Drug Development & Delivery

January/February 2021 Vol 21 No 1 www.drug-dev.com

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GATTEFOSSÉ

Melt Extrusion

Compritol® | Precirol® | Gelucire®

Solid Dispersions with Lipids

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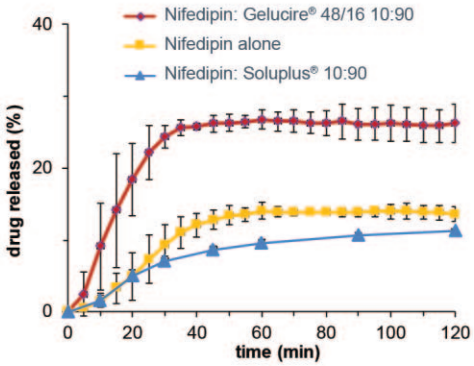
Depending on the choice of excipient and process, these excipients may serve as plasticizers, and carriers for a wide range of API.



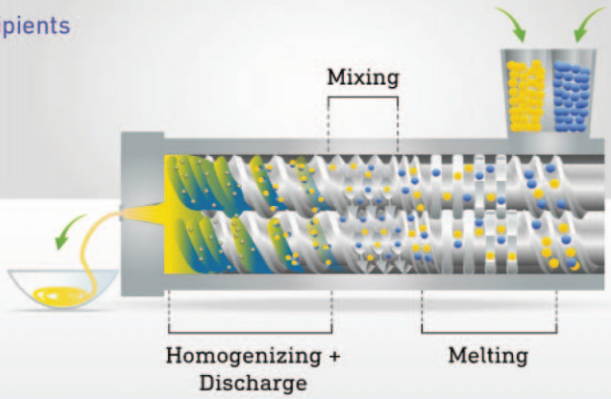
Drug release from Nifedipine milled extrudates filled into hard gelatin capsules

Contact Us

We help clients in various stages of drug development, beginning with drug solubility screening in solid lipid excipients, evaluating stability and compatibility with the API, and the characterization of the drug delivery system.

Melt extrusion with lipid excipients

Gelucire® 48/16
Extrudate



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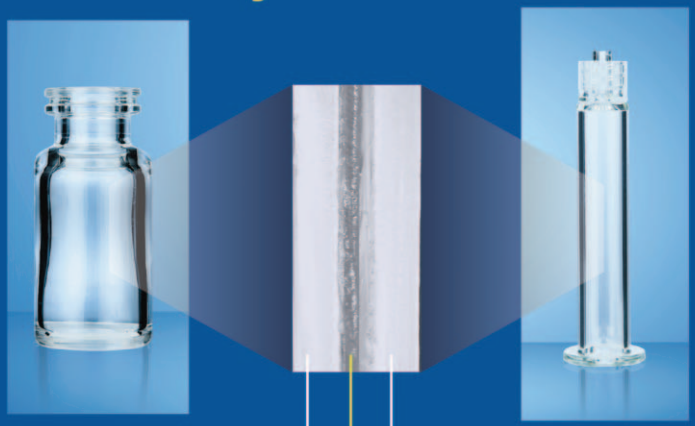
Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Regenerative Medicine

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E-mail: nb3.pharmapackage@mgc.co.jp

Drug Development & Delivery

January/February 2021 Vol 21 No 1

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Outsourcing Analytical Testing

"The global pharmaceutical analytical testing outsourcing market was estimated at $6.1 billion in 2019 and is anticipated to register a CAGR of 8.3% through 2027. Increasing demand for analytical drugs, biosimilars, and biopharmaceuticals are contributing to market growth. Other factors such as increasing investments in R&D for pharmaceuticals, rising demand for product safety and quality, and changing regulations for *in vivo* and *in vitro* tests are also expected to drive the demand for pharmaceutical analytical testing outsourcing services."

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ADARE PHARMACEUTICALS IS NOW ADARE PHARMA SOLUTIONS

DIFFERENT NAME. SAME CUSTOMER FOCUS.

Adare Pharma Solutions is a global, technology-driven CDMO providing turnkey product development through commercial manufacturing expertise focused on oral dosage forms for the Pharmaceutical, Animal Health and OTC markets. Adare's specialized technology platforms provide taste masking, ODTs, and customized drug release solutions. With a proven history in drug delivery, Adare has developed and manufactured more than 40 products sold by customers in more than 100 countries globally.

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"Orally disintegrating products are gaining increasing attention from the industry by offering distinct advantages in the development of both prescription and over-the-counter medicines. Many studies have already compared these dosage forms with standard tablet forms *in vitro* and *in vivo* and have found that orally dis¬integrating products offer superior compliance and drug solubility."

p.46

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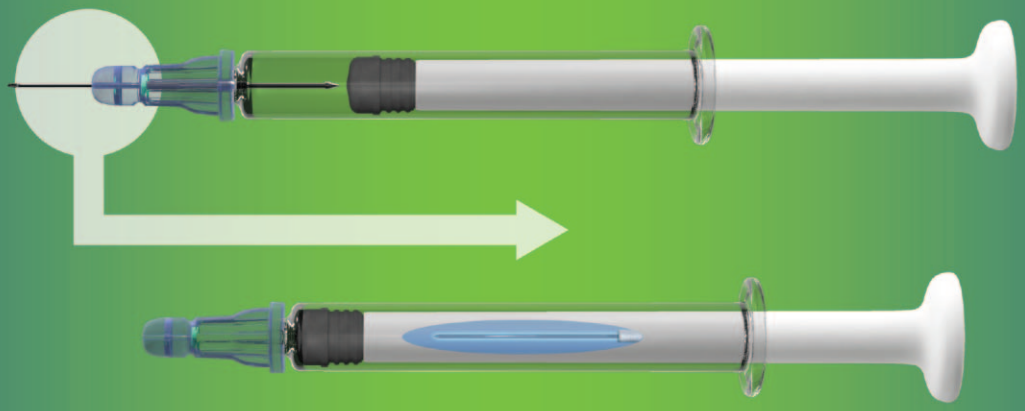
THE CREDENCE COMPANION

IMPRESS | PRESERVE | PROTECT



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YOUR sourcing strategy
YOUR filling process
YOUR practices, without disruption

INNOVATION WITHOUT CHANGE

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This product has not yet been evaluated by FDA

CREDENCE MEDSYSTEMS

Servier & X-Chem Announce Drug Discovery Collaboration

Servier and X-Chem, Inc. recently announced a partnership to identify and develop novel small molecules for the treatment of neurological disorders.

Under the terms of the multi-target agreement, X-Chem will utilize its DNA-Encoded library (DEL) platform to identify novel small molecule leads directed towards Central Nervous System (CNS) targets of interest to Servier. The parties may further progress identified leads into protein-degrading chimeric molecules, with X-Chem leading the design and synthesis of bispecific degrader molecules. Servier will be responsible for advancing any promising candidates through preclinical and clinical development and retains all rights for the commercialization of any products resulting from the collaboration. X-Chem will receive research payments and is entitled to additional payments upon the achievement of certain success milestones.

"Our partnership with X-Chem supports Servier's drive for innovative drug discovery approaches towards new treatments for the benefit of patients suffering from neurological diseases. Combining our expertise gives us a truly valuable opportunity to advance the expanding internal program of drug discovery projects here at Servier, with the ultimate goal of bringing forward new and effective treatments to slow the progression of these devastating diseases," said Ross Jeggo, Head of the Neurology & Immuno-Inflammation therapeutic area at Servier.

"We are delighted that Servier has chosen X-Chem as its partner for drug discovery in this challenging therapeutic area." said Matt Clark, Chief Executive Officer at X-Chem. "We look forward to a long-term scientific collaboration with the Servier team to make advances in the treatment of neurological diseases."

Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 150 countries and a total revenue of 4.6 billion euros in 2019, Servier employs 22,000 people worldwide. Entirely independent, the Group invests on average 25% of its total revenue (excluding generics) every year in research and development and uses all its profits for its development. Corporate growth is driven by Servier's constant commitment in five areas of excellence: cardiovascular, immune-inflammatory, and neurodegenerative diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs. Servier also offers eHealth solutions beyond drug development. For more information, visit www.servier.com.

Servier's innovation efforts in the US are enhanced by Servier BioInnovation, a joint initiative between Servier Group R&D and Business Development & Licensing, focused on external innovation in the U.S. BioInnovation's mission includes identifying early-stage R&D opportunities and expediting BD&L activities, increasing the group's visibility and attracting talent as well as establishing R&D partnerships in key life science innovation ecosystems.

X-Chem is the industry-leading provider of DNA-Encoded Library (DEL)-based discovery services. X-Chem has entered into drug discovery partnerships with numerous pharmaceutical companies, established, and early stage biotechnology companies, as well as research institutes and universities resulting in the licensing of hundreds of novel hits and leads across many target classes.

Ajinomoto Bio-Pharma Services & Revance Therapeutics Announce Manufacturing Agreement

Ajinomoto Bio-Pharma Services and Revance Therapeutics, Inc. recently announced a strategic commercial manufacturing agreement for the supply of DaxibotulinumtoxinA for Injection.

DaxibotulinumtoxinA for Injection is currently under Biologics License Application (BLA) review. Aji Bio-Pharma will serve as a dual supply source and provide drug product manufacturing services for Revance at the company's aseptic manufacturing facility in San Diego, CA.

"We are excited to partner with Revance and their efforts to establish a new standard in aesthetic and therapeutic neuromodulator offerings," said Jean-Baptiste Agnus, VP of Sales at Ajinomoto Bio-Pharma Services. "This partnership underscores our commitment to be a leading, trusted, innovative partner to our clients and reinforces our company mission to improve the health of humankind."

"We are delighted to be partnering with Aji Bio-Pharma for the production of our innovative product and bolstering our supply chain resiliency," said Brian Blagg, Vice President, Engineering & Supply Chain at Revance. "Aji Bio-Pharma's manufacturing infrastructure, long-standing experience, and customer-centric service, were important to this collaboration."

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, the US, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for pre-clinical and pilot programs to commercial quantities, including Corynex protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADC), high-potency APIs (HPAPI), biocatalysis, continuous flow manufacturing, and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's needs. For more information, visit www.AjiBio-Pharma.com.

Revance Therapeutics, Inc. is a biotechnology company focused on innovative aesthetic and therapeutic offerings, including its next-generation neuromodulator product, DaxibotulinumtoxinA for Injection. DaxibotulinumtoxinA for Injection combines a proprietary stabilizing peptide excipient with a highly purified botulinum toxin that does not contain human- or animal-based components. Revance has successfully completed a Phase 3 program for DaxibotulinumtoxinA for Injection in glabellar (frown) lines and is pursuing US regulatory approval. Revance is also evaluating DaxibotulinumtoxinA for Injection in the full upper face, including glabellar lines, forehead lines, and crow's feet, as well as in two therapeutic indications – cervical dystonia and adult upper limb spasticity. To accompany DaxibotulinumtoxinA for Injection, Revance owns a unique portfolio of premium products and services for US aesthetics practices, including the exclusive US distribution rights to the RHA Collection of dermal fillers, the first and only range of FDA-approved fillers for correction of dynamic facial wrinkles and folds, and the HintMD fintech platform, which includes integrated smart payment, subscription, and loyalty digital services. Revance has also partnered with Viatris (formerly Mylan N.V.) to develop a biosimilar to BOTOX, which would compete in the existing short-acting neuromodulator marketplace. Revance is dedicated to making a difference by transforming patient experiences. For more information, visit www.revance.com.

Argenx & Zai Lab Announce Strategic Collaboration

Argenx SE and Zai Lab Limited recently announced an exclusive license agreement for the development and commercialization of efgartigimod in Greater China, including mainland China, Hong Kong, Taiwan, and Macau.

"Through this collaboration with Zai Lab, we are expanding our global footprint in one of the world's fastest growing markets and reaching more people living with severe autoimmune diseases. By leveraging Zai Lab's strong local expertise within Greater China and proven development capabilities, we aim to provide broad access to efgartigimod in these important markets as well as accelerate the number of autoimmune indications in clinical development," said Tim Van Hauwermeiren, Chief Executive Officer of Argenx. "We believe that Zai Lab is the ideal partner for us ahead of our first potential approval of efgartigimod in generalized myasthenia gravis (gMG) in the US, and we are aligned in our mutual passion to bring potential innovative immunology therapies to patients in need."

"Argenx is building a leading immunology company, and we are excited to collaborate with them during this important time. Efgartigimod is being evaluated in a broad range of autoimmune diseases, and we look forward to bringing this potentially first-in-class product to patients in Greater China," said Dr. Samantha Du, Founder, Chairperson and Chief Executive Officer of Zai Lab. "This collaboration also significantly expands and strengthens our pipeline in severe autoimmune diseases, where there is an urgent and serious need for new therapeutic options."

Under the terms of the agreement, Zai Lab obtains the exclusive right to develop and commercialize efgartigimod in Greater China. Zai Lab will recruit Chinese patients to Argenx's global registrational trials for the development of efgartigimod. Additionally, this agreement is expected to allow Argenx to accelerate efgartigimod development by initiating multiple Phase 2 proof-of-concept trials in new autoimmune indications.

Argenx will receive $175 million in collaboration payments, composed of a $75-million upfront payment in the form of 568,182 newly issued Zai Lab shares calculated at a price of $132.00 per share, $75 million as a guaranteed non-creditable, non-refundable development cost-sharing payment, and an additional $25-million milestone payment upon approval of efgartigimod in the US. Argenx is also eligible to receive tiered royalties (mid-teen to low-twenties on a percentage basis) based on annual net sales of efgartigimod in Greater China.

Efgartigimod is an investigational antibody fragment designed to reduce disease-causing immunoglobulin G (IgG) antibodies and block the IgG recycling process. Efgartigimod binds to the neonatal Fc receptor (FcRn), which is widely expressed throughout the body and plays a central role in rescuing IgG antibodies from degradation. Blocking FcRn reduces IgG antibody levels, representing a logical potential therapeutic approach for several autoimmune diseases known to be driven by disease-causing IgG antibodies, including: myasthenia gravis (MG), a chronic disease that causes muscle weakness; pemphigus vulgaris (PV), a chronic disease characterized by severe blistering of the skin; immune thrombocytopenia (ITP), a chronic bruising and bleeding disease; and chronic inflammatory demyelinating polyneuropathy (CIDP), a neurological disease leading to impaired motor function.

University of Calgary Joins the Phase 2 Trial of LSALT Peptide for the Treatment of Complications in Hospitalized COVID-19 Patients

Arch Biopartners Inc. RECENTLY announced the University of Calgary Cumming School of Medicine has joined the Phase 2 trial of its lead drug LSALT peptide (Metablok), targeting the prevention of acute lung injury, acute kidney injury, and other complications caused by inflammation in hospitalized patients with moderate-to-severe cases of COVID-19.

"We are particularly excited in launching this study in Calgary given that this treatment has its roots in basic science work performed here at the University. This novel treatment adds to our local investigational therapeutic options for patients admitted to hospital with COVID-19 disease and has great potential to reduce complications from this and other severe diseases that frequently result in lung and kidney injury," said Alain Tremblay MDCM, Professor at the Cumming School of Medicine, Respirologist and site principal investigator for the LSALT Phase 2 trial.

The addition of the Canadian site increases the number of countries participating in the Phase 2 trial to three, joining sites in the US and in Turkey. Arch is currently exploring opportunities to add additional clinical sites in all three countries where the number of hospitalized COVID-19 patients has grown significantly.

Hospitalizations of COVID-19 patients have been on the increase as infection rates have surged throughout the world. In the last 2 weeks of December, Canada has had over 90,000 new infections and over 14,000 of these have been in Alberta.

The Phase 2 trial is an international, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of LSALT peptide (Metablok) as prevention of organ inflammation known to trigger acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) in patients infected with SARS-CoV-2 (COVID-19). ARDS is the leading cause of death in COVID-infected patients. AKI has been observed in approximately 35% of patients admitted to hospital with COVID-19 and is also a leading cause of mortality.

The composite primary endpoint of the Phase 2 trial reflects the severe effects often experienced by hospitalized COVID-19 patients and deemed appropriate for LSALT peptide's novel mechanism of action in blocking consequential inflammation in the lungs, kidneys, and other organs.

The Phase 2 results will be used to design the Phase 3 program, including greater patient numbers to more fully evaluate efficacy and safety in COVID-19 patients.

COVID-19 is the disease caused by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. Severe complications from COVID-19 are in large part due to excessive host immune responses to the virus that result in progressive lung inflammation and acute respiratory distress syndrome that often requires mechanical ventilation and critical care1. Patients with severe COVID-19 also experience multiple organ dysfunction including acute kidney injury, liver dysfunction, cardiac failure, and blood abnormalities. Currently, no effective antiviral drug or specific treatment exists for SARS-CoV-2 infection. Treatment of severe COVID-19 has been primarily supportive, relying heavily on respiratory, infectious diseases, and critical care medicine.

Survival rates and health care system capacity could both be improved with new treatments that prevent the severe manifestations of COVID-19, such as worsening lung inflammation (ARDS) and AKI experienced by patients infected with SARS-CoV-2.

Radius Health Announces Commercial Agreement With Paladin Labs

Radius Health, Inc. recently announced it has entered into definitive agreements with Endo Ventures Limited, a subsidiary of Endo International plc to register, commercialize, and distribute abaloparatide on an exclusive basis in Canada. Paladin Labs Inc., an operating company of Endo, will be responsible for all commercial activities related to abaloparatide. Under the terms of the agreements, Paladin will pay Radius upfront and milestone payments up to approximately $8 million and tiered royalties up to the mid-twenties on net sales in Canada.

In accordance with the terms of the agreements, Paladin will license Radius' abaloparatide subcutaneous injection, TYMLOS, and abaloparatide novel transdermal device (abaloparatide-TD) for the Canadian market. Paladin will be responsible for the registration distribution, sales, marketing, medical affairs, pricing and reimbursement activities in connection with abaloparatide. Radius will be responsible for supplying the drug to Paladin.

"Reaching an agreement with Paladin in Canada demonstrates both the interest in and opportunity to expand the global footprint of abaloparatide in select ex-US markets. This is one of several key priorities for us, and our goal is to make additional progress throughout 2021," said Cole Ikkala, Head of Business Development at Radius.

Paladin is targeting to file a New Drug Submission (NDS) to Health Canada for TYMLOS by the first quarter of 2022. The company will provide additional business updates as and when appropriate.

TYMLOS (abaloparatide) injection was approved by the US FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Abaloparatide-TD was developed in a collaboration between Radius and Kindeva Drug Delivery (formerly 3M Drug Delivery Systems) with the application of Kindeva's innovative microstructured transdermal patch technology. The Phase 3 wearABLe abaloparatide-TD study is the first pivotal study to evaluate treatment using a novel non-injectable delivery of an anabolic therapy. The wearABLe Phase 3 study is a pivotal, randomized, open label, active-controlled, bone mineral density (BMD) non-inferiority bridging study that will evaluate the efficacy and safety of abaloparatide-TD versus TYMLOS (abaloparatide) injection in approximately 500 patients with postmenopausal osteoporosis at high risk for fracture. The primary endpoint of the study is the percentage change in lumbar spine BMD at 12 months.

Radius is a science-driven fully integrated biopharmaceutical company that is committed to developing and commercializing innovative endocrine therapeutics. For more information, visit www.radiuspharm.com.

Endo is a specialty pharmaceutical company committed to helping everyone we serve live their best life through the delivery of quality, life-enhancing therapies. Our decades of proven success come from a global team of passionate employees collaborating to bring the best treatments forward. Together, we boldly transform insights into treatments benefiting those who need them, when they need them.

ViGeneron Signs Global Development & Commercialization Agreement With Biogen

ViGeneron GmbH recently announced a global collaboration and licensing agreement with Biogen Inc. to develop and commercialize gene therapy products based on adeno-associated virus (AAV) vectors to treat inherited eye diseases. The companies will use ViGeneron's proprietary vgAAV, novel engineered AAV capsids, to efficiently transduce retinal cells via intravitreal injections.

"Gene therapy has become a clinical reality. At ViGeneron, we are dedicated to developing innovative gene therapies to treat diseases with high unmet medical need. This collaboration exemplifies our strategy to develop in-house programs for selected retinal targets, while maximizing our proprietary technology platforms with additional collaboration programs for other targets in ophthalmology and further indications," said Dr. Caroline Man Xu, Co-founder and CEO of ViGeneron. "ViGeneron's recognized expertise in retinal gene therapy together with Biogen's leading research, drug development and commercialization experience is a powerful combination that we believe will allow us to deliver more novel gene therapies to patients in need."

Within the collaboration, ViGeneron will optimize and validate *in vitro* therapeutic candidates for an undisclosed target to treat inherited eye disease. Biogen has the right to add an additional reserved target within 2 years after the effective date. The companies will work together on the *in vivo* proof of concept (POC). Biogen will be responsible for all further development and commercialization of the selected therapeutic candidates.

ViGeneron will receive from Biogen an upfront payment and R&D funding for the mutually agreed workplan. In addition, ViGeneron will be eligible to receive development, regulatory and commercial milestone payments, and will also be eligible to receive tiered royalties on net commercial sales of products arising from the collaboration.

ViGeneron is dedicated to developing innovative gene therapies to treat ophthalmic diseases with high unmet medical need, as well as partnering with leading biopharmaceutical players in other disease areas. The company's pipeline is built on two proprietary adeno-associated virus (AAV) technology platforms. The first, vgAAV gene therapy vector platform, allows superior transduction efficiency and intravitreal, a less invasive treatment administration. The second, REVeRT vector platform, targets diseases caused by mutations in large genes. Privately-owned ViGeneron was founded in 2017 by a seasoned team with in-depth experience in AAV vector technology and clinical ophthalmic gene therapy programs and is located in Munich, Germany. For further information, visit www.vigeneron.com.

Kite & Oxford BioTherapeutics Establish Cell Therapy Research Collaboration

Kite, a Gilead Company, and Oxford BioTherapeutics Ltd. recently announced the companies have entered into a research collaboration to evaluate five novel targets for a number of hematologic and solid tumor indications.

Through this collaboration, OBT will validate five novel oncology drug targets, previously identified using OBT's OGAP discovery platform, and generate antibodies against these targets. Kite and Gilead will have the exclusive right to develop and commercialize therapies based on these targets or antibodies.

"As the leader in cell therapy, we are committed to continuing to bring its transformative potential to more patients with different kinds of cancers," said Mert Aktar, Vice President of Corporate Development and Strategy at Kite. "We're excited to partner with Oxford BioTherapeutics to help accelerate this research by identifying new targets in solid tumors and hematologic malignancies where novel approaches may help improve outcomes."

Dr. Christian Rohlff, OBT's Chief Executive Officer, added "Selecting the right target is fundamental for the successful development of first-in-class cell therapies. OBT's state-of-the-art platforms have refined this approach to address difficult-to-treat cancers. This has resulted in several candidates entering clinical development either by OBT or its development partners. We are delighted that Kite, the global leader in cell therapy, has recognized the potential of OBT's OGAP discovery platform and antibody capabilities through this partnership. On behalf of patients in urgent need of novel therapies, we look forward to working with Kite to advance cell therapies for the treatment of hematologic malignancies and solid tumors."

Under the terms of the agreement, OBT will receive an upfront payment and will be eligible to receive additional payments based on achievement of certain discovery, clinical and regulatory milestones, as well as royalties on future potential sales.

Oxford BioTherapeutics is a clinical-stage oncology company; based in Oxford, UK; Morristown, NJ, and San Jose, CA, with a pipeline of first-in-class immuno-oncology (IO) and antibody-drug conjugate (ADC)-based therapies identified using OBT's proprietary OGAP target discovery platform. OBT's approach aims to fulfil major unmet patient needs by targeting difficult-to-treat cancers. For more information, visit www.oxfordbiotherapeutics.com.

Kite, a Gilead Company, is a biopharmaceutical company based in Santa Monica, CA, with commercial manufacturing operations in North America and Europe. Kite is engaged in the development of innovative cancer immunotherapies. The company is focused on chimeric antigen receptor and T cell receptor engineered cell therapies. For more information, visit www.kitepharma.com.

Aurinia & Lonza Announce Exclusive Agreement for Dedicated Voclosporin Manufacturing Capacity

Aurinia Pharmaceuticals Inc. and Lonza recently announced they have expanded their exclusive manufacturing relationship. The parties entered into a collaborative agreement to build a dedicated manufacturing capacity within Lonza's existing small molecule API facility in Visp (CH). The dedicated facility (also referred to as "monoplant") will be equipped with state-of-the-art manufacturing equipment to provide cost and production efficiency for the manufacture of voclosporin, while expanding existing capacity and providing supply security to meet future commercial demand.

The new agreement builds on the parties' successful multi-year relationship. The agreement, which is conditional on regulatory approval of voclosporin, does not impact the launch supply for voclosporin as this is secured by existing capacity. The monoplant is estimated to be operational in 2023.

Following US regulatory approval of voclosporin, Aurinia will commence several capital expenditure payments. Upon completion of the monoplant, Aurinia will have the right to maintain unobstructed use of the monoplant by paying a quarterly fixed facility fee.

The US FDA accepted the filing of Aurinia's NDA for voclosporin in the treatment of lupus nephritis (LN), granted Priority Review, and assigned a Prescription Drug User Fee Act (PDUFA) target action date of January 22, 2021.

"This collaboration is a great example of how we can support both early and commercial-stage biopharmaceutical companies through innovation in manufacturing technology and flexible business models. We are looking forward to further developing our relationship with Aurinia into a long and productive collaboration to supply this innovative medicine to patients across the globe," said Gordon Bates, President Small Molecules Division, Lonza.

