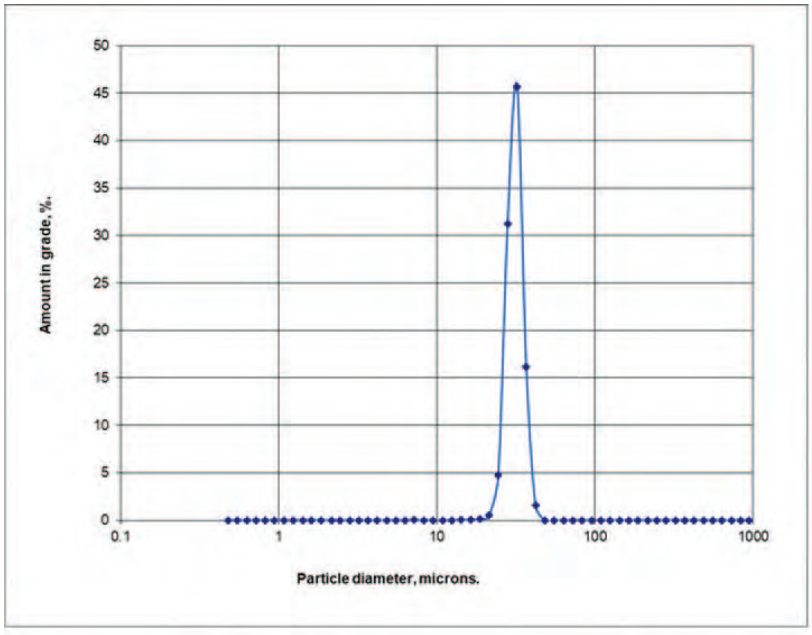
Solvent extraction kinetics are vital for creating a secure shell that depends on the solvent type used, temperature, and the type of PLGA. PLGA-solvent interaction also affects the PLGA coalescence and shell formation, determining the quality of microparticles formed. Crucially, the choice of solvent determines the drug solubility in the PLGA-drug mixture, particularly for hydrophobic drugs, and therefore affects drug loading, encapsulation efficiency (EE), and drug-release kinetics. As a result of each drug's unique physicochemical properties, each drug formulation needs a holistic consideration of PLGA specification, solvent type, and microparticle manufacturing conditions.

During the production of PLGA microspheres, slight changes in the formulation parameters can have radical effects on microsphere morphology and, in turn, drug release. With respect to double emulsion-solvent extraction, the mechanisms controlling microsphere internal porosity have been established for some time. In this instance, internal porosity is dependent on the stability of the primary emulsion.

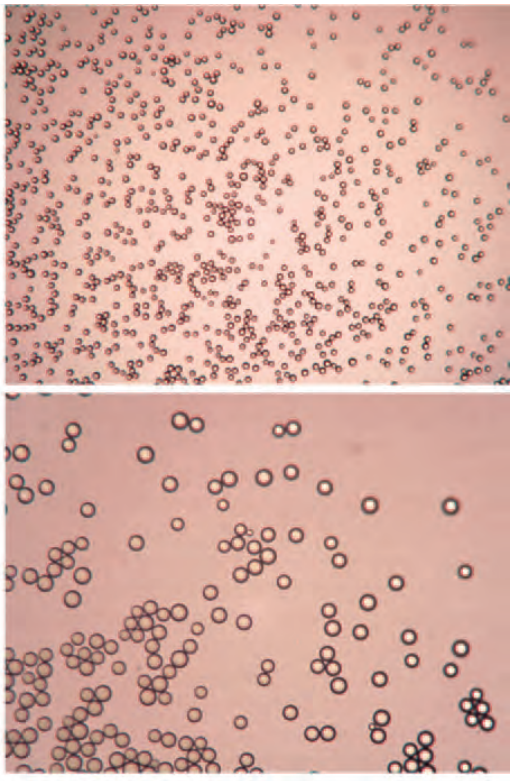
Traditionally, manufacturing methods have relied on high shear homogenization. This gives rise to a number of inefficiencies. The significant disruption of the secondary emulsion during emulsion manufacture results in low EE values. Additionally, this technique gives a wide size distribution of microspheres, which must be sieved, with significant waste arising, to give the correct size for administration. If this technique is applied to a sensitive API, the high shear will degrade a significant fraction rendering it therapeutically useless while adding to the regulatory compliance burden.

More recently, manufacture of highly precisely sized microspheres has been de-

FIGURE 2



Statistical Analysis	
StDev	3.19
Span	0.28
CV	11.67%
Uniformity Coefficient	1.2



Typical Narrow Dispersity PLGA Microspheres Produced by Membrane Emulsification (Micropore Technologies)

veloped using microfluidics technologies. Much has been written about these techniques, but they are all challenged when it comes to scale-up. The scale-up method of choice is to number up with consequently increased stringency of pumping and control systems and with no economies of scale benefits.

A third, well-established method that has the benefits of both homogenization and microfluidics but with few of their drawbacks offers precision at scale. Membrane emulsification was identified in Japan in 1985 but has come of age in the hands of Micropore Technologies Ltd.

Micropore harnesses the well-established solvent evaporation method of production with its multi-award-winning membrane emulsification technology. Micropore's precision engineered membrane emulsification technology robustly and reliably delivers a predictably narrow size distribution (coefficient of variation <15%) at a tuneable size between 5 to 500 µm through their precision-engineered, GMP-compliant technology.

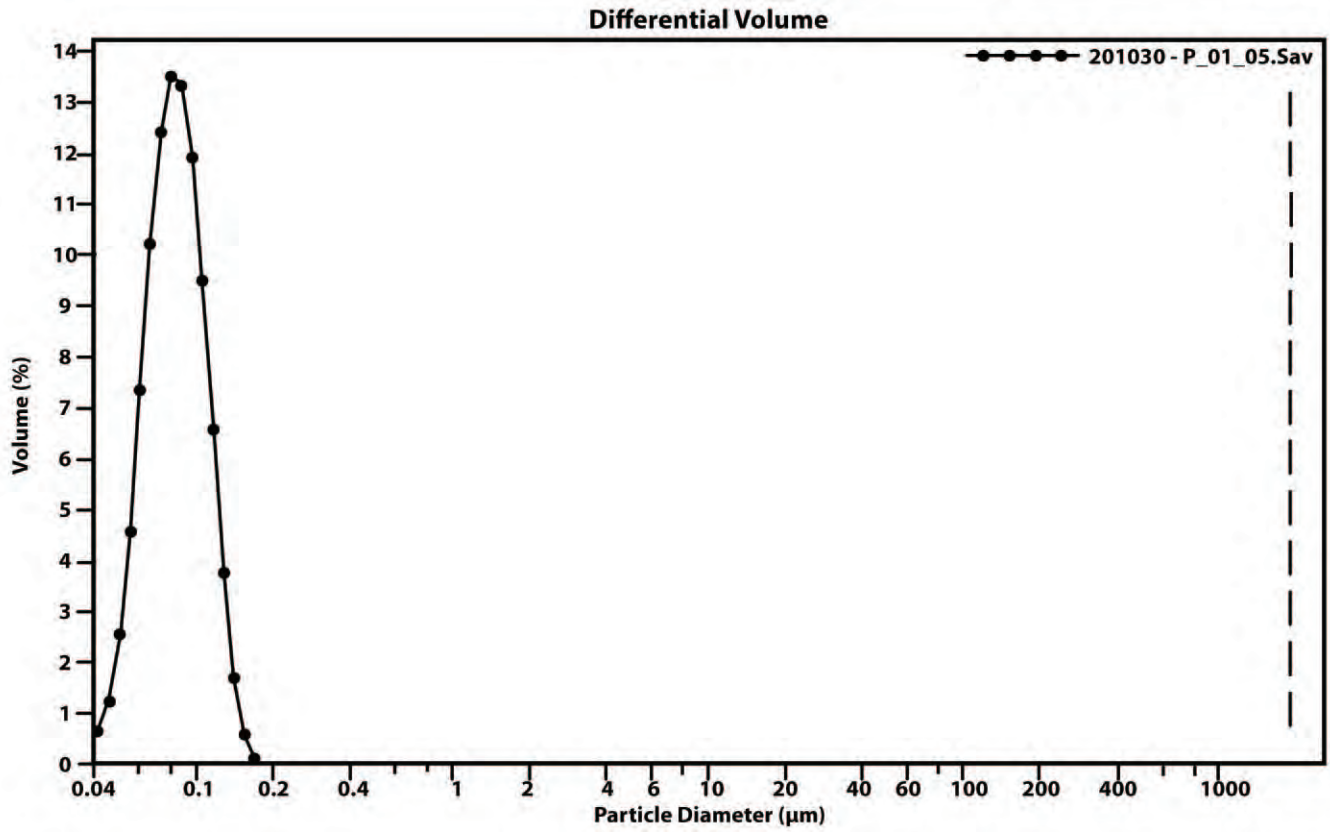
Client data highlights that it is common for 30% or more of microspheres produced using the traditional homogenization method to be over- or under-size and require removal through laborious and time-consuming sieving. The company has examples in which the material discard rate has been as high as 80% to 90%. Micropore's technology reduces this discard to zero, with consequent improvements in processing time and economics.

While biopolymers, such as PLGA, are most commonly associated with micron-size microspheres, PLGA nanospheres are emerging as interesting drug delivery vehicles. Such is the adaptability of Micropore's technology that it can be turned to the manufacture of this size of material.

The shear forces used in membrane emulsification are less than 50% of those required to lyse viable cells. This gentle process results in almost no degradation of sensitive APIs, retaining well above 90% biological activity compared with 37% to 67% degradation when rotor-stator homogenization is the method chosen for microsphere encapsulation.[7] Because Micropore's process is an inherently gentle process, the result is extremely high-quality microspheres when using a double emulsion process, as the primary emulsion is not broken during secondary emulsification. A gentle process enables enhanced microspheres, with high encapsulation efficiency of up to 99%, to be developed using a double emulsion-based membrane emulsification method.[8]

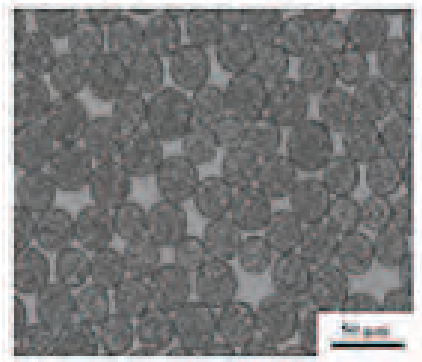
The simplicity and flexibility of Micropore's technology is such that develop-

FIGURE 3



PLGA Nanosphere Production (Micropore Technologies)

FIGURE 4



W/O/W Double Emulsion of Luperolide Acetate in PLGA (Unpublished data: M Dragosavac, Loughborough University)

ments can be transferred seamlessly from preclinical formulation development on the laboratory bench, through pilot scale and into full-scale GMP manufacturing, opening opportunities for more rapid development to explore the best way to optimize bioavailability for formulations.

Of course, reproducibility is vital in a full-scale manufacturing environment. In this respect the precision-engineered solution offered by Micropore excels.

