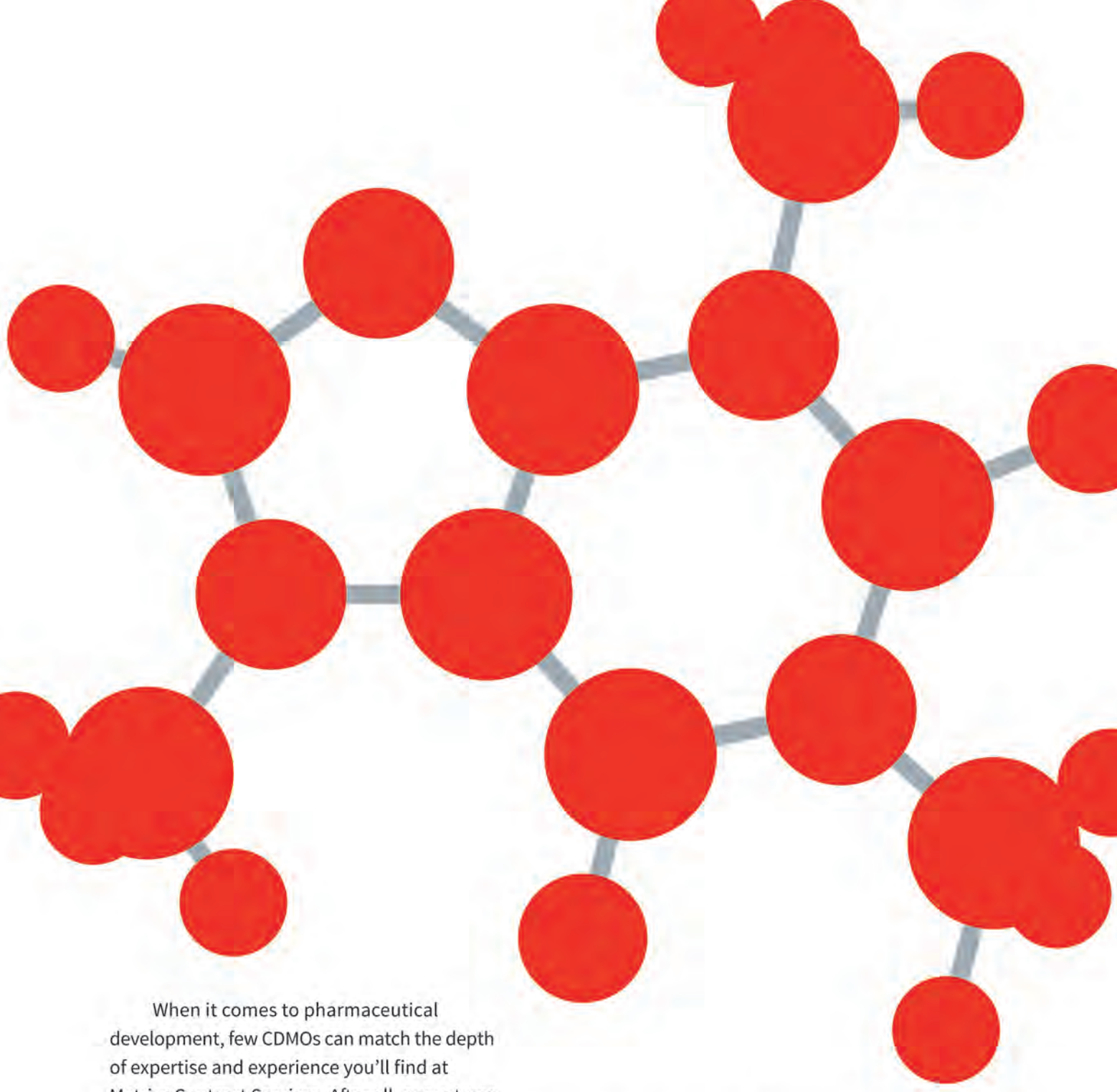

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Drug Development & Delivery

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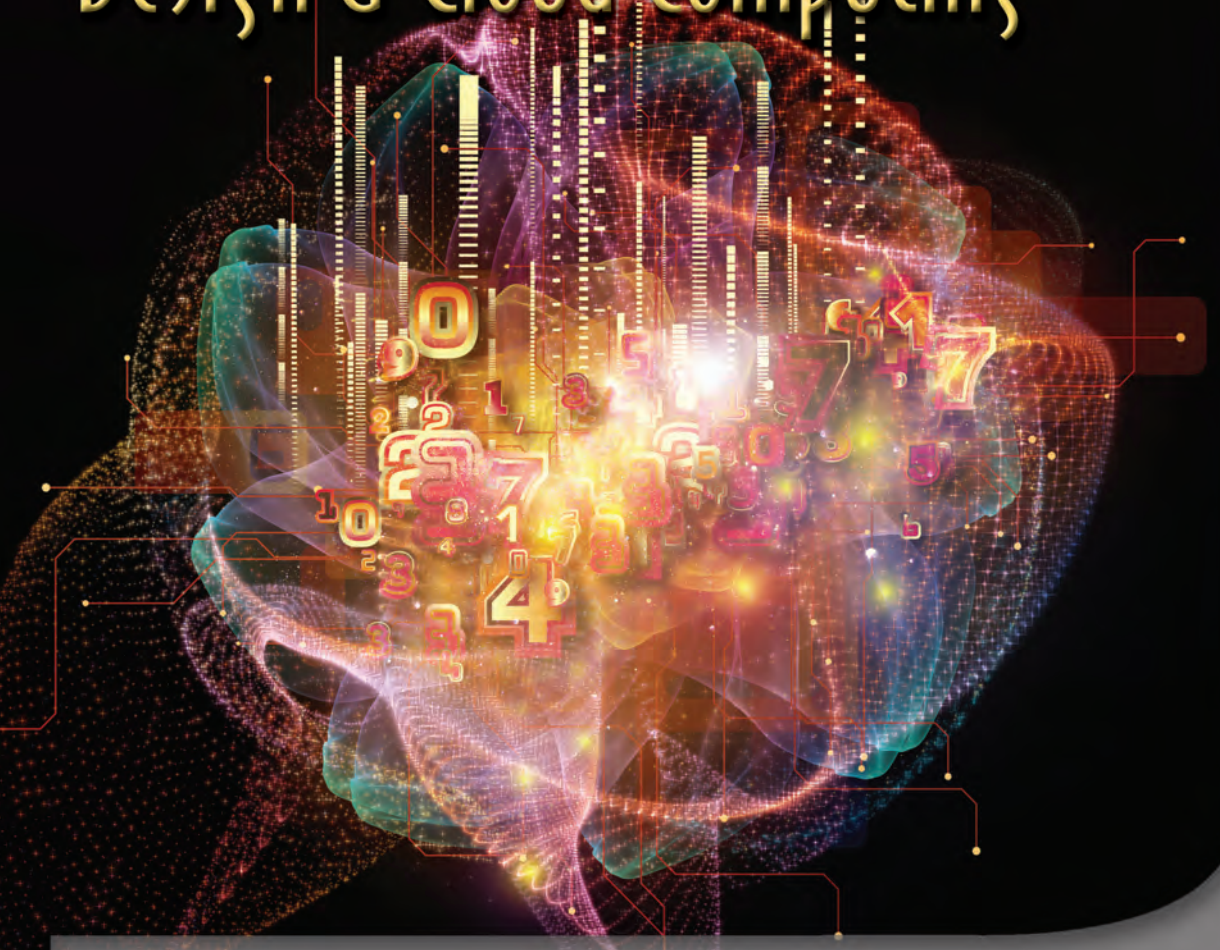
Quantum Molecular Design & Cloud Computing