"Lonza's world-class expertise and partnership have helped Aurinia to cost-effectively optimize the unique and complex manufacturing process required for the synthesis of voclosporin. We are currently well-poised and ready with adequate product supply for launch and anticipated market demand. A dedicated production capability will help keep our manufacturing costs down and ensure long-term flexibility to meet future demand for years to come," added Peter Greenleaf, President and Chief Executive Officer, Aurinia Pharmaceuticals.

At Lonza, we combine technological innovation with world-class manufacturing and process excellence. Together, these enable our customers to deliver their discoveries in the healthcare, preservation, and protection sectors.

We are a preferred global partner to the pharmaceutical, biotech, and specialty ingredients markets. We work to prevent illness and promote a healthier world by enabling our customers to deliver innovative medicines that help treat or even cure a wide range of diseases. We also offer a broad range of microbial control solutions, which help to create and maintain a healthy environment.

Aurinia Pharmaceuticals is a late-stage clinical biopharmaceutical company focused on developing and commercializing therapies to treat targeted patient populations that are impacted by serious diseases with a high unmet medical need. The Company is currently seeking FDA approval of voclosporin for the potential treatment of LN. The company's head office is in Victoria, British Columbia and its US commercial hub is in Rockville, MD. The company focuses its development efforts globally.

Apollomics & GlycoMimetics Granted Breakthrough Therapy Designation

Apollomics, Inc. and GlycoMimetics recently announced APL-106 (uproleselan) has been granted Breakthrough Therapy Designation (BTD) from the China National Medical Products Administration (NMPA) Center for Drug Evaluation (CDE) for the treatment of relapsed/refractory acute myeloid leukemia (AML).

"This Breakthrough Therapy Designation for APL-106 reinforces its potential and is an important regulatory milestone for Apollomics as we prepare to initiate our clinical development work in China for patients suffering from AML," said Guo-Liang Yu, PhD, Co-Founder, Chairman and Chief Executive Officer. "AML is an aggressive disease, and relapsed/refractory patients have an extremely poor prognosis. We look forward to initiating our Phase 3 bridging study this year and working with the CDE on a potentially accelerated clinical development program to address this important patient need."

In September 2020, the NMPA CDE granted Investigational New Drug (IND) approval for APL-106 enabling the initiation of a Phase 1 pharmacokinetics (PK) and tolerability study and includes acceptance of a Phase 3 bridging study of APL-106 in combination with chemotherapy in relapsed/refractory AML.

The BTD is part of the revised Drug Registration Regulation that became effective in July 2020 in China. The BTD is designed to expedite the development and review of therapies that are being developed for treatment of serious diseases for which there is no existing treatment or where preliminary evidence indicates significant advantages of the therapy over available treatment options.

Discovered and developed by GlycoMimetics, uproleselan (APL-106) is a late clinical-stage, potentially first-in-class, targeted inhibitor of E-selectin. Uproleselan (yoo' pro le' sel an) is designed to block E-selectin (an adhesion molecule on cells in the bone marrow) from binding with blood cancer cells as a targeted approach to disrupting well-established mechanisms of leukemic cell resistance within the bone marrow microenvironment. In 2017, the US FDA granted Breakthrough Therapy Designation to uproleselan for treatment of adults with relapsed or refractory AML. Apollomics licensed APL-106 from GlycoMimetics in January 2020 to develop and commercialize APL-106 in Mainland China, Hong Kong, Macau, and Taiwan, also known as Greater China.

Acute Myeloid Leukemia (AML) is a cancer of the blood and bone marrow. It is an aggressive disease that causes the bone marrow to produce immature cells that are unable to carry out their normal function and develop into leukemic white blood cells called myeloblasts. In the U.S., there are approximately 20,000 new cases of AML each year and a 5-year survival rate of 28.7%. The annual incidence of new cases of AML in China is 21,600, and relapsed/refractory AML has an extremely poor prognosis.

Apollomics, Inc. is an innovative biopharmaceutical company committed to the discovery and development of mono- and combination- oncology therapies to harness the immune system and target specific molecular pathways to eradicate cancer.

GlycoMimetics is a biotechnology company with two late-stage clinical development programs and a pipeline of novel glycomimetic drugs, all designed to address unmet medical needs resulting from diseases in which carbohydrate biology plays a key role.

Baxter Biopharma Solutions Announces Sterile Manufacturing Agreement for Novavax's Covid-19 Vaccine

Baxter International Inc. recently announced that Baxter BioPharma Solutions has entered into an agreement to provide sterile manufacturing services for NVX-CoV2373, Novavax's COVID-19 recombinant nanoparticle vaccine candidate with Matrix-M adjuvant. Baxter BioPharma Solutions is a premier contract manufacturing organization that specializes in parenteral (injectable) pharmaceuticals, including vaccines. The agreement is expected to advance commercial-scale manufacturing essential for the vaccine's production and distribution in the UK and European markets. Novavax's COVID-19 vaccine candidate is currently in Phase 3 trials and has not yet been authorized or approved for use.

"The quest to develop vaccines for COVID-19 has reinforced the opportunity for industry partners to work together and contribute their unique capabilities and expertise for the benefit of all," said Marie Keeley, Vice President, Baxter BioPharma Solutions. "We welcome the opportunity to work with an innovative company like Novavax and look forward to helping bring their vaccine candidate to the market."

According to Novavax, NVX-CoV2373 contains a full-length, prefusion spike protein made using Novavax's recombinant nanoparticle technology and the company's proprietary saponin-based Matrix-M adjuvant. The purified protein is encoded by the genetic sequence of the SARS-CoV-2 spike (S) protein and is produced in insect cells. It can neither cause COVID-19 disease nor can it replicate, is stable at 2°C to 8°C, and is manufactured in a ready-to-use liquid formulation that permits distribution using standard vaccine supply chain channels.

"Our priority is to bring a safe, effective COVID-19 vaccine to people around the world," said Rick Crowley, Executive Vice President, Chief Operations Officer, Novavax. "Partners like Baxter BioPharma Solutions are enabling Novavax to quickly establish a commercial supply chain network to ensure access for global populations, and ultimately help bring about an end to the global COVID-19 pandemic."

Baxter's manufacturing services for NVX-CoV2373 will take place at its state-of-the-art facility in Halle/Westfalen, Germany. The site has broad sterile manufacturing capabilities and areas of focus, offers current good manufacturing practices (cGMP) manufacturing with dedicated production areas, and is designed to deliver products with optimum efficiency and speed to market. Baxter's recently expanded Halle/Westfalen facility has been in operation for more than 60 years.

Baxter's BioPharma Solutions business supports leading pharmaceutical companies in meeting their commercialization objectives by providing scientific expertise, sterile manufacturing solutions, parenteral delivery systems, and customized support services needed to meet the unique challenges that parenteral products face.

Every day, millions of patients and caregivers rely on Baxter's leading portfolio of critical care, nutrition, renal, hospital, and surgical products. For more than 85 years, we've been operating at the critical intersection, where innovations that save and sustain lives meet the healthcare providers that make it happen. With products, technologies and therapies available in more than 100 countries, Baxter's employees worldwide are now building upon the company's rich heritage of medical breakthroughs to advance the next generation of transformative healthcare innovations.

Rhythm Pharmaceuticals Announces Sale of Priority Review Voucher for $100 Million

Rhythm Pharmaceuticals, Inc. recently announced it has entered into a definitive agreement to sell its Rare Pediatric Disease Priority Review Voucher (PRV) for $100 million.

The PRV was granted to Rhythm by the US FDA with the approval of IMCIVREE (setmelanotide) for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing.

"Rhythm is focused on transforming the care of people living with rare genetic diseases of obesity," said David Meeker, MD, Chair, President, and Chief Executive Officer of Rhythm. "The non-dilutive capital from the sale of our PRV provides an important source of additional funding to advance the continued development of setmelanotide as a precision medicine for people whose severe obesity and insatiable hunger may be caused by genetic variants associated with the melanocortin-4 (MC4R) receptor pathway."

According to the agreement, Rhythm will receive an upfront payment of $100 million upon the closing of the transaction, which is subject to customary closing conditions and is expected to occur following expiration of the applicable US antitrust clearance requirements. Jefferies LLC acted as exclusive financial advisor to Rhythm on this transaction. Latham & Watkins LLP acted as legal advisor to Rhythm.

The non-dilutive funds expected from this transaction are in addition to the $201.8 million in cash, cash equivalents, and short-term investments Rhythm reported as of September 30, 2020.

The program is intended to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. A PRV may be issued to the sponsor of a rare pediatric disease product application and would entitle the holder to priority review of a single New Drug Application or Biologics License Application, which reduces the target review time and could lead to an expedited approval. The sponsor receives the PRV upon approval of the rare pediatric disease product application and it can be sold without limitation, subject to applicable FDA requirements for filing and use.

Rhythm is a commercial-stage biopharmaceutical company committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. The company's precision medicine, IMCIVREE (setmelanotide), has been approved by the FDA for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing. IMCIVREE is the first-ever FDA approved therapy for these rare genetic diseases of obesity. Rhythm is advancing a broad clinical development program for setmelanotide in other rare genetic diseases of obesity. The company is leveraging the Rhythm Engine and the largest known obesity DNA database – now with more than 30,000 sequencing samples – to improve the understanding, diagnosis and care of people living with severe obesity due to certain genetic deficiencies.

Formulation Forum

Oral Controlled Delivery of Poorly Water-Soluble Drugs

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

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INTRODUCTION

In the pharma industry, there is a very high failure rate in new drug development. Only one in 5,000 discovery compounds will reach the market. Most failures in early development are mainly due to drug toxicity, safety, and efficacy issues. A significant increase in the percentage of new chemical entities (NCEs) with poor physical, chemical, and biopharmaceutical properties (BCS II and IV) in the drug pipeline has played a significant role in attributing to those high failure rates. Around 50% of drugs on the market and nearly 90% of molecules in the discovery pipeline are poorly water soluble. Poor solubility can lead to low bioavailability, resulting in suboptimal drug delivery, ineffective drug efficacy, and side effects. As a result, various drug delivery nanotechnologies, such as nano-suspensions, lipid microemulsions, nano-emulsions, and amorphous solid dispersions, have been found critical in overcoming these bioavailability challenges faced by the pharma and the biotech industries.

In addition, because immediate-release formulations normally having a wide fluctuation of drug plasma concentration and causing unwanted toxicity and poor efficiency, oral controlled-release formulations, which could maintain a steady concentration of the drug in the plasma within the therapeutic index, have been adapted for early drug development to overcome compound toxicity issues (Figure 1). Controlled-release formulations can optimize the pharmacokinetic and pharmacodynamic properties of drugs, and thus can improve the safety and efficacy of NCEs that otherwise might fail due to safety reasons. In addition, controlled-release dosage forms have proven very useful in lifecycle management of approved drugs via NDA 505(b)(1) or 505(b)(2) regulatory pathways. Reformulation of immediate-release dosage forms with multiple daily doses into a once-daily modified-release product can simplify dosing regimens, improve patient compliance, and enhance product safety.

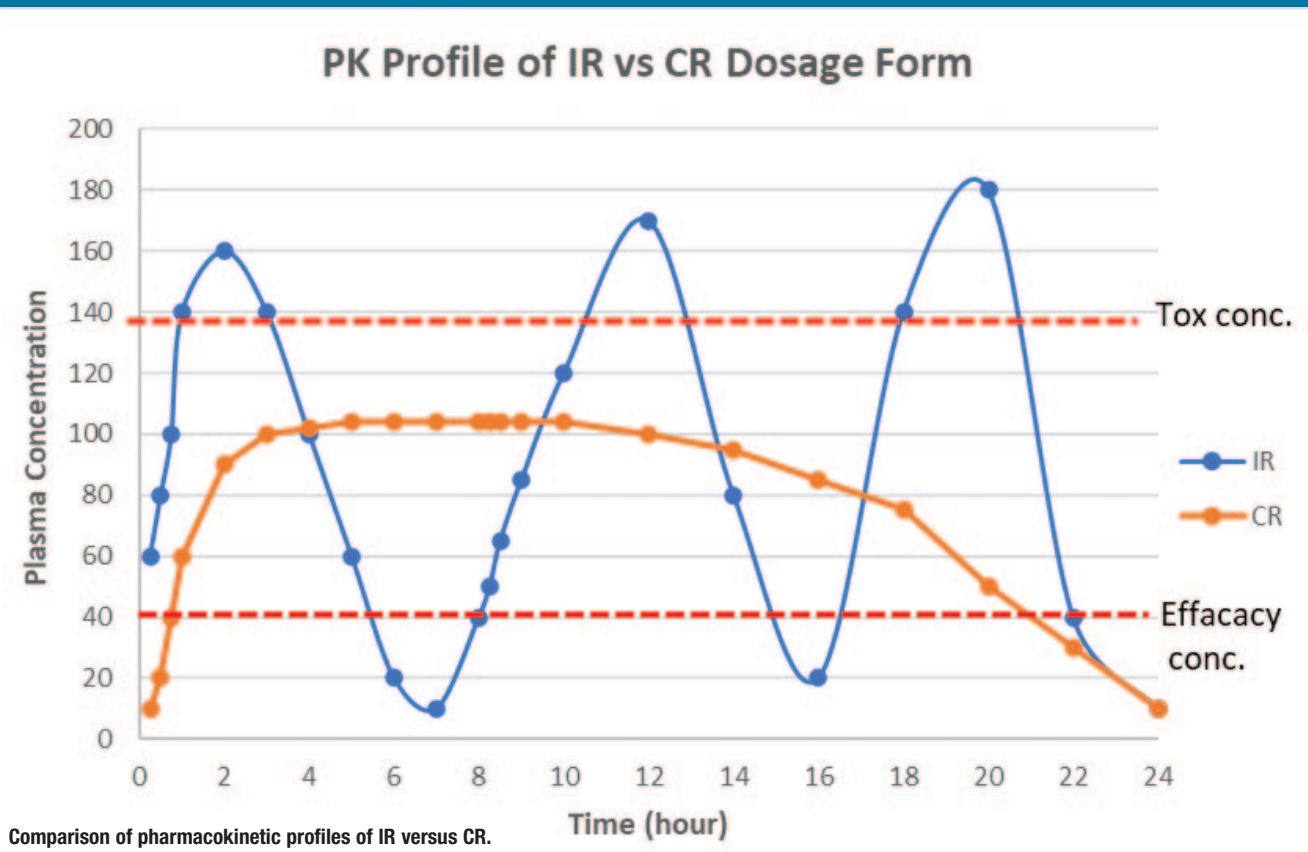
KEY CONSIDERATIONS FOR CR DOSAGE FORM DESIGN

Every NCE possesses its unique properties that require special considerations for rational design of a CR drug delivery system. CR dosage form development should define its target pharmaceutical profiles based on medical need, physiochemical/biopharmaceutical properties, and applicability of formulation technology. Figure 2 shows the key considerations for design of CR dosage forms.

TARGET PHARMACEUTICAL PROFILES

The main goals in early phase modified-release dosage form development is to enhance efficacy by increasing duration of C_{min} plasma concentration above the effective concentration and to minimize toxicity by reducing the C_{max} plasma concentration to below the toxicity level. In addition, controlled release can reduce the dosing frequency and thus improve patient compliance. The modified-release duration varies between 2 to 24 hours depending on the goals of the CR dosage form: 1) if the CR formulation is needed to blunt the C_{max} plasma concentrations in order to reduce C_{max}-related side effects, a 4- to 6-hour delivery will be sufficient; 2) if a CR formulation is to improve efficacy by increasing duration of C_{min} above the efficacious concentration and to reduce dose frequency, a 6- to 24-hour release will be desirable depending on the drug body half-life

FIGURE 1



Comparison of pharmacokinetic profiles of IR versus CR.

and regional absorption of the drug in the lower GI tract; and 3) if a CR formulation is to reduce local irritation or to avoid drug degradation in the gastric fluid, a delay release of ~2 hours will be sufficient.

When designing a CR dosage form, ease of administration, dose accuracy, and swallowability should be always considered for specific patient populations, including for Alzheimer's disease, pediatric, and geriatric populations. Multi-particulate dosage forms, such as coated beads and powder for reconstitution, are popular for those populations due to ease of swallowing and reproducibility in drug-release rate.

Depending on body half-life, regional absorption in the GI tract, dose/solubility, bioavailability, matrix type, or membrane-coated CR dosage forms can be selected for development with an aid of modeling and simulation.

BIOPHARMACEUTICAL CONSIDERATIONS

An ideal candidate for CR dosage form has the following biopharmaceutical properties:

- Adequate solubility in the physiological pH range
- Minimal first-pass metabolism
- Uniform absorption throughout GI tract (no site specificity)
- Optimal partition coefficient (log PC o/w > 1.0)
- Low dose (< 500 mg)
- Short half-life (4 to 8 hours)
- Relatively high therapeutic index

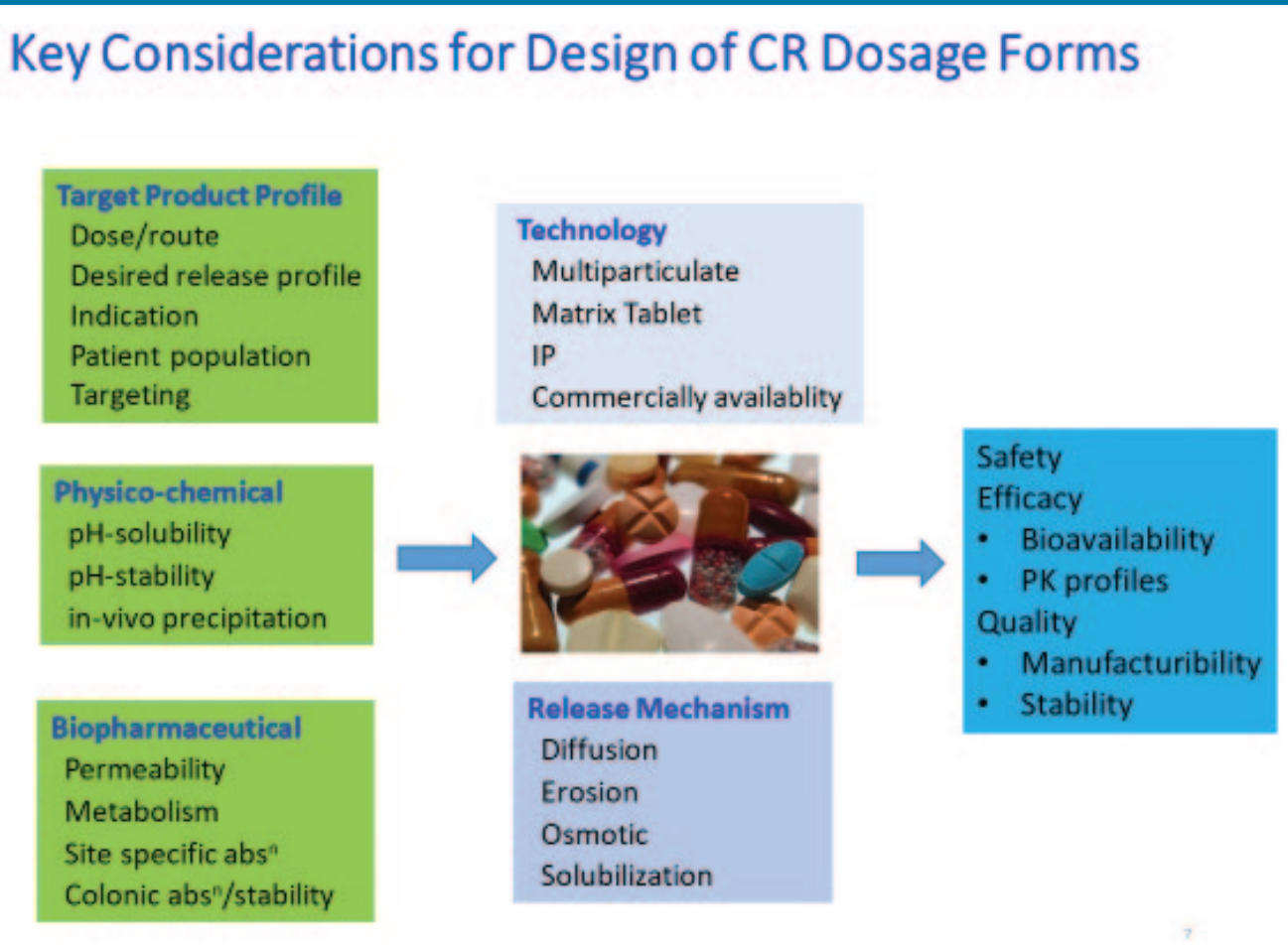
A compound that has difficulty for CR dosage form development has the following properties:

- High first-pass metabolism
- Large dose (> 500 mg)
- Site-specific absorption
- Drug having narrow therapeutic index
- pH dependent solubility/low aqueous solubility

SOLUBILITY

For compounds with low water solubility, even though drug absorption of the original crystalline form is generally extended due to the slow drug dissolution, it is not an ideal way to achieve modified release by controlling API particle size because of potential variation in particle size distribution for different batches and potential issues in poor bioavailability. It will be challenging to develop a CR dosage form for compounds with low solubility at a

FIGURE 2



Key considerations in design of CR dosage forms.

high dose level (dose/solubility >250). One way to resolve the issue is to use enabling formulation technologies, such as Ascendia's nanotechnology platoforms, such as NanoSol, AmorSol, and EmulSol, to enhance API solubility, and thereafter to incorporate the active soluble intermediate into a CR dosage form.

STABILITY

Compounds that are unstable in GI tract (various pH levels) and are subject to enzymatic degradation in the GI tract should consider ways to stabilize the compound by using a buffer, protecting reagent and coating the API. A compound that is subject to colonic microflora digestion should not consider drug release in the lower GI tract with a release duration longer than ~6 hours.

PERMEABILITY

For BCS class III drugs, absorption of drug is limited by its permeability through the GI tract membrane, whereas for BCS class IV drugs, drug dissolution and permeation influence drug absorption. Absorption enhancers and solubility enhancement should be utilized for enhancement of the drug absorption of BCS class IV drugs.

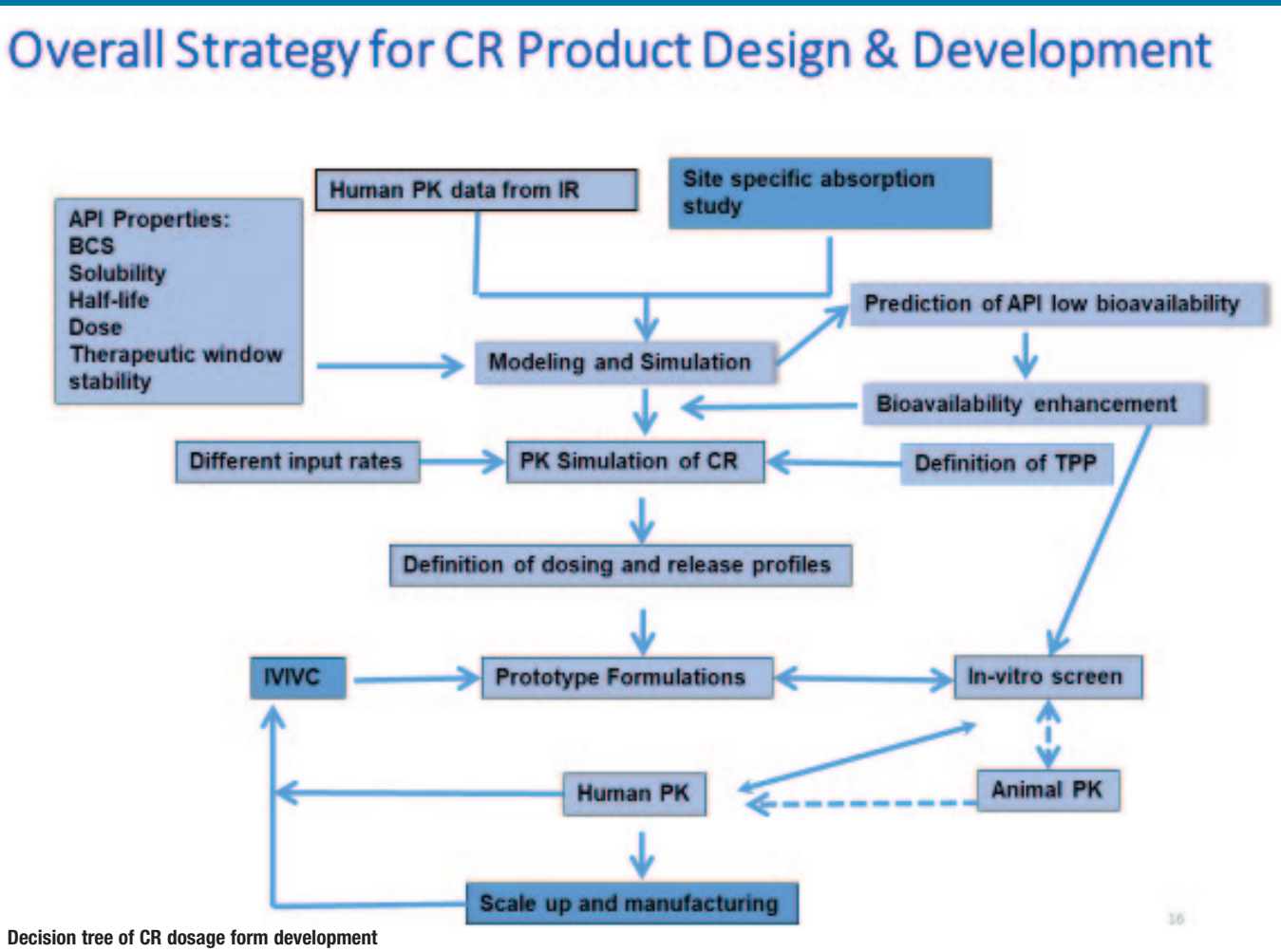
RATIONAL DESIGN OF CR DOSAGE FORMS

The overall design and development process for controlled-release dosage forms of insoluble drugs can be divided into the following steps: (1) to enhance the solubilities and dissolution rates as to the bioavailability of insoluble drugs; and (2) to incorporate the drug intermediate with enhanced solubility in an oral controlled-release dosage form, wherein the drug-release rate is controlled by the dosage form other than by the intrinsic low solubility of the API. Figure 3 shows the decision tree for rational design of CR dosage form for fast translation of discovery compounds into the clinic.