SUMMARY

In summary, and to quote G2GBIO Inc., South Korea, who have licensed Micropore's technology, "The traditional method of manufacturing microspheres faced the challenge of difficulty in achieving uniformity and mass production. There also were limitations, such as lowering the predictability of drug efficacy as a result of low manufacturing reproducibility. The existing microsphere manufacturing method additionally had a problem of difficulty in cleaning and sterilizing, which are essentials for sterile GMP production. Micropore's microsphere manufacturing technology using membrane equipment overcomes the aforementioned problems. By introducing the newly developed membrane equipment in the GMP manufacturing process, 1 kg of uniform particles can be produced within an hour. This is a mass production scale of about 1,000 vials for Alzheimer's disease treatment and about 30,000 vials for animal neutering drugs."[9]

Together, recent advances in biopolymers and manufacturing technology now enable formulation of injectable drug products to be tailored at will to achieve a target bioavailability in a shorter development time with robust and low cost of manufacture, thereby delivering significantly improved therapeutic outcomes against the target disease. ◆

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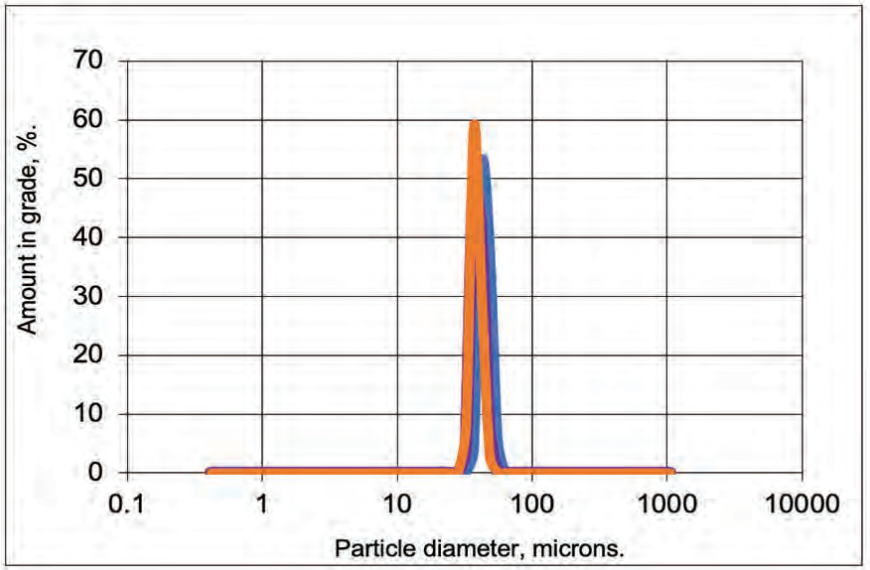
FIGURE 5



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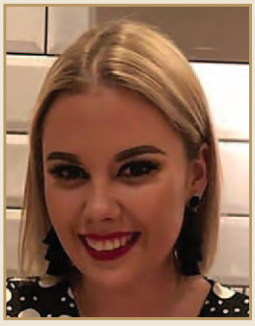
BIOGRAPHIES

Alex Kerr is a specialist in the field of encapsulation and formulation and heads up Micropore's formulation development team, investigating a range of techniques relevant to Micropore's award-winning technology.

Sam Trotter has a Masters degree in Chemical Engineering and heads up operations for Micropore, overseeing day-to-day lab operations, working with customers, and developing equipment design.



Poppy Maley has a Masters in Clinical Psychology and heads lead generation and customer relations management for Micropore Technologies.

PRODUCT DEVELOPMENT STRATEGY

ESCP, Estimating Product Performance Part 2 – Choosing a Seesaw

By: Josef Bossart, PhD

INTRODUCTION

In last month's introductory article, the concept of **ESCP (Efficacy, Safety/Tolerability, Convenience, Pricing)**, seesaws, and buckets was introduced as a visual and intuitive way to understand and estimate the marketplace potential for new pharmaceutical products. The very real-world example of "balancing" branded and generic products helped visualize the process. In this month's article, we will look at the importance of choosing the proper seesaw to play on.

THE INFINITELY LARGE PLAYGROUND

Most physicians and gatekeepers have their own sense of playgrounds and seesaws. Companies need to understand exactly what playground and seesaw they are planning to "play" on and whether it is consistent with their customers' perspectives. It doesn't make sense for an anticancer product to compete on the general "anticancer" seesaw. That seesaw doesn't exist. Rather, there is a large anticancer playground with dozens of seesaws. These seesaws are defined by a variety of characteristics, including, tumor type, disease marker, and disease stage. To play here, you need to decide exactly what seesaw(s) you want to compete on, generally not a decision made early in the development process, but which needs to quickly come into focus.

A common error smaller companies make when defining their product strategy is assuming there is a single seesaw rather than a playground full of seesaws. Assuming a single seesaw of undefined characteristics makes it impossible to sharpen focus on the key product benefits. Who exactly are you assuming is sitting on the other side of the seesaw?

Another error made by companies is choosing the wrong seesaw or choosing a seesaw that no longer exists. It is possible to create a new seesaw as I will discuss in a future article, but that is a challenge requiring resources often beyond the reach of smaller companies.

A look at the experiences of Exubera and Afrezza, both inhaled insulin products indicated for the treatment of Diabetes, shows the importance of picking the right seesaw and then creating the necessary leverage in development.

THE DIABETES PLAYGROUND

While not as large as the Cancer playground, Diabetes as a disease condition represents a remarkably large playground in terms of disease treatment objectives and options. Among Type 1, Type 2, and Gestational Diabetes patients, there is a varied population with any number of co-morbidities. Trying to get a handle on exactly what segment, or seesaw, to benchmark or compete in can be challenging.

NEKTAR, PFIZER & EXUBERA

Exubera, Nektar's inhaled formulation of insulin, was conceived and initially developed while it was a small company. The underlying product concept of Exubera was to provide a more convenient dosing presentation that avoided the need for multiple

daily injections. At the time of its conception and development, the 1990s and early 2000s, there was a sense that many patients with Type 2 diabetes who might benefit from insulin were put off by the injection requirements.

Exubera, with its large and ungainly bong style delivery device, was intended to compete directly with injectable formulations of insulin, most of which had not yet introduced the less-intimidating pen type devices with dialed-in dosing. At the time, taking insulin generally involved pulling out a new syringe, measuring and withdrawing the appropriate amount of insulin from a multidose vial, and then injecting the insulin subcutaneously. The prospect of a premeasured amount of insulin in unit-dose packaging that was slipped into a delivery device, the bong, and then inhaled was much more attractive to insulin naïve Type 2 patients.

That this was an improvement in patient dosing, and represented a significant commercial opportunity, was validated by Pfizer's early investment in the program. Returning to the seesaw analogy, it is likely that Nektar and Pfizer both imagined that they would be competing on the Type 2 seesaw, with injectable insulin on the other side as shown in Figure 1. It was probably imagined that the Efficacy, Safety, and Pricing buckets would be similar for both products, but the benefit of the inhaled, non-injected, dosage form would tip the balance in the favor of Exubera. While this might not significantly tip the balance, it might well be enough to carve out an attractive market share for Pfizer, which up to that point was not active in the insulin sector.

The reality was that while the balance might have tipped in favor of Exubera with improved convenience, it was counter balanced and overwhelmed by safety concerns. These safety issues were probably recognized during development but not fully appreciated. The largest concern was that long-term exposure of the pulmonary system to insulin, a growth factor in its own right, might exacerbate or stimulate malignancies. There also was a requirement for pulmonary testing on a regular basis, especially for patients with pre-existing res-

FIGURE 1

Exubera Versus Injectable Insulins, the Hope

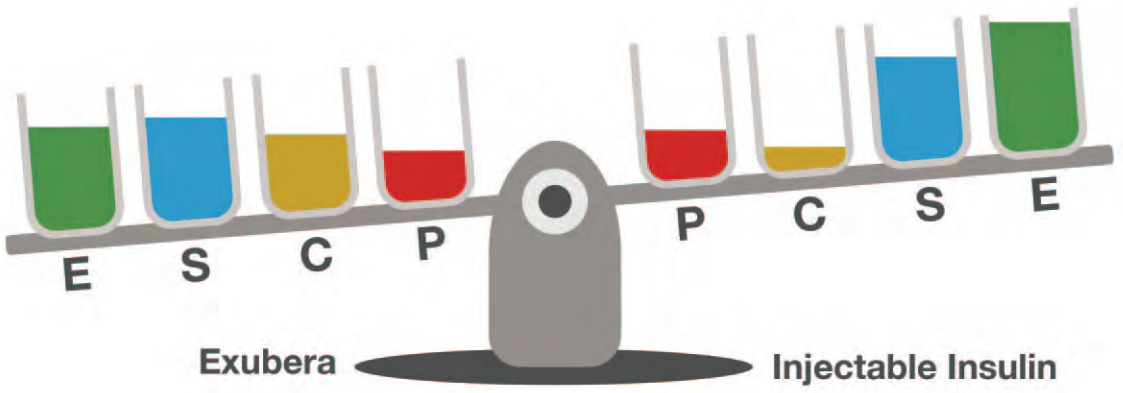
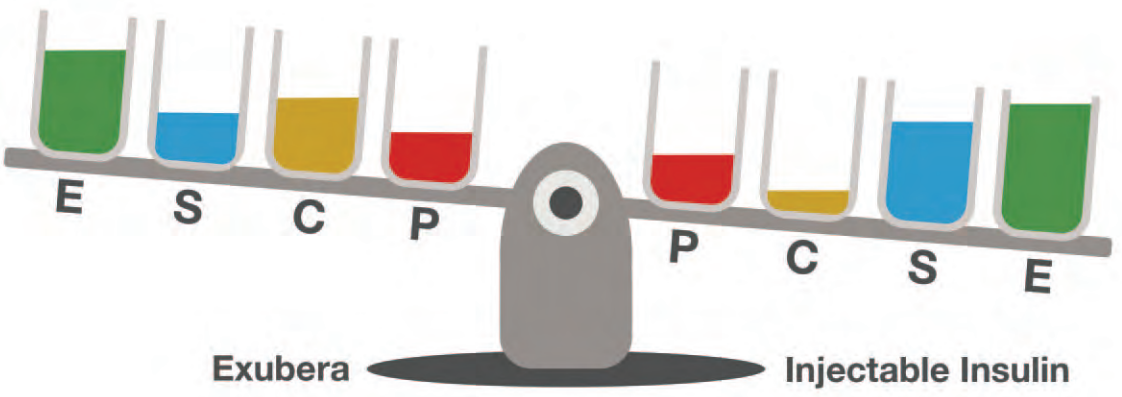


FIGURE 2

Exubera Versus Injectable Insulins, the Reality



piratory conditions. This testing was less an inconvenience for patients than it was for physicians, often general practitioners who often did not have the necessary familiarity and equipment to do the testing. In the end, despite the considerable weight of Pfizer's commercial resources, Exubera was withdrawn from the market less than 2 years after approval. The expectation of a commercially exploitable patient convenience benefit with Exubera was outweighed by safety concerns and perhaps also by an unexpected convenience disadvantage, at least with physicians (Figure 2).

MANNKIND, SANOFI & AFREZZA

It might be argued that Exubera failed, not because of any real failure of strategic and product planning, but the reality of the tolerability and safety concerns surrounding the chronic inhalation of insulin. There are few excuses for MannKind's strategy and execution.

It's worth reviewing the key development timelines for Exubera and Afrezza. The Exubera program was started in the early 1990s with the Pfizer deal in 1996, initial clinical results in 1998, and US FDA approval in January 2006. The partnership was terminated in October 2007 following the acknowledgement of safety concerns that limited commercial prospects for Exubera.

The Afrezza program reported first clinical results in 2004, with results from a Phase 3 trial presented in September 2006 and an NDA submitted to the US FDA in March 2009. Following multiple submissions and rejections, Afrezza was approved by the FDA in June 2014 for the treatment of patients with Type 1 and Type 2 diabetes. Sanofi entered into a partnership with MannKind for Afrezza in August 2014 with a US product launch in February 2015.

MannKind and Sanofi were certainly aware of Exubera and the reasons for its commercial failure, largely safety concerns, pulmonary testing requirements, and the large cumbersome bong-like delivery device. The answer was Afrezza, featuring a device that was small and discreet. The labeling for Afrezza was somewhat less restrictive than Exubera, with more limited pulmonary testing requirements, but also a warning about use with patients suspected of having, or being at risk for, lung cancer. The product also carried a dreaded black box warning regarding bronchospasm, a contraindication in patients with chronic lung disease, and a requirement for initial lung testing.

It is quite possible that MannKind considered Exubera to be their competitor on the other side of the seesaw. With a Convenience bucket for Afrezza that was filled almost to the top, and slightly fuller Efficacy and Safety buckets, things would surely tip in Afrezza's favor (Figure 3).

The reality of course was that Afrezza at launch was competing not against Exubera, but injected insulins with decades of clinical experience and increasingly patient friendly delivery devices. It has not gone well for MannKind. Afrezza is still marketed in the US with forecast sales of $40 million in 2021, an estimated cost of goods of 50%, and annual operational losses of about $100 million.