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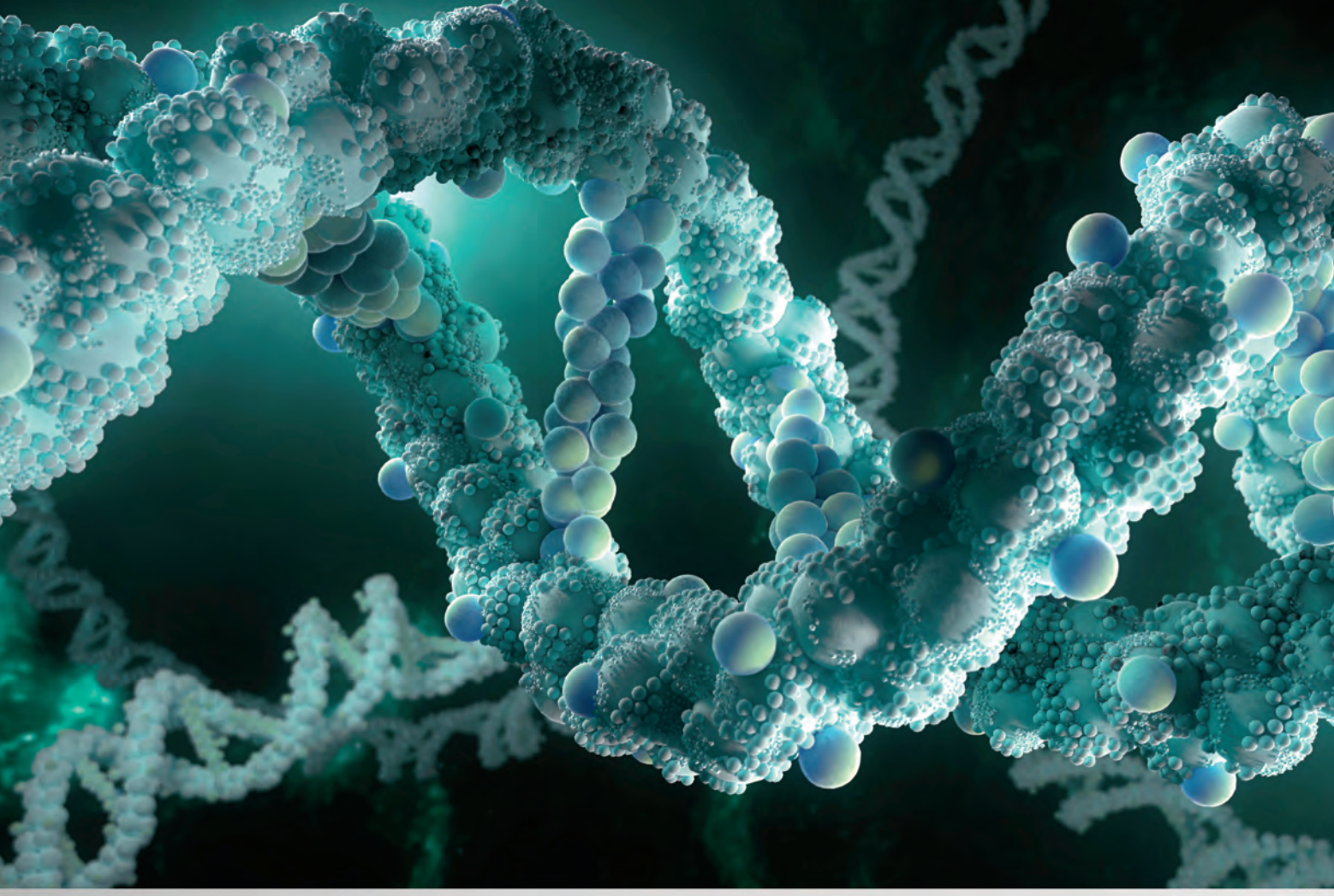