CR formulation development normally go through the following steps:

1. Definition of the target pharmaceutical profile and unmet medical need.
2. Assessment of drug physical-chemical and biopharmaceutical properties relevant to CR dosage form design and paper feasibility analysis.

FIGURE 3



Decision tree of CR dosage form development

3. Modeling and simulation to define the dose and the drug-release profiles.

4. Selection of an appropriate CR technology and in vitro test methods to evaluate formulations with different release rates that bracket the target release rate in vitro.

5. Identification of controlled-release mechanisms that are suitable for the compound under study. Drug-release mechanism includes osmotic pressure, matrix system, and reservoir system. Drug release of different release mechanisms involve desorption from surface; diffusion through the matrix; diffusion through coated membrane; matrix erosion; and a combined erosion and diffusion process. For insoluble drugs, its bioavailability could change with different release mechanisms as drug absorption is influenced by the way of dosage form distribution in the GI tract and the site of drug release.

6. In vivo study in animal or human models using prototype formulations with different release rates.

7. Development of in vitro/in vivo relationship (IVIVR) or correlation (IVIVC) to aid product development and to obtain a BE waiver for SUPAC changes.

SUMMARY

Controlled-release formulations improve the safety and efficacy of NCEs that otherwise might fail due to safety and efficacy reasons. Controlled-release dosage forms have proved useful in life cycle management of approved drugs via the NDA 505(b)(1) or 505(b)(2) regulatory pathways. Rational design of CR dosage forms for insoluble drugs involves: (1) to enhance the solubilities and dissolution rates as to the bioavailability of insoluble drugs; (2) to incorporate the drug intermediate with enhanced solubility in an oral controlled-release dosage form.

Understanding of key biopharmaceutical properties in relationship to drug absorption and elimination plays a critical role in successful design of CR dosage forms from discovery to first-in-human with a shorter timeline and lower development costs. ◆

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TUB PACKAGING

Why Double-Bagged Tubs are an Issue for High-Speed Filling

By: Tilman Roedle

INTRODUCTION

Fully automated production is fast becoming the standard for the biopharmaceutical manufacturing industry. At the same time, many fill and finish businesses are still struggling with a consistent source of variability in their automated production processes: inconsistently double-bagged tubs of pre-sterilized syringes.

Variation in tub packaging continues to create financial and operational challenges for the entire downstream supply chain. It's time for our industry to align on packaging configuration requirements that make tubs fully processable on automated lines.

INCREASING DEMAND FOR PRE-STERILIZED FORMATS & QUALITY REQUIREMENTS

When pre-sterilized systems were introduced in the early 1980s, they were intended primarily for labs and small filling. They were packaged in a bag that simply had to keep its contents clean and sterile until it was opened. Unbagging a tub of syringes was a manual process with little impact on the small-scale use cases of the time.

But much has changed in 40 years. Today, pre-sterilized syringes are the requested industry standard for filling of prefilled syringes, which now make up a significant portion of the pharmaceutical injectables business. With the growing demand for these products, the aseptic production processes as well as quality and regulatory requirements have also changed. Pharmaceutical fill finish companies now increasingly rely on high-speed syringe-filling machines. This machinery can have a nominal output of >50,000 units per hour, or about six tubs of syringes every minute.

Production volumes this large have only been made possible by automating as many production steps as possible, including the process of unbagging tubs. Like any mechanized manufacturing system, today's advanced filling lines depend on reproducible characteristics and precision, in both the filling steps they perform and the components they process. Variability of any kind can create significant challenges – and double-bagged nested syringes are one of the troublesome culprits.

Aseptic quality requirements are tightening, especially with new Annex 1 contamination regulations on the way. Double-bagging syringe tubs is a valuable sterility solution for these businesses, especially for those who aren't using E-Beam sterilization equipment to sanitize the outside of the bag before a tub is introduced to a higher-level cleanroom. For drug manufacturers who don't rely on this equipment, double-bagged tubs help enable compliance with aseptic quality requirements. As tubs move along the filling process, one bag can be removed each time the tub enters a higher cleanroom level.

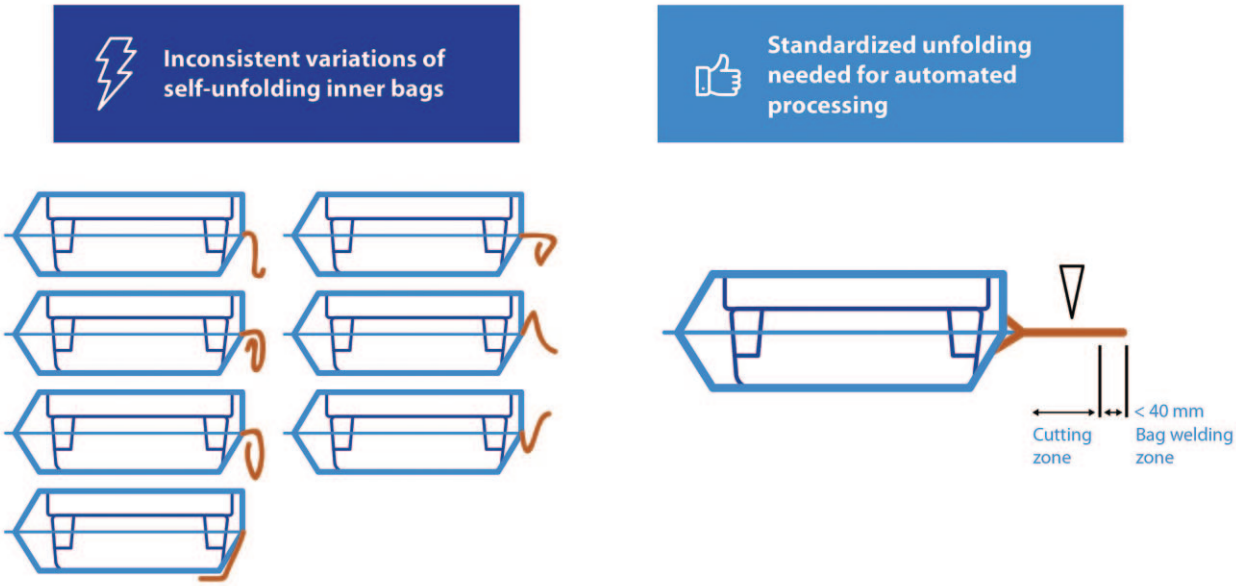
THE DOUBLE BAGGING PROCESS: SOURCE OF VARIABILITY

The production challenges begin well upstream from the automated production lines, starting with the way primary containers are packaged by their manufacturers.

Nested, ready-to-use syringes are typically packaged in tubs that are sealed with a gas permeable foil and then bagged. Downstream production challenges often originate with the bagging process, which is still a manual one for most syringe suppliers. The process usually involves the following several steps:

- An operator places the tub in an inner bag, which is then sealed

FIGURE 1



Spectrum of unfolding inner bags observed during filling process (often different patterns within in a single delivery batch). The different bag flap patterns clearly demonstrate the various folding methods. Due to this many ways, any one of these unfolding configurations can occur once the outer bag is removed and relaxing forces take effect on the inner bag.

- Since the inner bag is typically the same size as the outer bag, the sealed flaps of the inner bag are then folded up and fixed in position while the operator inserts the tub into the outer bag
- The outer bag is then also sealed for delivery

Unfortunately, this manual approach inevitably leaves these processes susceptible to inconsistency in the bagging results.

This lack of packaging standardization can be challenging for automated processing facilities, which depend on the repeat precision of every input to deliver the rigorous efficiency and distinctive quality that our industry now expects. For drug manufacturers who use mass volumes of pre-sterilized syringes, the biggest problem often begins when the outer bag is opened – the moment when challenges unfold along with the inconsistently packaged inner bag.

THE AUTOMATED UNBAGGING PROCESS AT THE FILLING SITE

In theory, this ought to be a straightforward process. Here's how it's typically designed to work:

- First, the outer bag is cut open and transferred.
- The tub with the remaining inner bag is pushed through an opening ("mouse hole") into the cleanroom area.
- At this point, the folded inner bag should relax and unfurl before the tub reaches the cutting station at the mouse hole entry to the Class A cleanroom area. While most inner bags partially unfold due to restoring forces, process aids like mechanical guides and compressed air nozzles can help further unfold the bag to a flat flap that can be readily opened by a cutting device.

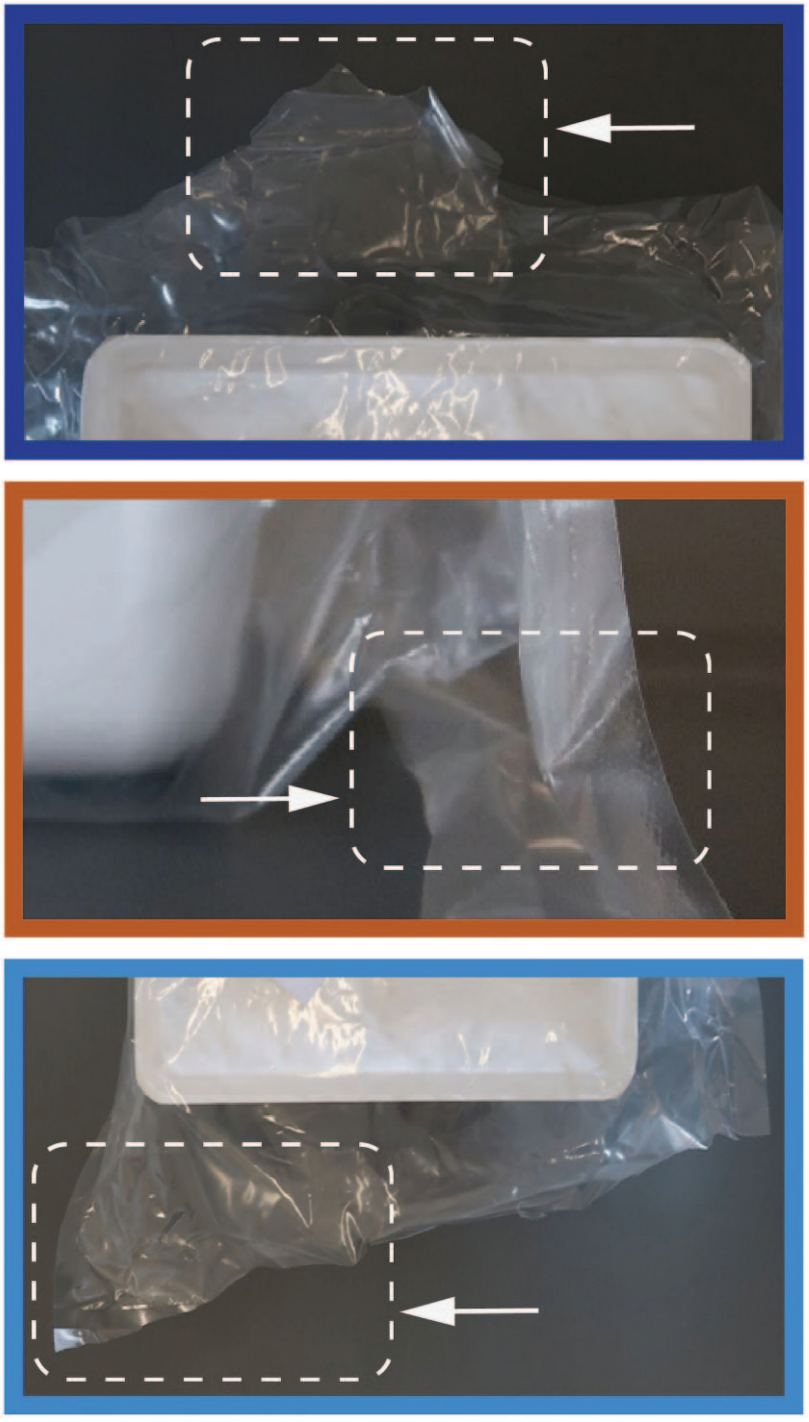
In reality, the results are often far less satisfactory. So where do the issues arise? In a nutshell, it is the incompatibility between the alignment of manual and automated process.

MANUAL BAGGING: A CHALLENGE FOR AUTOMATION

Most suppliers for primary packaging container continue to manually bag their tubs according to their own internal packaging specifications. This approach relies heavily on operating instructions and the frequency and quality of operator training to enable consistent outputs. The predictable result: considerable variability in the tub packaging, especially in the position and folding of the inner bag.

These variances create an impossible challenge for automated bag-opening machinery. No combination of relaxing forces and assistive equipment can resolve this level of variability to the point that

FIGURE 2



This shows typical situations in which the cutting tool was only able to partially open inconsistently folded inner bag flaps. Each of these bags presented a different flap configuration to the cutting tool or a mispositioned tub in the inner bag, resulting in angular cuts that left the bag welding intact at the edge or even the middle of the bags. Every unpredictable result like these makes it impossible for the tub to leave the partially sealed bag – again leading to process disruption, manual intervention, and a discarded tub.

every inner bag is fully compatible with the cutting step.

This challenge is then further compounded by three key factors: the way the inner bag flaps are folded, the position of the tub in the inner bag, and the inner bag material. Let's take a closer look at how each one can impact an automated production line.

FOLDING PATTERN INNER BAG FLAPS

This challenge is most acutely clear when tubs arrive at the cutting station that will open the inner bag and release the tub through the filling room mouse hole. At this critical process step, partially or inconsistently unfolded inner bags create a cascade of disruptively variable cutting results.

Some bags will be cut partly open and then get stuck when high resistance forces prohibit the forwarding mechanism from advancing the tub. Sometimes the cutting tools strike misaligned inner bag folds at an angle to the axis of the tub, resulting in torsional force that twists the bag and tub and stops the processing machinery. At this process step, manual intervention to open the inner bag is not possible, as the inside and content of the bag must remain sterile to enable contamination-free presentation to the Class A area. Instead, the partially opened tubs must be removed by hand and discarded.

POSITION OF THE TUB IN THE INNER BAG

Furthermore, not all tubs approaching the cutting station are properly positioned in their inner bags, which can also affect the consistency of the rectangular

bag cut resulting in machine stoppages and manual intervention.

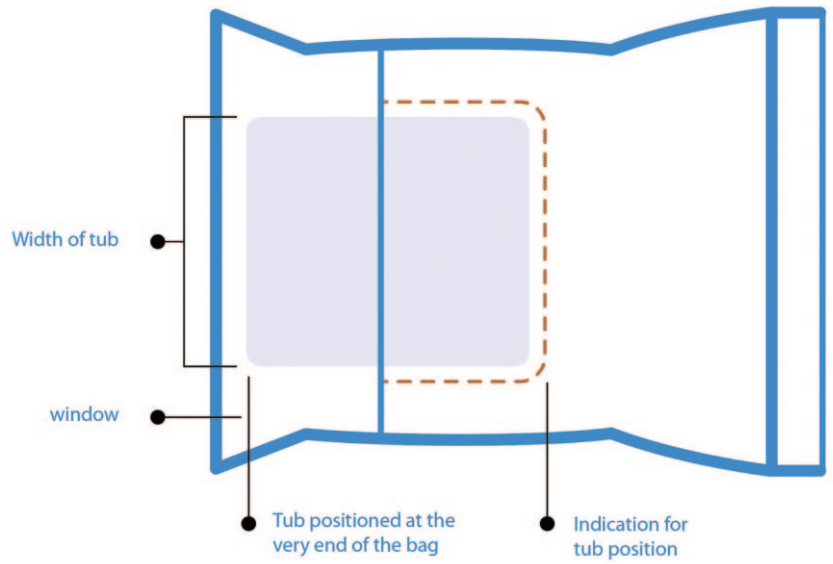
This begs a natural question: had the bagged tubs been decentered during earlier processing steps, or had the tubs been misaligned during manual packaging? Tracing tubs back to the input station quickly demonstrates that the latter is usually the case. When tubs arrive at the drug manufacturer, many of them have being found not centered relative to the inner bag or inserted as far into the bag as possible, the correct position for automated unbagging.

Unfortunately, these inconsistencies in the folding pattern of the inner bag flaps and the position of the tub in the bag are both difficult for an operator at the filling site to assess from the outside of the bag. Auditing and presorting tubs based on bag alignment is neither practical nor feasible at the filling machine entry, when the operator is focused on loading the conveyor belt and has no control over the alignment of the tub inside its bag. At this point, not even optimal operator instruction or training will compensate for misaligned tubs or inconsistent bag folding. Ultimately, the quality of the output depends on the consistency of the input.

THE INFLUENCE OF THE INNER BAG MATERIAL

Different qualities of the inner bag material can strongly impact the way bagged tubs behave in the manufacturing area, as well as in the subsequent unbagging process in the filling site. The material compound, foil thickness, and the stiffness of the plastic foil can all influence the way relaxing forces take effect on the unfolding bag flaps. The material's surface friction

FIGURE 3



Indication of correct tub position on the inner bag, to assist both supplier and filler operators with quality control.

properties and adhesiveness can also vary significantly. These machinability variables can not only require adjustments in standard processing parameters, but also demand hardware modifications when bag material properties differ widely enough.

Variable bag characteristics can be especially challenging for mechanical guides or travers feeding devices designed help unfold inner bags or direct them with a controlled movement (like on a cutting station). Outlet belts for cut-off bag sections can also be critically impacted: if these sections are too stiff or tacky, they may not readily bend or slip through channels or tubes on their way to a disposal box. Because the machine parts associated with these steps are typically integrated into the machine bed, they are not as readily replaceable as format parts. Consequently, bag characteristics that require hardware modifications are often a reason for declaring syringe tubs "non-processable."

In our experience, automated unbagging processes are consistently successful for some bag materials, but far less so for others. The cost and efficiency implications are all too clear. Not surprisingly, the question comes up whether it's reasonable to expect pharmaceutical filling lines to absorb the impact of this lack of standardization.

ECONOMIC IMPACT

Folding pattern of inner bags, positioning in the inner bag, inner bag material: all these variables can contribute to a significant number of production interruptions.

An inner bag that cannot be properly cut stops the machine. Because manually opening the bag will break sterility protocol, the tub must be removed by hand and then discarded. One hundred and sixty syringes are lost. At that point, the machinery will have experienced about 40 seconds of downtime. During this time, another four tubs could have been processed. The fill and finish business

loses not just the value of the syringes and production time, but also sees a severe impact on machine utilization and overall equipment efficiency (OEE).

And what is the economic cost involved? Consider the progressive ratio of lost high-value syringes for biotech applications, to lost production time, to unplanned extension of batch manufacturing times. Calculating this model, a 10% rate of non-processable tubs caused by inconsistently folded bags correlates with a roughly 50% increase in batch production time – with a corresponding and significant impact on production costs and customer satisfaction.

STEPS TOWARD SOLVING THESE CHALLENGES

Fortunately for our industry, the issues created by inconsistent bagging processes are readily addressable with the right approach. The position of the tub is particularly important. Figure 3 shows a schematic drawing with important criteria:

- The tub is inserted all the way to the end of the bag
- The tub is centered in the bag
- Bags have a printed indicator of the correct tub position to help operators achieve consistent results
- Air is expelled from the inner bag in order to avoid "loose" tubs that can change position during the unbagging process consistently
- Bag weld is consistently flat
- The bag material is specified always the same to enable consistency

And finally, the folding method for the inner bag flaps is specified and uniform to enable that the inner bags can be fully and consistently unfolded before they reach the cutting station.

Today, none of these steps are subject to specification or standardization. From our point of view, this must be changed.

AUTOMATED BAGGING PROCESS & STANDARDIZATION

The efficiency and productivity of pharmaceutical producers is handicapped by "plastic bags." Fortunately, there's a solution to this challenge: automated bagging equipment. This investment can lead to the consistent, reproducible bag configurations that the drug manufacturer relies on, without the variable folding and unpredictable configurations of manual bagging processes. But again: Which folding scheme (according to Figure 1) is this machine equipment is designed for?

The 2015 ISO 11040-7, Packaging Systems for Sterilized Sub-Assembled Syringes Ready for Filling, agreed among other things on measures for tubs, nests, and bags. However, to support fully automated handling of double-bagged tubs, all the specifications described here – inner flap folding schemes, the tub position in the bag, smaller tolerances of the bag dimensions – are preferable to incorporated into the next revision of the ISO. These changes can help our whole industry drive down inefficiency and waste in the processing of pre-sterilized syringes.

Today, double-bagging processes have some distance to go to reach this valuable goal. We hope to soon see some progress toward the same level of standardization that our industry continues to aspire to and achieve. ◆

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BIOGRAPHY

Tilman Roedle is Lead Expert Drug Delivery Systems for Vetter. He deals intensively with strategic industry collaborations on innovative drug delivery systems and Quality Management for medical device development. He joined Vetter in 2003 as Project Manager, Packaging Development and was appointed Director of Packaging Development in 2005. In this position, he was responsible for primary packaging materials for parenterals and drug delivery systems, later including secondary packaging as well as automated visual inspection implementation and process qualification to help ensure cGMP. His career began in 1996 as a Design Engineer in special machinery for the automotive industry, and later worked as a Project Manager for special machinery investment projects. He earned his Master's degree in Mechanical Engineering at the University of Stuttgart, Germany, in 1995, focusing his studies on key aspects of design and materials sciences.

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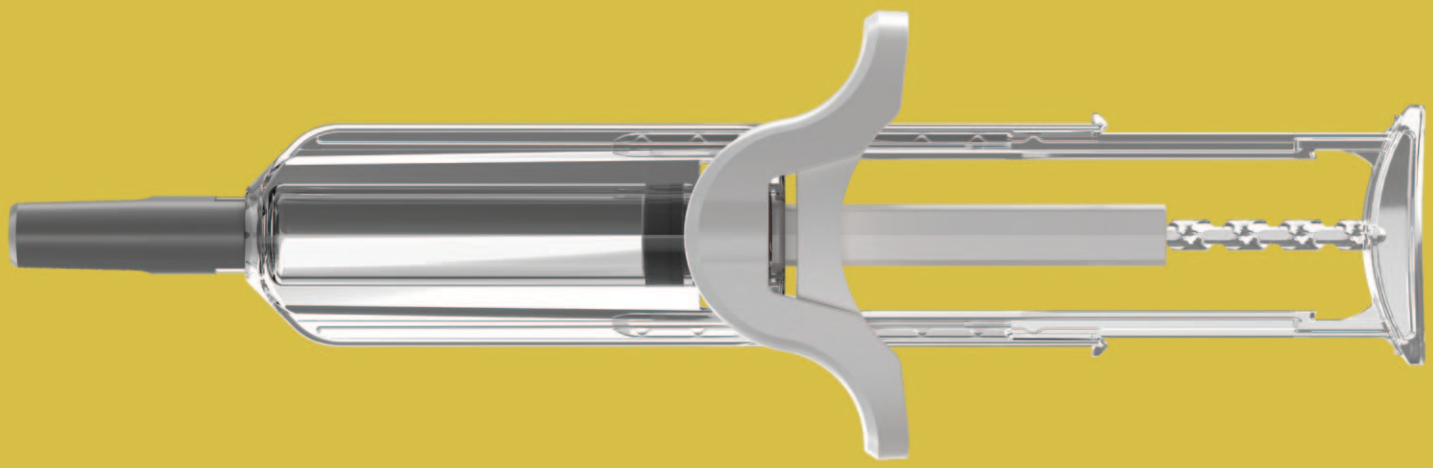

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MULTI-PARTICULATE MANUFACTURING

How Does Experiment Design Affect Multi-Particulates Manufacturing?

By: Namrata Vora, MS, Danica Cartwright, Karthikeyan Selvaraj, MPharm, and Ryan Larmon, MS

INTRODUCTION

Multiparticulate dosage forms are gaining popularity and have many potential advantages over single-unit dosage forms, including reduced risk of dose dumping, increased bioavailability for compounds with short biological half-lives, predictable gastric emptying, less inter- and intra-subject variability, and better control over release patterns.[1] Pellets are one of the most common of the various multi-particulate dosage forms. Pelletization is an agglomeration process that converts bulk powder or active pharmaceutical ingredient (API) blends with excipients into free flowing spherical or semi-spherical units, referred to as pellets, of desired size. Pellets range in size, typically, between 0.5 mm and 1.5 mm.[1] Pellets as a drug delivery system offer not only the aforementioned therapeutic advantages, but also process advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution (PSD), ease of coating, and uniform packaging. The reproducibility of the drug blood levels is an additional advantage with the use of a pellet formulation. Pellets are commonly filled into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules, but can also be compressed into tablets in some cases if desired.