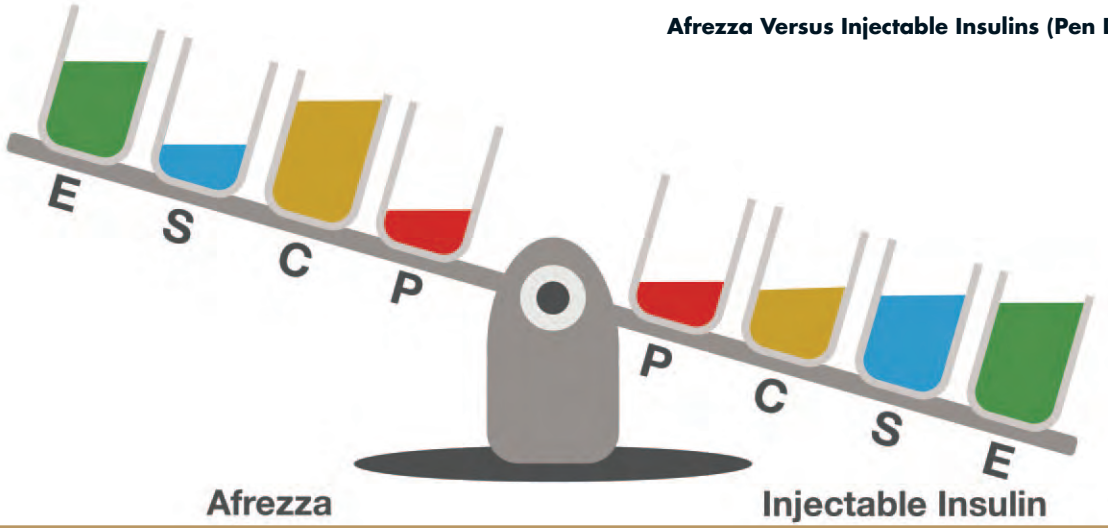
MannKind was competing with insulin injectables (Figure 4), not Exubera, a situation that was very obvious as early as 2006 when Exubera was floundering. Perhaps MannKind never really bothered to do the appropriate assessment or decided they had too much invested, financially or reputationally, to discontinue Afrezza's development. Regardless, Afrezza has been,

FIGURE 3

Afrezza Versus Exubera, the Hope

FIGURE 4

Afrezza Versus Injectable Insulins (Pen Devices)



and continues to be, a commercial failure that could have been avoided with an appropriate review, even a simple seesaw analysis, once the fate of Exubera was obvious. As Pfizer and Nektar understood, sometimes a company needs to walk away from sunk costs that will never pay off, ego be damned.

FINAL THOUGHTS

A critical analysis a decade and a half ago, even a simple seesaw comparison that compared Afrezza against the injectable insulins, would have provided important insights. While the bucket weights of Afrezza and Injected Insulin for Efficacy and Price might have been about the same, any Convenience benefit for Afrezza would have been overwhelmed by its Safety liabilities. The MannKind choices would have been to either kill the program or find a way to overcome the Safety gap.

Lessons provided by the experiences of Exubera and Afrezza include the following:

1. Pick the proper seesaw(s) to model.
2. Acknowledge the relative leverages provided by E, S, C, and P.
3. If things don't tilt your way, pick a different seesaw, figure out how to better fill your buckets, or walk away.

Next month, we examine the impact of friction at the pivot point. ◆

Drug Development
EXECUTIVE

Laura Brand

VP, Medical & Pharmaceutical Business

Celanese Corporation

Celanese

The chemistry inside innovation™

Celanese: Better Therapeutic Outcomes From Better Drug Delivery

In the evolving world of medicine, long-acting dosage forms are becoming more prevalent in the drug development pipeline. These forms are ideal for providing targeted drug release with continuous drug administration, ensuring patient adherence, which is of particular importance when compliance is crucial to treatment response. In addition, these dosage forms contribute to improved safety and efficacy through better dosing. Celanese Corporation's pharmaceutical business works closely with its customers to create innovative drug-eluting implants, inserts, and transdermal films delivering biologics and small molecules to meet the goals of patient-centric therapies, improved medicine, and better healthcare economics. *Drug Development & Delivery* recently spoke with Laura Brand, Vice President of Celanese's Medical & Pharmaceutical Business about it drug delivery platform and the value it brings to the industry.

Q: You recently joined Celanese as the new leader for Medical & Pharmaceuticals. Can you tell us about your background and area of expertise?

A: My area of expertise is primarily in the large molecule oncology space encompassing drug product differentiation for new molecular entities and for biosimilars. I started developing my expertise at the Boston Consulting Group (BCG)

predominantly in the healthcare business, and I worked with a wide variety of clients to support launch strategies, post-merger integrations, and measuring the effectiveness of launch spend. After 10 years at BCG, I moved to Amgen, where I held a variety of roles. However, the majority of my time was spent on the commercial side of the oncology business developing a strong understanding of the full spectrum of challenges of growing specific oncology drugs. From clinical trials though regulatory and reimbursement hurdles ending with product differentiation and both physician and patient education, I was able to establish a strong knowledge of both innovative and biosimilar oncology assets. Now with Celanese, I am using my experience to drive a stronger understanding of these challenges, enabling Celanese to be a true partner in our customer's drug pipeline development.

Q: We don't often see a move like yours from a Pharma company to a Specialty Materials company. What drew you to the Celanese organization?

A: Celanese is much more than just a materials company. When I was introduced to the company, I was amazed to see how broadly Celanese's materials were used. What I saw was the POTENTIAL. Our business is in a lot of interesting spaces from inhalation and injection devices as well as more complex orthopedic implants and glucose monitors. Even more complex is the drug-eluting platform for implants and inserts and the significant impact they can have on the improvement of healthcare, in patient therapeutics, and ultimately on patient's lives due to improved efficacy through better dosing and a more targeted therapeutic approach. Patient adherence is such an important aspect of a medicine's efficacy. Oftentimes, you will see great results in a clinical trial, but they are not replicated in the real world because the patient doesn't take his/her dose on time or misses it for various reasons. The idea of taking this issue out of the equation and having an implant or insert that can release the drug over time is fascinating. Whether the delivery form is used in the eye, contraceptives, oncology, or various other applications, it just has great potential.

In addition, Celanese's vision to "improve the world and everyday life through our people, chemistry, and innovation" is strongly supported through its emphasis on sustainability and diversity with strong environmental, social, and governance initiatives, making it a leading company to be at the forefront of positive change, and that is a type of company I am happy to be associated with.

Q: Could you please tell us more about Celanese's healthcare business as well as your drug-eluting platform?

A: What's interesting about Celanese's Health Care business is how well diversified it is within the medical and pharmaceutical industries. Our materials are used in essentially every type of medical device you can think of, from drug delivery and administration (eg, auto-injectors and inhalers), to interventional and surgical devices, to pharmaceuticals. Two key application area highlights include: (1) Patients' self-administration, such as wearable infusion pumps in which Celanese's technology enables smaller and more reliable devices that are more cost-effective to produce, and (2) Drug delivery in the form of drug-eluting durable implants or insert. This second focus area is an area for disruption that is very important. Our durable drug-eluting implants allow our customers and innovation partners to rethink how many medications are currently delivered and open the door to opportunities to enhance the drug's impact on patient outcomes. We strive to create value of a drug product through improved quality of a therapeutic via more safe and efficacious delivery as well as lower the total net costs of healthcare.

Getting a pharmaceutical company to incorporate a new technology is viewed as high risk. They see a new technology can lead to additional time-to-market. However, with a proven technology demonstrating that our delivery platform works in existing drugs, we can provide peace of mind for customers to incorporate these delivery concepts into their drug development process. Moreover, we expect our durable delivery platform will drive better patient adherence, which will then drive better outcomes. This improvement in outcomes is due to the patient having the right dosage continuously, which should in turn drive a positive outcome from a reimbursement perspective and ultimately, can be a strong path for pharmaceutical companies to extend the lifecycles of their products.

Q: What are some of the advantages of Celanese's Long-Acting Dosage durable delivery platform versus other controlled-release mechanisms?

A: Let me first address the value of durable implants. With a durable implant, you can better control the release of the drug at a more stable rate. It provides the ability to deliver controlled dosing over a long duration especially when continuous dosing

is critical to achieve the expected outcome. Because of its biostable and durable nature, our platform allows clinicians to reliably interrupt the therapy due to such issues as toxicity, side effects, or life changes. In addition, the need to remove the implant or insert ensures dosing clarity when it comes to subsequent dosing.

With a biodegradable system, you don't have as much control over the release, and removing the device is often not possible. Both have their benefits and drawbacks as you don't want to have to explant something unnecessarily. However, we believe our delivery platform is complementary and better suited for many indications and situations.

Celanese's VitalDose® EVA copolymer is a delivery platform that has a long clinical history of use and is used in a number of products undergoing clinical trials as well as marketed products. The drug delivery platform is very flexible making it compatible with both biologics and small molecule APIs for local or systemic drug administration. It also allows for very high drug loading (~75% max) and is ideal for treatment durations from months to years. We don't just supply the material. We work closely with our customers in a development partnership.

Q: You mentioned you don't just "supply material." Can you elaborate on the partnerships you established with your customers?

A: In a typical supplier-customer relationship, a customer calls a supplier up and asks for a material because they already know what they want. However, Celanese works directly with its customers to understand what the true needs are and customize the materials to fit those needs. We support our customers from early feasibility through development so we can help their drug successfully reach commercialization. Once commercialized, we provide customers with quality material tailored for their application.

We are committed to providing our customers with extensive development support as can be seen by our recent investment in our technical resources. Earlier this year, we opened our new pharmaceutical lab in Kentucky, which has been designed to support our customers with early stage feasibility work. We are equipped to create functional API-loaded prototypes, the ability to characterize and measure in vitro drug release, as well as to provide technical transfer support to our customers and their partners. In addition, Celanese is committed to providing strong regulatory support. Backed by years of experience working with global regulatory bodies, we provide customers with relevant certifications and documentation needed throughout various stages of their drug development and approval process.

With our breadth and depth of experience in polymer technology, Celanese continues to make it a high priority to apply that expertise in servicing our customers in the pharmaceutical and medical industry now and in the future. ◆

Special Feature

Excipients: Far From Inactive

By: Cindy H. Dubin, Contributor

Once defined as the inactive ingredient of a pharmaceutical drug, formulators are finding that excipients are anything but inactive, significantly impacting manufacturing, quality, efficacy, and delivery. Thus, industry experts predict the global pharmaceutical excipients market to reach upwards of $10 billion b7 2027.[1] The pros expect these effecting excipients to play a role in generics and biosimilar development, and even COVID-19 as more companies are engaged in developing coronavirus vaccines.

As excipients become more "active," research suggests that this may cause unintended reactions. A study conducted by the University of California San Francisco School of Pharmacy and the Novartis Institute for BioMedical Research portends that some excipients in common drugs may be biologically active and lead to unanticipated side effects. According to the scientists, excipients are generally accepted to be biologically inactive because they do not produce any obvious toxicity in animal studies, however a few studies have looked for more subtle effects of long-term exposure to these compounds and how they might interact in people who take multiple different medicines that include these ingredients.

In response, excipient manufacturers stand by the safety and quality of their drug ingredients. Dr. Yukiko Suganuma, Pharma Solutions, Daicel Corp., says: "Our co-processed excipients are composed of conventional ingredients that meet JP, USP-NF, and EP and are designed with reference to the Co-processed Excipient Guide for Pharmaceutical Excipients. Therefore, it seems that our co-processed excipients are satisfied in the view of quality and safety."

And, Jasmine Musakhanian, Scientific and Marketing Director, Gattefossé USA, says: "In designing our existing and

Gattefossé Gelucire® 48/16, a multifunctional solid excipient.

new excipients, Gattefossé always focuses on the excipient's safety, biocompatibility, purity, and consistency of quality. More importantly we have spent decades accumulating extensive safety data in different animal models. The information is readily shared with the clients, in the form of Safety Overview dossiers and preclinical guides, with clear indication of maximum daily intake limits and precedence of use allowed by regulatory bodies. Our clients also have access to the market references, where our excipients are safely incorporated approved therapies to improve drug pharmacokinetics."

In addition to Daicel Corp. and Gattéfosse, the companies highlighted in this annual report by *Drug Development & Delivery* assert that novel excipients – agglomerated, co-processed, and multifunctional – actively and safely affect formulation stability, solubility, and bioavailability as well as foster faster drug disintegration.

Caption: galenIQ™ can be used to improve the stability of oral solid dosage forms at low compression forces, which facilitates high-speed tableting.