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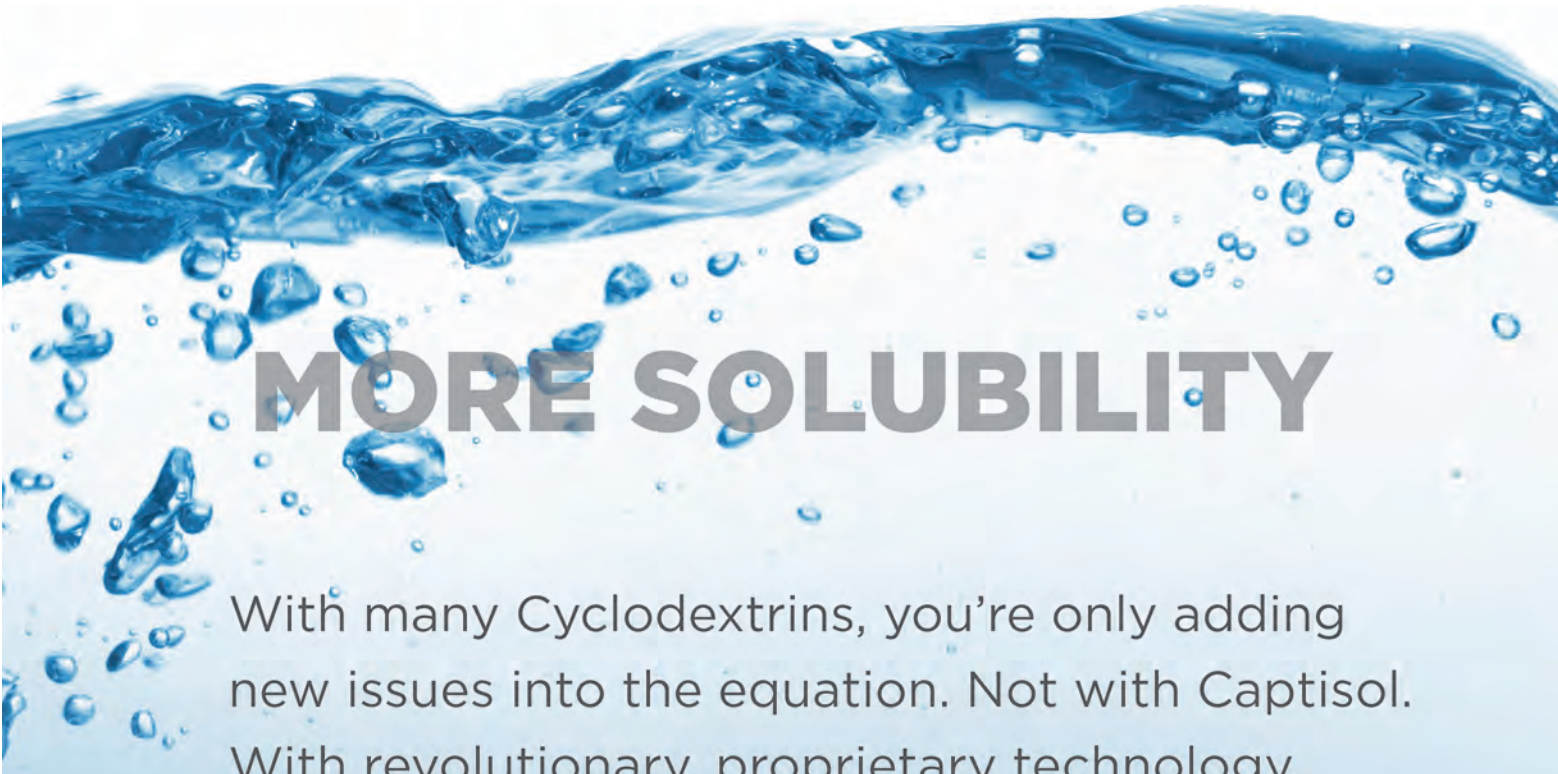
MORE TECHNOLOGY.



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"Quantitative Polymerase Chain Reaction (qPCR) technology is a core technique within NGS, employed for the robust quantification of library target molecules. It is essential that qPCR instrumentation deliver precise data at this point, or users risk ruining the NGS run before it even gets started. Unfortunately, many traditional qPCR systems suffer from imprecise temperature control, uniformity, and light bleedthrough, which compromise the reliability of each run."

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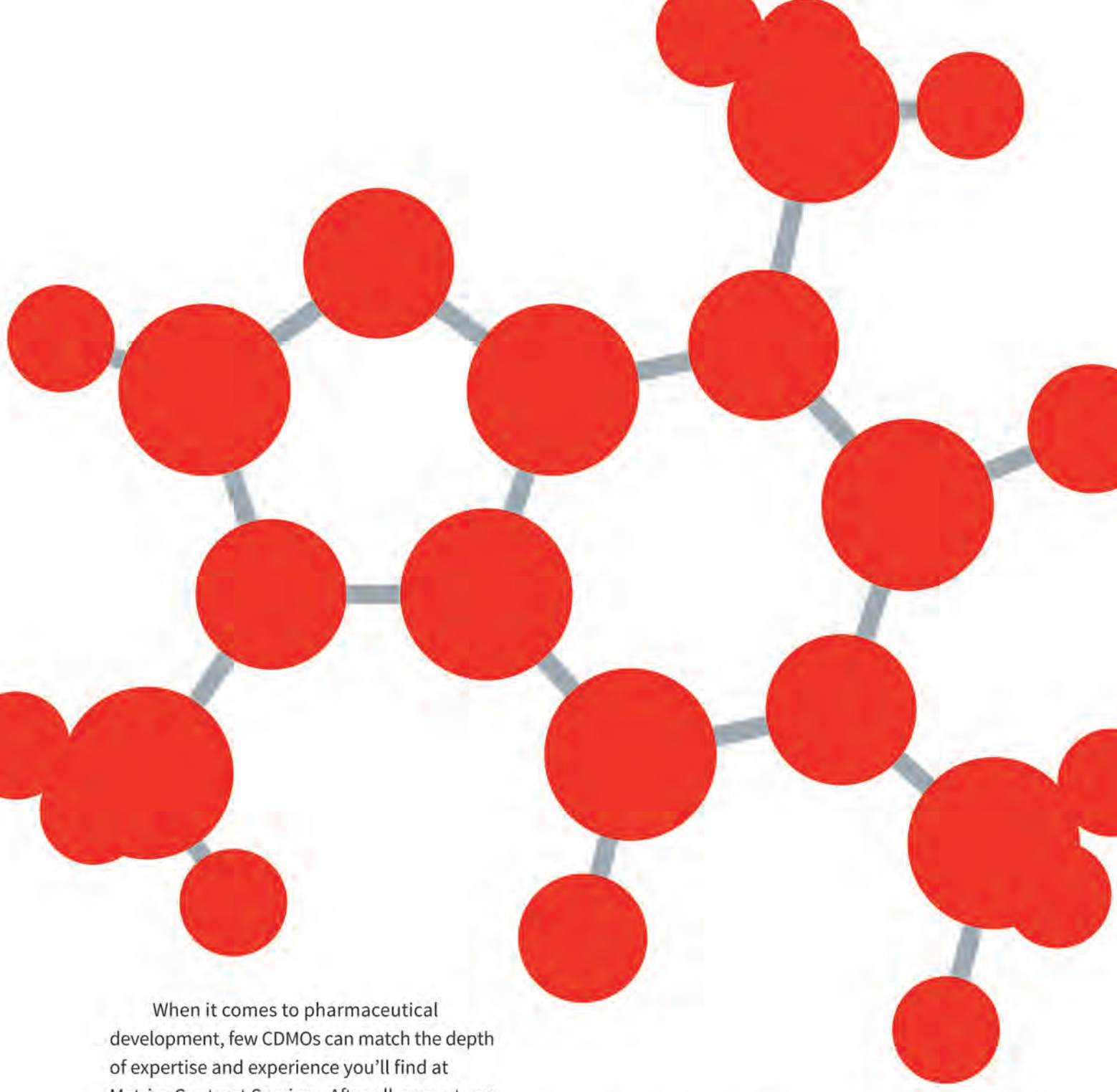

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"Organizations that develop drugs cannot afford to stick to traditional costly and time-consuming methods of drug discovery. Nor can they remain mired in outdated thinking that focuses on the past failures of computational drug discovery. A number of newer approaches are yielding faster, more accurate, and more affordable results. Cloud computing combined with the continued influence of Moore's Law has provided an unprecedented opportunity to apply inexpensive high-performance computing to drug discovery."