Several factors affect drug product quality, inspiring the regulatory authorities worldwide to modernize good manufacturing practices such that quality is built-in by design, defining it as quality-by-design approach. Quality can be built into the drug product by comprehensive understanding of each unit operation in manufacturing as well as each quality attribute of the finished product, helping to gain understanding about the process as well as finished product during the development stage. The manufacturing process can be well understood when the target product profile is defined and the process flow is established after the initial development trials. Among the many development strategies, statistical design of experiments (DOEs) is considered the most beneficial tool for multi-factorial relationships investigations. Generally, for the test of k factors each at two levels, the factorial design requires 2^k runs of experiments. As the number of factors or levels increases, the number of runs increases rapidly. Thus, it is advantageous to establish the critical process parameters (CPPs) that impact the drug product quality. The CPPs are parameters whose variability in limited range impact drug product critical quality attributes (CQAs) and hence should be monitored or controlled to ensure that the process produces finished product with acceptable quality. Statistical software packages are available to generate multi-level fractional factorial design of experiments, thereby reducing the number of experiments to be performed before obtaining an optimized range for the various CPPs selected. Sophisticated approaches to multi-particulate manufacturing can help ensure proper quality standards are met, while also speeding the development of innovative drug products. This is especially true as a growing proportion of small molecules in the drug development pipeline are being administered as combination therapies in which multi-particulate technology can play a role in development.

USING DOE TO ESTABLISH CRITICAL PROCESS PARAMETERS IN MULTI-PARTICULATE MANUFACTURING

Lonza researchers set out to investigate optimal multi-particulate manufacturing process design by focusing on a drug product containing a high drug load of a model water-insoluble [Biopharmaceutical Classification System (BCS) class 2 compound API]. The pellets were manufactured using the high shear granulation followed by extrusion spheronization techniques. This process involves wet granulation, extrusion, spheronization, fluid bed drying, and screening of dried beads through desired sieve stack to obtain the pellets of desired PSD.

Plackett-Burmann Design – DOE

This study was specifically designed to evaluate the impact of select processing parameters from the high shear granulation process toward the manufacturing of drug product, and their impact to critical quality attributes such as yield and dissolution. The data from this evaluation were designed to identify the processing parameters that need to be considered as CPPs and establish a proven acceptable range for each. All other manufacturing process parameters were constant for all the batches.

Several CPPs were identified based on prior knowledge of the unit operations involved, out of which three wet granulation CPPs were evaluated and optimized in the current study. Impeller speed, mixing time, and amount of binder solution used were identified as the process variables, whereas the percent yield and percent dissolution at 15 minutes were measured as response variables. The impeller speed was evaluated between 250-350 rpm, the mixing time was evaluated between 3-10 minutes, and the binder solution was evaluated in the range of 30%-45% w/w (Table 1).

TABLE 1

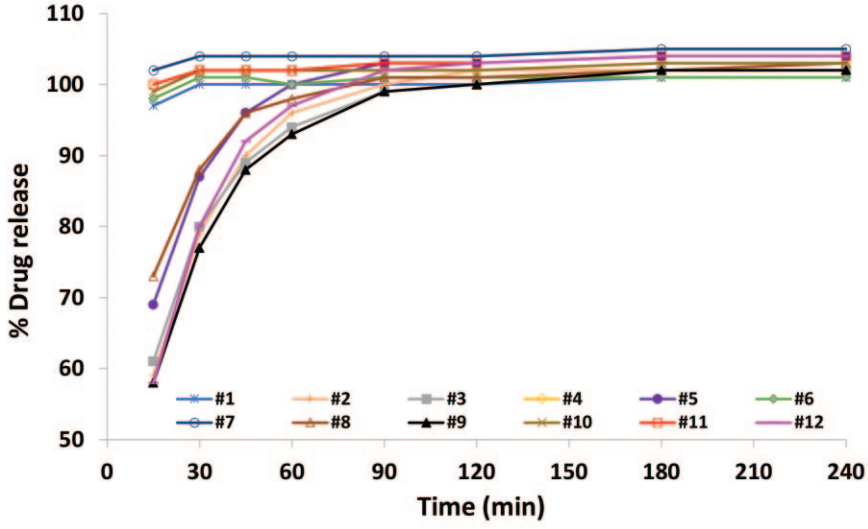
	Wet granulation process variables/parameters			Response parameters	
	Impeller speed (rpm)	Amount of water added (% w/w)	Water addition time (min)/Flow rate (g/min)	Dissolution profile	% Yield
Low	250	30	3/125	% drug released on 60 min	Acceptable beads between 16/30 sieve cut
Target	300	37.5	5/75		
High	350	45	7/53		

Wet granulation process parameters and response parameters evaluated.

Experiments were designed using the Plackett-Burman experimental design to evaluate the parameters. Plackett-Burman designs are usually resolution III, two-level designs. In a resolution III design, main effects are aliased with two-way interactions. The design selected was two-level factorial design for three factors with no center points or replicates. Table 2 represents the design of experiments generated by Minitab 17 following the Plackett-Burman half factorial design.

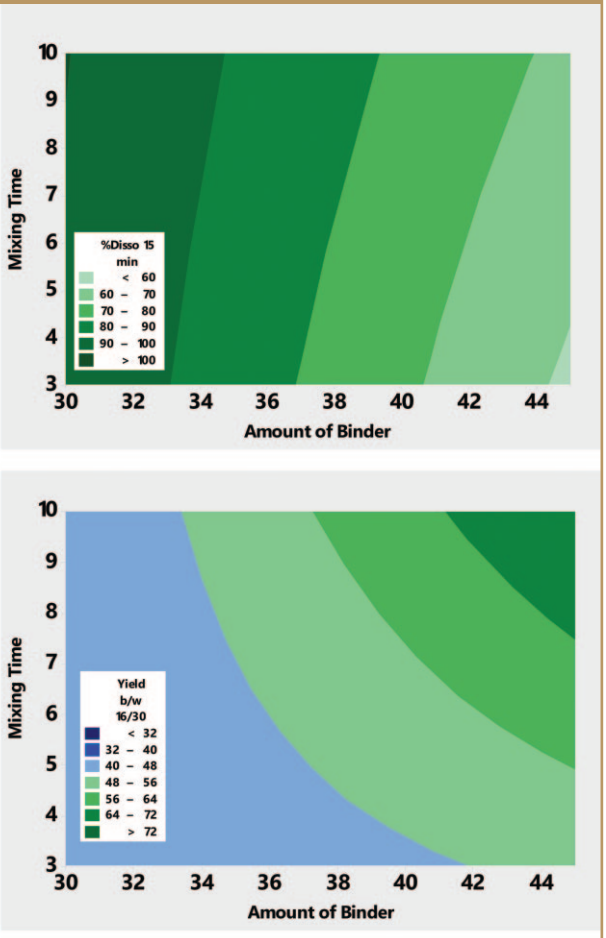
DOE runs 1-12 were executed, and the data generated were monitored for their effects on two critical quality attributes. First, the yield or the amount of beads generated in the acceptable particle size distribution range of 16 mesh to 30 mesh, and second, the amount of drug released within 15 minutes from the drug product generated in each experiment. Dissolution at t=15 minutes was monitored as part of heightened scrutiny of the processing parameters under consideration; however, the acceptance criteria is set at Q 75 in 45 minutes. This data was evaluated by plotting 2D contour plots using Minitab 17 software. Contour plots were formatted in accordance to the acceptability level of the critical quality attributes. The

FIGURE 1



Dissolution Profile for Capsules From DOE Run Nos. 1-12.

FIGURE 2



Contour Plots for the CQAs Versus the CPPs Evaluated in the Current Study

data were analyzed to evaluate the main effects as aliased with two-way interactions of the processing parameters. This information was used to decipher if a given processing parameter was considered a critical processing parameter and define a proven acceptable range for it.

The optimized range obtained for the CPPs was further challenged for reproducibility as a similar batch size level as well as a 10x batch size scale up level. Thus, two additional batches were manufactured, one at 300-g level and another one at 3-kg level and evaluated for the CQAs to confirm the results obtained in this study.

RESULTS & DISCUSSIONS: IDENTIFYING EFFECTS OF SPECIFIC CPPS & PROVING BATCH REPRODUCIBILITY

Results of Factorial Design & DOE Analysis

This study identified the amount of binder solution as the most critical parameter that affects the dissolution profile from the granulated multi-particulate formulation. The dissolution profile was also affected by the mixing time and impeller speed when evaluated at constant amount of binder solution added. The yield was found to be significantly affected by a combination of all three variables. The current formulation presented differences in dissolution profiles with changes in the processing parameters, but passed the acceptance criteria of 75% (Q) in 30 minutes, therefore the ideal set-up for maximum yield was identified in the range of 275-300 rpm impeller speed with 8-10 minutes of mixing time and 42%-45 % w/w binder solution.

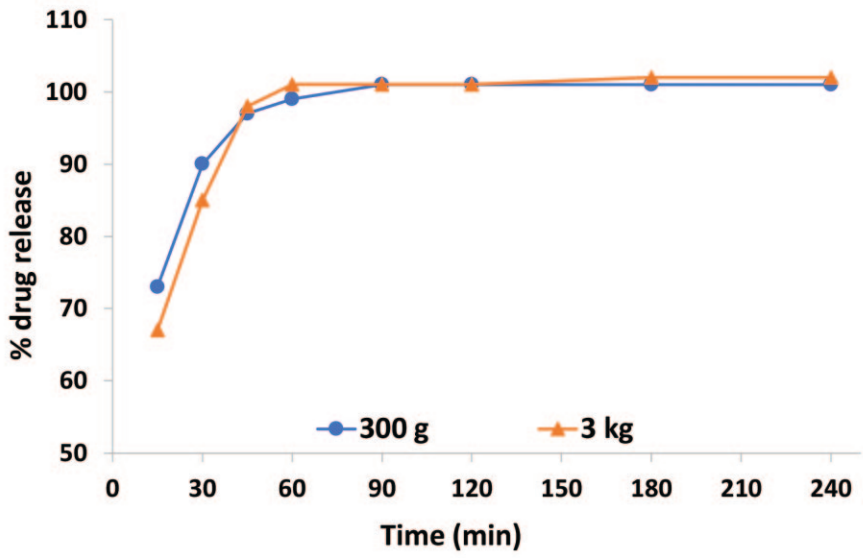
Yield between 16/30 mesh as well as dissolution profiles for each DOE run 1-2 were obtained and evaluated. The current formulation presented differences in dissolution profiles with changes in the processing parameters (Figure 1), but passed the acceptance criteria of 75% (Q) in 30 minutes. Thus, dissolution at 15 minutes was used to evaluate the effect of process parameters. The yield values between 16/30 mesh as well as percent drug released at 15

TABLE 2

Plackett-Burman design		CPPs			CQAs	
StdOrder	RunOrder	Impeller Speed	Mixing Time	Amount of Binder	%Disso 15 min	Yield b/w 16/30
12	1	250	3	30	97	43.1
4	2	350	3	45	59	65.7
7	3	250	10	45	61	70.3
5	4	350	10	30	100	34.8
3	5	250	10	45	69	68.7
10	6	350	3	30	98	35.7
2	7	350	10	30	102	37.9
6	8	350	10	45	73	76.5
8	9	250	3	45	58	30.1
11	10	250	10	30	99	50.0
9	11	250	3	30	100	41.8
1	12	350	3	45	58	54.5

Plackettburman design generated by Minitab 17 and the response parameters obtained for each run.

FIGURE 3



Dissolution Profile of the Optimized 300-g & 3-kg batches; Batch Nos. N3041-38, 39.

minutes time point has been compiled for all DOE runs in Table 2. Contour plots as prescribed in Figure 2 were generated in Minitab 17 for each response factor versus each possible combination of the CPPs.

Response Factors versus amount of binder and impeller speed

No significant effect of impeller speed on dissolution or yield for a constant amount of binder was observed in the test. Increasing the amount of binder improved the yield but was observed to slow down the dissolution. This could be explained by the increase in density of the granulation following increased amount of binder, which in turn can lead to denser extrudates and beads leading to slower dissolution rates. The increased yield could also be explained by denser granules and beads leading to a lower amount of fines being generated during spheronization as well as fluid bed drying process, increasing the amount of beads retained on 30-mesh sieve.

Response Factors Versus Mixing Time & Amount of Binder

There was no significant effect of mixing time on the dissolution rate for a constant amount of binder. However, a mixing time of 8 minutes or higher favored a greater yield. The increase in amount of binder and mixing time from 30% w/w and 3 minutes to 45% w/w and 10 minutes, respectively, improved the yield from 40% to 72% (or higher). The increase in binder solution from 30% to 45% reduced the amount of drug released in 15 minutes from 100% to 60%, but was unaffected by the mixing time.

Response Factors Versus Mixing Time & Impeller Speed

Optimum dissolution was obtained with impeller speed between 250- 300 rpm and mixing times between 3-8 minutes. A maximum yield was obtained with a 250-300 rpm impeller speed and 8-10 minute mixing time.

Summary

For the formulation used in this study, the amount of binder was identified as the parameter with the most significant impact on CQA followed by mixing time and impeller speed. Combining the observations from the preceding discussion, the ideal set-up for maximum yield was identified in the range of 275-300 rpm impeller speed with 8-10 minutes of mixing time and 42%-45% w/w binder solution at 300-g scale.

MULTI-PARTICULATE PROCESS DESIGN IMPROVEMENTS CAN BE REPRODUCED & SCALED UP

Reproducibility Batch

The reproducibility of the manufacturing process was evaluated at a 300-g scale to verify the aforementioned design space using the optimized range of the parameters as mentioned in the summary. Maximum yield was obtained for this batch as compared to all of the DOE runs, which ascertains optimization and the accurate selection of the design of experiments. Refer to Figure 3 to see results obtained using the optimized CPP values in the verification batch at 300 g and scale-up batch at 3 kg.

Scale-Up Batch

A 10x scale-up batch was manufactured to evaluate the ability of design space to predict the scale-up parameters at 10x scale without impacting the CQAs. Yield as well as dissolution results obtained were in line with the results of smaller scale batches, further proving the reproducibility as well as the extension of the DOE run results to larger scale batches Refer to Figure 3 to see results obtained using the optimized CPP values in the verification batch at 300 g and scale-up batch at 3 kg.

CONCLUSION

Understanding the manufacturing process as well as finished product is of key importance in identifying the CPPs as well as CQAs for a multi-particulate drug product. High and low levels of CPPs (minimum and maximum settings of the operational ranges of CPPs) can be used to generate specification limits during the manufacturing process within which CQAs can be found to be acceptable. Operational ranges of critical parameters should be optimized in order to produce quality product in a repeatable manner. It could be concluded from the current study that the DOE approach can be used to optimize the critical process parameters that are reproducible at similar scales as well as 10 x scale-up. This study can be used as a guide in identifying an optimum range of CPP to be used during scale-up without impacting the CQAs. Additionally, it can be concluded that for the current process and the product, the amount of the binder solution had the maximum effect on the dissolution profile as well as percent yield.

These findings and other investigations into optimal process design may be of service to drug manufacturers seeking to rapidly advance new chemical entities from clinic to commercial stage. The careful application of design of experiment studies is an invaluable tool in proving the design space of complex formulations and manufacturing processes. Pharma & biotech companies developing combination therapies of incompatible APIs or modulated drug-release profiles can benefit from access to multi-particulate expertise, both in terms of product quality and faster development.

ACKNOWLEDGEMENTS

The authors acknowledge colleagues Nithin Vidiyala, Naveen Mangu, James Evans, Parag Ved, and Jeffrey Williamson for their efforts, contribution, and support provided in enabling this research. ◆

REFERENCES

1. Muley, S., Nandgude, T. and Poddar, S., 2016. Extrusion–spheronization a promising pelletization technique: In-depth review. Asian Journal of Pharmaceutical Sciences, [online] 11(6), pp.684-699. Available at: <https://www.sciencedirect.com/science/article/pii/S1818087616300721#ac0010>.

BIOGRAPHIES

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Richard Vellacott
Chief Executive Officer
BiologIC Technologies

BiologIC Technologies: The Future Microsoft of Cell Therapy

BiologIC Technologies is a world leader in the development of 3D architectures for powerful, miniaturized, and highly integrated life science automation. These proprietary architectures enable entirely novel workflows with extreme power, integration, and flexibility and will empower scientists driving the future of synthetic biology to configure bespoke systems, in a manner analogous to the Custom System on Chip proposition offered in the electronics sector. The company is on a mission to provide scientists with novel applications to innovate, develop, and run biological workflows "at the speed of thought." *Drug Development & Delivery* recently interviewed Richard Vellacott, Chief Executive Officer of BiologIC Technologies, to find out more about the technology and its applications in the future of medicine and wider fields of synthetic biology.

Q: Can you give us an overview about the company and tell us how and why BiologIC Technologies was started?

A: Humanity faces three enormous challenges: feeding 9.8 billion people by 2050, mitigating climate change, and mitigating the existential threat of disease. But we now also have a once-in-a-generation opportunity to solve these challenges. We are at the start of a bio-revolution in which 60% of the world's physical inputs could be made using "biology-by-design," including new foods, materials, fuels, and medicines that will be significantly more powerful and more sustainable.

BiologIC's pioneering vision, inspired by insights from the semiconductor industry, is to become the enabling architecture that drives this bio-revolution. Our breakthrough digital hardware allows rapid development and execution of novel, high-value, and high-volume biological workflows in powerful, affordable, and highly integrated application-specific 3D bioprocessing units. Our architectures are

being developed to advance research, diagnostics, and therapies, such as new vaccines, and will power the next generation of synthetic biology at scale.

Q: Could you tell our readers about your grand vision?

A: Our grand vision at BiologIC – which is deliberately bold and disruptive – is to build a powerful new digital hardware platform that can run many different protocols and help scientists produce "biology by design" – that is, make it much easier to produce whatever biology they want, whenever they want it. This approach of biology by design will enable much more insightful, reproducible, and scalable discovery and development of new therapies.

Why is BiologIC's approach important? Well, if you can picture the old photos of mainframe computers in the 1950s – big, complicated machines that needed a lot of expertise to run and were not very versatile – that's how we see biology labs operate today. They are big labs with specialist but difficult-to-use robots and poorly integrated instruments that stifle the creativity and productivity of highly trained scientists and constrain the pace of innovation.

We are building a system to fast forward biology into a much more creative, collaborative, and productive future and unleash the biological creativity of brilliant scientists. They might use the BiologIC system to discover new biology, manufacture vaccines or other treatments, or make the next generation of foods and biofuels that reduce climate change.

Q: Could you tell our readers about BiologIC's proprietary platform technology and how it was developed?

A: The core of our product is our flagship three-dimensional (3D) bioprocessing unit. It's about the size and shape of a Rubik's Cube and, if you look inside this cube, it contains complex 3D fluidic circuitry that performs all the functions of a biological laboratory. This "lab-in-a-box" plugs into a universal instrument, in the same way computer chips plug into a motherboard, and gives a powerful system that lets you program biology. We've drawn a lot of inspiration from how silicon chips are designed.

BiologIC exploits additive manufacturing and what's really exciting about it is that – for the first time – this enables "digital hardware," with all the design information held on a computer. This means the hardware design can be developed and rolled out very rapidly, in the same manner as software updates. Our system is designed to speed up work in laboratories on everything from new vaccines to fight coronavirus or lab-grown food to more environmentally friendly biofuels that will have a big impact on the future of global challenges related to health, climate change, energy, and so on.

Q: Can you tell us more about your intended markets and applications?

A: Our main applications are in synthetic biology – designing biology to solve some of the world's biggest challenges in food, fuel, and medicine. Ever since the industrial revolution, we have made incredible progress, but it is taking a heavy toll on climate change and environmental sustainability – and only providing very limited access to incredible new medicines, such as the latest vaccines, and cell and gene therapies. The synthetic biology future will be about solving these global challenges through more efficient food production, greener biofuels, and more accessible precision medicines.

This is where BiologIC comes in. We are helping to enable the next wave of synthetic biology through powerful new ways to integrate and operate biological processes that are capable of producing biology by design at any scale. In much the same way mainframe computers have reduced in size to laptops, tablets, and smartphones, we are creating a lab within a Rubik's Cube-size unit. Modern laboratories are often essentially collections of very sophisticated but poorly connected machines, with scientists employed to perform mindless tasks rather than engaged in mindful creativity. What we are trying to do is miniaturise the lab and let the scientists do what they are most interested in – collaborate and break new ground in science.

Q: Can you provide an update on your development status and how COVID-19 has affected your business?

A: COVID-19 has underlined the existential importance of biology – it impacts everybody on the planet every second of every day. COVID-19 also provides a once-in-a-generation opportunity to rapidly accelerate the major trends that had already been emerging and to shift to fundamentally new paradigms – for example, sustainable new solutions in food production, energy generation, and accessibility to precision medicines. The pandemic has highlighted in stark terms where our classical approaches fall short and has provided a rare window of opportunity for disruptive innovation.

BiologIC is uniquely placed to enable these major global vectors and create significant disruptive value through powerful new applications of synthetic biology. Our technology gives us

the ability to integrate many multidisciplinary capabilities in powerful new ways that allow us to take a holistic approach in unlocking the power of biology. For example, our approach enables dynamically adaptive and highly integrated new workflows, the ability to operate artificial intelligence and machine learning directly on the biology, and the ability to rapidly scale out from the research lab to the patient or consumer. In short, our digital hardware allows us to put the biology first.

In precision medicine, for example, because we integrate in-line metrology into our system, we can monitor the performance of the biology and use this information to adapt the workflow on a real-time basis. Furthermore, we can exploit a benefit of additive manufacturing – that "complexity is free" – giving us the ability to parallelise many workflows. These technical features provide many direct benefits, including in-line quality control of therapies, efficient use of expensive reagents, more effective selection, engineering and expansion protocols, greater throughput and so on.

We are fortunate that our proprietary digital toolchain has meant we have not suffered any significant disruption from the pandemic, and our product development continues to progress very rapidly. We have been able to build exciting new partnering opportunities with disruptive pioneers to develop solutions from proof-of-concept to commercial products, and we are building a world-leading network of collaborators across academic, biotech, pharma, and technology communities to develop the powerful new biological systems of the future.

Q: What are the unique features and advantages of your business model?

A: We like to refer to our platform as "physical firmware." Because our hardware designs are digital, they can be evolved and iterated very rapidly. In fact, the rapid but precise approach enabled by our proprietary digital toolchain aligns particularly well with synthetic biology's pioneering mindset. Synthetic biology adopts an engineering approach to biology, whereby it is treated as a complex system that can be analysed into predictable – or at least highly characterized – components. In the field of medicine, this synbio engineering approach is being used to develop sophisticated new precision therapies that might incorporate, for example, multiple gene-editing events.

Development of synthetic biology products is predicated on a clearly defined design-build-test-learn cycle to explore and deploy these constituent biological parts. However, using classical approaches, this cycle is relatively slow, poorly integrated, and expensive – and suffers from low throughput. Because BiologIC can integrate these workflows in new ways and, moreover, iterate the hardware as rapidly as the biology, scientists can explore a much greater experimental space with high-quality characterization data, at greater throughput and attractive economics.

This approach also allows our customers to "scale out" their research into manufacturing rather than undertake a high-risk endeavor to scale up the biology, allowing them to retain much more of the value of their bioproduct as it is commercialized. Unlike classical manufacturing, our approach also enables what is known as "mass customization" in that our fabrication process is agnostic as to whether we produce thousands of standard units or thousands of custom units. This is of great benefit where customers combine a number of standard lab protocols with certain proprietary processing steps, meaning we can truly enable the hardware to be optimized around the biology.

This approach also allows bioproduction to be located wherever is most appropriate as the particular therapy dictates. As we transition from the blockbuster therapy model to the latest niche-buster precision medicines – where each therapy is produced as a discrete batch – there is a strong argument for greater decentralization of manufacturing capability. Our response to this is that the patient dynamics and specific treatment regime should dictate the location and scale of bioproduction – our intention is to enable this bioproduction anywhere in the continuum of centralized or decentralized locations.

Q: Can you tell us more about what we can expect from BiologIC in the future?

A: If I were to make a prediction, it is that the next big global technology company will be a biological technology company. There are so many clear and pressing needs for new solutions to global problems, and many of the solutions lie in synthetic biology.

The world can't wait 10 or 20 years for classical technologies and approaches to make a difference. We imagine a future where scientists are free to do what they do best, which is work together to understand biology, develop new treatments, and produce new foods and fuels that make a difference to the biggest global problems. And we hope BiologIC will play an important role in that future by driving new biological capabilities that are orders of magnitude more powerful than they are today. ◆

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Special Feature

Outsourcing Analytical Testing: Innovative Drugs Spike Demand for Advanced Analysis

By: Cindy H. Dubin, Contributor

The global pharmaceutical analytical testing outsourcing market was estimated at $6.1 billion in 2019 and is anticipated to register a CAGR of 8.3% through 2027, according to Grand View Research, Inc.[1] Increasing demand for analytical drugs, biosimilars, and biopharmaceuticals are contributing to market growth. Other factors such as increasing investments in R&D for pharmaceuticals, rising demand for product safety and quality, and changing regulations for *in vivo* and *in vitro* tests are also expected to drive the demand for pharmaceutical analytical testing outsourcing services. Additionally, the development of combination products, biosimilars, and other innovative medicines has led to an increase in demand for specific types of pharmaceutical analytical tests, such as bioanalytical testing, method development and validation, active pharmaceutical ingredient testing, and stability testing.

The annual *Drug Development & Delivery* report asked some of the key analytical testing providers to describe their offerings in these areas and what advanced analytical testing techniques they can offer to pharma clients.

Ajinomoto Bio-Pharma Services: Customizing Phase-Appropriate Analytical Programs

Advanced analytical testing techniques are rapidly gaining significant interest from pharma and the CDMOs that support them. The more data an innovator company has on their molecule of interest, the better prepared they and their partners are for characterization, process development, manufacturing, and quality control. Additionally, they are then well-equipped to present comprehensive data packages for submission to the FDA, which better positions pharma companies to pass regulatory scrutiny.