BENEO: Filler-Binder Excipient Improves OSDF Stability

Oral solid dosage forms (OSDFs) remain the preferred and most convenient delivery method for drugs and supplements. It is to be expected, perhaps, that some biosimilar drugs that are currently administered by injection could also be formulated into OSDFs. In that case, inert and compatible filler-binders are required. It seems that relatively new excipients such as agglomerated galenIQ™, which are chemically inert, could be suitable because of their compaction properties and surface structure, which promotes high content uniformity. BENEO's pharma team is investigating the use of galenIQ in some new and emerging pharmaceutical technologies, including how it can be used to make 2mm orodispersible minitablets that disintegrate in the oral cavity within 30 seconds.

"Filler-binder excipients such as galenIQ can be used to improve the stability of OSDFs at low compression forces, which facilitates high-speed tableting and makes it more efficient," says Dr. Michael Black, Head of Sales Pharma, BENEO. "Moreover, galenIQ is water-soluble and can be used in tablets without having to add a super-disintegrant. Using galenIQ could simplify both formulation development and production for pharmaceutical manufacturers."

Dr. Black explains how BENEO works closely with customers during the formulation development phase and provides them with data and sample material to ensure the suitability of agglomerated galenIQ grades for processes such as continuous manufacturing and direct compression. As an example, one customer wanted to formulate a tablet containing two herbal extracts and a mineral. Each of these components had a different compaction profile. He says: "By using galenIQ 721, the customer was able to achieve good compaction, high content uniformity, and long-term stability."

Cyclolab Ltd.: Evading Thermodynamic Constraints of Cyclodextrin-Drug Formulations

Applying cyclodextrins (CDs) in drug formulations helps form non-covalent, reversibly dissociating inclusion complexes with lipophilic drugs or their lipophilic moieties (via partial complexation). As a consequence, the aqueous solubility of the included substance may significantly increase. In solution, the constituents of the complex are in dynamic equilibrium, i.e. the free and bound species constantly undergo rapid association/dissociation governed by thermodynamic factors such as the association constant, temperature, and concentration of the host

cyclodextrin and guest drug molecule. Determining these parameters is the key for successful classical complex composition design. Nevertheless, such factors often demonstrate limitation of CD complexing capacity, resulting in unacceptably high amounts of CD needed to encapsulate the therapeutic dose of some drugs.

"By evading the thermodynamic constraints of cyclodextrin-drug formulation design – by preparing supersaturated, but kinetically stabile compositions – even an apparently weak drug-CD interaction might be exploited to yield a practically applicable pharmaceutical product," says Dr. István Puskás, a formulation expert at Cyclolab Ltd.

Two examples illustrate how to prepare such oversaturated solution in which the low rate of drug crystallization enables the administration of the composition within a reasonable time limit. First, hydroxypropyl betadex (HPBCD) is a peculiar CD soluble in ethanol. Ethanol-soluble guest drug molecules might be co-processed with HPBCD in their common ethanolic solution. By exhausting removal of the solvent, a glassy, amorphous coevaporate forms containing the drug in a solid HPBCD matrix in molecularly dispersed state. Upon contact with water, this coevaporate might dissolve and produce drug concentration over the thermodynamic equilibrium value. The chaotropic nature of multicomposite HPBCD hinders drug precipitation in aqueous solution. The oversaturated composition can then be stabilized by freeze drying, resulting in another amorphous composition that can be reconstituted prior to patient administration into a still oversaturated, but kinetically, stabile aqueous solution.

Volumes of solutions to dissolve 10mg model drug (Cyclolab Ltd.).

A second example is betadex sulfobutyl ether sodium (SBECD), as an ionic CD derivative often shows great pH-dependent variation on its solubilizing performance. If the chemical durability of the drug permits, complex formation can be performed at very low pH value (even exceeding the physiologically relevant range) to reach thermodynamic equilibrium at highly acidic medium. After successful complete dissolution, the pH might be raised to a physiologically acceptable pH range, resulting in an oversaturated solution having a composition that could not be spontaneously attained without this pH excursion, ensuring kinetic stability of the composition.

Another strategy applicable for native alfa-, beta-, and gamma-CDs to cope with low stability constant interactions is offered by the application of a third component like a polymer or hydroxy acid. In these ternary systems, a new stability constant applies that might be significantly higher than that obtained for binary drug-CD compositions. The stability of the reconstituted ternary system may be of thermodynamic or kinetic nature, says Dr. Puskás.

Daicel: Two ODT Formulations Offer Strength & Fast Disintegration

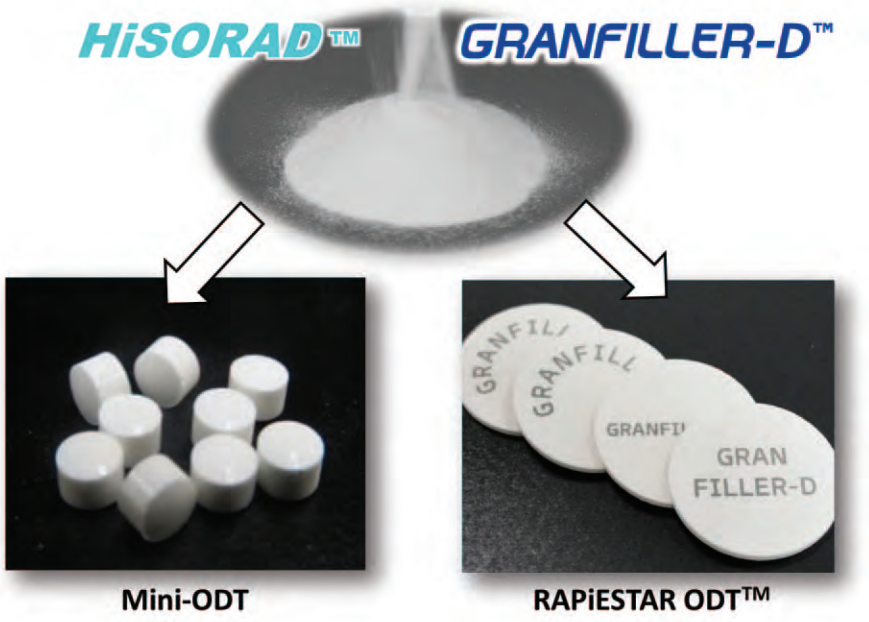
The number of available pediatric formulations are limited. Orally disintegrating tablets (ODTs) that disintegrate in the oral cavity within 30 seconds are a preferred choice for children, however even rapid disintegration of conventional ODTs is not necessarily enough for pediatric use. Daicel Corp. offers two types of ODTs for pediatric formulations by direct compression process using co-processed excipients.

One formulation is a mini-ODT. These miniaturized tablets are approximately 2 to 4mm in diameter and are considered to provide improved acceptability by children, says Dr. Yukiko Suganuma, Pharma Solutions, Daicel Corp. Moreover, by adjusting the number of tablets, the dose can be controlled according to weight and age of pediatric patients.

Mini-ODTs can be produced using DC co-processed excipients such as GRANFILLER-D™ or HiSORAD™ without any special preprocessing. A 2018 study revealed that tablet weight of the mini-ODTs with GRANFILLER-D or HiSORAD was uniform and disintegration time of <3 seconds was achieved. They also exhibited sufficient hardness and friability for any mini-tablet measuring devices.

The other formulation is an ultra-fast disintegrating tablet, RAPiESTAR™ ODT. RAPiESTAR ODT is approximately 14mm in diameter and ≤1mm thick. Its large surface allows rapid disintegration; a placebo tablet disintegrated in less than 5 seconds. Unlike other commercially available ultra-fast disintegrating tablets using lyophilization technologies, RAPiESTAR ODT can be produced by DC with GRANFILLER-D, explains Dr. Suganuma. "Although thin tablets are typically fragile in response to external impact, RAPiESTAR ODT with GRANFILLER-D had practical strength that exceeded expectations. This thin tablet with enough strength is derived from the unique mechanical property of GRANFILLER-D."

RAPiESTAR ODT is applicable to a variety of APIs. A feasibility study of RAPiESTAR ODT for commercial launch is currently in progress. "Thus, mini ODTs and RAPiESTAR ODTs prepared using GRANFILLER-D or HiSORAD disintegrate in several seconds, indicating excellent disintegratability far beyond that of conventional ODTs," says Dr. Suganuma. "These tablets provide not only the advantages of ODTs, such as safety, convenience, and reliability, but also the special shape considered for suitability to children taking medications."



Two types of ODTs for pediatric formulations with Daicel's co-processed excipients.

Gattefossé: Lipid Excipients as Delivery Systems that Enhance Solubility & Bioavailability

Gelucire® series by Gattefossé are multifunctional excipients for solid self-emulsifying drug delivery systems (SEDDS) and low-temperature melt extrusion.

Given the low oral bioavailability and complex nature of the emerging chemical entities, there is a need for excipients that act as drug delivery systems on their own, simultaneously addressing the drug solubility, dissolution rate, and eventual absorption. This is possible with self-emulsifying liquid as well as solid lipid excipients.

For example, Gattefossé's Gelucire 48/16 is a solid excipient that may be used in a variety of processes serving as solid drug delivery matrices in direct capsule filling, melt granulation, and preparation of solid amorphous dispersions using hot melt extrusion. The resulting powder or granules may be dry filled into capsules or compressed into tablets.

In the case of one poorly soluble drug, conventional formulation approaches were failing to produce the required drug release rate, explains Jasmine Musakhanian, Scientific and Marketing Director, Gattefossé USA. "Following a thorough solubility screening, our Technical Center of Excellence in Paramus, NJ, proposed a combination of two liquid excipients, including Labrasol®. The proposed formulations were able to release the entire dose within the first five minutes of dissolution."

Shin-Etsu Chemical Co.: Multifunctional Excipients with High Binding Capability

With the advent of material science and particle engineering, various excipients with multifunctional properties for pharmaceutical applications have been introduced. Such excipients are Shin Etsu's AQOAT (Hypromellose Acetate Succinate or Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)) and L-HPC (Low substituted hydroxypropyl cellulose).

HPMCAS was first commercialized by Shin-Etsu Chemical Co., Ltd. in Japan in 1986 under the commercial name of Shin-Etsu AQOAT. It was originally developed as an enteric polymer for aqueous coating, explains Anisul Quadir, PhD, MBA, RPh, Technical Director, Pharmaceutical Excipient, Pharmaceutical Application Laboratory, SE Tylose USA, Inc., A Shin-Etsu Chemical Group Company.

"However, with recent advancements in solubilization techniques, such as spray drying and hot melt extrusion to prepare amorphous solid dispersion (ASD), HPMCAS became a polymeric carrier of choice for improving solubility and bioavailability of poorly water-soluble drugs," he says.

Currently more than 25 marketed formulations consist of HPMCAS as a solid dispersion carrier. The distinct advantage of HPMCAS from other solid dispersion carriers is its ability to maintain the supersaturation of a drug for a long period of time, thus avoiding precipitation. For instance, it has been demonstrated that with HPMCAS, an extremely high apparent supersaturation has been achieved for almost 5 hours with poorly soluble APIs like Itraconazole and nifedipine. Additionally, having a higher glass transition temperature (Tg~1220C), HPMCAS makes a suitable carrier for a stable ASD formulation and inhibiting recrystallization of the drug until it has reached its shelf life, says Dr. Quadir. "The availability of optimum particle sizes (fine, medium as well as granular grade) and three different levels of acetyl/succinoyl substitution (low, medium and high) for HPMCAS gives more flexibility to the formulation scientist. The recently introduced mid-particle size grade of HPMCAS (70-300µm) helps to overcome the challenges of particle segregation and ensures consistent content uniformity in HME application."

L-HPC is another multifunctional excipient with high binding capability and fast disintegration abilities. Different grades of L-HPC based on morphology, particle size, and % hydroxypropyl substitution have been introduced. Depending on the physical and chemical substitution, L-HPC can be used in both wet (LH-21) and in direct compression (NBD-021). However, smaller particle and higher compressibility grade would be better for dry granulation such as roller compaction. Therefore, LH-31 (and NBD grades) would be recommended for dry granulation says Dr. Quadir..

In a recent study, it was found that compressibility and compactibility of L-HPC is equivalent to a commonly used diluent like microcrystalline cellulose; water absorption and swelling capability is higher when compared to popular disintegrants like croscarmellose sodium and crospovidone, explains Dr. Quadir. "Higher compressibility, along with pH independent disintegration ability and no detectable peroxide content, makes L-HPC one of the most suitable and smart excipients for robust formulation development of solid dosage forms."