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Complex packaging? Vetter is the simple choice.

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Drug Development & Delivery

Wednesday, April 6th

KEYNOTE: CRISPR Versus AI: Which will have a more profound impact on humanity within the next 50 years?
Derek Hennecke, *President & CEO, Xcelience*

TOPIC: Strategic & Emerging Therapeutic Markets
Amy Duda, *Director of Strategic Planning, Sudler New York*

TOPIC: Innovative Drug Platform & Formulation Technologies
Kurt Sedo, *Vice President of Operations, PharmaCircle LLC*

TOPIC: Drug Devices: Current & Future Directions
Adrienne Lovink, *Partner, Consulting, Decision, Resources Group (DRG)*

TOPIC: Contract Services: Trends & Industry Landscape
Nitin Naik, *Global Vice President, Frost & Sullivan's Life Sciences Practice*

Thursday, April 7th

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9:00 AM - 12:00 PM

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ZIOPHARM Announces First Patient Enrolled in Phase I Study; Drug Uses Sleeping Beauty Platform

ZIOPHARM Oncology, Inc. recently announced that the first patient has been enrolled in a Phase I clinical study of its second-generation non-viral CD19-specific chimeric antigen receptor (CAR) modified T-cell therapy in patients with advance lymphoid malignancies. The CD19-specific T cells were modified using the Sleeping Beauty system to stably express the CAR in T cells.

The Sleeping Beauty transposon-transposase is a unique non-viral system for introducing genes encoding CARs and T-cell receptors (TCRs) into lymphocytes and is exclusively licensed by Intrexon Corporation through The University of Texas MD Anderson Cancer Center and accessed as part of ZIOPHARM's collaboration. This non-viral approach may play an important role in immunotherapy and has several potential advantages over viral delivery systems, including: lower cost of generating genetically modified T cells, generate T cells with minimal ex vivo processing, conduit to targeting solid tumor neo-antigens using TCRs, and pathway to overcome regulatory hurdles

"The survival benefit seen in early clinical results with our first generation CD19-specific CAR+ T cells were highly encouraging, and preclinical results to date suggest that our next-generation CAR structure may improve upon these outcomes," said Laurence Cooper, MD, PhD, Chief Executive Officer of ZIOPHARM. "These studies continue to strengthen our understanding of the application and benefit of the Sleeping Beauty platform, the only efficient non-viral gene transfer system in clinical application. Sleeping Beauty offers the potential to significantly reduce the expense and simplify the implementation of genetically modified T cells, both of which are critical to the personalization and broad application of immunotherapies based on CARs and TCRs."

In two prior trials the first-generation CD19-specific CAR+ T cells, patient-derived (autologous) or donor-derived (allogeneic) T cells were administered to recipients with advanced CD19-expressing leukemias and lymphomas after hematopoietic stem-cell transplantation (HSCT). Results demonstrated an apparent doubling of survivals compared to historical controls.

The second-generation Sleeping Beauty CAR+ T cells employ a revised CAR construct designed to improve persistence and anti-tumor response over the first generation therapy. Additionally, this investigational treatment is independent of HSCT. This trial is being conducted at MD Anderson.

ZIOPHARM Oncology is a Boston, MA-based biotechnology company employing novel gene expression, control, and cell technologies to deliver safe, effective, and scalable cell- and viral-based therapies for the treatment of cancer. The company's synthetic immuno-oncology programs, in collaboration with Intrexon Corporation and the MD Anderson Cancer Center, include chimeric antigen receptor T cell (CAR-T) and other adoptive cell-based approaches that use non-viral gene transfer methods for broad scalability.

Protea Announces Collaborative Partnership With Protein Metrics

Protea Biosciences Group, Inc. recently announced it is collaborating with Protein Metrics Inc., a premier provider of software solutions for the comprehensive characterization of proteins, to advance new analytical capabilities for use in the development of protein biotherapeutics.

"We are positioning Protea to be a leader in the next generation of bioanalytics, focused on the needs of the biotherapeutics industry," said Greg Kilby, PhD, Protea's Vice President and Chief Operating Officer. "Our Protein Metrics collaboration will provide Protea access to advanced software for comprehensive protein characterization, PTM analysis, and sequence variant analysis. We will combine our technologies, including our proprietary LAESI mass spec imaging platform, with Protein Metrics software to provide novel, big data services to identify, characterize, and quantify biologically important molecules. Biopharma is in need of these new bioanalytical capabilities."

"The rapid adoption of our suite of software is entirely thanks to the input from our customers who have helped us design tools that are directly applicable and tailored to their needs. We are delighted to partner with Protea Biosciences and are looking forward to seeing our software advance the results they provide their clients," added Chris Becker, President and CEO of Protein Metrics.

Protea Biosciences Group, Inc. provides innovative bioanalytical solutions to the pharmaceutical and life science industries by applying the company's proprietary technology to identify and characterize the proteins, metabolites, lipids, and other biologically active molecules that are the byproducts of all living cells and life forms. Protea is the leader in mass spectrometry imaging services (MSI), providing a revolutionary capability that enables the identification and spatial display of biologically active molecules in tissue and cells. MSI can be performed without sample preparation, labeling or antibody techniques, thereby integrating for the first time direct identification of molecules with anatomic pathology. For more information, visit www.proteabio.com.

Protein Metrics Inc. is a privately held company serving biopharmaceutical development professionals. The company focuses on the analysis of mass spectrometric and other analytical data on proteins, peptides, and glycans. Seeking to ensure that software to analyze mass spec and other analytical data keeps pace with the rapid advances in instrumentation, Protein Metrics leverages its experience in mass spectrometry, computer science, and bioinformatics to make analytical results more complete, sensitive, accurate, and easier to achieve. For more information, visit www.proteinmetrics.com.