Ajinomoto Bio-Pharma Services offers a variety of biophysical characterization and support capabilities, ranging from compendial methods such as pH and osmolality to more in-depth analyses that probe deeper into a protein's makeup. Some of these assays include peptide mapping for a molecular fingerprint, circular dichroism for secondary structure, and size exclusion chromatography with multi-angle light scattering for first principle molecular weight and radius measurements.

In addition to compendial method testing, Aji Bio-Pharma has a wide suite of analytical instrumentation to meet the needs of large-molecule clients. Separation and quantification of impurities is of high importance. Aji Bio-Pharma is equipped with HPLC and field flow fractionation capabilities, along with downstream UV, CAD, mass spectrometry, light scattering, and refractive index detection for further characterization after separation. Alternative separation is also available via capillary electrophoresis, capillary isoelectric focusing, and traditional SDS-PAGE gels with Western blotting as desired.

Aji Bio-Pharma's scientists develop and optimize analytical methods to the specific molecule needs.

Characterization of particles is also of critical importance, as the number and size of particles in a given formulation needs to minimized, says William Wittbold, Director of Analytical Technologies, Ajinomoto Bio-Pharma Services. The company offers particle size measurements in the submicron range via dynamic light scattering, with laser diffraction and micro-flow imaging options for particles larger than one micron.

"Recently, we worked with a client who needed to use our full suite of analytical tools, from initial characterization to full development of in-process and release assays," Mr. Wittbold explains. "We worked closely with our Process Science team, which was scaling up production of the client's molecule, providing immediate feedback on protein concentration and impurities using several HPLC techniques. Using this information, the team was able to adjust subsequent runs to help increase yield and purity. Concurrently, we were able to refine the analytical methods for this molecule, allowing us to promptly validate the methods and transfer them to the QC department."

Alcami Corp.: Demonstrate Control Over Biologics Manufacturing

Analytical testing of biologics presents unique challenges relative to small-molecule APIs and drug products. Manufacturing biologics using cellular systems results in a mixture of molecules from the expression of the biologic within the cells. This mixture makes it critical to demonstrate control over the manufacturing process. As a result of the size and complexity of biologics, multiple methods are required to detect the different types of potential in-process and degradation products. Control over the process can be demonstrated using both chromatographic and electrophoretic tech-

niques as well as assays demonstrating that the desired activity of the biologic is maintained.

William Boomershine, PhD, Senior Manager, Biologics, Alcami, explains Alcami's chromatographic/electrophoretic techniques, such as in the case of charge state variants, which can arise during the fermentation process in the form of various glycans containing differing sialic acids. Charge state variants can also arise as degradation products on stability. Deamidation of aspartic acid or glutamic acid residues to yield asparagine or glutamine residues change the overall charge of the protein. Charge state variants can be separated chromatographically using ion-exchange chromatography (IEX). The decision to use cation-exchange or anion-exchange chromatography will depend on the isoelectric point of the protein and the overall charge of the protein in the formulation buffer. Charge state variants can also be separated using electrophoresis. Traditional iso-electric focusing and capillary iso-electric focusing can provide an orthogonal method to IEX for separation of charge state variants.

Dr. Boomershine goes on to explain how molecular weight variants can be in-process impurities formed during the purification or refolding steps of drug substance manufacturing, and can be degradation products, forming in the drug product on stability. Size exclusion chromatography can monitor both dimers and higher order aggregates, as well as smaller impurities in buffers that can closely mimic physiological buffers. Electrophoresis – both traditional SDS-PAGE and capillary – can separate impurities based on molecular weight. Non-reduced SDS is utilized to monitor molecular weight variants that use disulfide bonds to form dimers and other higher order aggregates while reduced SDS can detect molecular weight variants of the light and heavy chains from monoclonal antibodies.

"While the above chromatographic and electrophoretic techniques can be used to look at charge state and molecular weight variants of the biologic as a whole, these techniques may not easily see specific, individual changes that can impact activity," he says.

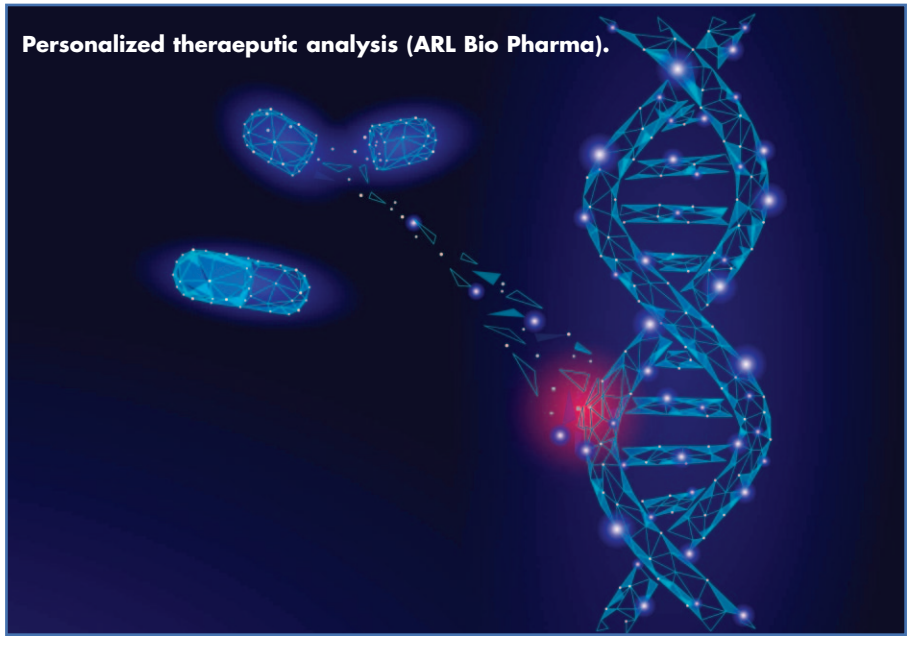
Detecting and quantitating local changes require techniques with higher resolution, such as a peptide map. The individual peptides from a peptide map can be more easily separated from each other using reversed-phase HPLC. "Chromatography for a peptide map can be optimized to target the separation and quantitation of a specific process impurity or degradation product, such as methionine oxidation, N-terminal variants, or deamidation of a specific residue," he says.

ARL Bio Pharma: Test Services for Therapeutics

ARL Bio Pharma is a contract laboratory that provides analytical and microbiological testing to pharmaceutical companies and research scientists. Its laboratory provides test services for all phases of the product lifecycle following USP, FDA, and ICH guidelines. ARL's approach to industry quality requirements, analytical systems, and data integrity provides the scientific results needed to launch small molecules, biologics, protein therapeutics, and cell and gene therapies to market.

"ARL validates analytical methods based on ICH, USP, cGMP guidelines, and high-quality industry practices," says Thomas C. Kupiec, PhD, President and CEO, ARL Bio Pharma."

ARL also works with pharmaceutical companies to test for the presence of residual host cell proteins (HCPs) left in a drug or therapeutic protein



Personalized theraeputic analysis (ARL Bio Pharma).

following purification. Residual HCPs have the potential to affect product quality, safety, and efficacy. "It is important that product purification processes are optimized to consistently remove HCPs to make the product as pure as possible," says Dr. Kupiec.

ARL provides product testing to ensure drugs maintain the same product characteristics throughout all phases of the product lifecycle. Analytical and microbiological testing services include: *E. Coli* and CHO residual DNA quantification, human residual DNA quantification, protein aggregation, protein-size and charge variant, stability studies, method development/validation, USP monograph testing, and more.

Ascendia Pharmaceuticals: Analytical Services Support Formulation Development

Ascendia Pharmaceuticals strives to be on the forefront of acquiring new technologies and at this point offers LC-MS, HPLC-CAD (Corona Aerosol Detection), and HPLC-ECD (Electrochemical Detection) testing services in-house. The new highly sensitive CAD detector has universal application and has advantage over traditional detection techniques for compounds that lack chromophores, says Muhammad Asif, PhD, Executive Director, Analytical R&D and Quality Control, Ascendia Pharmaceuticals.

Ascendia also offers the ICP-MS analysis service through one of its partners. Due to heightened concern about metal ions safety, the highly sensitive ICP analysis makes tighter controls possible. "ICP-MS stretched the lower limits for innocuous metal ions about two decades ago and advances in technology have made it feasible to gain a better understanding of metabolic pathways for drug candidates," says Dr. Asif.

Wenjiao Song, PhD, Senior Scientist at Ascendia Pharmaceuticals, is analyzing a drug product for potency and control of impurities using an ultrasensitive CAD (Charge Aerosol detector). The API used in this product does not have any chromophores and cannot be analyzed using UV/Vis detection. The Ultrasensitive CAD detector that is designed for use with uHPLC systems is coupled with a UPLC system that allows quick and sensitive analyses.

The next step, he says, is to develop methodologies and design experiments that *in vitro* testing can align with, and predict, *in vivo* behavior of a drug moiety and its metabolites. "The new FDA guidelines provide a list of recommended studies that make it easier for large and small pharmaceutical companies to help design their experiments," he says.

Ascendia also has a strong analytical support mechanism in place for API manufacturers, providing impurity identification service and method development and validation for final drug substances, intermediates, and in-process controls. "The in-process controls ensure that a mistake is caught before a lot of time and funds are invested to finish the manufacturing cycle," he says. "These controls also help establish Quality by Design parameters to build quality into the manufacturing process, resulting in a better and consistently high purity drug substance."

Aztech Sciences Inc.: Addressing Complexity in Drug Development

Complex development has been gaining interest in the pharmaceutical industry, therefore specialized analytical techniques are often needed to address this complexity. These specialized analytical techniques include pre- and post-column derivatization for drug materials that cannot be detected by ultraviolet-visible (UV-Vis) light or photodiode array chromatography, says Alvin Persad, PhD, President, Aztech Sciences Inc. "Performing these derivatization methods allows drug materials to bond with a chromophore molecule that will be detected by UV-Vis chromatography."

Additional chromatography approaches used for non-chromophore drug materials are U/HPLC combined with refractive index (RI) that does not depend on light-absorbing molecules. Another analytical technique includes

Preparation of a topical cream in Aztech Sciences Inc.'s clean room followed by sample analysis using HPLC refractive index.

gas chromatography with flame ionization detector for low-level residual solvents in the parts per million.

Dr. Persad says there have been increased requests for size exclusion and gel permeation chromatography (SEC, GPC). "These analytical methods are more complex and higher cost due to standards, sample preparation, instrumentation set up, and longer elution time," he says. "SEC/GPC in combination with RI and multi-angle light scattering detectors are used to analyze water soluble or non-water soluble polymers and peptides characterization, size distribution, and molar mass."

In addition to analytical development and testing solutions, Aztech Sciences offers API development services for form identification and selection. This includes salt screening, co-crystal polymorphic/amorphous solid forms, high-energy co-precipitates, and API-polymeric drug solid solutions. "Whether preclinical or life cycle management, our goal is to identify leads and candidates suitable for the appropriate phase of drug development," says Dr. Persad.

Pion Inc.: Biorelevant Drug Testing Services

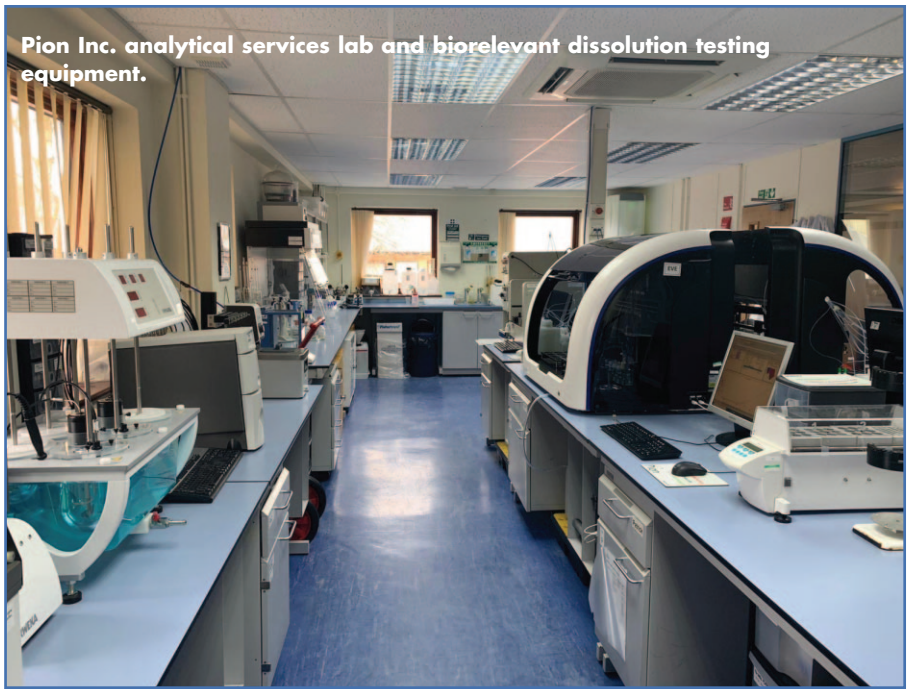
Currently, there is a growing demand for *in vitro* tests on drug compound and formulation behavior that can be linked to *in vivo* behavior. This has necessitated the use of biorelevant conditions and media that more closely represent the environment that a drug experiences in the human body, for example, through the use of biorelevant dissolution media, e.g., Fasted State Simulated Intestinal Fluid (FaSSIF) or subcutaneous extracellular matrix components.

Due to the complex interplay between solubility and permeability, there are many cases where dissolution experiments alone cannot correctly predict the *in vivo* response to drug products, says Karl Box, CSO Europe, Pion Inc. Simultaneously, measuring concentration on both sides of a bio-mimetic membrane improves the assessment of the absorption potential and provides more realistic IVIVC modeling.

Pion has introduced the addition of a stirred absorption chamber to the USP I/II apparatus that functions as a 'receiver' chamber with the MacroFLUX™ and BioFLUX™ systems. The USP vessel serves as a "donor" compartment and provides the media volume needed to test finished dosage forms under sink conditions. The donor media is selected to mimic the absorption site along the gastrointestinal tract, and the Acceptor Sink Buffer (pH of 7.4) used in the receiver vessel mimics blood chemistry. FLUX systems are also available for the microDISS Profiler™ using media volumes of just 15mL for the donor and receiver chambers and for the miniDISS system, which has a biorelevant 250mL volume vessel. "This offers a great advantage when outsourcing testing services when customers have small sample quantities available," he says.

A subcutaneous injection site simulator (Scissor) is an instrument developed by Pion that mimics the chemical, physical, and physiological properties of the subcutaneous tissue. It supports analytical techniques for monitoring post-injection stability and diffusional properties of subcutaneously administered biopharmaceuticals. "Using Scissor, scientists can evaluate formulation performance of subcutaneously administered biopharmaceuticals without performing *in vivo* tests using animals," says Mr. Box. "The instrument has shown good applicability for the development of monoclonal antibody and insulin formulations."

Pion works with pharma companies and CROs to facilitate drug discovery and development through its Analytical Services Team for assays, data analysis, and interpretation. According to Mr. Box: "Once your outsourcing needs are completed and



Pion Inc. analytical services lab and biorelevant dissolution testing equipment.

you are ready to move to the next stage of development in your lab, you have the option of utilizing the same instruments your studies were performed with and our scientists will continue to partner with you long after your samples have left our lab."

Recipharm: Identifying Impurities Using Advanced Analytics

Market demand for the fixed dose combinations (FDCs) used in treatment of fever and common cold rose significantly during the course of the COVID-19 outbreak. In response, a number of Recipharm's customers needed to update their analytical methodologies to ensure they are workable throughout the lifecycle of the drug product.

One customer approached Recipharm to support it in developing a single chromatographic release method to determine product quality and purity – a challenge, because FDCs may not have similar molecular weight or polarity. Ramesh Jagadeesan, Assistant Vice President at Recipharm, explains that the customer had five different methods to determine purity and impurity profiles. Recipharm worked to simplify this by developing two different methods capable of delivering a high resolution between the impurities and the active components. These were found to be accurate, precise, and robust, and were validated as per current ICH guidelines in significantly less time. As a result, the contract provider was able to fill the drug product in the tight timeframe required to get approval and bring to market.

Increased demand for advanced analytical techniques, such as LC-MS, LC-MS-MS, GC-MS, FT-IR-TGA, are proving powerful in identifying impurities. Mr. Jagadeesan explains that chromatographic methods, coupled with mass spectroscopy, is becoming more widely used for investigating the co-elution of peaks and peak purity. For example, LC-MS-MS techniques are powerful in the identification and characterization of impurities, as well as monitoring impurity profiles during the development stage.

"The recent recall of pharmaceutical drug products, including Valsartan, Losartan, and Irbesartan put the regulatory spotlight on nitrosamine impurities in drug products," he says. "LC-MS-MS based methods provided by agencies can help to ensure that drug products are sufficiently tested to ensure that absence of nitrosamine impurities."

Finally, there is always a risk that impurities will be present in drug substances and drug products, and, in accordance with guidelines, these must be identified to remove contaminated batches from the supply chain. In addition to the suggestion of molecular structures impurity based on the HRMS/MS and 13C and 2D NMR analyses results, Recipharm offers confirmation of the proposed structure by comparative UPLC-HRMS/MS analysis, employing the synthesized reference material and subsequent *in silico* toxicology.

Recipharm also offers method development and qualification for small molecules. The company is embarking on a growing number of projects to develop bioanalytical methods for large molecules, such as oligonucleotides, ADCs, and proteins. The company offers bioanalysis of blood, plasma, cell, and tissue samples from individual compound testing to high throughput screening for multiple compounds. Blood/plasma stability testing plays an important role in drug discovery and development.

"Recipharm's protein binding assays help customers to determine which compounds bind to blood pro-

teins," says Mr. Jagadeesan. "The degree of binding might affect a drug's efficacy, making it vital to understand this behavior as early in the project as possible."

Analytical scientist at SGS Life Sciences in Lincolnshire, IL.

SGS: Assuring APIs Meet Quality Standards

To cut cost of API production, many small- and medium-sized pharmaceutical companies choose to outsource API manufacturing overseas. To confirm that APIs comply with USA quality standards, those APIs should be tested independently. SGS labs comply with cGMP practices and provide a variety of analytical services to test APIs, excipients, finished products, and medical devices.

"Our labs have successfully verified dozens of monographs for known APIs per USP and Eur.Pharm. pharmacopoeias," says Natalia Belikova, PhD, Analytical Services Director, SGS. "We also have experience in compendial testing per Japanese Pharmacopoeia and Chinese Pharmacopoeia. In addition to the compendial testing, we offer development and validation methods to support release testing."

SGS analytical techniques include simple wet chemistry like loss on drying, residual on ignition, bulk density, and titrations to more complicated wet chemistry testing like identification tests by fourier transformation infrared, X-Ray Powder Diffraction, melting point by differential scanning calorimetry, instrumentational color testing, particle size distribution by laser diffraction, and heavy metal testing by inductively coupled plasma technology. SGS also offers chromatography techniques with ultraviolet/visible light, refractive index, fluorescence, charged aerosol detector, evaporative light scattering detector, and conductivity detectors.

"More and more drugs on the market, such as those for combinational therapies, have multiple APIs to treat different symptoms or act in different ways," says Dr. Belikova. "In that case, we can develop and validate chromatography methods that will separate both actives in the same run and potentially known impurities for both actives will be evaluated on case-by-case basis."

For newly discovered/developed APIs not yet listed in the available compendia, SGS performs forced degradation studies. She says: "By developing stability-indicating assay methods, we have assurance that any possible degradants are chromatographically separated from the main API peak and do not contribute to the overall label claim for the assay."

SGS has successfully worked to assist in bringing known and new APIs to market and provide assurance that APIs are of acceptable quality and can be used in further manufacturing processes to create final drug products, claims Dr. Belikova.

Triclinic Labs, Inc.: Solid-State Testing of Small Molecules

Triclinic Labs offer advanced solid-state analytical testing techniques, which include hyphenated techniques such as thermogravimetry-infrared spectroscopy, IR-microscopy, Raman-microscopy, and turbidity-low frequency Raman spectroscopy. "The real advantage lies in the fact that we offer a multi-disciplinary testing approach by utilizing our full suite of solid-state analytical techniques because a single technique or a single hyphenated technique alone often does not provide a complete answer to various problems that arise during drug development," says Triclinic's Chief Scientific Officer Aeri Park, PhD. "Our analytical techniques allow us to probe the physical and chemical properties, identity, quantity, stability, and purity of pharmaceutical drug substances and drug products, and

other materials."

According to Dr. Park, one of the fastest growing areas of *in vitro* testing is cGMP solid state analytical testing. More companies are developing formulations containing amorphous drugs or amorphous solid dispersions to improve bioavailability of the drugs. In response, Triclinic has developed a propriety technology to predict the physical stability of amorphous formulations to help clients select the best formulations quickly without time-consuming full stability studies. In addition, Triclinic develops and validates highly sensitive solid-state analytical methods to detect crystalline forms in amorphous formulations in order to meet the regulatory requirements for amorphous drug formulations.

In one situation, Time-Temperature-Transformation (TTT) studies performed in Triclinic's labs showed that the physical stability of a client's amorphous formulation was predicted to be greater than hundreds of years at ambient storage conditions. Simon Bates, PhD, Head of the Materials Modeling Group at Triclinic, explains that when the product crystallized during ambient storage, it was postulated that there was nothing wrong with the formulation but that there was heterogeneous nucleation in the system.

"Because the amorphous formulation was manufactured by hot melt extrusion, Triclinic recommended that the client increase the hot melt extrusion temperature slightly (based on the melting point of the API and interconversion studies) to remove any nucleation seeds," Dr. Bates says. "The client increased the hot melt temperature by 5°C, which was allowed within their processing guidelines. This resulted in a stable formulation. The resulting product was predicted to be stable over millennia."

Upon further investigation, the failed product was found to be from a scale-up process at smaller scale compared to the commercial hot melt extrusion process. At the same temperature, the larger process was not as effective in removing all crystalline seeds as seen in the smaller scale. Says Dr. Bates: "Without the TTT information, the client would not have been able to resolve the issue easily." ◆

Reference

1. Pharmaceutical Analytical Testing Outsourcing Market Size, Share & Trends Analysis Report By Service (Bioanalytical, Stability, Method Development & Validation), By Region, And Segment Forecasts, 2020 – 2027), February 2020, https://www.grandviewresearch.com/industry-analysis/pharmaceutical-analytical-testing-outsourcing-market.

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FORMULATION DEVELOPMENT

The Role of Excipient Selection in the Development of Orally Disintegrating Tablets

By: Torkel Gren, PhD

INTRODUCTION

Orally disintegrating tablets (ODTs) offer multiple benefits to patients that have difficulty swallowing medicines in tablet or capsule form. They can be swallowed without the need for water, making them highly convenient for taking "on the go". The ability of the active ingredient to rapidly dissolve in the mouth also means they provide a faster onset of action in comparison to other delivery formulations that can be highly useful for products that are required to work quickly such as pain relief medications.

Excipients play an incredibly important role in all formulation development; however, they are even more crucial in ODTs as they can affect multiple characteristics, including taste, odor, and mouthfeel. The following looks at the benefits that orally disintegrating products can bring to patients and developers and assesses the impact that excipient selection can have on the development of successful products.

BENEFITS FOR PATIENTS & DEVELOPERS

There are many patients who struggle to consume standard tablet dosage forms. It can be difficult to persuade young children to swallow them, and they could pose a choking hazard. Adults with a swallowing disorder (dysphagia) or Parkinson's disease, as well as elderly patients, may also struggle to administer medicines in this form. ODTs present an alternative option that are more easily swallowed and reduce the risk of drug-induced oesophagitis, which can occur when a tablet is caught in the oesophagus

FIGURE 1

and dissolves while remaining in contact with the oesophagus lining. As well as being pleasant tasting, they are easy and convenient to take, and are supplied in a single dose, which removes any need for measuring prior to administration.

ODTs present an ideal platform for active ingredients for the treatment of pain, migraine, allergies, diarrhoea, Parkinson's disease, insomnia, travel-related sickness, and psychiatric incidents amongst other indications in which rapid dosing and absorption are required. These formulations are also ideal for dialysis patients that need to reduce their daily liquid intake. As well as the patient groups already identified, a significant proportion of the general population finds swallowing tablets difficult, and a disintegrating product can greatly increase compliance. For active patients, they present a useful strategy to take a drug in situations when water is not available, for example during travel or in meetings.

FIGURE 2

From a development perspective, orally disintegrating medicines may offer excellent bioavailability as they are dissolved and dispersed in the mouth. If the drug is absorbed within the oral cavity rather than digested, it also avoids first pass of the liver. This pre-gastric absorption can reduce side-effects caused by metabolites formed in liver enzymes.

Depending on need and indication, ODTs can offer the option of immediate active pharmaceutical ingredient (API) release, suitable for fast-acting painkillers. They also provide a user-friendly dosage form for many compounds, including poorly soluble APIs. They can also be formulated as fixed dose combinations (FDCs), combining two or more drugs in a single dosage form to increase patient compliance and experience.

MANUFACTURING TECHNIQUES

Orally disintegrating products are all tablets in the sense that they have solid bodies. While some products are manufactured using techniques, including freeze drying, moulding, cotton candy process, and mass extrusion, they can also be manufactured via conventional tabletting technologies, such as direct compression. More advanced technologies are generally patent protected and should only be considered if a less-complex technology cannot offer the necessary product properties.

Most frequently, a conventional compressed tablet technology will be used due to better cost efficiency and a reduced risk of development delays. In addition, this conventional technology offers a better mechanical stability and more packaging options than special techniques, such as freeze drying and the cotton candy process.