Dr. Saurabh Mishra, a formulation scientist at the Shin-Etsu pharmaceutical application laboratory, says that L-HPC, in combination with PHARMACOAT 603 (HPMC, 3 m.Pas), could be ideal excipients to develop a robust platform for continuous manufacturing using twin screw wet granulation. Using a Quality by Design approach, using 5% LH-21 and 1% PHARMACOAT 603 achieved an immediate-release, robust formulation complying with critical quality attributes of a poorly flowable and compressible API like acetaminophen. "This could be attributed to the higher binding capability of L-HPC and lower viscosity of PHARMACOAT 603, which make it suitable for continuous manufacturing applications," Dr. Mishra says. ◆

Reference

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NUCLEAR β-CATENIN INHIBITOR

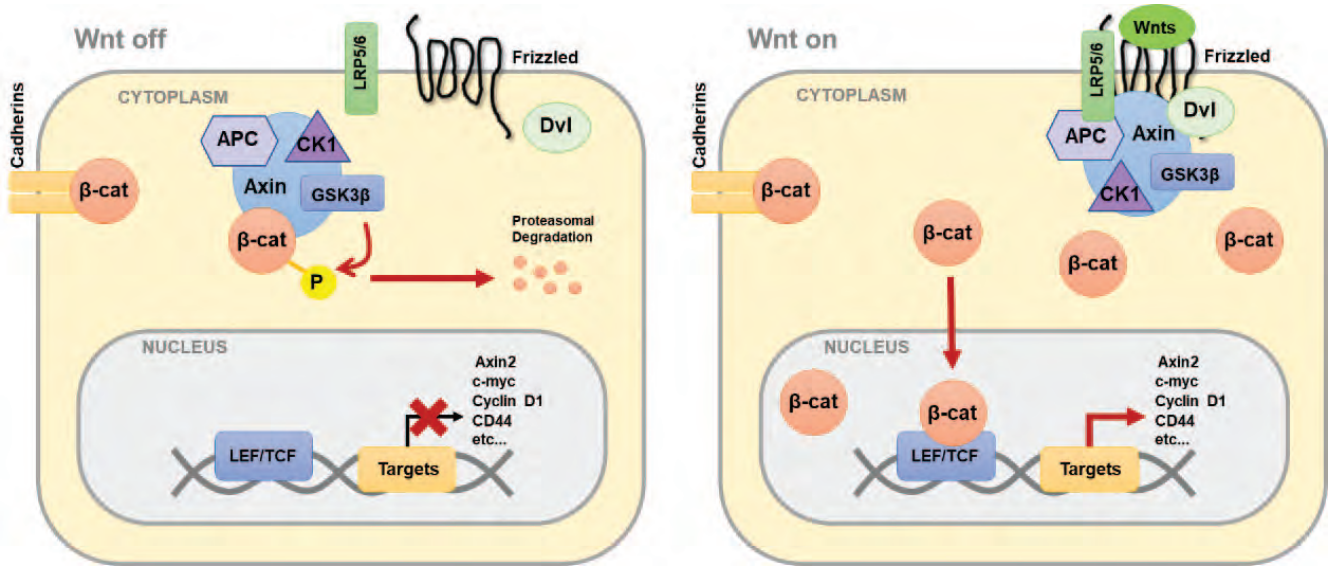
TBL1 - A Novel Target for Safe & Effective Blockade of the Nuclear β-catenin Signaling Pathway

By: Ruolan Han, PhD

INTRODUCTION

The canonical Wnt signaling pathway, mediated by the nuclear transcription factor β-catenin, is a primary signaling pathway that orchestrates various biological processes, such as cell proliferation, differentiation, organogenesis, tissue homeostasis, tissue regeneration, tumorigenesis, and tumor immune evasion. Aberrant Wnt-activation and nuclear β-catenin up-regulation drive oncogenic gene transcription in many human cancers. Mutations in key components of this pathway have been found in a significant number of sporadic and familial cancers. Inhibition of this pathway in various oncogenic model systems further validates its critical role in

FIGURE 1



The Wnt/β-catenin Signaling Pathway: In the absence of Wnt ligand, cytoplasmic β-catenin is maintained at low levels by its constitutive degradation. β-catenin degradation occurs primarily via its association with a complex consisting of glycogen synthase kinase 3 (GSK3), casein kinase 1α (CK1α), adenomatous polyposis coli (APC) and Axin. Within this destruction complex, β-catenin is phosphorylated by GSK3 and targeted for degradation by the ubiquitin-proteasome pathway. Upon binding of Wnt ligand to Frizzled and low-density lipoprotein-related receptors 5 and 6 (LRP5 and LRP6), β-catenin destruction is inhibited and the scaffold protein Axin is degraded. Thus, Wnt signaling increases cytoplasmic levels of β-catenin, which enters the nucleus and interacts with other factors to activate a TCF/LEF1–mediated transcriptional program. Alternatively, the pathway can be turned on by mutations in the phosphorylation site of β-catenin, or loss-of-function mutations in the destruction complex, resulting in cytoplasmic accumulation and nuclear translocation of free β-catenin even in the absence of wnt ligand binding.

cancer growth and metastasis. Therefore, the Wnt/β-catenin pathway has long been considered a high-value oncology target.

However, since the discovery of the Wnt/β-catenin pathway involvement in cancer in the 1980s, more than 40 inhibitors targeting this pathway have been reported in the literature, with nearly 20 proceeding to clinical evaluation, yet none have made it to FDA approval.

Reasons for this failure center around two major issues. The first is that the key effector of the Wnt/β-catenin pathway, nuclear transcription factor β-catenin, lacks enzymatic activity and possesses no surface structures suitable for drug binding. Hence, drug development strategies must target other, more druggable components of the pathway either upstream or downstream of this pathway.

UPSTREAM CHALLENGES IN TARGETING THE WNT/β-CATENIN PATHWAY

Upstream approaches include reduction of Wnt ligand signaling, either at the receptor level, or the subsequent transduction of the Wnt signal by Dishevelled (Dvl). However, these approaches are limited in their specificity due to cross-regulatory effects on other signaling events activated by Wnts, such as the non-canonical Wnt pathways that lead to PKC and JNK activation. Moreover, these therapeutics are ineffective in cases where the aberrant Wnt signaling is activated by mutations in downstream components, such as Axin, APC, or β-catenin.

Finally, several of the enzymatic components of the Wnt signaling cascade that could potentially serve as attractive targets for small molecules, such as GSK-3β, CK1α, and β-transducin repeat containing protein (β-TrCP), have broad activity and regulate multiple other signaling pathways, thereby diminishing their suitability as specific Wnt/β-catenin pathway targets.

An even more global challenge to upstream approaches is that β-catenin is also found in the cell membrane and cytoplasm of normal cells where it is an important structural protein in cell-cell adherence junctions. So, compounds that reduce the global cellular levels of β-catenin (such as targeting WNTs, RNAi therapeutics and tankyrase inhibitors) have a significant risk of disrupting these junctions. Such perturbations in cell-cell adhesion is often associated with the initial stages of tumor metastasis. Moreover, disruption of the adherence junctions might be deleterious to the structural integrity and viability of cells, such as the mucosal barrier in the gut and tight junction barrier in the epidermis, resulting in adverse systemic effects such as GI toxicities and skin reactions.

TABLE 1

	Upstream Approaches			Downstream Approaches		
Target	Porcupine	LRP5/6	Frizzled Receptors	CREB-Binding Protein	Phospho-p68	TBL1/TBLR1
INDs	LGK974 (Novatis/Pyridines) CGX1321 (Curegenix) XNW7201 (Sinovent Pty Ltd.) ETC-159 (EDDC, Singapore)	BI 905677 (Boehringer Ingelheim)	OMP-18R5, OMP-54 F28 (OncoMed) Foxy-5 (WntResearch AB) OTSA 101 (OncoTherapy Science)	PRI-724, E7386 (Prism/Eisai)	RX5902 (Rexahn)	Tegavivint (Iterion Therapeutics)
Activity Level	Wnt ligand	Wnt receptor	Wnt receptor	Nuclear coactivator of β-catenin	Nuclear transporter/coactivator of β-catenin	Nuclear transporter/coactivator / stabilizer of β-catenin
Selectivity	Propensity for on-target toxicity as a result of cross-regulation of non-canonical Wnt and other signaling pathways important for normal cell function			More selective for nuclear-β-catenin-dependant signaling; Avoided toxicity resulted from upstream signaling cross-talks; may cross-regulate other transcription factors		
Efficacy	Ineffective against APC loss-of-function or CTNNB1 gain-of-function mutations			Effective against APC loss-of-function and CTNNB1 gain-of-function mutations		
				Inhibits nuclear β-catenin signaling on the nuclear level	Inhibits nuclear β-catenin signaling and promotes degradation of nuclear β-catenin	

"Tegavivint (BC2059, Iterion Therapeutics) is a first-in-class small molecule inhibitor of TBL1 and the only TBL1 inhibitor reported to date. Tegavivint was discovered through cell-based screening strategy for inhibition of nuclear β-catenin activity and subsequently shown to target the TBL1/R1 interaction with β-catenin. Tegavivint has been shown to potently inhibit nuclear β-catenin-dependent signaling through binding to TBL1, thus disrupting the TBL1/β-catenin association."

LOOKING DOWNSTREAM FOR OPPORTUNITY

Given these challenges, other development efforts focus downstream at the nuclear β-catenin level by targeting the nuclear transporters and coactivators of β-catenin. Because the oncogenic functions of β-catenin are derived from the nuclear transcriptional activation of the protein, this strategy has a greater promise of specifically disrupting cancer cells.

Compared to the upstream approaches, these therapeutics are also more effective for loss-of function mutations in APC and gain-of-function mutations in CTNNB1 (the gene that encodes β-catenin protein). However, the selectivity for Wnt/β-catenin pathway may vary, because these nuclear factors may have other functions, including interactions with other transcription factors, thereby potentially influencing many signaling pathways besides Wnt/β-catenin pathway, leading to various off-target effects.

Table 1 illustrates a comparison of the therapeutics targeting the Wnt/β-catenin pathway currently being evaluated in clinical trials.

TBL1/TBLR1 AS ATTRACTIVE TARGETS FOR NUCLEAR β-CATENIN SIGNALING

Transducin Beta-like protein 1 (TBL1) and its highly homologous family member TBLR1, have recently emerged as attractive targets for altering nuclear β-catenin signaling. TBL1/TBLR1 are evolutionarily conserved proteins that share high structural and functional similarities from yeast to human. TBL1/TBLR1 are F-box/WD-40 repeat containing scaffold proteins that associate with members of coactivator or corepressor complexes, including NCoR/SMRT and NFkB through its N-terminus hydrophobic pockets.

In response to Wnt pathway activation, TBL1 and TBLR1 are SUMOylated and released from the NCoR/SMRT corepressor complex. SUMOylated TBL1/TBLR1 subsequently binds β-catenin and translocate to the nucleus. The direct physical interaction between TBL1/TBLR1 and β-catenin inhibits β-catenin degradation in the nucleus.

Binding of TBL1/TBLR1 to β-catenin also facilitates the localization of β-catenin to the oncogenes and activates β-catenin-dependent gene transcription. The recruitment of TBL1-TBLR1 and β-catenin to the Wnt target gene promoter is mutually dependent. The positive synergistic mechanism of Wnt activation→TBL1 SUMOylation→BL1/β-catenin interaction→Wnt activation provides a unique opportunity to preferentially target oncogenic Wnt/β-catenin signaling amplification while leaving other normal physiological processes that depend on this signaling intact.