Portola Pharmaceuticals Enters Licensing Agreements Worth Up to $120 Million

Portola Pharmaceuticals recently announced it has licensed lead development and commercial rights to its investigational agent andexanet alfa in Japan to Bristol-Myers Squibb Company and Pfizer Inc. to be developed as an antidote for apixaban and other Factor Xa inhibitors. Separately, Portola has entered into a clinical collaboration agreement with Bayer HealthCare to include its Factor Xa inhibitor rivaroxaban in this clinical development program in Japan.

Three oral Factor Xa inhibitors are currently on the market in Japan – Bristol-Myers Squibb and Pfizer's apixaban, Bayer HealthCare's rivaroxaban, and Daiichi Sankyo's edoxaban – but an antidote is not yet approved. A universal antidote for Factor Xa inhibitors is needed for certain patients in Japan, as the clinical use of these novel oral anticoagulants is growing.

"These agreements allow Portola to expand the development and commercialization of andexanet alfa into Japan, which is a new country for us and the third largest market for Factor Xa inhibitors after the United States and EU 5 countries," said William Lis, Chief Executive Officer of Portola. "Bristol-Myers Squibb, Pfizer and Bayer all have extensive infrastructure and experience in Japan. With Bristol-Myers Squibb and Pfizer leading development and commercialization activities and Bayer providing support, the path forward for andexanet alfa as a Factor Xa inhibitor antidote in Japan will be accelerated."

Portola is developing andexanet alfa, a US FDA-designated breakthrough therapy, for patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed, such as in life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures. Portola retains full, worldwide commercial rights to andexanet alfa outside of Japan.

Under the terms of the agreement with Bristol-Myers Squibb and Pfizer, Portola will receive an upfront payment of $15 million and is eligible to receive potential regulatory and sales-based milestone payments totaling $90 million, as well as double-digit royalties based on andexanet alfa net sales in Japan. Bristol-Myers Squibb and Pfizer will be responsible for all development and regulatory activities for andexanet alfa in Japan and for commercializing the drug in Japan, assuming it receives regulatory approval from the Japanese Ministry of Health, Labor and Welfare (MHLW).

Portola previously entered into two separate non-exclusive clinical collaboration agreements with Bristol-Myers Squibb and Pfizer to support Phase II and Phase III development of andexanet alfa and apixaban in the United States and EU. Portola may receive additional milestone payments under these agreements based on developments in the United States and EU. Portola has completed a Biologics License Application (BLA) submission with the FDA and is awaiting acceptance for filing. The FDA assigned a PFUDA date of August 17, 2016, under an Accelerated Approval pathway. Portola plans to submit an EU application in 2017. Bristol-Myers Squibb and Pfizer continue to provide development and regulatory guidance to Portola for the andexanet alfa program in the United States and the EU.

Under the terms of the Bayer Clinical Collaboration agreement, Portola will receive an upfront payment of $5 million and is eligible to receive an additional milestone payment based on Japanese MHLW approval of andexanet alfa as an antidote for rivaroxaban. Bayer will provide technical support as well as fund clinical studies of andexanet alfa with rivaroxaban in Japan. Bayer will receive no commercial rights under this agreement.

Portola previously entered into two separate non-exclusive clinical collaboration agreements with Bayer HealthCare and its development partner, Janssen Pharmaceuticals, Inc. to support Phase II and Phase III studies of andexanet alfa and rivaroxaban in the United States and Europe. Portola may receive additional milestone payments under these agreements based on developments in the United States and EU.

Commensurate with the increase in use of Factor Xa inhibitors, the number of hospital admissions due to bleeding associated with these agents continues to grow. Annually, 1% to 4% of patients treated with Factor Xa inhibitors may experience major bleeding, and an additional 1% may require emergency surgery. Currently, use of the Factor Xa inhibitor class in Japan is substantial and growing. Based on data from IMS Health, in the 12 months ending September 2015, sales of novel oral anticoagulants in Japan were more than $800 million. There is an unmet need for an antidote for some patients.

RedHill Biopharma Announces Collaboration With Germany's Fraunhofer Institute

RedHill Biopharma Ltd. recently announced a research collaboration with Leipzig-based Fraunhofer Institute for Cell Therapy and Immunology (IZI), a research unit of the Fraunhofer Society for the evaluation of RedHill's Phase II-stage oncology drug candidate, RP101.

The research collaboration tests RP101 in preclinical oncology models, including pancreatic cancer, in combination with standard-of-care chemotherapies to support existing Phase I and Phase II clinical data. RP101 is a proprietary, first-in-class, orally administered, heat shock protein 27 (Hsp27) inhibitor intended to prevent the induction of resistance to chemotherapy (chemo-resistance), thus maintaining sensitivity of the tumor to chemotherapy and potentially enhancing patient survival. RP101 has completed several clinical studies, including a Phase II study in pancreatic cancer and has been granted Orphan Drug Designation for the adjunct treatment of pancreatic cancer by the US FDA and the European Medicines Agency (EMA).

As part of the collaboration, Fraunhofer IZI is conducting real-time monitoring of tumor engraftment, tumoricidal efficacy, and response to treatment with RP101 in combination with standard-of-care chemotherapies. Results from the studies are expected during the first half of 2016. The preclinical program is intended to support the existing Phase I and Phase II clinical data with RP101 and to assess the drug's clinical development path.

In August 2014, RedHill entered into an exclusive option agreement with RESprotect GmbH, a privately held Germany-based biotech company, under which RedHill obtained the option to acquire the worldwide exclusive rights to RP101 for all indications, other than for the pancreatic cancer indication in South Korea. RedHill announced in July 2015 that it had extended the term of the exclusive option agreement for an additional year.

RP101 is a nucleoside analogue found by Prof. Rudolf Fahrig at the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) in Hannover, Germany, to inhibit development of chemo-resistance in various cancer models. It is an orally administered, patent-protected small molecule which binds to heat shock protein 27 (Hsp27) and inhibits its anti-apoptotic effects. Hsp27 is a chaperone protein which is found in abnormally high levels in cancer cells. The overexpression of Hsp27, which results in anti-apoptotic effects, has been linked to tumor resistance to cytotoxic drugs and the development of metastasis. By inhibiting Hsp27, RP101 may prevent the induction of resistance to chemotherapy (chemo-resistance) and maintain sensitivity of tumors to chemotherapy, thus potentially enhancing patient survival. RP101 has been studied in several Phase I and Phase II clinical studies with a total of 249 subjects treated, including a Phase II study in pancreatic cancer. RP101 has been granted Orphan Drug Designation for the adjunct treatment of pancreatic cancer by the US FDA and the EMA.