The process of scaling-up these techniques for commercial manufacture is also more straightforward than other technologies. Usually, a high-production speed can be achieved. By modifying well-characterized process parameters and varying excipients, a wide spectrum of characteristics can also be achieved via this method in terms of disintegration, dissolution, and mouthfeel.

EXCIPIENT SELECTION

The excipients used for orally disintegrating products can be divided into two groups. These include the usual excipient types that are always required for the development of tablets, such as disintegrates, binders, fillers, and lubricants. Filler selection is important as it is often present in significant quantities and will heavily impact final taste and mouthfeel. Lubricant is even more crucial than in standard tablets as sticking problems are widely associated with these products.

The second group includes excipients that are not normally found in conventional tablets and capsules, such as high-intensity sweeteners (aspartame, acesulfame K, and sucralose), pH modifiers, and flavoring agents. All of these are well established and widely accepted ingredients in pharmaceutical formulations.

A product's taste should be developed in line with the tastes of the intended patient population. For this reason, it is important that a development team works in close collaboration with their company's marketing professionals when selecting the flavoring agents. Sugar alcohols and mannitol are incredibly useful in orally dis-

FIGURE 3

integrating products due to the contribution of sweetness and a pleasant mouthfeel, as well as favorable technical properties.

Today, the industry is seeing the launch of new and more advanced excipients, with many bringing advantageous properties. These excipients do, however, come hand in hand with higher costs, which will need to be balanced against the benefits that they bring. For example, a more expensive excipient may allow a developer to avoid complex process steps and, therefore, can contribute to reductions in manufacturing costs.

CHALLENGES IN EXCIPIENT SELECTION

In the development of orally disintegrating products, the type and amount of excipient used needs to be carefully identified to achieve the right balance between several technical characteristics. These include stability, dose homogeneity, and dissolution rate. Not less important but more difficult to measure are flavor and mouthfeel. Here, it can be very useful to work with taste panels to ensure that the new product will be appealing to the intended patient population. The use of a Quality-by-Design (QbD) approach and multivariate methods may be helpful. This will result in a better understanding of the optimal process parameters and the robustness of the process. This will also offer the advantages of a more stable process with higher yield and less risk of rejected batches.

FINAL THOUGHT

Orally disintegrating products are gaining increasing attention from the industry by offering distinct advantages in the development of both prescription and over-the-counter medicines. Many studies have already compared these dosage forms with standard tablet forms in vitro and in vivo and have found that orally disintegrating products offer superior compliance and drug solubility. Pre-gastric absorption can also have considerable advantages in terms of both a faster onset of action and a reduction of side-effects.

Successful development of these products requires careful selection of the right excipients. Excipient manufacturers can offer valuable information and support on their products, and wise developers will look to use this insight to their advantage. By taking the time to fully understand how each excipient works in their formulation, manufacturers can ensure they achieve the best selection for their product. ◆

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BIOGRAPHY

Dr. Torkel Glen is Senior Director, Science & Technology Officer at Recipharm AB. He earned degrees in Pharmacy and Business Administration as well a PhD in Pharmaceutics (Uppsala University). He has worked in the pharmaceutical industry since 1988, and has held a number of scientist and manager positions in Europe and the US. He was lead formulator and co-inventor of Detrol OD/Detrusitol SR. Dr. Glen is Vice Chairman of the Board of the Swedish Pharmaceutical Society.

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Lindsay A. Rosenwald, MD
Chairman, President & CEO
Fortress Biotech

Fortress Biotech, Inc.: Looking for the Muffin Tops

Fortress Biotech, Inc. doesn't create new molecules or develop new medicines. Fortress Biotech looks for programs – drug development candidates – that already have very good human data, acquires those assets, finances the rest of their development, and builds companies around them to get them on the market.

The biopharmaceutical company, which ranked number 10 in Deloitte's 2019 Technology Fast 500™, has five marketed prescription pharmaceutical products and over 25 programs in development, at its majority-owned and majority-controlled partners and at partners it founded and in which it holds significant minority ownership positions. Such product candidates span six large-market therapeutic areas, including oncology, rare diseases, and gene therapy. Fortress Biotech's net revenue for year-end 2019 totaled $36.6 million.

Lindsay A. Rosenwald, MD, is Chairman, President, and CEO of Fortress Biotech. He earned a degree in finance and economics from Penn State University, graduated medical school at Temple University, and then found himself on Wall Street just as biotech was emerging as an industry. He decided he wanted to be in the business of acquiring clinical-stage programs and building companies around those assets. Several years before taking control of what became Fortress Biotech, he retired and became a passive investor. Then in 2014, Dr. Rosenwald realized he missed searching out those programs and assumed leadership of Fortress Biotech and has been building the business ever since.

Dr. Rosenwald recently spoke with *Drug Development & Delivery* magazine about how his medical and financial knowledge come together to find successful drug candidates, the Fortress Biotech partnership model, and the inefficiencies he sees in the biotech industry.

Q: Please describe Fortress Biotech's business model and why that model is unique.

A: It's extremely unique. Most biotech companies are built around either a platform technology or just focus on products. Biotechs are mostly financed by venture capitalists with a 7- to 10-year time horizon. So, when they make an investment in a company, they are already trying to figure out how to get out of it profitably. We are not a platform company. We don't look for platform technologies. We have 11 partner companies – one does happen to be a platform tech company – and the others are single- or multi-product oriented. We mostly focus on clinical-stage medicine. As an MD myself, with mostly MDs and scientists working for me, we understand human biology and pharmacology. We often find drugs that big companies, as well as small, were developing and failed, so the companies gave up on the drugs, yet there was data available to show the drug's viability. We go to that drug company, buy the drug for a few million dollars or less, and plan a quick clinical trial if it's the right indication. If it works, it might be worth hundreds of millions of dollars. We like compounds that already have human data or for which it will be inexpensive to obtain human data. Consider going to a bakery to buy a muffin. Some people just eat the muffin tops. Now bakeries sell muffin tops. We're looking just for the muffin tops, the easy stuff. If it's already in the clinic and already looks like it works, it has been meaningfully de-risked. When we find the asset, we either put it into an existing partner company we control and have a continuing economic interest in, or, if it doesn't fit one of our companies, we'll create a new partner company. These partner companies are a big part of our future. They provide long-term economic gain in exchange for our ability to help run those companies. So, it's a very scalable business. I don't believe anyone else does it this way.

Q: Can you describe the relationship with your partner companies?

A: Wall Street can only focus on one or two lead programs at a single company. So, by setting up separate partner companies for each asset, we get better long-term value. It's very expensive to develop drugs, so setting up partner companies gets capital dedicated for specific product development. We get equity in these partner companies and we get royalties. As the partner companies grow in value, our equity holdings grow. Once they launch their products, we get royalties on those products. It incentivizes us to find really great product opportunities, show them to the partner companies, and, if they want them, we give it to them. Three of our partners are public. The goal is to find more of these assets, create more partner companies, and just keep growing the business that way. It's like building multi-family housing, collecting rent, building more multi-family houses, and renting them. Eventually, you have unbelievable cash flow. Same with us. But instead of multi-family housing, it's multiple partner companies.

Q: Your partner company, Checkpoint Therapeutics, appears to be pursuing a "fast follower" strategy. What does that entail?

A: Fast follower means that we aren't inventing anything new. We went after a big market, but we were not the first ones in the market. There is a technology called checkpoint antibodies. Checkpoints are receptors (PD1 and PDL1). If you can block these receptors, then you can unblind the immune system to the cancer cell. Antibodies bind to the checkpoint and once they bind to the site, the body's immune system sees the cancer cell and kills it. It's becoming the biggest market in cancer therapeutics. It is competitive, and in five years this could be a $65 billion a year market.

This situation is different than our usual business model, which looks for drugs already in clinical trials. In this case, we met with a scientist that created an anti-PDL1 antibody and we set up Checkpoint Therapeutics around the antibody. We own 20% of the company and get a 4.5% royalty and an equity dividend every year of 2.5% of the outstanding shares. So, it's a very important holding to us. We are just finishing enrollment in our pivotal clinical trial of cosibelimab and hope to have the drug on the market by 2023. If we just get 1% of the $65 billion market, that's $650 million in sales. That would make that company worth potentially billions of dollars.

Q: Can you identify a partner situation where Fortress Biotech took little risk but reaped significant benefit?

A: In the case of our partner company Mustang Bio, we aren't followers, we are pioneers. We have a drug for bubble boy disease. One of my team members identified a very sophisticated gene therapy at St. Jude Children's Research Hospital in Memphis. When a baby is born with the disease, doctors take a sample of the bone marrow and send it to the

lab, which then modifies the marrow by injecting a healthy gene to replace the broken gene and puts it back into the baby. In April 2019, Mustang announced the gene therapy for bubble boy disease had restored full immune systems in eight babies suffering from the condition. St. Jude was the pioneer because we didn't take the risk to invent the drug and do the early development. But we did enable St. Jude to move much more quickly towards the market. It is still a substantial investment.

Q: With COVID-19 affecting every aspect of life, can you explain the possibilities that your partner Oncogenuity Inc.'s oligonucleotide platform has for treating coronaviruses?

A: This was the exception to the rule, as we don't usually do platform technology. But, we are risk takers. Several years ago, one of my business development people found this technology at Columbia University as a way to theoretically suppress bad DNA. Sometimes bad genes are inherited. Or a gene spontaneously mutates. That's what cancer is. The mutated gene causes a mutated protein that causes a cell to become malignant and metastatic. The potential Holy Grail in medicine would be to stop the expression of a mutated gene or an inherited bad gene. This is a hot area in life sciences, and there are many ways to approach this. It's called antisense, where you block messenger RNA and prevent the manufacture of bad protein from the bad gene, which in turn prevents the cell from doing bad things. Columbia researchers said they could block the expression at the DNA level. We took an option on it because if it worked in one disease, it could work in many. We don't like to take bets like that on single products because the odds are often against you from an early-stage perspective. In this case, however, we felt if it worked, the payout would be huge because of the potential for other areas beyond cancer such as neurological disorders and even coronaviruses. The company is studying replacement sequences, which could help combat COVID-19 and provide proof-of-concept as a treatment for coronaviruses. These ongoing experiments would validate the technology as a possible treatment for COVID-19, as well as potentially expedite the discovery of treatments for future coronavirus outbreaks. Last year, Columbia presented compelling data so we decided to set up Oncogenuity around the platform. We won't be ready for clinical trials for another 18-24 months, but we are generating data.

Q: With 11 partner companies, which drug candidates are you most excited about and where are they in development?

A: In addition to the work at Mustang Bio, I am excited about a drug called CUTX-101, which is a small molecule for a genetic disorder called Menkes disease, a rare X-linked recessive pediatric disease caused by gene mutations of copper transporter ATP7A. Note that this is not a gene therapy. CUTX-101 is a subcutaneous injectable formulation of Copper Histidinate developed by a professor at Nationwide Children's Hospital. When my team found the drug at National Institutes of Health (NIH), it was in a Phase 3 clinical trial. We licensed the rights from the NIH, and the data look really good. In fact, we recently announced positive topline clinical efficacy results, which demonstrated statistically significant improvement in overall survival for Menkes disease subjects who received early treatment with CUTX-101 when compared to an untreated historical control cohort. It could be a real life-saving drug for the kids affected by Menkes disease. Cyprium Therapeutics, our partner company, is developing CUTX-101.

Q: How did you navigate the sale of Cougar Biotechnology to Johnson & Johnson as the country was coming out of an economic recession?

A: Life science is immune to the vagaries of the economy, so a recession doesn't really impact biotech much. It's a data-driven business. So, in the case of Cougar, there was a small English biotech developing a drug called abiraterone acetate for prostate cancer that showed it could prolong the life of men with metastatic prostate cancer. This was a great compound with really great human data. But there were no patents. The bulk of our competition tends to have bureaucratic tendencies, so if there isn't a patent, or there isn't a long period of exclusivity on the market, they won't look at it. But I know if you can find a drug that has been almost completely de-risked, and it might sell hundreds of millions or more a year, it is a great opportunity. Even if you only get five years of exclusivity and it's an unmet medical need, the product launch can go quickly and there is enormous value. So, we bought the compound for $500,000, got new patents issued, and, after a Phase 2 trial, the data were very compelling. J&J made us an offer we couldn't refuse. The drug is now marketed as Zytiga under J&J's auspices; we sold it for $1 billion, and it became a $4 billion a year drug. When we

sold Cougar, it woke up the stock market to the undervalued nature of biotech.

Q: What are the major upcoming milestones for Fortress Biotech and its partner companies?

A: We expect to begin a rolling submission to file an NDA by the end of this year for CUTX-101 for Menkes disease. We plan to launch four Phase 3 pivotal trials soon for some of our other drugs. And we plan to complete enrollment in our pivotal clinical trial for cosibelimab, the Checkpoint Therapeutics antibody. No company our size could ever have so many milestones so fast without our business model. It would take too much capital and too many people. Our business model lets us take on all these programs because we can keep expanding as long as the assets are really good.

Q: Where do you see Fortress Biotech in the next 5-10 years and where do you see the company making the most impact?

A: Ten years from now, the hope for Fortress Biotech is that we further the development of drugs that save lives, improve lives, and make a great return for our employees, our shareholders, and our partner companies. Our goal is to get lots of great drugs to the market in order to treat disease and alleviate suffering.

This is a noisy market with hundreds of billions spent on R&D annually and lots of things that fall through the cracks without being developed. You can find great drug candidates and pay a small fraction of what their intrinsic value is – if you know how to look for them. This business is about finding strong candidates or creating them, depending on your tolerance for risk, patience, and amount of capital. Fortress Biotech is always looking for talented and driven business development people to find these opportunities under rocks and around the world. ◆

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TURNAROUND CASE STUDY

A Pharma Industry Outsider's Perspective - Turning Around the "ABCDMO" Company

By: Paul Fioravanti, MBA, MPA, CAGS

INTRODUCTION

I'd previously worked for the private equity (PE) firm that owned it on another business experiencing challenges. Prior to working on companies owned by this particular private equity group, I'd worked on more than 50 such assignments, ranging in size from smaller, lower middle market companies owned by founders or families, up to public companies, in a mix of industries.

In the fall of 2018, it would turn out that this PE firm had another business that was failing fast, a pharmaceutical contract development and manufacturing organization (CDMO) that grew rapidly from one production location to eight in just 4 years; but it was a few weeks away from running out of cash when I was asked to join as CEO.

I've never cared about titles. This one came with a significant amount of responsibility, risk, and opportunity. It was in a highly regulated industry that focuses on patients relying on their medicines. I'll call the company ABCDMO.

ABCDMO was simply, a roll-up of several unrelated legacy assets that were divested from big pharma. Unless I was missing something, I saw no apparent synergy in this $350-million global CDMO roll-up business. All I saw was a business struggling under the weight of a variety of challenges, not the least of which was poorly structured asset acquisition deals and teetering on insolvency.

Other challenges included rigid employment and workforce contracts and assurances, financial and operational disconnects in the sites that were acquired, wild spending - including high IT spend, enormous looming cash requirements to fund high payrolls, and balloon and installment payments for acquiring the sites through creatively financed seller notes.

Like an unfortunate healthcare patient, it was bleeding. ABCDMO needed first responders. Those first responders would be our turnaround team and a cadre of key legacy employees who embraced the challenge and the change and who came alive and came to action. Did I have prior experience fixing and turning around companies? Yes. Did I have prior experience in healthcare and other related industries? Yes. Was I willing to outwork everyone to be successful and transform this business? Yes. Did I have prior experience in pharma? Zero!

But it didn't matter. We (ABCDMO) had people. We had

fearful people. Not many of them, but those that were, ran away, terrified. We also had fearless, brilliant, resilient people. Great employees. They just needed to be led toward clearly articulated goals to fix this business. There was no other choice. Right now, you're thinking about the corn-ball cliché, but, no, failure was not an option. We had to reassemble the puzzle and put the right pieces together. Sure, every industry believes it is unique. Every industry bathes in self-adulation. Every industry places disproportionate weight on its traditions and experience. This one wasn't any different, at least up front.

So, we began the transformation. I had the good fortune to work with a team of strong advisors. While the personalities and egos often clashed, in the end, the results were stellar, and it was only through building on the basics of Plan, Organize, Motivate, and Control (POMC) that sound management practice, tireless work, and the ability to humbly admit all I/we didn't know and focus people much smarter than I on all we needed to fix, were some of the ingredients to our success. In this article I'll point out a few letters. A little bit of alphabet soup. This was, after all, the pharma industry, which loves acronyms.

In addition to the POMC - there was one more C – Communicate. I figured out that if I didn't reach out, get out there and communicate and earn the trust and confidence of the customers, the regulators, the employees, the bank, the other stakeholders, I, we, and the turnaround itself, were doomed.

One thing resonated with me above everything else – the P - the Patients. We were all ultimately accountable to them. That was the foundation of our program of change – that we shared with our stakeholders – especially the big pharma companies whose names and brands were on the bottles, boxes, packages, vials, ampules, and pills we produced – that we were unified in the drive for the big S - Sustainability. Here's a little glimpse into the transformation of ABCDMO.

A TWO-SIDED LADDER

When you do turnaround work, interim CEO work, and/or any kind of organizational change, you inevitably find yourself in the midst of a two-sided Ladder of Inference problem. The Ladder of Inference was first put forward by organizational psychologist Chris Argyris and used by Peter Senge in The Fifth Discipline: The Art and Practice of the Learning Organization. The Ladder of Inference describes the thinking process that we go through, usually without realizing it, to get from a fact to a decision or action.[1]

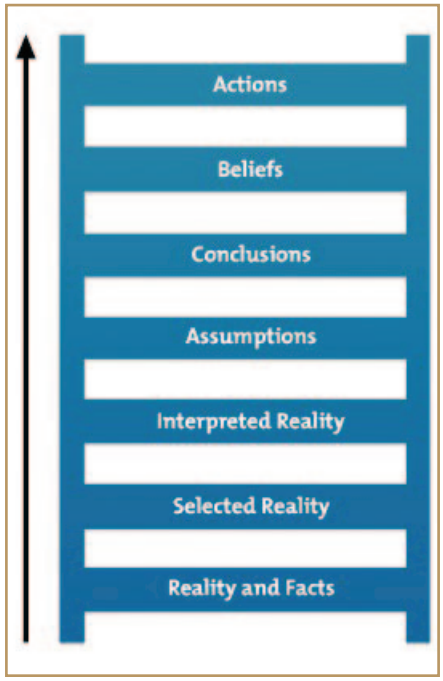
On the one hand, you can easily jump to conclusions and have preconceived notions, as the change agent; on the other side, the industry veterans can quickly dismiss your lack of industry knowledge as a major risk or failure factor, or it just may be a response to their own fears.

Why two sides? Well, you as the change agent view the steps and the sequence of the rungs in the ladder one way, and the other folks see it differently. But that's ok. From either side, success can only come from being rooted in reality. Reality and facts (and factual evidence) are at the base of the ladder. From this point of "safety," where we're closest to the ground, we begin to ascend. As we go up, we must look at facts, isolate our beliefs and prior experience, and draw conclusions based on hard data, and be prepared to take objective actions. That's hard for people to do. Change is difficult. It's human nature to page ahead in the test, to skip scenes while watching Netflix, to wanting to know what happens at the end of a book.

A challenge in the company in question is across sites and geography, "sets" of employees would undoubtedly have preconceived ideas. That is further complicated by what a prior management team (most of whom aren't there anymore) told them, and whether they identified, or disagreed with, those perspectives. Did they know what a plan was? Did they agree with it? It doesn't matter because now they were in the midst of another change – a new CEO and perhaps other new executives, site heads, functional heads, etc.

All of the stakeholders of the CDMO – the bank, lenders, vendors, employees, shareholders, customers, former legacy owners (some of whom are creditors with seller notes) – have wildly varied beliefs, experiences, judgment, and degrees of openness of mind.

The point of The Ladder of Inference is to force objectivity and get consensus to move a team of people forward in unison, to respond to and manage challenges.



Some of the employees thought I was insane. Some thought our entire team was insane. Some didn't understand what we were doing. Some didn't care. Some just left. Some checked out. But most dug in, buckled up, let go, and hung on. And when they first witnessed positive impacts, they realized they didn't have to be fearful.

ABCDMO: LIKE OTHER CDMOS, A VICTIM OF FLAWED ASSUMPTIONS

ABCDMO was one of many companies with business models that worked better in theory than in practice. Why? Flawed assumptions. When big pharma began selling off their large plants, the premise was that some entrepreneurial companies called CDMOs would own the plants, and the former cost centers would magically become vendors overnight.

The reality was that the legacy cultures had high inertia. How do you magically turn a 20- or 25-year employee of some huge global pharma company into an overnight entrepreneur? It's like taking a person who has played hockey for 25 years and asked them to be a pilot or Formula One driver the next day. You might have a new business card that says you work for an airline or a race team, but you're still probably thinking about playing hockey.

The transition to get former legacy-owned plants to independence and profitability has been a challenging one, and, like most industries that have been through deregulation, or whose largest players have spun off or spun out assets, the devil is in the details, normally embodied in the fine print of the contracts the divestiture was "papered" with, such as an asset purchase agreement (or asset sale agreement), master services agreement, or transitional services agreement.

Legacy plants are overbuilt, inefficient assets that were run as cost centers of big pharma. After acquisition by a CDMO, they are magically supposed to be efficient, low-cost production centers. This poses challenges from a number of perspectives, the capital itself (buildings, facilities, equipment, machinery) and the workforce.

Transitioning the workforce culture from a bureaucratic pharmaceutical industry to an entrepreneurial "low-cost but high-quality" nimble CDMO model poses many challenges. Pharma employees are highly compensated, and benefits are extremely generous, compared to most subcontracting businesses in other industries. With such high direct, indirect, and SG&A labor cost input into the model, it becomes very difficult to be profitable as a true low-cost provider.

Pharma organizational structures and staffing models are robust – with high span of control duplication, further bolstered by regulatory requirements and the pharma mindset, which was to overbuild, overstaff, and throw resources and people at problems and inefficiencies. The most profitable CDMOs have embraced a culture shift, injecting the mindset with new methodologies, operational excellence, more laser-focused KPIs, and flatter organizations, to cut cost, improve margins, and ultimately lower the cost of drugs for their customers, the pharma companies, and the ultimate customers – the P - Patients.

Workforce culture can be a major stumbling block for companies looking to make the transition from former big pharma cost center, or a purpose-built production facility dedicated to a single blockbuster drug, to a nimble, flexible low-cost provider. These two realities exist in conflict. Getting a long-term employee who's never felt career risk or who has never been asked to double or triple their productivity over a period of time to embrace change remains a challenge.

In order for this turnaround to be successful, we had to accelerate the rate of change and the adoption of new mindsets within the company as a whole, but in more granular fashion, at the sites. The sites are where the culture is most embedded.

The large legacy pharma companies divesting the plants, and many of the

"By strategically downsizing to four sites from eight, ABCDMO shed loss-making entities and improved EBITDA from FY 2018 to FY 2019 by increasing it from negative $45,000 to positive $30 million. The majority of the 1,900 jobs were preserved as employees left through attrition or returned to prior legacy company payrolls for those sites divested or returned."

CDMO startups that have acquired them, have found out that the typical 2- or 3-year transitional services agreement – a window of time that the acquirer presumes it can drive new business to the plant – is simply not enough time to transition the business.

Professionals on both sides of the arrangement – the supply chain and procurement people at pharma companies, and the people now working for the CDMO that was once a pharma cost center – agree that the time it takes to stabilize the spun off plant with enough diversified commercial business to produce net income and EBITDA – the main profitability KPI for CDMOs – is more like 6, 7, or 8 years.

A jointly crafted, fair, flexible, longer term site acquisition/supply agreement/asset purchase agreement, which places patient needs, sustainability of supply, and product quality above a hastily conceived divestiture/acquisition to get a plant off the books (or on the books in the case of the acquiring CDMO), would be most important to ensure future success. We had to point in that direction – pragmatic sustainability – as "true north."

THE TURNAROUND OF ABCDMO

Our turnaround team immediately went to work on all aspects of operations in the US, Canada, and Europe, which included a deep review of the purchase agreements and supply contracts under which these former legacy sites had been acquired from the elite top list of "big pharma" companies. While the CDMO's revenues grew rapidly in just a few years, the facilities had not yet been integrated to save costs and leverage capabilities. Most of the sites were unprofitable, and the company had severely missed its internal forecasts on revenues, gross and net profits, EBITDA, and new customer sales.

The turnaround took a multi-pronged, site-specific approach to remedying the business model challenges along with the accompanying reputational issues. At the exact same time, mold was detected in a European operation, necessitating an immediate shut down and expensive eradication program, for an additional combined loss of 2 million Euros/month. The company's prime lender, a bank, was soon fatigued, which brought new pressures to the situation. While vendors started holding shipments, the company was locked into rigid supply agreements, labor contracts, and other constraints that made it difficult to operate and nearly impossible to generate profits. EBITDA was negative. The media and the European unions were beating us up. In some cases, so were the executives from the legacy owners, but we pushed through it.

The plan to restore ABCDMO took dramatic measures to optimize revenue and margins while cutting costs. A discrete diagnosis and turnaround plan were created for each subsidiary of ABCDMO. I and other new management personally met with each key customer, legacy company management contacts, and key supply chain vendors in order to build credibility and establish trust and retain vital lifelines to new commercial opportunities. As the turnaround took hold, ABCDMO restructured corporate and site-based staff to make sure every key management function was efficiently and effectively covered.