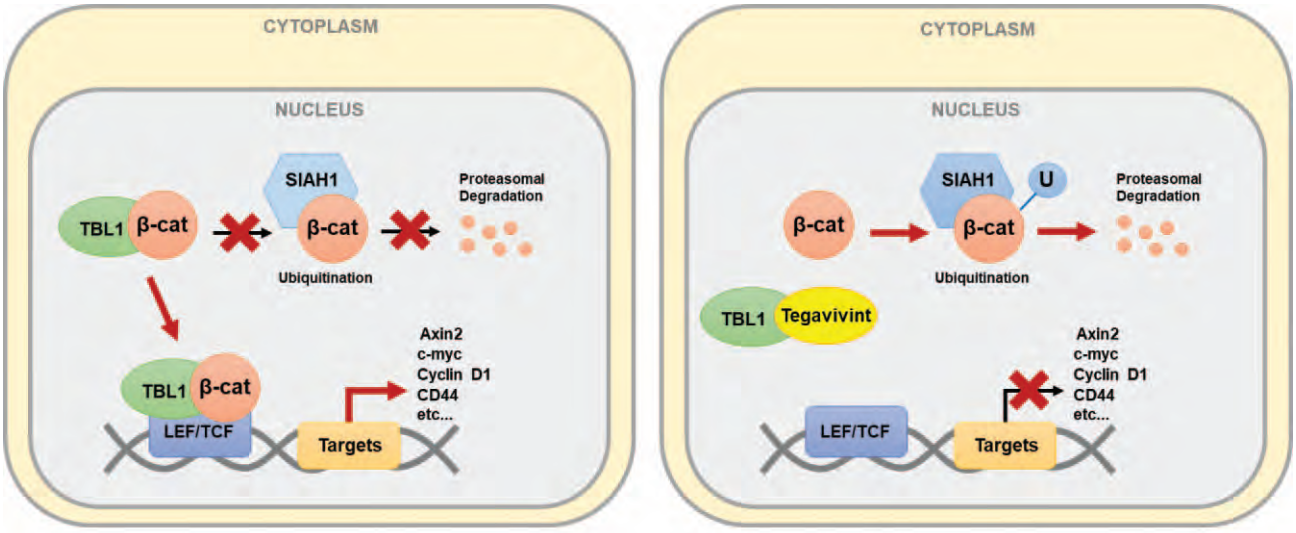
Experimental evidence supports that overexpression of TBL1 or TBLR1 can lead to significantly enhanced β-catenin-mediated transcription. Conversely, depletion of TBL1 or TBLR1 abolished the activation of β-catenin.

TBL1/TBLR1 ARE MULTIFUNCTIONAL ONCOLOGY TARGETS ON THEIR OWN RIGHT

TBL1 and TBLR1 are also mutated and upregulated in multiple types of cancers, including breast, lung, pancreatic, and colon cancers, and their overexpression is often associated with poor prognosis and metastasis. These and other accumulating data provide increasing evidence that TBL1/TBLR1 are promising oncology targets for therapeutic intervention.

TBL1/TBLR1 are intrinsic components of the SMRT/NCoR co-repressor com-

FIGURE 2



TBL1 binds nuclear β-catenin to protect it from SIAH1 mediated ubiquitination and degradation, and promote β-catenin mediated target gene expression

Tegavivint binds TBL1, inhibiting its interaction with β-catenin, resulting in specific nuclear β-catenin degradation, and silencing of target gene expression

plexes and act as exchange factors of corepressors for coactivators to control the transcriptional switch between gene repression and gene activation. Transcriptional activation mediated by liganded nuclear hormone receptors (NHRs) and other regulated transcription factors (TFs) requires the release of co-repressors followed by the recruitment of a series of coactivator complexes harboring specific enzymatic activities. A recent study has shown that both TBL1/TBLR1 are required for transcriptional activation by estrogen receptor (ER), androgen receptor (AR), thyroid hormone receptor (THR), and peroxisome proliferator-activated receptor (PPAR).

TBLR1 is also required for the activation by RAR (retinoid acid receptor) and AP-1 (activator protein-1). TBL1/TBLR1 both serve as adaptors for the recruitment of the ubiquitin conjugating/19S proteasome complex to the promoter in a ligand-dependent fashion, mediating the exchange of corepressors for coactivators. The functions and the specificity of TBLR1 and TBL1 are regulated by signaling specific phosphorylation events at target gene promoters.

Additionally, TBL1/TBLR1 regulates the NF-κB pathway, an important signaling pathway that has been implicated in autoimmunity, chronic inflammation and cancer. A recent study has shown that both TBL1 and TBLR1 are required for the NF-κB mediated activation on canonical sites. TBL1 is critical for the recruitment of p65 to NF-κB target genes to mediate activation. NF-κB transcription requires IKKalpha to phosphorylate SMRT on chromatin, stimulating the exchange of co-repressor for coactivator complexes. The recruitment of TBL1/TBLR1 to the target promoters coincides with SMRT phosphorylation. Moreover, TBLR1 can directly interact with BCL-3 and is involved in BCL-3 degradation through a GSK3 independent pathway. These data suggest that TBL1/TBLR1 plays a critical role in NF-κB mediated activation through both canonical and non-canonical pathways.

TBL1 has also been recently shown to regulate the prost-transcriptional stability of critical oncoproteins through modulating the activity of the Skp1-Cul1-F-box (SCF) complex in diffuse large B cell lymphoma (DLBCL). These data revealed an additional post-transcriptional oncogenic pathway mediated by TBL1 besides its transcriptional regulatory functions as a nuclear exchange factor and coactivator.

TARGETING TBL1/TBLR1 WITH TEGAVIVINT

TBL1 interacts with a portion of the β-catenin armadillo domain (residues 133-467) at its N-terminus (residues 1-142). Protein structural studies have identified a hydrophobic pocket in this region that is involved in binding to β-catenin in addition to other proteins like the members of the NCoR complex and NFkB family.

This defined interaction pocket in TBL1/R1 provides a structural basis for small molecule inhibitor binding designed to target disruption of these protein-pro-

tein interactions. TBL1/β-catenin interaction requires TBL1 to be SUMOylated in response to activated Wnt/ β-catenin signaling, while the interactions with p65 and NcoR are regulated by specific phosphorylation events. Such distinction in protein modifications and subsequent conformational changes may provide a basis for designing small molecule inhibitors that are selective for different pathways regulated by TBL1.

Tegavivint (BC2059, Iterion Therapeutics) is a first-in-class small molecule inhibitor of TBL1 and the only TBL1 inhibitor reported to date. Tegavivint was discovered through cell-based screening strategy for inhibition of nuclear β-catenin activity and subsequently shown to target the TBL1/R1 interaction with β-catenin. Tegavivint has been shown to potently inhibit nuclear β-catenin-dependent signaling through binding to TBL1, thus disrupting the TBL1/β-catenin association.

Tegavivint preferentially inhibits TBL1/β-catenin interaction with high potency, only partially inhibits TBL1/p65 interaction, and it does not inhibit TBL1/NcoR interaction. This selective activity allows Tegavivint to preferentially target β-catenin oncogenic signaling. Tegavivint treatment results in downregulation of oncogenic Wnt target genes, cell cycle arrest, apoptosis, and tumor growth inhibition in multiple preclinical cancer models driven by activated nuclear β-catenin signaling, including desmoid tumor, osteosarcoma, AML, multiple myeloma and lung cancer. Recent data also indicates that binding of Tegavivint to TBL1 led to conformational changes of the SCF complex, resulting in proteasomal-mediated degradation of critical oncogenic regulatory proteins that contributed to its antitumor activity in preclinical models of DLBCL.

Tegavivint is currently being evaluated in a first-in-human Phase 1/2 clinical study in patients with progressive desmoid tumors. Significantly, desmoid tumors are almost entirely driven by CTNNB1 mutations that lead to oncogenic activation of the Wnt/β-catenin signaling pathway; additional mutations in these tumors are not common.

As observed in preclinical models of desmoid tumor, the pharmacological blockade of TBL1-TBLR1/β-catenin interaction by Tegavivint decreased β-catenin protein levels in the nucleus of desmoid tumor cells with activated β-catenin signaling, without significantly affecting β-catenin levels in the cytosolic and membrane compartment. Thus, this approach has the potential to minimize toxicity from the disruption of membrane-bound β-catenin.

Consistent with preclinical data, accumulating clinical data of Tegavivint demonstrate a better safety profile compared with previous Wnt inhibitors tested in cancer patients. Early signs of antitumor efficacy have also been observed. The lack of GI, bone, and hematopoietic toxicities and skin reactions that were frequently associated with upstream Wnt/β-catenin pathway inhibitors supports the targeting TBL1 as a safe and effective novel approach to drugging the Wnt/β-catenin pathway.

SUMMARY

Previous attempts to drug the Wnt/β-catenin pathway have been hampered by toxicity and/or lack of potency due to β-catenin's multiple cellular roles and complexity of the signaling cascade. Targeting TBL1/TBLR1 enables specific silencing of oncogenic Wnt target gene expression without affecting other necessary cellular functions that are disrupted when targeting higher up the Wnt pathway. This avoids toxicity issues common to other drugs in this pathway. Tegavivint's ability to disrupt TBL1/β-catenin interaction makes it unique among nuclear β-catenin inhibitors and clinical data has confirmed that its novel and differentiated mechanism of action is a potentially safe and effective approach to drugging the Wnt/β-catenin pathway. ◆

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BIOGRAPHY

Dr. Ruolan Han is the Director, Translational Research at Iterion Therapeutics, a privately held, Houston-based clinical-stage biotechnology company developing novel cancer therapeutics. Dr. Han earned her BS in Genetics from Fudan University, Shanghai, China, and her PhD in Pharmacology from the University of Rochester. She has more than 15 years of combined experience in research and development of cancer therapeutics, including broad-based training in the field of cancer/stem cell biology and neuroscience.

CLINICAL TRIALS

Considering Recurrent Events in Clinical Trials Statistical Analysis

By: Jennifer Rogers

INTRODUCTION

Many chronic diseases are characterized by non-fatal recurrent events. Examples of such include asthma attacks in asthma, epileptic seizures in epilepsy, and hospitalizations for worsening condition in heart failure. Typically, in clinical trials for heart failure, composite outcomes (eg, heart failure hospitalization or cardiovascular death) are adopted as the primary endpoint and then analyzed as a time-to-first-event analysis using the Cox proportional-hazards model. These composite outcomes combine fatal and non-fatal events, thereby providing more comprehensive information about the impact of the treatments compared. Combining multiple endpoints into one composite outcome also increases the event rate and avoids the multiplicity issues surrounding the analysis of multiple endpoints. However, composite outcomes that only consider the first event are suboptimal for a chronic disease such as heart failure, which is characterized by recurrent heart failure hospitalizations, since repeat events within individuals are ignored in analyzes. Recurrent hospitalizations are an indication of worsening condition, so analyzing all these repeat events within individuals is more representative of disease progression. Furthermore, recurrent hospitalizations are distressing for patients and thus outcomes that consider all these events more accurately estimate the effect of treatment on the true burden of disease. If we consider the CHARM-Preserved trial, we can examine the impact of analyzing only the time-to-first event, ignoring repeat hospitalizations.[1]

TABLE 1

HF Hospitalisations	Candesartan (N=1513)	Placebo (N=1508)
≥ 1 admissions	230	278
≥ 2 admissions	95	114
All admissions	392	547
'Unused' admissions	162	269

THE CHARM-PRESERVED TRIAL AS A CASE IN POINT

There were 508 patients presenting with at least one heart failure (HF) hospitalization and 209 of these presenting with two or more (Table 1). Patients presented with a total of 939 HF hospitalizations, meaning that a time-to-first-event analysis throws away 431 hospitalizations. This is data that is relevant to patients and costly to collect, it shouldn't just be ignored. The effect of treatment on these non-fatal, recurrent events is important to quantify, but there is controversy as to which statistical methods of analysis are the most appropriate.[2] Time-to-first-event analysis of composite endpoints remain the gold standard in many indications as the statistical approaches are well established, and there is substantial experience in regulatory assessment. There is notably less regulatory experience for recurrent event endpoints, and the statistical approaches are more complex, but it is important to consider these methodologies because of the many advantages they present.

Methods for analyzing recurrent events are well developed and can be split into two broad categories: time-to-event approaches and methods based on event rates. Time-to-event methodologies include the Wei-Lin-Weissfeld (WLW), the Prentice-Williams-Peterson (PWP), and the Andersen-Gill. Methods based on event rates discussed here are the Poisson and the negative binomial.