RedHill Biopharma Ltd. is an emerging Israeli biopharmaceutical company primarily focused on the development and commercialization of late clinical-stage, proprietary, orally administered, small molecule drugs for the treatment of inflammatory and gastrointestinal diseases, including cancer.

The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops specific problem solutions at the interfaces of medicine, life sciences, and engineering. The Institute practices contract research for biotechnological, pharmaceutical, and medical-technological companies, hospitals, diagnostic laboratories, and research facilities.

Inovio Pharmaceutical's DNA Vaccine for Zika Virus Induces Robust Immune Responses

Inovio Pharmaceuticals, Inc. recently announced that preclinical testing of its synthetic vaccine for the Zika virus induced robust and durable immune responses, demonstrating the potential for a SynCon vaccine to prevent and treat infections from this harmful pathogen. Health authorities have observed neurological and autoimmune complications potentially associated with Zika virus, including microcephaly in newborns and Guillain-Barre syndrome. Inovio is developing its Zika vaccine with GeneOne Life Sciences (KSE:011000) and academic collaborators.

"Using our SynCon technology, we rapidly generated a synthetic vaccine candidate that shows promise as a preventive and treatment. With robust antibody and killer T cell responses generated by our vaccine in mice, we will next test the vaccine in non-human primates and initiate clinical product manufacturing. We plan to initiate phase I human testing of our Zika vaccine before the end of 2016," said Dr. J. Joseph Kim, Inovio's President and CEO.

In this preclinical study, DNA vaccine constructs targeting multiple Zika virus antigens were synthetically generated using Inovio's SynCon vaccine technology. These SynCon constructs were administered using Inovio's CELLECTRA electroporation delivery technology. Inovio's Zika DNA vaccine resulted in seroconversion, or the development of detectable specific antibodies in the blood, in all vaccinated mice. Researchers also observed that vaccination generated robust and broad T cell responses as analyzed by the standardized T cell ELISPOT assay. These findings are vital given the potential importance of neutralizing antibodies in preventing infection and the role T cells play in clearing infection by killing cells that harbor the virus.

Zika virus belongs to the flavivirus family, which includes dengue and West Nile virus (WNV). Inovio previously published robust immunogenicity and challenge protection data for its SynCon dengue and WNV vaccine candidates. Inovio's Zika program builds on its extensive previous preclinical development experience with flavivirus-related vaccines.

First identified in Uganda, Zika virus subsequently spread to equatorial Asia and over the past 2 years has rapidly spread through the South Pacific, including Hawaii, and to South America, Central America, and the Caribbean. Zika virus is a flavivirus, a family of viruses including yellow fever, dengue, and West Nile virus, which are introduced to people through mosquito bites. Because the Aedes species of mosquitoes that spread Zika virus is found throughout the world there is concern that outbreaks will spread to new countries. There is also concern that Zika can spread sexually, as has been reported for some returning travelers. In February 2016, WHO stated that 39 countries had reported locally acquired circulation of the Zika virus since January 2007. Geographical distribution of the virus has steadily expanded.

The most common symptoms of Zika virus are fever, rash, joint pain, and conjunctivitis. More seriously, a possible link to a severe birth defect called microcephaly has recently been observed resulting from infected mothers. Microcephaly is a rare condition marked by an abnormally small head and incomplete brain development. There may also be a link with Guillain-Barré syndrome, a disease in which the body's immune system mistakenly attacks peripheral nerves. Symptoms start with muscle weakness. In severe cases the person is almost totally paralyzed and the disorder can be life threatening.

No vaccine or therapy currently exists for the Zika virus.

GeneOne Life Science Inc. is an international DNA vaccine developer and leading contract manufacturer of DNA plasmid-based agents for preclinical and clinical trials for global companies and institutions. It researches and develops DNA vaccines to prevent and treat incurable diseases in South Korea and internationally. The company is headquartered in Seoul, South Korea. VGXI, Inc., GeneOne's wholly owned manufacturing subsidiary located in Texas, is the largest pure-play cGMP DNA plasmid manufacturing facility in the world.

Inovio is taking immunotherapy to the next level in the fight against cancer and infectious diseases. It is the only immunotherapy company that has reported generating T cells in vivo in high quantity that are fully functional and whose killing capacity correlates with relevant clinical outcomes with a favorable safety profile. The company is advancing a growing clinical- and preclinical-stage product pipeline. Partners and collaborators include MedImmune, Roche, University of Pennsylvania, DARPA, GeneOne Life Science, Drexel University, NIH, HIV Vaccines Trial Network, National Cancer Institute, US Military HIV Research Program, and University of Manitoba. For more information, visit www.inovio.com.

Galapagos Starts SAPHIRA Phase II Study With GLPG1837 in Cystic Fibrosis Patients

Galapagos NV recently announced the first dosing in its Phase II exploratory program of GLPG1837 in patients with cystic fibrosis (CF). GLPG1837 is a candidate CFTR potentiator drug in clinical development for the treatment of Class III mutations in cystic fibrosis. The SAPHIRA Phase II program will explore the safety, tolerability, and efficacy properties of GLP1837 in CF patients with a G551D (SAPHIRA 1) or S1251N (SAPHIRA 2) Class III mutation. Topline results from the SAPHIRA Phase II program are expected in Q4 2016.

"Today's announcement is a landmark achievement in our CF program, with the first CF patient being treated with a Galapagos potentiator," said Onno van de Stolpe, CEO of Galapagos. "Recruitment for the SAPHIRA program is rapid, and we look forward to seeing to what extent our promising in vitro data translates into clinical results. We aim to start and report a number of clinical studies with additional compounds in the CF portfolio throughout 2016."

SAPHIRA 2, an open-label study of two doses of GLPG1837 in at least six CF patients with the S1251N mutation, was first dosed in a patient last week. SAPHIRA 1, an open-label study of three doses of GLPG1837 in at least 12 patients with the G551D mutation, is expected to begin dosing soon. The SAPHIRA Phase II program will explore the safety, tolerability, efficacy, and medicine-like properties of GLPG1837 in patients in six EU countries and Australia. Primary objectives are to evaluate the safety and tolerability; secondary objectives are to assess changes in sweat chloride from baseline as the biomarker of cystic fibrosis transmembrane conductance regulator (CFTR) ion channel function and to explore the changes in pulmonary function (forced expiratory volume in 1 second [FEV1]) from baseline. Both studies will include subjects treated with Kalydeco as well as those who are naïve to this drug. In each study, different doses of GLPG1837 tablets will be administered twice daily for a total duration of 4 weeks.