ABCDMO's eight global sites varied by location, legacy company, production focus, company culture, and most importantly, the relative sustainability of the contracts associated with the acquisition of each unit. It would prove the best strategy to turn the company around would be to focus on each site's unique pluses and minuses, and determine which sites would be retained and fixed, and which ones divested.

The newly energized and focused team went to work on revenue improvement and cost reduction opportunities, while ensuring compliance with intensely regulated quality and delivery guidelines, with the main metric being "on time and in full, or OTIF," THE contract pharma benchmark KPI.

PROBLEMS TO SOLVE

There were numerous issues plaguing the acquisitions which included the following:

- Rigid asset purchase agreements that restricted commercial opportunities, prohibited headcount reductions, and titular changes
- Sites that were grossly underutilized, with large excess capacity, producing

late lifecycle products approaching or past the dreaded pharma "patent cliff"
- Contract pricing and volume design that frontloaded obligations from former legacy owners for sustainable volumes for a very short term
- An unrealistic forecast for commercial opportunities coupled with a grossly undersized sales team
- Sizeable capex obligations due to deferred maintenance, poorly executed contracts for new business requiring ABCDMO to expend large sums to "buy business" from other pharma companies willing to transfer their commercial production (manufacturing and packaging) in exchange for low pricing, and large commitments to buy machinery and equipment
- Large deferred obligations, such as balloon payments, substantial seller note obligations, and other acquisition financing arrangements that severely impaired near-term and long-term cash flow
- Excessive spending on IT (opex and capex)
- Excessive spending on HQ staff
- Ineffective sales and marketing – the company was focused on brand leadership above its size and scope when what it really needed was sales
- In addition, ABCDMO was in covenant violation with its bank, and the relationship was strained

THE FIRST 10 DAYS

1. Reduce headquarters line and staff officers' headcount - Complete
2. Recruit global restructuring team - Complete
3. Cease all non-critical spending - Complete
4. Contact Customers/Seller Note holders - Complete
5. Cease payments and begin negotiation of seller notes - Complete
6. Freeze all past due payables - Complete
7. Model Proforma forecast 2019 - Complete
8. CEO to visit every facility - Complete
9. Cease IT projects and reduce IT spend - Complete
10. Replace law and accounting firms at lower rates - Complete
11. Replace overpriced IT through insourcing - Complete
12. Move HQ; sublease corporate office - Complete
13. Establish supply chain credit programs with vendors - Complete
14. Stop losses in factory No. 8 within 30 days - Complete
15. Stop losses in factory No. 7 within 30 days - Complete
16. Gain customer financial support for Factory No. 6 - Complete
17. CEO to visit every customer - Complete
18. Accelerate A/R Collections - Complete
19. Limited headcount reductions/consolidation/attrition - Complete
20. Wage and benefit alignment - Complete
21. Consolidate certain senior management positions - Complete

Of those action steps:

- HQ headcount reductions produced an annual EBITDA improvement (Salary, Bonus, and Perquisites)
- Lease termination generated a savings, boosting annual EBITDA
- Cancellation of certain corporate events and trade shows produced an annual EBITDA improvement
- Divestiture/administration of certain European sites created tens of millions of annual EBITDA improvement
- Reduction of marketing expense
- Renegotiation of supply agreements at four US sites improved EBITDA by millions annually
- Renegotiation of the maturities of seller notes and certain accounts payable
- Restructuring and insourcing of the expensive IT program
- Negotiated stretch-out of the high accounts payable related to prior IT expense with legacy IT vendors
- In-depth, on-site review of each operation to explore opportunities to reduce costs and drive production and revenue
- Freeze on all hires
- Review of all insurances and health care policies with a new Broker of Record to eliminate excess costs and improve coverages and increase employee participation in premiums

- Consolidation of executive roles and elimination of duplicate roles
- Reduction of millions in IT capex spend
- Reduction in IT contractor fees
- Reduction in audit and legal fees
- Streamlining and consolidation of common vendor contracts
- Drawdown sale and shipment of excess inventory to customers to reduce on-hand materials and improve cash flow and cash on-hand

And the digging in, and the savings and EBITDA restoration, would continue to bear fruit.

RESULTS: ABCDMO SAVED & RESTORED: SUSTAINABILITY FOR PATIENTS

In less than 1 year, ABCDMO was successfully transformed, improving its relationship with its lender and vendors, maintaining critical mass with employees, retaining and improving (through contract renegotiation) all supply contracts with its customers, and regaining the confidence of its current as well as pending and new commercial customers. By strategically downsizing to four sites from eight, ABCDMO shed loss-making entities and improved EBITDA from FY 2018 to FY 2019 by increasing it from negative $45,000 to positive $30 million. The majority of the 1,900 jobs were preserved as employees left through attrition or returned to prior legacy company payrolls for those sites divested or returned.

ABCDMO was efficiently and promptly restructured without resorting to a bankruptcy court filing for the entire group and without a change of control transaction. Administration court filings were made only for certain European subsidiaries, but an out-of-court restructuring for the ABCDMO Group was possible due to frequent communications and negotiations with ABCDMO's bank and other key creditors.

Our major risk was from an IT vendor that threatened to shut down computer systems, wiping out supply in over 40 countries. After sensible, calm negotiation, this too was resolved peacefully. The community and industry in general were positively impacted by this turnaround. Industry supply was secured. Communities were protected even through the process, one of the European facilities was restored to health with mold eradication, Canadian and European facilities were sold, which protected those communities and the accompanying union jobs.

As a consequence, customers were happy, jobs were protected and secured, employees had been stabilized, and the bank was pleased. Most importantly, patients can depend on a stable supply of their medicines from a quality-driven, compliant, sustainable business operated by skilled, motivated, passionate employees. That's the win!

SUMMARY: ALPHABET SOUP

The X factor in this transformation of ABCDMO was the openness of employees. It was their willingness to embrace the agents of change and to listen and learn. I wasn't the solution. The rest of the turnaround team wasn't the solution. The employees were the solution and deserve the lion's share of the credit. They accepted the challenge. They accepted the change. They accepted me. They accepted us.

It was my pleasure to serve as the CEO of ABCDMO, and I back and take pride in what we were able to do and look forward to my next challenges. And meanwhile, the CDMO industry will likely continue to consolidate, creating both competitive intensity and opportunity, and hopefully greater focus on sustainability as patients rely on the industry for life-saving and life-enhancing medicines.

POMC works in the CDMO. POMC delivers OTIF. Nobody in the industry can ever forget the big P – the Patients, and the big S - the Sustainability of CDMOs.

At this writing, the turnaround of the CDMO has been submitted to the TMA - Turnaround Management Association - for the 2019 International Turnaround of the Year, a tremendous honor. I hope the case wins. Not for anyone's resume or ego, or for my peers, but for the employees, especially the ones who looked beyond the team's lack of pharma experience and embraced new ways of thinking, and new approaches to an industry and legacy organizational structures that they'd grown up in. ◆

REFERENCE

1. Argyris, C. Overcoming Organizational Defenses: Facilitating Organizational Learning, 1st Edition,© 1990. Printed electronically and reproduced by permission of Pearson Education, Inc., Upper Saddle River, New Jersey. and Sons, Inc.

BIOGRAPHY

Paul Fioravanti, MBA, MPA, CAGS, is the Founder and Managing Partner of Qadent Management Services, LLC, a US-based turnaround, restructuring, business optimization and interim management firm. He is a proven turnaround CEO with experience in a variety of industries and situational challenges. He earned his MBA and MPA from the University of Rhode Island, and completed advanced post-masters research in finance and marketing at Bryant University. Mr. Fioravanti can be reached at paul@qadentmanagement.com.

BIOSIMILAR DEVELOPMENT

Biosimilars: The Process & Quality System Approach to Clinical Applications

By: Kaiser J. Aziz, MB, MS, PhD, FACB, FACS

INTRODUCTION

Biosimilars are medicines that are highly similar to their approved reference biologics as they claim to have no clinical differences in purity, potency, and safety. For regulatory approval for a biosimilar in the US, a sponsor must demonstrate that its product is highly comparable to an FDA-approved biologic, and that any residual differences do not affect the biosimilar's safety and effectiveness. The sponsor's claim plays a pivotal role for use of biosimilars in specialty therapy categories, such as immunology, endocrinology, and oncology. The new discoveries of innovative biosimilar products continues to challenge the clinical treatments for patients suffering from chronic diseases (ie, carcinoma, sarcoma, lymphoma, etc). These new innovative treatments have placed immense economic burden on emerging market developments and healthcare systems delivery. According to the European Medicines Agency (EMA), there are assessment reports showing a decrease in costs and marketing of biosimilars, leading to ease of access for patients. The following addresses biosimilar developments and future innovations. Emphasis is placed on quality system approaches to the development and availability of new biosimilar products. For approvals of new biosimilars, the sponsors of premarket applications must present analytical and biological characterization to demonstrate that a proposed biosimilar is highly similar to a licensed reference product. The premarket application protocol requires a sponsor to describe the biosimilar product's PK/PD clinical data comparing its safety, efficacy, and immunogenicity to that of the reference product. Emphasis is placed on design of studies, extrapolations, interchangeability, and c-GMP risk-based monitoring criteria. A brief description is presented on risk-benefit analysis that guides the clinical use of the new biosimilar drug product by providing patients' organized data and appropriate labeling information in conformance with the new biosimilar drug's intended clinical use.[1,2]

DEVELOPMENT STRATEGIES FOR BIOSIMILAR PRODUCTS

Biosimilar medicines have a profound impact on patients suffering from many debilitating and life-threatening diseases, such as rheumatoid arthritis, cardiac myopathies, leukemias, lymphomas, multiple sclerosis, and various oncogenic cancers. Biosimilars are copies of biological medicines and require stringent comparison against their licensed reference products (design controls, CMC, GMP, nonclinical, and clinical). Biosimilars share the same amino acid sequences as their comparative biologics, but may consist of proteins having post-translational changes due to manufacturing processes (ie, glycosylation, phosphorylation, etc) These types of modifications may impact immunogenicity. The impact of post-translational changes require similarity studies, such as analytical/biological, nonclinical, and clinical in order to ensure the safety and efficacy profiles of the resulting new biosimilars. Thus, developing new biosimilars require robust strategies to achieve the goal of reduced development costs. From GMP perspectives, Chemistry, Manufacturing, and Controls (CMC) will require comprehensive comparison data requirements

along with nonclinical and clinical studies. When the final data and information are available, then a global strategic roadmap can be constructed to pursue the ultimate goal of providing quality biosimilars for patients in need of treatments for debilitating and life-threatening diseases. For clinical assessment, the comparative PK and/or PD data in addition to comparative immunogenicity, safety, and efficacy data become essential for evaluation purposes. However, the PD measures should be relevant to clinical outcomes after dosing to ascertain PD response in terms of sensitivity and specificity to detect clinically meaningful differences. When all of the aforementioned essential elements are addressed, a strategy can be developed with regard to manufacturing process development, biosimilarity testing, scale-up, nonclinical testing, clinical studies, marketing, and clinical utility outcomes.[1-8]

CLINICAL ASPECTS OF BIOSIMILAR DRUGS EVALUATION

Biosimilar medicines have been essential in the treatment of diseases ranging from autoimmune diseases to various types of cancers. The US biosimilar approval process requires a thorough characterization of the molecular structure of the proposed biosimilar product with clinically meaningful outcome. In other words, the proposed biosimilar is expected to produce clinical outcomes that are not significantly different from those expected with licensed reference biologic drug approved by the FDA. This publication is intended to present guidances in reference to FDA's regulatory framework for organizing sponsor's data in biosimilar 351(k) application. An example is the anti-CD 20 monoclonal antibody, rituximab, which has revolutionized the treatment of patients suffering from non-Hodgkin's lymphoma (NHL). In 2014, the National Cancer Institute (NCI) stated that since 1997, deaths due to NHL decreased each year and continue to fall. Recent information in regard to immune-oncology therapies have provided new treatment examples for patients with advanced cancers, such as lung cancer and melanoma. Other biologic medicines, such as epoetins, infliximab, and filgrastims have played important roles in the treatment of patients with serious life-threatening situations. These types of biologic medicines were developed based on data presented in comparison to approved reference products. These developmental paradigms have the potential to improve the affordability and accessibility and cost of biosimilar medicines (ie, TNFa inhibitors known as Humira, Enbrel, and Remicade). These studies have provided opportunities for developers and providers to make it available to patients and payers potentially significant cost savings. Neverthless, these kinds of advancements and opportunities make it possible for patients with clinical outcomes that are meaningful in comparison to original biologic-innovator drug products.[9,11]

DEVELOPMENT PERSPECTIVES

The developmental perspectives consist of characterization of basic structures, such as protein backbone (physicochemical) properties of the biosimilar product and biological activities associated with it. It may not be limited to primary, secondary, tertiary, or quaternary protein structures, but post-translational modifications may occur due to manufacturing processes, which may influence the functionality of the protein. For instance, effector mechanisms associated with monoclonal antibodies may require assessing the biological activity of the biosimilar product in terms of receptor binding and pharmacodynamic effect. Finally, other properties of the biosimilar poduct, such as formation of residual aggregates may require testing and acceptability.[8]

Sponsors of innovative new biosimilar drugs follow the appropriate ICH guidance in regard to preclinical characterization of safety and effectiveness.[4,6,9] These studies involve testing in a relevant animal species, which represent appropriate receptor binding studies. The developmental paradigm for a new biosimilar drug emphasizes clinical evidence to demonstrate that safety and efficacy of each indication for use is similar to the reference product's clinical safety and efficacy information. While development of innovative biosimilars usually focuses heavily on clinical studies, the FDA's guidances describe similarity studies at the physicochemical and biological level using a variety of analytical techniques (ie, cellular bioassays are considered to be useful in comparing receptor binding kinetics and bioactivity).[8]

CLINICAL STUDIES

The sponsors of biosimilar 351(k) applications have shown that clinical studies usually include side-by-side comparisons of pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy as described below:

Pharmacokinetic Studies: The pharmaco-

kinetic (PK) profiles of biosimilar biologic drugs are dependent on many factors, including product-specific characteristics, such as small differences in the quality attributes of a candidate biosimilar in comparison to a reference product, which may potentially lead to differences in drug absorption, distribution, metabolism, or excretion.[11] These types of clinical studies (ie, human PK/PD studies) play a central role in the biosimilar developmental process. Furthermore, these studies provide sensitive tools to assess potentially clinically relevant differences between candidate biosimilar and reference biologic. Human PK studies are generally conducted in a well-defined healthy-sensitive population who are not prescribed other medicines that could interfere with baseline human PK studies.[8,12]

Clinical immunogenicity studies in a healthy-sensitive population also provides information in regard to duration studies (antibody titers) after extended exposure to biosimilar product.[8,9] Confirmatory safety and efficacy studies are helpful in assessing clinically relevant differences between the candidate biosimilar and reference product. These types of studies depend on whether PK studies are designed and conducted in settings to detect sensitivity to change. The type of study performed depends on whether that study is designed for parallel or cross-over groups. Generally cross-over studies are not feasible due to the long half-lives associated with many biologic products, particularly monoclonal antibodies. For biosimilars with relatively short half-lives, such as filgrastims, insulin, or certain fusion proteins, cross-over studies are preferred. Additionally, host factors, such as receptor affinity and patient status, may affect the disposition and clearance of biosimilar. Furthermore, concomitant medications (ie, immunosuppressants) may affect the PK of the biosimilar products and could mask differences between the candidate biosimilar and the reference product. For those situations, particularly where monoclonal antibodies are used for cancer treatment, patients receiving first-line therapy with minimum heterogeneity/prior therapies may show minimum impact on the clinical PK profile of candidate biosimilar and reference product.[8,11]

It is important to consider the design of study for biosimilar's route of administration and absorption kinetics for comparative PK profiles. Bioequivalent testing protocols are very helpful to assess PK similarities. Many biologics biosimilars are usually administered via intravenous injection or infusion, making bioavailability approximately 100% possible. However, for a candidate biosimilar intended to be administered subcutaneously, simply comparing Cmax and AUC methods may not be suitable to assess the PK similarity of the candidate biosimilar and its reference. In those situations where there are differences in absorption and distribution modes, analysis and comparison of additional PK parameters (ie,T1/2, Ke, and Cl) distribution and clearance of biologics biosimilars may be useful. From a clinical perspective, methods used to determine serum concentrations in test results from volunteers/patients need to be validated with the guidelines and standards based on (National Committee for Clinical Laboratory Standards-NCCLS). Notably, NCCLS recognized ligand-binding assays are used for the detection of patient sample analytes for US FDA premarket approvals.[1-14]

Pharmacodynamic Studies: Human pharmacodynamic (PD) profiles play a central role in detecting any clinically relevant differences that may exist relating to the assessment of biosimilarity between a biosimilar and reference biologic.[13] PD testing is aimed at determining a safe dose range in which a biosimilar drug can be administered and the methods of absorption and distribution in the body are determined. A primary consideration in these studies is limiting risk to the subjects and determining safety or toxicity limits. These studies usually include PK and PD testing to help establish the relationship between biosimilar drug dose and plasma concentration levels, as well as therapeutic or toxic effects.[8,12,13]

Clinical Safety & Efficacy Studies: Clinical safety assessment for biosimilar products consist of a comparison of the overall adverse event profile inclusive of specific types of adverse drug reactions occurring after the initiation of treatment. It is useful to compare the types of hazards and severity levels of adverse reactions in those events that have been observed throughout the reference product's life-cycle in order to determine whether the candidate biosimilar product has shown new safety concerns. This type of study helps selecting a patient population that determines likelihood of detecting a difference in critical control points in the assessment of clinical differences. This may become an issue for the assessment of safety profile parameters for testing the biosimilar product's side-by-side comparison for monotherapy versus concomitant therapies. This type of testing in a relatively homogeneous population may increase the ability to detect differences in safety parameters by reducing perplexity that may occur due to the use of concomitant medications and/or presence of concomitant conditions. This type of

testing is helpful in detecting meaningful differences between safety profiles of biosimilar assessment. For this perspective, appropriate risk management study design and post-marketing surveillance for new biosimilars are crucial for the strengthening of the safety database. Therefore, this type of approach, for the proposed labeling of the biosimilar product indicates the same risks to patients as the reference product's labeling.

Clinical efficacy assessment for a biosimilar product is a key component of the FDA's approval process. When designing the clinical efficacy studies, it is important to consider the relevant mechanism(s) of action considering all the indications for use sought for approval. It is known that some biologics can function through multiple mechanisms of action, and the mechanisms involved in the treatment of one disease may not be the same as mechanisms involved in the treatment of other diseases. The ability to detect a difference is of utmost importance for the candidate biosimilar's development. In order to maximize the sensitivity of a clinical efficacy study, sponsors should perform a thorough review of the available clinical data for the reference product in order to determine the population-endpoint associated with the study database. By performing a thorough systematic review of data available for the reference product, the biosimilar product's sponsor can identify critical control points of the new biosimilar product in terms of magnitude of effect and the timing of response that are necessary to guide study design in establishing clinically meaningful similarity margins. The primary endpoints should provide adequate sensitivity margins to detect differences in efficacy of the candidate biosimilar in comparison to the reference product. The clinical sensitivity protocol (ie, ability to detect the endpoint differences) is important for the candidate biosimilars. In order to achieve the maximum clinical efficacy sensitivity, the protocol should include both selection of well-defined populations and endpoints that in combination will be sensitive to detect differences that may provide clinical efficacy profile of candidate biosimilar in comparison to the licensed reference product. This type of data comparison provides assessment of candidate biosimilar's population endpoints that may be associated with a large effect size and a robust historical reference product's available dataset. These studies performed in comparison to reference product, the sponsor of candidate biosimilar 351(k) application can identify manufacturing critical control points inclusive of the magnitude of effect and the timing of response that are necessary to establish clinically meaningful similarity margins. The primary goal for determining endpoint(s) should be to provide acceptable sensitivity to detect differences/similarities in clinical efficacies of the comparative data. For instance, there are several endpoints commonly used to assess the efficacy of biosimilar products.[15,16]

Generally, overall survival is considered a quality indicator for the demonstration of clinical efficacy for innovative new biosimilars for oncology treatments. Comparing endpoints for early applications, such as response rates or progression-free survival may be more appropriate in some oncology settings. The important factors being the overall affect of study population endpoints and the timing of therapeutic effects in regard to duration of treatment and follow-up. The comparative studies to demonstrate clinical efficacy of new biosimilars should be designed and powered to test a hypothesis of equivalence, and this should include randomization and double-blinded factors. The selection of equivalence margins should be part of predesigned protocols based on statistical applications and historical data available for the reference product. Predefined equivalency margins include differential criteria for efficacy determination considered clinically meaningful.[17]

Immunogenicity: Immunogenic studies have an impact on PK/PD, safety, and efficacy of biosimilars. Structural and manufacturing changes in a biosimilar can have different immunogenic responses. For instance, formulation changes in a product containing epoetin alfa have been reported to show a significant rise in the number of cases of red cell aplasia in chronic kidney disease patients due to generation of neutralizing antibodies that cross-reacted with endogenous proteins.[18] The formation of anti-drug antibodies (ADA) has been reported with severe acute infusion reactions affecting immunogenicity responses in patients.[19] Furthermore, anti-drug antibodies (ADAs) have been shown to interfere with the clinical efficacy of biologic drugs, such as the anti-TNF antibodies that are useful in the treatment of a number of autoimmune diseases.[20] The modified complexity of biosimilar structures has been reported that differences in post-translational modifications, such as folding and conformational changes, could lead to differences in the elicit response to immunogenicity.[21,22] Therefore, it is essential that sponsors of new biosimilar applicants assess the formation of ADAs in comparative clinical studies in order to determine whether processed molecular differences might lead to differences in the immune responses, which

subsequently could affect safety/efficacy of the new biosimilar product.

In designing immunogenicity studies, patient-specific factors play a key role in the interpretation of data (ie, genetic factors, age, concomitant medications, duration, and route of administration, previous exposure to similar products - any or all of these factors may contribute to patient's risk of developing ADA against the candidate biosimilar). Also the underlying diseases of study participants may influence the rate of ADA against a particular biosimilar product. It has been reported that infliximab had shown rate changes from 7% to 61% in patients with psoriasis, ankylosing spondylitis, Crohn's disease, and rheumatoid arthritis.[14,23] All of these factors should be considered in design and interpretation of the immunogenicity studies for the new biosimilar product.[24]

Extrapolation: The concept for extrapolation is based on the principle that biosimilar product has demonstrated that intended clinical use and its outcome will not differ meaningfully whether a patient receives the candidate biosimilar or its reference product. Extrapolation must be supported by scientific evidence of the candidate biosimilar's human PK/PD, safety, and efficacy data in a well-defined patient population based on a similar safety and efficacy profile as reference biologic. It is essential that both the candidate biosimilar and licensed reference product share the same mechanism of action.[10] The biosimilar sponsor need not conduct clinical studies in every indication for use described in the reference product's labeling. Instead, the FDA guidance advises the biosimilar applicant to conduct clinical evaluations in one or two indications, then provide scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought. The underlying rationale under the concept of extrapolation is the scientific principle that biosimilar protein structure determines the molecular (output) function, clinical PK/PD data, safety, and efficacy outcome of the proposed biosimilar product.

The essential biosimilar parameters of extrapolation are listed below:

- The uncertainty margin or acceptable analytical/functional differences between the candidate biosimilar and the licensed reference product
- The mechanism of action (MOA) of each indication for use and the justification that the residual differences will not contribute to any meaningful differences in the clinical safety and efficacy of the biosimilar's intended use sought by extrapolation
- High similarity in PK/PD comparisons of the candidate biosimilar and the reference product's established indications for use and the justification that any residual differences will not contribute to misinterpretation of data (extrapolation justification that residual differences will not lead to any meaningful differences in safety, effectiveness, and immunogenicity sought by extrapolation)
- Clinical safety and immunogenicity profiles of the new biosimilar and licensed reference product are compared for indications for use, and the justifications are provided that residual differences will not contribute to safety and effectiveness bias under extrapolation studies

The FDA's guidance for extrapolation states that data derived from clinical studies should be sufficient to demonstrate purity, potency, safety, and the intended use of the proposed biosimilar product in comparison to licensed biologics.[10] The sponsor of biosimilar 351(k) application may apply for licensure for one or more indications for use based on MOAs for which the reference product is licensed. MOAs for safety and efficacy for different indications present a major challenge for extrapolation.[25] For instance, MOAs for hormonal protein drugs may be different from antibody drugs. Hormonal protein drugs, such as human growth hormone (hGH) somatropin, generally have similar structure and function as the corresponding endogenous hormones, and their MOAs are considered to be identical with the same binding receptor with identical biological effects. Whereas MOAs for antibody drugs may be different due to complexity of antibody structure, especially the complexity of post-translational modifications, such as glycosylation causing different structural variations of the same antibody whose residual mixture could be different from batch to batch technically making it difficult an exact copy of antibody drug. Structural residual uncertainties in the antibody structure could be detected during the physico-chemical characterization step in the manufacturing process.[10] Glycosyation may have potential impacts on the PK/PD of the biosimilar drug antibody.[25,26] Remicade (infliximab) biosimilar was approved for inflammatory diseases, such as ankylosing spondylitis (AS), inflammatory bowel diseases (IBD), psoriatic arthritis (PsA), plaque psoriasis (PsO), and rheumatoid arthritis (RA). Clinical studies for the proposed biosimilar Inflectra/Remsima (CT-P13) were conducted for AS and

RA and extrapolation to IBD. In these studies, the structural uncertainties reached to lower levels of glycans, which caused to lower antibody-dependent cell-mediated cytotoxicity (ADCC) responses.