THE WLW MODEL (WEI-LIN-WEISSFELD)

The WLW model examines the cumulative time from randomization to *K* ordered events considering each event in turn as the outcome in a sequence of applications of the Cox proportional-hazards model.[3] The distinctive feature of the WLW model is that each individual's time at risk for events (ie, first, second, third event, etc) is considered to start at randomization, so full randomized treatment groups are compared. Thus, in the case of heart failure hospitalizations, time-to-first hospitalization would be analyzed for all randomized patients and an estimated hazard ratio and associated p-value obtained. Then the total time from randomization to second hospitalization would be analyzed separately, again including everyone randomized, even if they hadn't yet had a first hospitalization, giving a second estimated hazard ratio and associated p-value. Analysis continues in this manner giving *K* distinct estimated treatment effects for each ordered hospitalization, which can be considered in isolation, or these hazard ratios can be combined using weights to give an "average effect." The advantages of the WLW model are that it preserves randomization, and it is semi-parametric meaning that there is no assumption on the baseline hazard. The disadvantages include issues surrounding the interpretation of the estimated hazard ratios. The treatment effect for the second hospitalization, for example, includes the effect on the first. If a large treatment affect is observed for the first hospitalization, this will have impact on the treatment effect for subsequent events. It is also difficult to interpret global effects if the estimated hazard ratios are combined. This methodology also still doesn't allow analysis of all hospitalizations. Because there are fewer higher order events, analysis must be restricted to a *K* subset of all hospitalizations. If we consider the CHARM-Preserved data, for example, we see that it may only be sensible to consider the first three or four hospitalizations for analysis. So those patients who have five or more hospitalizations will still have some of their events ignored.

TABLE 2

	Candesartan (N=1514)	Placebo (N=1509)
Follow-up years	4424.62	4374.03
Deaths	244	237
CV deaths	170	170
HF Hospitalisations:		
1	135	164
2	56	55
3	23	25
4	9	13
5	4	9
6	1	4
7	2	2
8	0	2
≥9	0	4
All admissions	392	547

THE PWP MODEL (PRENTICE-WILLIAMS-PETERSON)

The PWP model is similar to the WLW, but rather than considering total time to each ordered event, gap times (ie, the times between consecutive events) are considered with conditional risk sets.[4] Analysis continues in the same manner; however, and distinct hazard ratios are estimated with associated p-values for *K* gap times. These can once again be combined using appropriate weights and an average global treatment effect obtained. The PWP model presents with many of the same advantages and disadvantages as the WLW model, the main difference being that conditional risk sets in the PWP model better reflect the true disease progression, but do not maintain randomization like the WLW model.

THE ANDERSEN-GILL MODEL

The Andersen-Gill is an extension of the Cox proportional-hazards model, which analyzes gap times.[5] In the Cox proportional-hazards model, each individual's time to event contributes independently to the partial likelihood, but in the Andersen-Gill model, it is each gap time that contributes independently giving a hazard ratio-like intensity ratio for the treatment effect. Hospitalizations within individuals are likely to be related to each other with some patients being inherently more/less frail than others,

subsequently presenting with increased/fewer hospitalizations respectively, meaning that heterogeneity is often present in the data. The independence assumption ignores this heterogeneity, meaning that analysis can result in standard errors that are too small with corresponding confidence intervals that are too narrow, p-values that are too optimistic, and an increased in the Type I error rate. Robust standard errors must be used to accommodate overdispersion when adopting the Andersen-Gill methodology.[6] Advantages of the Andersen-Gill model include the fact that it is a semi-parametric approach, and it can analyze all hospitalizations for all individuals. A disadvantage of this methodology, however, is that it assumes a common baseline hazard for all of the gap times, which may not be true in practice.

ANALYSIS BASED ON EVENT RATES: POISSON & NEGATIVE BINOMIAL DISTRIBUTIONS

Methods based on event rates include the Poisson and negative binomial distributions. The Poisson model is a very simple model that considers the total number of events divided by the total follow-up in each group, giving a rate ratio for recurrent events. This distribution assumes that the underlying event rate is the same across all subjects (and follows a Poisson process) and assumes independence of events, which as has already been discussed, is not a sensible assumption in the case of HF hospitalizations. An alternative approach is to use the negative binomial distribution, which naturally induces an association between repeat events within individuals through a random effect term, which is assumed to follow a gamma distribution. The negative-binomial assumes individual-specific Poisson event rates conditional on a random effect for each patient's true underlying rate. The negative binomial distribution is easy to implement and does not require complex data files. The resulting estimated rate ratio is also easy to interpret and can comfortably be communicated to non-statistical audiences. This methodology, however, comes with a strong distributional assumption for the underlying event process: event rates within individuals are assumed to follow a Poisson process with a constant event rate.

CONSIDERATIONS OF STATISTICAL METHODOLOGY FOR RECURRENT HEART FAILURE HOSPITALIZATIONS

So, which statistical methodology should be used in the analysis of recurrent HF hospitalizations? There are of course many statistical considerations that must be addressed when answering this question. Would it be preferable to use a modeling framework that is semi-parametric over fully parametric? What assumption do we want for the event rate? Constant, time-varying, or leave it completely unspecified? And what should be done to handle the over-dispersion that is often present in this recurrent HF hospitalization data? Often, I believe too much emphasis is placed on these statistical considerations, when in fact, I would prefer to see the most appropriate methodology being used to answer the question of interest. Many of these methodologies answer slightly different questions. Perhaps we are interested in the effect of treatment on times to particular events. Maybe we are interested in the effect of intervention on subsequent events among those who had a preceding event. Or we could be interested in the effect of treatment on rates of events. All too often in the analysis of recurrent events I see the question being driven by the chosen analysis method. Surely, it's time to turn this around and use the methodology that best answers the question of interest.

ELEVATED RISK OF CARDIOVASCULAR DEATH: HOW TO ANALYZE USING COMPOSITES

Another key characteristic of heart failure is that an increase in HF hospitalizations is associated with a worsening condition and a subsequent elevated risk of cardiovascular (CV) death, meaning that subjects may die during follow-up. Consequently, any censoring due to CV death is not independent of the recurrent event process. A comparison of heart failure hospitalization rates, between treatment groups, can be confounded by this competing risk of death and ignoring the dependent censoring can result in bias in estimated treatment effects. Therefore, any analysis of recurrent events must take into consideration informative censoring that may be present.

One simple strategy for incorporating CV death into analysis of recurrent heart failure hospitalizations is to consider this outcome as an additional event in the recurrent event process. That is, one considers a composite of recurrent heart failure hospitalizations and CV death. This updated recurrent event process can then be analyzed using all standard recurrent event techniques, and the subsequent estimated treatment effect that is obtained is

an intensity/rate ratio for the composite of repeat heart failure hospitalizations and death. Note that any death that occurs during a heart failure hospitalization would be treated as a single event. This methodology has received positive reaction from the regulators and was adopted as the primary outcome in the PARAGON-HF trial.[7] Regulators seem to like this outcome as it isn't too far away from the current status-quo; they are used to seeing composite endpoints, and this is an extension of the current gold standard methodology. But this approach isn't without its disadvantages. This composite endpoint is composed of many more recurrent HF hospitalizations than CV deaths, meaning that the estimated treatment effect is going to be dominated by the effect of treatment on these non-fatal events. A marginal treatment effect in CV death could be masked by a large treatment effect on HF hospitalizations, and thus it is crucial that any such composite endpoint analysis is also presented with corresponding analysis of the component parts and careful attention is paid to attributing common treatment effects to each of the different types of event.

THE GHOSH & LIN METHOD

The Ghosh and Lin non-parametric analysis of heart failure hospitalizations takes mortality into account while also adjusting for different follow-up times and multiple hospitalizations per patient.[8] This method considers the marginal expected number of recurrent heart failure hospitalizations up to some particular timepoint, t, acknowledging the fact that death is a terminal event after which no further recurrent hospitalizations can be experienced. This means that although a patient stays in the risk set beyond time to death, their associated recurrent hospitalization count stays constant, fixed at whatever value it was just prior to death. The stochastic structure of the recurrent hospitalizations process is left completely unspecified and there are no assumptions regarding the dependence between the recurrent hospitalizations and death. The mean frequency function is defined as the marginal expected number of recurrent heart failure hospitalizations up to some timepoint, *t*, acknowledging that no further recurrences occur after death.

JOINT MODELING TECHNIQUES

An alternative approach is the use of joint modeling techniques to obtain estimates of treatment effects on heart failure hospitalization rates while allowing for informative censoring.[9] Joint modeling techniques are appropriate when analyzing rates of recurrent events whilst allowing for association with a potentially informative dropout time, or when each of the outcomes is of scientific importance to the investigators and the dependence between the two processes needs to be accounted for. One approach to joint modeling is random effects models, which assume that the recurrent hospitalizations and time-to-death are conditionally independent given a latent variable. Models of this kind are intuitively appealing as they can give a tangible interpretation that an individual's independent frailty term measures their underlying, unobserved severity of illness, which proportionately affects both their heart failure hospitalization rate and their time-to-death (or CV death). Joint models allow distinct treatment effects to be estimated for each of the processes, while taking account of the association between the two. Joint frailty models can also be parametric or semi-parametric, allowing flexibility in the underlying assumptions. One of the disadvantages of joint modeling methodologies is that two co-primary primary endpoints must be specified in the statistical analysis plan. Regulatory experience in this area suggests that preference is given to analysis that consider only one primary endpoint that incorporates both non-fatal and fatal events (such as the composite outcome of recurrent HF hospitalizations and CV death), rather than two co-primary endpoints that must be considered together. Additionally, if it were required to power studies on CV death as well as HF hospitalizations, very large sample sizes would be needed as treatment effects on CV death are typically marginal, compared with larger treatment effects for HF hospitalizations.

SUMMARY

The world of recurrent events in HF studies is complex, and there is no obvious right answer. This is perhaps why it is so interesting! There is also still a significant amount of work to be done in this area. The methodologies considered here either assumed a constant HF hospitalization rate or left the underlying rate completely unspecified. But what if we wanted to explicitly model a non- constant rate? Clinicians believe that hospitalizations may cluster and that the event rate may increase just prior to death. It may be desirable to develop methodology that captures these features of the data so that these aspects can be quantified. All these analysis have also assumed that events are instan-

taneous, which is obviously not true for the case of hospitalizations. It may be that treatment not only affects if a patient is hospitalized, but also how long they must subsequently stay in the hospital. Multi-state models would allow us to model the effect of treatment on transitions into and out of the hospital, as well as transitions to death. I look forward to seeing how this field of statistics develops in the future. ◆

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BIOGRAPHY

Jennifer Rogers is Head of Statistical Research and Consultancy for the CRO PHASTAR, and has broad portfolio of achievement, particularly in the development of clinical trial methodologies. She provides leadership and advice to statistical consultancy activities, and directs the statistical research strategy helping the company stay at the cutting edge of new methodological advances. She joined in 2019, following a move from the University of Oxford, where she was Director of Statistical Consultancy Services and an Associate Professor in the Department of Statistics. She had previously worked as a post-Doctoral Research Fellow in the Department of Statistics funded by the National Institute of Health Research. She is Vice President for External Affairs at the Royal Statistical Society and has made numerous appearances on UK TV and radio.

Drug Development EXECUTIVE

David J. Bearss, PhD

Chief Scientific Officer & Global Head of Research*

Sumitomo Dainippon Pharma Oncology, Inc.

Sumitomo Dainippon Pharma Oncology

SDP Oncology: Uncovering New Biology

In recent years, the oncology community has seen a shift in understanding how the immune system interacts with cancer cells. Researchers have learned that people's immune systems may help fight cancer, as evidenced by the approval of multiple immune checkpoint inhibitors. While these drugs have revolutionized the treatment of cancer for some people, they don't work for everyone. As one of its many areas of focus, Sumitomo Dainippon Pharma Oncology, Inc., a wholly-owned subsidiary of Sumitomo Dainippon Pharma Co. Ltd. based in Japan, has been committed to learning why some people benefit from immune-targeted agents and others do not. Through this research, the company has discovered that the tumor microenvironment plays a crucial role in the immune response to a tumor.

David J. Bearss, PhD, Chief Scientific Officer and Global Head of Research* at SDP Oncology recently spoke with *Drug Development & Delivery* about the company's unique structure that has supported its robust research in the tumor immune microenvironment as well as its investigational assets being studied in this space.

Q: What is SDP Oncology's business model and what are the benefits of being a wholly-owned subsidiary of Sumitomo Dainippon Pharma?

A: We are a global oncology-focused company that is dedicated to developing novel cancer therapeutics that will make a meaningful difference in the lives of patients with cancer. Our efforts encompass moving programs from very early drug discovery

through clinical development and commercialization. Often, big companies acquire smaller companies and then integrate them into the parent company. Recently, there's been a movement towards keeping the smaller companies more independent, which allows the smaller company to maintain its culture, environment and nimbleness while having the infrastructure, financial support and value that comes from a large organization. You have the best of both worlds.

In addition, we have the power that comes from being in multiple geographic locations. We have research and development teams in Japan that are part of this new oncology focus. From the research side, it's exciting for us to think that all day, every day, there's someone working on these programs. Cancer doesn't sleep and neither should we. SDP Oncology is always working on our programs and there is constantly somebody actively pushing forward the research behind them.