In September 2013, Galapagos and AbbVie, a global biopharmaceutical company, entered into a global collaboration agreement focused on the discovery and worldwide development and commercialization of potentiator and corrector molecules in a potential triple combination therapy for the treatment of CF. Under the terms of the agreement, AbbVie made an upfront payment of $45 million to Galapagos. Upon successful completion by Galapagos of clinical development through to completion of Phase II, AbbVie will be responsible for Phase III, with financial contribution by Galapagos. Galapagos has earned $20 million in milestone payments to date and is eligible to receive up to $340 million in total additional payments for developmental and regulatory milestones, sales milestones upon the achievement of minimum annual net sales thresholds, and additional tiered royalty payments on net sales, ranging from mid-teens to 20%.

Galapagos is a clinical-stage biotechnology company specialized in the discovery and development of small molecule medicines with novel modes of action. Its pipeline comprises three Phase II, two Phase I, four preclinical, and 20 discovery studies in cystic fibrosis, inflammation, fibrosis, osteoarthritis, and other indications. It has discovered and developed filgotinib: in collaboration with Gilead they aim to bring this JAK1-selective inhibitor for inflammatory indications to patients all over the world.

Galapagos is focused on the development and commercialization of novel medicines that will improve people's lives. The Galapagos group, including fee-for-service subsidiary Fidelta, has approximately 400 employees, operating from its Mechelen, Belgium, headquarters and facilities in The Netherlands, France, and Croatia. For more information, visit www.glpg.com.

Biota Commences Dosing in Phase II Trial of Antiviral Therapy

Biota Pharmaceuticals, Inc. recently announced that the first patient has been dosed in a Phase II double-blind, randomized, placebo-controlled trial to evaluate the safety, tolerability and efficacy of BTA074 5% gel in male and female patients with condyloma, or anogenital warts, caused by human papillomavirus (HPV) types 6 & 11.

"We are excited to progress BTA074 into a well-powered proof-of-concept study. The currently approved topical treatments for condyloma lack consistent efficacy and cause a considerable amount of undesirable local skin reactions, such as erosions and edema, often leading to the need to stop treatment. With this larger Phase II study, we hope to further validate the clinical activity of BTA074 seen in its earlier Phase II trial, which showed evidence of overall clearance and a benign side effect profile," said Joseph M. Patti, PhD, President and Chief Executive Officer at Biota. "We now have three direct-acting antiviral programs in the clinic, each of which has the potential to help patients by attacking the root cause of their viral infections."

BTA074 is a potent and selective inhibitor of the interaction between two viral proteins from HPV6 and HPV11, and is designed to prevent HPV DNA replication. The Phase II trial is expected to enroll approximately 210 patients with anogenital warts and will have a 2 to 1 randomization of BTA074 5% gel to placebo gel. The patients will be dosed twice daily for up to 16 weeks. The primary efficacy objective is to determine the complete clearance rate for baseline anogenital warts from the commencement of therapy to the end of the treatment period. Secondary efficacy endpoints include various assessments of clearance and wart area reduction for both baseline warts and post-baseline emergent warts.

Condyloma infections from human papillomavirus (HPV) represent the most frequent viral sexually transmitted disease in adults worldwide. In the United States, approximately 1% to 2% of sexually active adults between the ages of 15 to 49 develop condyloma as the primary clinical manifestation of HPV infection. Currently available treatments for anogenital warts typically are divided into two categories, ablative/destructive therapies and topical therapies. Existing topical therapies are associated with significant mucosal toxicities manifesting as erosions and ulcerations, which can result in therapy discontinuation. Ablative options can be painful and scarring, and can lead to sexual dysfunction. Another significant limitation with current therapies is a high incidence of recurrence after successful primary treatment.

Biota Pharmaceuticals is focused on the discovery and development of direct-acting antivirals to treat infections that have limited therapeutic options and affect a significant number of patients globally. The company has three product candidates in active clinical development. These include vapendavir, an oral treatment for human rhinovirus infections in moderate-to-severe asthmatics, currently being evaluated in the company's ongoing Phase IIb SPIRITUS trial; BTA585, an oral fusion protein inhibitor in Phase I development for the treatment and prevention of respiratory syncytial virus (RSV) infections; and BTA074, a topical antiviral treatment in Phase II development for condyloma caused by human papillomavirus types 6 & 11. For more information, visit www.biotapharma.com.

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Management Insight

Why I Sold Xcelience: The Non-Linear Path of Decision-Making

By: Derek Hennecke, CEO & President, Xcelience

I started writing for *Drug Development & Delivery* in 2008 with a six-part series on the lessons learned from the management buy-out that created Xcelience. Now I've sold the company to Capsugel. Some of you may be wondering, did I sell out? I plan to stay on with Xcelience/Capsugel, and to continue writing these articles, so it only seems fitting that I start the new year off by sharing with you some of the thought process that brought me to this momentous and very emotional decision, as well as some of the lessons I learned in the process.

I hope that you will follow my reasoning. I'm not going to give you a chronological story. The decision didn't come about in an orderly fashion.

I remember when I was a student of Microbiology in the 80s in Canada. All science students were required to read Thomas Kuhn's influential scientific philosophy book, The Structure of Scientific Revolutions. At the time, I couldn't imagine a duller book. Upon review, it hasn't changed. And yet, something Kuhn said stayed with me through the decades.

Kuhn says that science doesn't proceed in an orderly linear direction. We don't progress from one theory to the next gradually, as each new piece of evidence arrives and alters the course of thought. Instead, Kuhn proposes thinking of an existing theory as a long-standing house. Each piece of evidence that arises to contradict that theory is like a new stone set on the roof of that house. More and more stones are placed on the house, but as long as the roof holds, the theory stands. Oftentimes, the roof stands long after the weight of evidence bearing down upon it seems unbearable. Then, one day, the roof collapses. A new theory is built in its place, using the new

stones. Inevitably, we all look back with wonder at how that old house managed to stand so long when the new evidence clearly should have destroyed it long ago.

Major business decisions are no different. In August of last year, Xcelience was absolutely not for sale. Xcelience was my house, in more ways than one. There were four rather stupendous rocks upon the roof of this paradigm in my mind, and yet the roof held. A fifth was about to break it.

The first stone on my roof was technological innovation. To be able to offer complete solubility solutions, we were missing one piece of the puzzle: spray-dried dispersion (SDD) technology. Through its 2013 acquisition of Bend Research, Capsugel was a clear leader in this area. Other players desperate to move into the field have bought SDD equipment, but without experienced staff and engineers operating it, you are acting as hands and tools. I would not be one of them.