Adalimumab biosimilar ABP501, biosimilar of Humira, was approved for rheumatoid arthritis (RA), Juvenile idiopathic arthritis (JIA) in patients approximately 4 years or older, AS, PsA, UC, adult CD, and PsO, while the clinical studies for the proposed biosimilar ABP501 was conducted in PSO and RA. The physico-chemical characterization (with no major residual uncertainties reported) provided justification for extrapolation in comparison to CT-P13.[27] The clinical studies supporting the similarity of ABP501 included single-dose PK similarity study in healthy subjects, which was conducted to assess PK parameters simply because these subjects were not under concomitant medications treatments and did not have medical conditions that could potentially affect PK. The study showed PK equivalence assessed by AUCinf and Cmax between ABP501 and US approved licensed product.[28] Additional study in subjects with moderate to severely active rheumatoid arthritis and plaque psoriasis demonstrated clinical similarity (safety, efficacy, and immunogenicity) for ABP501and the reference product.[28] Additionally, the study results indicated that there was no increased risk to safety, efficacy, and immunogenicity switching from reference product to ABP501.[28]

Scientific justification for the biosimilar candidate's extrapolation is based on the totality of evidence presented to demonstrate the analytical characterization of high similarity coupled with high similarity in functional testing for a solid extrapolation justification.[9,10] The justification goal for extrapolation of safety is dependent on reducing the residual uncertainty. It is critical that residual uncertainty will not contribute to any significant difference in clinical safety and efficacy in indications sought by extrapolation.

Interchangeability: The FDA requires switching studies (at least three switches) with primary endpoints measuring PK/PD providing assessments for sensitive changes in immunogenicity and efficacy.[8] The FDA guidance (FDA 2017b) addresses the use of post-marketing data for a biosimilar product with real-time evidence providing sensitive PK/PD information as a part of post-marketing surveillance process.[5,6,8] Current biosimilars include Humira, Enbrel, Rituxan, Remicade, Avastin, Herceptin, and Lantus in their respective lists of top drugs that are widely available through the FDA's approval process.[29] A biosimilar applicant can apply for interchangeability status (1 year interchangeability exclusivity is allowed). To achieve interchangeability approval, the biosimilar applicant is required to show substantial switching studies between the candidate biosimilar and RP. However, the 1-year exclusivity applies only to interchangeability status. Biosimilar candidate product is expected to produce the same clinical result as the RP in any given patient and also not to pose excessive risks to patients if they switch between the RP and interchangeable product without the intervention of the biosimilar product's prescriber – the interchangeable product may be given in place of the RP at the pharmacy level (Interchangeability Guidance, US FDA 2017a). The FDA expects minimum immunogenicity risk-related outcomes by switching candidate biosimilar and RP products. The PD/PK endpoints become essential sensitivity indicators in the switching studies. The important point of the FDA's stepwise approach is to consider the outcome supporting biosimilarity assertions in its totality of evidence (ie, filgrastim and bevacizumab interchangeability studies)[13,16,22,30]

CONCLUSION

Biosimilars have recently emerged as a new class of biologic drug that has the potential to have access to many critical medicines through the reduction of costs. Furthermore, there is need to ensure that new biosimilars are as safe and effective as their innovative counterparts. To date, there are approved biosimilar drugs, spanning a variety of indications for use-from autoimmune disease to growth deficiency, that have fulfilled the needs for the treatment of diseases/abnormalities. It is expected that future biosimilar developments will provide robust pipeline for biosimilars intended to be used in oncology and other severe diseases. At the same time, the manufacturers of biosimilars will have to stay abreast of these biosimilar drugs development and the new technologies, such as the interpretation of data from switching and interchangeability studies. The FDA's guidance on demonstration of interchangeability emphasizes that alternating use of a proposed biosimilar in comparison to the reference product would not incur more risk than the use of the reference product alone. This article is primarily focused on considerations for the quality system approach to design of studies for clinical applications for designated patient populations and selection of conditions of use.

ACKNOWLEDGEMENT

The views and opinions expressed in this article are those of the author and do not represent official views of the US FDA. ◆

REFERENCES

1. Aziz KJ. Drug Monitoring: Modern Approaches to Quality Assurance. CRC Handbook of Analytical Therapeutic Drug Monitoring and Toxicology, 1997;19:335-349.
2. Aziz KJ. Global harmonization & quality system application for medical products. Clin Lab Med. 2001;39:76-78.
3. Aziz KJ. The FDA's critical path initiative for medical products. J Clinic Ligand Ass. 2006;29:171-176.
4. Aziz KJ. Globalization: Challenges and Solutions (Seventh Annual FDA Inspections Summit). 2012:19-21.
5. Aziz KJ. The FDA's new drug approval process. Drug Development & Delivery. 2016;3:50-56.
6. Aziz KJ. The FDA's quality risk management approach to new drug applications. Drug Development & Delivery. 2019;19:1-4.
7. Aziz KJ. The FDA's design control requirements for biomarkers in drug development. Drug Development & Delivery. 2019;3:39-43.
8. Aziz KJ. Biosimilar drug development and approval process. J Pharmaceut Sci & Emerg Drugs. 2019;7:2;1-5.
9. Cohen H. Biosimilar development: approval of biosimilar medicines through totality of evidence. Drug Development & Delivery. 2019;19:40-45.
10. Aziz KJ. Biosimilar biological products: development & applications. Drug Development & Delivery. 2019;19:1-6.
11. Rader RA. An analysis of the US biosimilars development pipeline and likely market evolution. Bioprocess Inter. 2013;11:16-23.
12. Putnam WS, et al. Pharmacokinetic, pharmacodynamic and immunogenicity comparability assessment strategies for monoclonal antibodies. Trends Biotechnol. 2010;28:509-516.
13. Desai K, et al. Confirmation of biosimilarity in a pharmacokinetic/pharmacodynamic study in healthy volunteers for an analytical highly similar pegfilgrastim. Clin Pharmacol Drug Dev. 2016;5:354-363.
14. Ducourau E, et al. Antibodies toward Infliximab are associated with low Infliximab concentration at treatment initiation and poor Infliximab maintenance in rheumatic diseases. Arthritis Res Ther. 2011;13:R105.
15. Hobbs KF, et al. Rheumatoid arthritis disease measurement: a new old idea. Rheumatol. 2012;51:21-27.
16. Moots R, et al. Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. Curr Rheumatol Rep. 2017;19:37.
17. NIH National Cancer Institute. Using the Immune System in the fight against Cancer: Discovery of Retuximab. 2014, available at : https://www.Cancer.gov/research/progress/discovery/blood cancer. Accessed 22 Nov, 2017.
18. Casadevall N, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. NEJM. 2002;346:469-475.
19. Steenholdt C, et al. Severe infusion reactions to infliximab: etiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2011;34:51-58.
20. Kalden JR. Immunogenicity and loss of response to TNF inhibitors: implications for rheumatoid arthritis treatment. Nat Rev Rheumatoid. 2017;13:707-718.
21. Maas C, et al. A role for protein misfolding in immunogenicity of biopharmaceuticals. J Biol Chem. 2007;282:2229-2236.
22. Jahn EM. How to systematically evaluate immunogenicity of therapeutic protein. New Biotechnol. 2009;25:280-286.
23. Perdriger A. Infliximab in the treatment of rheumatoid arthritis. Biologics. 2009;3:183-191.
24. Brinks V. Immunogenicity of biosimilar monoclonal antibodies. GaBI J. 2013;2:188-193.
25. Suzuki MK, et al. Therapeutic antibodies: their mechanism of action and the pathological findings they induce in toxicity studies. J Toxicol Pathol. 2015;28(3):133-139.
26. Liu L. Antibody glycosylation and its impact on the pharmacokinetics and pharmacodynamics of monoclonal antibodies and Fc-fusion proteins. J Pharm Sci, 2015;104(6):1866-1884.
27. FDA Guidance for Industry: scientific considerations for CT-P13 Infliximab biosimilar. 2016(a). https:www.fda.gov/downloads/drugs/guidances/ucm 484859.Pdf.
28. FDA briefing for Adalimumab. (https//www.fda.gov/downloads/drugs/guidances/ucm 397017.pdf. Accessed Jan 18, 2017.
29. US Food and Drug Administration (FDA) Biosimilar Product Information (2019). Available at https://fda.gov./drugs/biosimilars/biosimilar-product-information. Accessed May 7, 2019.
30. Ha K, et al. Statistical considerations in evaluating a biosimilar product in an oncology clinical study. Clin Cancer Res. 2016;22:5167-5170.

BIOGRAPHY

Dr. Kaiser J Aziz completed a 30-year career with the FDA as a clinical regulatory scientist and manager of drug and device evaluations, approvals, reengineering, standards, good manufacturing and quality system applications. He worked with individual and industry organizations in design and total product life cycle (TPLC) approaches to premarket applications for medical devices, pharmaceuticals, and combination products (510ks, NDAs, and PMAs). Prior to joining the FDA, he developed and implemented quality assurance standard operating procedures and protocols for medical diagnostic systems in hospitals, physicians' offices, and clinical reference laboratories. During his tenure at FDA, he served as an adjunct faculty in the Department of Medicine and Physiology, NIH Graduate School, where he developed and taught courses in Clinical Pharmacology, Toxicology, Therapeutic Drug Monitoring, and Clinical Laboratory Medicine. Currently, he serves as an adjunct faculty at Virginia Tech's Medical HACCP Alliance Program, where he teaches Quality Risk Management courses and workshops using HACCP principles for the pharmaceutical industry. He was an invited guest editor on Nanotechnology and Clinical Trials in the journal of Clinical Ligand Assay. He is the author of book chapters, textbooks, and over 70 publications in professional and trade journals. His expertise includes Quality System Approach to Medical Device and Pharmaceutical Premarket Applications.

REAL ESTATE

How Biopharma M&A Can Uncover Hidden Value in Real Estate

By: Roger Humphrey, MBA

INTRODUCTION

A new era of deal-making is accelerating breakthrough therapy development, making now a prime time to look for breakthrough real estate and facilities concepts as well. As life sciences ventures grow, so do the challenges — and opportunities — for newly combined firms to leverage real estate to engage the talent it takes to deliver life-changing medicines, while uncovering the value needed to stay competitive.

Today's industry leaders are extending the cutting edge of innovation by continuing to invest in strategic mergers and acquisitions (M&A). Throughout the past 5 years, almost every major industry player has been involved in at least one deal. In 2018 alone, life sciences M&A activity totaled $198 billion, according to EY's 2019 *M&A Firepower Report*.[1] Recent highlights include Bristol Myers Squibb's $74-billion acquisition of Celgene and Takeda's $62-billion acquisition of Shire Pharmaceuticals. All told since 2012, 31 biotech companies have been acquired with valuations exceeding $1 billion each. And continued deal-making is all but ensured throughout the next 5 years, given pending patent expiries, competitive headwinds, and growing technology needs.

This rampant M&A coincides with a meaningful all-time high investment in therapeutic innovation. According to JLL's eighth

FIGURE 1

Exterior of Boston University's BioSquare Research Park
(Credit: JLL Project & Development Services)

FIGURE 2

Interior of a lab at Boston University's BioSquare Research Park
(Credit: JLL Project & Development Services)

annual Life Sciences Outlook, biopharmaceutical firms spent a record-breaking $179 billion on research and development (R&D) in the US alone.[2] In fact, the top 10 pharma companies spent an average of 35% of their total R&D investments on M&A transactions throughout the past 10 years.

The ripple effect of such investment is evident across the drug development landscape, with the total number of drugs in development having jumped up a whopping 46% in the past 5 years. Looking ahead, R&D investment is expected to rise by another $34 billion by 2024, a signal that firms are serious about improving future pipelines, now.

Bold new deals, together with record-breaking investment, provide invaluable opportunity to broaden product lines. But the full promise of these actions can only be realized when leaders also give due attention to the complex real estate strategies that accompany M&A.

HOW REAL ESTATE STRATEGY CAN HELP UNLOCK M&A VALUE

Even the most pioneering ideas can only become real when innovative people are inspired to show up for work each day. And these days, prize employees aren't likely to accept anything less than the best when it comes to facility location, technology, and workplace experience — particularly in times of change like an M&A.

But the boom in funding has ramped up the competition for the right spaces, in the right places. It can be harder and costlier than ever to find the production and lab facility you need in a coveted innovation center, where talent, capital, and other essential resources flow freely.

Even the most profitable life sciences firm cannot afford to simply throw money at this problem. Each real estate and facilities decision matters in a world where R&D returns have dropped to their lowest levels in 9 years. Returns among 12 large-cap biopharma firms sank to 1.9% in 2018 – down from 10% in 2010. Meanwhile, the cost of bringing a new therapy to market has surged to record highs, rising from $1.2 billion in 2010 to nearly $2.2 billion in 2018.

Fortunately, new real estate concepts offer a new source of hidden value that can give your firm an advantage after a merger is complete. First and foremost,

consider how the deal can empower your corporate real estate team to improve operational efficiencies while giving talent what they want.

Next, let data and industry insights guide decisions over the fate of the acquired company's real estate portfolio. By cutting expenses like redundant lab or office space and optimizing distribution systems and supply chains, real estate teams can significantly reduce a combined company's occupancy costs. And, in such decisions, operational costs are just the tip of the iceberg. If redundant facilities are in premium locations, for example, can one be used for other purposes? What do employee retention rates look like? Is it best to keep teams spread across multiple locations, or to unite them in a single, state-of-the-art campus? Advanced analytics can help teams make the right call in prioritizing locations to keep, drop, or right-size.

Outsourcing facility management is another promising way to unlock agility and efficiency in a newly integrated portfolio. A seasoned facility management team, with deep experience in sensitive production and R&D environments can help apply leading practices in maintenance, security, and compliance — while adding all-new value in energy and sustainability performance. These technical wins can also support the employee experience, adding pride in workplace and driving individual comfort and choice.

Location and facility sophistication are also important to attracting and retaining the talent firms need for future growth. High-demand researchers, data scientists, and engineers flock to pricy cities like Boston, San Francisco, and Seattle. Securing a spot in the center of the action can support talent and innovation. Yet, for many companies, finding enough high-quality space is cost-prohibitive--and, in many cases, the space is simply not available. Fortunately, a new crop of coworking R&D labs and incubator spaces are helping make room for smaller outfits, too.

IN A FAST-GROWING INDUSTRY, GROW WISELY

Despite broader uncertainty in the political and economic arena, the outlook is bright for life sciences. Demand for life-saving therapies is not going anywhere, and every day, new investment supports new breakthrough development. Forward-looking firms can ensure their real estate strategies do, too.

By seizing M&A as an opportunity to consolidate facilities wisely, today's leaders can spark innovation, and offset its high cost, all at the same time. ◆

REFERENCES

1. EY, 2019 *M&A Firepower Report*, https://www.ey.com/Publication/vwLUAssets/ey-2019-ey-m-and-a-firepower-report/$FILE/ey-2019-ey-m-and-a-firepower-report.pdf. Accessed January 23, 2020.
2. JLL, Life Sciences Outlook, https://www.us.jll.com/en/trends-and-insights/research/2019-life-sciences-outlook-innovation-is-alive-and-well. Accessed January 23, 2020.

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Technology & Services Showcase

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Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 11 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

Oral Dose Design & Development

Catalent is the global leader in drug development and delivery, and offers partners end-to-end solutions in formulation, development, and dose design. Its tools, experience and expertise ensure the right decisions are made at each stage of development, creating oral dose forms that can improve a drug's clinical efficacy and commercial success: including softgels, fast-dissolving tablets, modified-release capsules, and stick packs. Catalent's Better Treatments by Design™ service aims to combine the needs of innovators, prescribers, and patients to create superior products. Using the widest array of drug delivery technologies to overcome each product's unique challenges and requirements, solutions can be matched to molecules to maximize the potential of a drug, from Phase 2 through to commercial supply. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com.**

Testing Services

DDL®

Testing experts.
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DDL is an independent third-party, ISO 17025-accredited testing laboratory that provides package, medical device, and combination products testing. For nearly 30 years, DDL has provided extraordinary service and specialized testing expertise to the medical device and pharmaceutical industries. We employ a team of engineers, technical, and quality experts devoted to helping our customers bring medical device and combination products to market. Our single source, totally integrated approach enables organizations of all sizes from start-ups to globally recognized corporations maximize product performance, reliability, and safety while seamlessly achieving regulatory compliance. We work hard to build strong partnerships with our clients and have an unwavering commitment to assist in getting products to market on time. For more information, visit DDL at **www.DDLTesting.com.**

Technology & Services
SHOWCASE

FORMULATION TECHNOLOGY

Enteris BioPharma is an independently operated and wholly owned subsidiary of SWK Holdings Corporation [NASDAQ: SWKH]. The organization's headquarters and 32,000- square-foot cGMP manufacturing facility is based within the heart of New Jersey's "Life Sciences Corridor." Through its pioneering and proprietary Peptelligence® technology, Enteris BioPharma partners with pharmaceutical and biotech organizations to develop bespoke solutions, including robust oral formulation development and clinical cGMP manufacturing. For more information, visit Enteris BioPharma at **www.enterisbiopharma.com.**

CMC TESTING SERVICES

Eurofins BioPharma Product Testing offers complete CMC Testing Services for the Bio/Pharmaceutical industry, including all starting materials, process intermediates, drug substances, drug product, packaging, and manufacturing support through our broad technical expertise in Biochemistry, Molecular & Cell Biology, Virology, Chemistry and Microbiology. With a global capacity of more than 1,600,000 square feet of facilities and 35 locations worldwide, our network of GMP laboratories and vast experience allow us to support projects of any size from conception to market. For more information, visit Eurofins BioPharma Product Testing at **www.EurofinsUS.com/BPT.**

GLOBAL MANUFACTURING PARTNER

Flex is a global manufacturing partner that helps a diverse customer base design and build products that improve the world. Through the collective strength of a workforce across 30 countries and responsible, sustainable operations, Flex delivers technology innovation, supply chain, and manufacturing solutions to various industries and end markets. Flex Health Solutions provides design, engineering, manufacturing, real-time supply chain insight, and logistics services to pharmaceutical and medtech companies. It focuses on medical device and drug delivery design, development and manufacturing solutions, including extensive work in injection pens, auto-injectors, wearable pumps, and smart inhalers. Our approach is supported by FDA-registered and ISO 13485- compliant and ISO 11608-1-accredited faciilties, with a world-class single quality system across sites. For more information, visit Flex Health Solutions at **www.flex.com/health.**

FORMULATION SUPPORT, LIPID-BASED TECHNOLOGIES

With application and R&D Centers in the United States, France, India, and China, the **Gattefossé** group is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we are able to support your development efforts and stay at the forefront of research both in basic and applied sciences pertaining to lipids and related drug delivery technologies. Our support covers all stages of development, from solubility screening and preclinical to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.com.**

Technology & Services Showcase

Functional Chemicals

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and the division created OXYCAPT™ Multilayer Plastic Vial & Syringe to solve some issues of existing primary packaging for injectable drugs. OXYCAPT Vial & Syringe consists of three layers. The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharmaceutical industry. The middle layer is made of state-of-the-art polyester developed by MGC. The oxygen-barrier property is almost equivalent to glass and much better than COP. OXYCAPT also provides an ultra violet (UV) barrier. For more information, visit Mitsubishi Gas Chemical at **www.mgc.co.jp/eng/products/abd/oxycapt.html.**

Patient-Focused Delivery Devices

Nemera

With over 1,600 people and four plants across two continents, **Nemera** is a world leader in the design, development, and manufacturing of drug delivery devices for the pharmaceutical, biotechnology, generics industries. Nemera's services and products cover several key delivery routes: Ophthalmic (multidose eye droppers for preservative-free formulations), Nasal, Buccal, Auricular (pumps, valves, and actuators for sprays), Dermal & Transdermal (airless and atmospheric dispensers), Parenteral (autoinjectors, pens, safety devices, and implanters), and Inhalation (pMDIs, DPIs). Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including off-the-shelf innovative systems, customized design development, and contract manufacturing. For more information, contact Nemera at information@nemera.net or visit **www.nemera.net.**

Injectable Drug Delivery

Owen Mumford
Pharmaceutical Services

Owen Mumford Pharmaceutical Services is a specialist in the design, development, and manufacture of injectable drug delivery systems for the pharmaceutical, biotech, and generics industries. These include single-dose and multi-dose reusable and disposable auto-injectors, pens, and syringes for subcutaneous and intramuscular administration. Our innovative products are designed to meet both the need of our pharmaceutical partners and their patients by facilitating ease of use and improving safety and patient compliance. Our devices are also designed with the aim of reducing complexity and risk for the pharmaceutical and biotech industry in the development of their combination products. Our products are supported by our services, and we work with our partners every step of the way, supporting and guiding from initial concept stage through to taking the solution to market. For more information, visit Owen Mumford Pharmaceutical Services at **www.ompharmaservices.com.**

Global Data & Analytics

PharmaCircle is a leading provider of global data and analysis on the pharmaceutical, biotechnology, and drug delivery industries. PharmaCircle's premier database delivers an integrated scientific, regulatory, and commercial landscape view with unprecedented access to hundreds of company, product, and technology attributes. PharmaCircle connects product and pipeline information for drugs and biologics with formulation and component details, and provides due diligence level data on nearly 6,000 drug delivery technologies and devices. Drug label comparison tools and full-text document search capabilities help to further streamline research. No other industry database matches PharmaCircle's breadth of content and multi-parameter search, filtering, and visualization capabilities. To learn more, email contact@pharmacircle.com, call (800) 439-5130, or visit **www.pharmacircle.com.**

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Captisol	5	cdinfo@captisol.com	www.Captisol.com
Catalent Pharma Solutions	76	888-SOLUTION (USA)	www.catalent.com
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Although meeting physically at conferences, trade shows and corporate facilities has been significantly changed, Drug Development & Delivery has remained open and committed to providing digital and print solutions for drug developers around the world.

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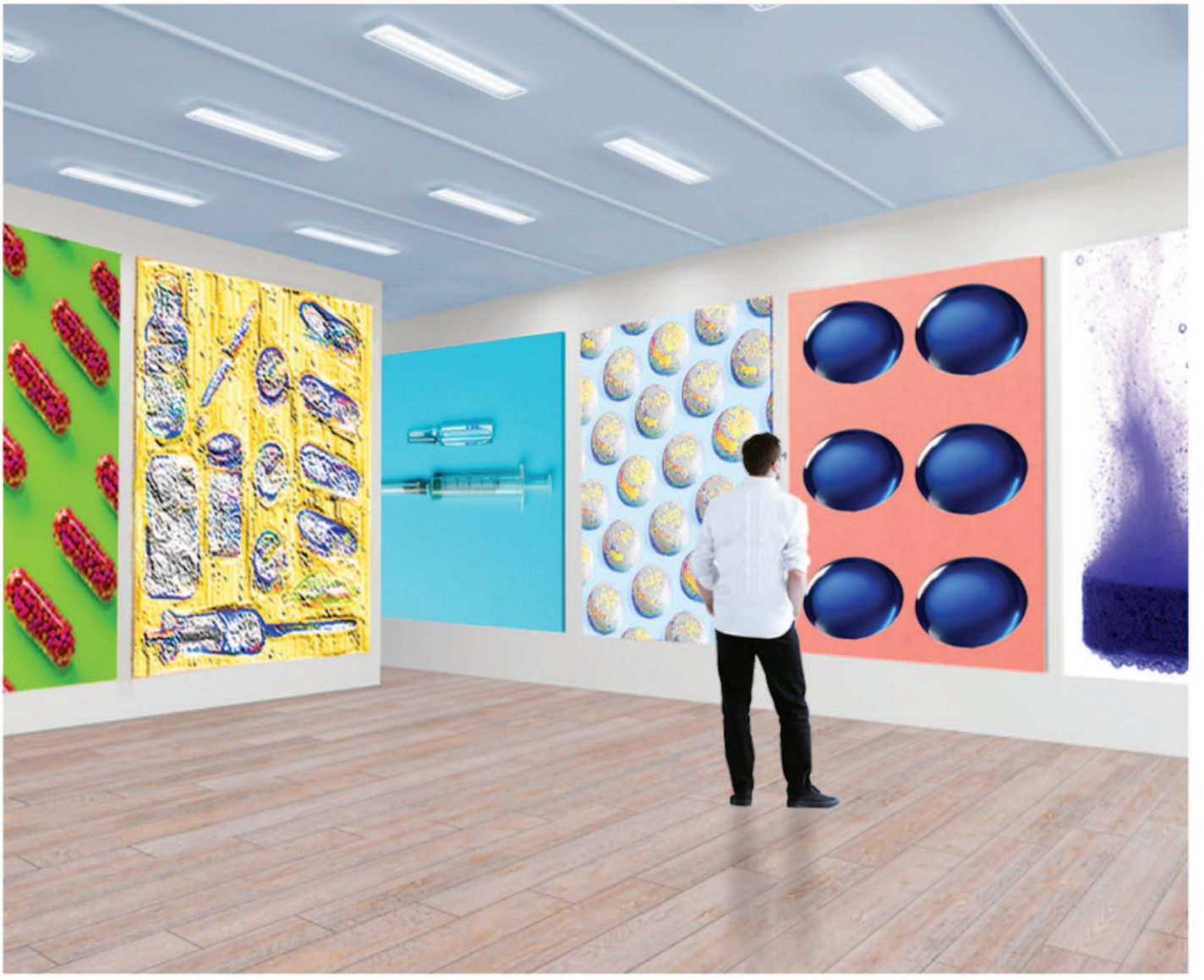

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Successful treatments are built on drug development science, superior formulation technologies and the art of dose form design that meets the needs of patients, doctors and innovators.

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