Q: SDP Oncology is a company with multiple platforms. What does this mean for your portfolio and the types of novel drugs you are discovering?

A: Because we have a multitude of drug modalities – the technologies that serve as the platform –we are not limited to the types of targets that we can pursue. I've always been a believer that we will follow the best biology that's available to us. Having multiple drug modality platforms gives us access to technology that allows us to pursue any target that we think is novel and has potential. We have access to a number of drug delivery technologies as well as several approaches for target engagement. We are not constrained to just small molecules, for example. We have nanomedicine technology that allows us to change the pharmacokinetics and distribution of a drug. We have peptide conjugation technology, aptamer technology, antibody-drug conjugate technology, biomolecule conjugates and polymer conjugates, just to name a few. The proprietary technology that exists within SDP Oncology doesn't put any limits on us with respect to pursuing biology that we find interesting.

Q: Can you describe SDP Oncology's focus on the tumor immune microenvironment and why it is important in creating novel oncology drugs?

A: Over the past several years, there has been a shift in understanding how the immune system interacts with cancer cells. The immune checkpoint inhibitors that have been approved are among the most successful oncology drugs that we have in our arsenal today. The oncology community has discovered that our own immune system is probably the best medicine we have in fighting cancer. These drugs have been revolutionary and provided benefit for a lot of people, but they don't work for everybody. As we've tried to understand why it is that some people benefit from immune-targeted agents and others do not, we've discovered that the microenvironment of the tumor is important.

Most tumor cells interact with the surrounding normal cells, what is called the "tumor microenvironment," and these interactions are critical to the survival of the tumor. The cancer cells influence the cells they interact with, and that microenvironment determines if a patient will respond to an immune-targeted agent. We've been trying to understand what targets exist, both on cancer cells and non-cancer cells, that create an immune microenvironment that competes for resources in the tumor. We want to target the right biology that will change that microenvironment and the behavior of both the cancer cells and the immune cells within the tumor to activate an immune response.

Q: What strides has SDP Oncology made in studying the tumor immune microenvironment?

A: We've identified a number of new targets that we think are crucial in modulating interactions that immune cells have with cancer cells. It's been such a dramatic change in the way that we develop drugs. In the old days, therapeutics were focused on just killing cancer cells or putting those cells into a more sensitive state so that they can be either targeted with a single agent or in combination with different types of therapy. The new biology that we are trying to uncover might not necessarily have a direct effect on the cancer cells. In fact, they may not kill cancer cells at all, but they change that microenvironment. It is challenging as a drug discovery research group to develop the right systems, the right assays, and the right models to test these types of agents. Most of the models that we use preclinically are focused on killing cancer cells and shrinking tumors that are grown in animal models. We've had to change those model systems to assess mechanistically what new agents are doing.

Q: Can you describe dubermatinib and its role as an AXL kinase inhibitor and the role of TP-1454 as a PKM2 activator, within the context of the microenvironment?

A: Dubermatinib is a compound we discovered in a model system that involved the zebrafish. We used the fish as a screening tool to look for a very specific biology to target the AXL protein. AXL is a receptor expressed in many cells in our body and it is responsible for sensing cell damage and cell death. When it gets activated in tumor cells, it changes the behavior of these cells, making them less differentiated, more aggressive and resistant to therapy. We refer to this state as the "mesenchymal phenotype." We screened thousands of compounds and found that dubermatinib was the only one – in this particular model – that can reverse this mesenchymal change. AXL kinase is a tumor immune microenvironment target because not only does the cancer cell express the protein, but so do the surrounding immune cells. When activated in immune cells, it changes their behavior and makes it harder for the body to mount an immune response against the cancer. Dubermatinib has a specific effect on the cancer cells, changing this aggressive behavior, and targets the immune cells at the same time by pushing them into a more responsive state to mount an appropriate immune response against the cancer.

TP-1454 is another compound unique in its biology. Almost every drug inhibits protein activity. In this case, our drug is an activator of the PKM2 protein. PKM2 is a metabolic enzymatic "switch" that gets turned on in cancer cells. As cancer cells become more aggressive and the tumor starts to grow, the tumor changes its metabolism and its ability to utilize different types of nutrients to adapt to the changing environment in which cancer cells find themselves. PKM2 is expressed but it's not a very active enzyme, which is of metabolic benefit to the tumor cells. TP-1454 makes this enzyme become highly active, shifting the metabolism of the cancer and starving it of certain essential building blocks necessary for growth. For years, we thought a characteristic distinguishing cancer cells from normal cells was the metabolic requirements and changes that occur during tumor formation. If you could exploit these differences, it could serve as an Achilles heel for those cancer cells. Unfortunately, as industry tried targeting these metabolic pathways, the cancer cells were quick to adapt to the changing environment. PKM2 looked like an attractive target. As we started to think about this target in the tumor immune microenvironment, we questioned whether other cells inside the tumor express the enzyme and what happens to those cells. While we know cancer cells can adapt, normal cells are restricted in what they can do. It turns out the normal immune cells inside the tumor are competing with the cancer cells for resources. To mount a reaction against the cancer, you have to take off the "brake," which is the immune checkpoint. But there also needs to be fuel for immune cells to proliferate quickly, in terms of energy production. It turns out that access to fuel is suppressed in the tumor immune microenvironment, in part through PKM2.

Q: Are you saying the AXL inhibitor and the PKM2 activator work together in the tumor immune microenvironment?

A: We developed them separately to target very different pathways. It's possible these compounds may work in combination with existing agents, which we are evaluating. It's challenging to develop two novel drugs at the same time. If we are looking at combination activity, we will take an already approved therapeutic and combine it with the new compound. It's easier to study that because the approved drug has been validated in terms of efficacy and safety. There may be opportunities in the future to develop two novel drugs for combination at the same time.

Q: What is the status of these assets in clinical development and what can you share about the results of preclinical studies?

A: TP-1454 has an active IND and will move forward with the first-in-human study, which is just getting started. It's a first-in-class compound that we hypothesize will change the metabolic microenvironment of the tumor and make it more permissive to an immune response. We've shown in animal models that treatment with TP-1454, which activates PKM2, in combination with an immune checkpoint inhibitor, produced a dramatic response. We are excited to see what happens in the clinical studies.

Dubermatinib just completed a Phase 1 study where we treated over 150 patients. Half of the patients were part of the dose escalation evaluation where we determined the safety and the maximum tolerated dose of the drug. We did an expansion from the dose escalation study to explore specific tumor types. We examined biopsies from some of the patients in this expansion study before they received treatment with dubermatinib and then took another biopsy after. We can use these to determine changes not only in the tumor, but also in the

tumor microenvironment. We have analyzed these data and they were presented at ESMO 2020 Virtual Annual Congress. This data showed that dubermatinib produced changes consistent with AXL inhibition and will help us design the next clinical study as we move this program forward.

Q: Are you targeting specific cancers?

A: Every cancer is unique from a genetic and mechanistic standpoint. We are interested in identifying the characteristics of an individual patient's cancer that make it susceptible to a specific therapy. Most cancer types, like breast cancer, share some common characteristics, so we do a lot of drug development around specific tumor types. We are also trying to group cancer types that are similar to one another at the molecular or mechanistic level. We have some ideas on why certain kinds of cancers may be more susceptible to treatment than others and we are trying to validate those quickly in early clinical development to set a clinical development path that will be most effective. We want to deliver therapy that will be as effective as possible for the individual. We also want to develop tools to identify those patients who will respond to particular therapies.

Q: What are your feelings about licensing these drug assets or working with partners?

A: Partnerships can be opportunistic if it makes sense from a development and commercialization standpoint. Part of our strategy in the short term, as programs mature, if appropriate, may involve looking for partners to address different parts of the world where we don't yet have a presence. Part of my goal leading the research team is to develop our programs internally and to look for partners on specific programs that may not fit our clinical development strategy. ◆

**Note: This interview was conducted before Dr. Bearss made the decision to leave his role as Chief Scientific Officer and Global Head of Research at Sumitomo Dainippon Pharma Oncology and return to academia at the University of Utah. Dr. Bearss will remain at the company as a member of its Scientific Advisory Board.*

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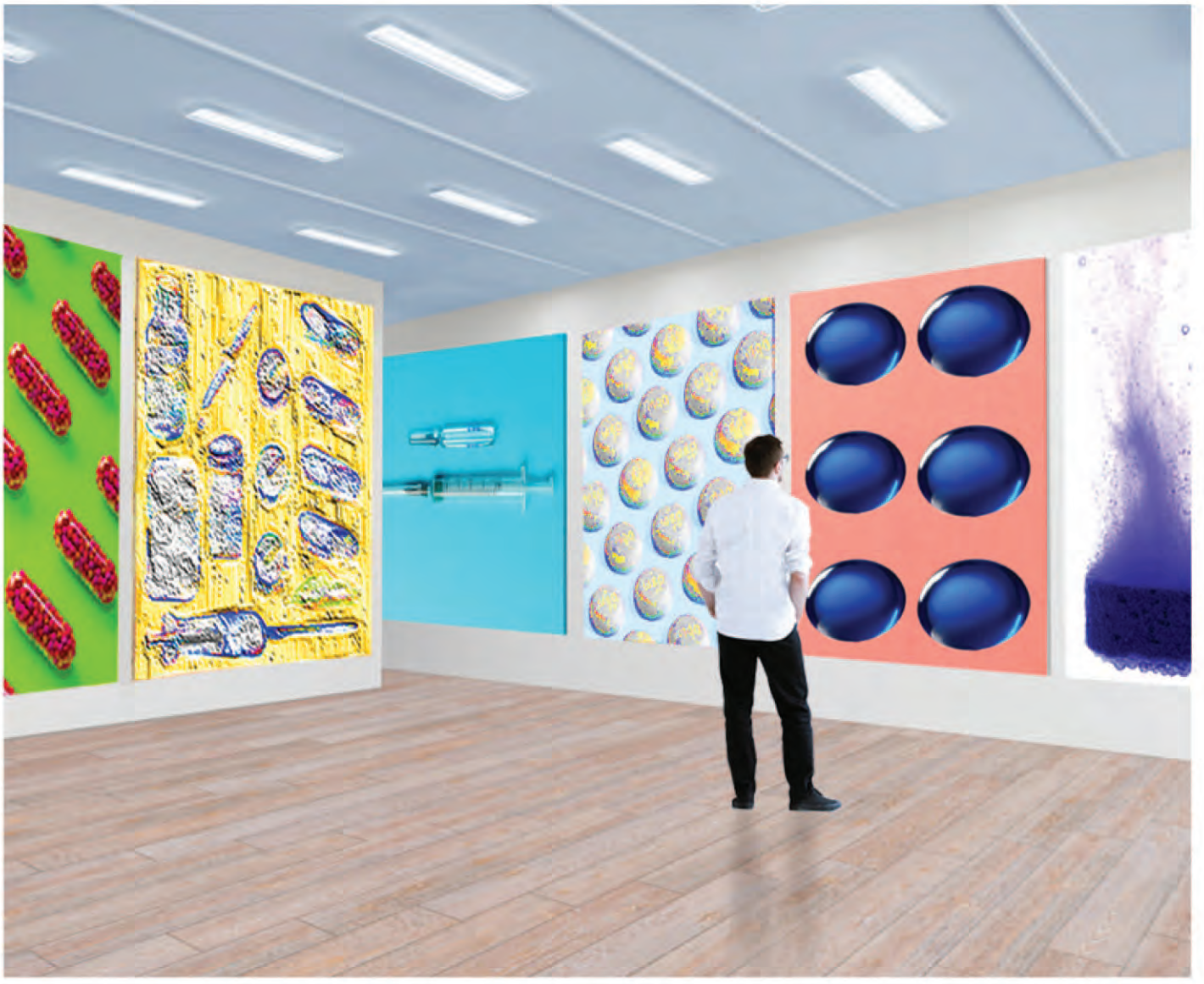

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Catalent's NEW OptiDose® Design Solution helps deliver a comprehensive assessment of your Molecule, Patient, and Market. Our scientific advisors will combine expertise across dose forms, thousands of molecules and advanced delivery technologies to deliver optimal dose form, scale-up and manufacturing solutions. We aim to help differentiate your product, improve patient acceptance, and turn your science into commercially successful medicine.

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