The second stone was disruptive technology. Uber is a disruptive technology that upended the taxi industry. I've been writing about this quite a bit lately, so it has always been near the edge of my thoughts. If such a disruptive technology were to hit drug development, being at the helm of a small business in such stormy waters is not a secure place to be.

The third stone was the hunger for capital. This is a really big stone, but I had been able to bear it so far. Xcelience was a private company with very little debt, but as the company got bigger, that was going to become harder and harder to maintain. The fees to play in the big leagues are proportionately big. Building a large lab, for example, costs a lot more than building a small one. Daily capital requirements grow with company size as well. You have to pay employees, vendors, and equipment suppliers before you can even begin working for clients, and then you have to wait to be paid. Quick access to working capital is imperative.

The fourth stone was market uncertainty. We've had 6 solid years of market expansion as an industry. What would the future hold? I remain optimistic, but also realistic. Nothing lasts forever. The next recession, big or small, will come at some point. What happens if we need capital and interest rates have gone much higher? What if I am forced to sell to a buyer that doesn't know MY business. I would be relinquishing managerial control to people who don't know my business like I do, and may not want to run it the way I do.

The stone that would eventually bring the house down is going to sound trivial in comparison to the others, but bear with me. It isn't. I'm going to call it "the quest for an authentic partner." Like a bachelor who tells himself he isn't looking for a bride until he meets the right woman, I wasn't looking for a buyer until I found the right one. Capsugel's authenticity made me finally consider settling down for a sale.

Authenticity is what you want in a buyer, but it's more than that. It's what good, successful companies in the modern world are. It's what customers increasingly look for. The days of slick, emotional mottos are slipping away. In the age of the Internet, customers are more sophisticated and educated in their buying choices. Even if you believe people can't intuitively spot a fake, the digital age has given the market more transparency than ever. Facebook, Twitter, blogs, and 24-hours news are forcing companies to live up to their claims. No ad campaign can survive a thousand blog entries trashing your company.

Authenticity means you don't oversell or undersell. You impart a true understanding of your product or service and what it can do for clients. Rather than making unrealistic – or unsustainable – claims, an authentic company speaks to its effort, its commitment, and its genuine capabilities. Any company that over promises is a red flag to clients. On the other hand, consumers are more forgiving of an authentic company when it makes a mistake.

In the pharma industry, authenticity is ascertained by word of mouth. Word of mouth is far more powerful than any ad or sales visit.

Unbeknownst to me, four of the five stones rested placidly on the roof of my house on a sweltering Florida day last August, when the knock on the door came. My paradigm stood. I was not for sale.

I was accustomed to the knock. About once a month for the past couple of years, I've had suitors call. I always listen. It's good business to keep evaluating your options for the future. And let's face it, it's flattering. I'm not above vanity.

I always knew we would have to sell someday. Eventually the capital needs of our growth would force us to. The management team had a 5-year plan to prepare us for that moment. We were 2 years down that road, and right on target. To sell now would be to sell short. We had great plans, as yet unrealized. We weren't ready.

Guido Driesen, President and CEO of Capsugel, was a familiar face. Guido has worked at Capsugel for over 30 years. Capsugel has a long-standing reputation as a dependable research-based manufacturer of high-quality capsules. In recent years, it has significantly broadened its capabilities with a comprehensive suite of technologies for designing, developing, and manufacturing a wide range of finished dosage forms. I also had first-hand experience with them as we had been working with Capsugel since 2006. Xcelience made a name for itself back then as the first company in North America to offer the Xcelodose® micro-dosing systems; a piece of equipment we purchased from Capsugel.

When Guido left my office, I turned to my network to confirm my impressions by word of mouth. In 2013, Capsugel bought two of my industry friends. First, it bought Encap Drug Delivery, in Scotland, led by Stephen Brown. I'd visited Stephen in Edinburgh in 2009 and we'd often enjoyed swapping stories about the Great Recession. Stephen assured me that Capsugel had allowed the company to operate with a great degree of independence, and no one had been laid off. In fact, Encap had increased both its sales and its headcount.

Later that same year, Capsugel bought Bend Research. We'd worked with Bend since 2010 and knew quite a few scientists there. I gave a call to Rod Ray, former CEO of Bend Research and current Scientific and Business Advisor to Capsugel, and asked him about his experience selling to Capsugel. He confirmed that the company had also given them great latitude for independence, and hadn't let anyone go. As with Encap, Bend Research had increased both its sales and headcount.

Rod also told me that Capsugel had negotiated with Bend Research in good faith. As a small business owner, this was extremely important to me. There are only so many hours in a day, and running a company takes most of them. I knew that if I entered into this process with Capsugel, I couldn't do so lightly. It would be draining.

In truth, it took even more hours than I imagined. First, I decided to open the process up to other bidders. I hired investment banker Neil McCarthy, of Fairmount Partners. Again, this is just good business; a fair process would give me peace of mind that I was getting the best deal possible for the company. That meant creating a bid book; a slick little book that provides an overview of operations. The bid book flushed out more serious bidders, including one which also would have made an excellent buyer. It was difficult to close that other door, but ultimately Capsugel made the best match for our capabilities and had the resources to take us to the next level.

Throughout the process, Capsugel was straightforward and trustworthy – just as Rod had said – in a way that is uncommon in the business world. When Guido presented his offer, he asked only that I not move forward myself unless I was serious and willing to follow through with selling the company.

I remember where I was when we had that conversation. I was in an Airbnb apartment in Bilbao, Spain; a stopover on the way to the CPhI. The cool fall air came in through the cracks of the windows. My wife swung in a little hammock in the living room beside me, listening to my half of the conversation with Guido. She had once wisely told me we had no choice but to put our life savings into Xcelience; we could never live with ourselves if we didn't try.

It seems so obvious to me now, but that was the moment when I first realized it. I had to sell. ◆

Derek G. Hennecke
President & CEO
Xcelience

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PULMONARY DELIVERY

Afrezza – Another Lesson for Drug Delivery Professionals?

By: Josef Bossart, PhD

INTRODUCTION

Often when discussing financial and geopolitical events, we use the expressions "history repeats itself" and "those who do not learn from history are fated to repeat it." But perhaps a more realistic assessment is offered by the statement that "history doesn't repeat itself, but it does rhyme." Mannkind's recent announcement that Sanofi has decided to return the marketing rights for Afrezza may not exactly be history repeating itself, but it certainly feels as though it rhymes.

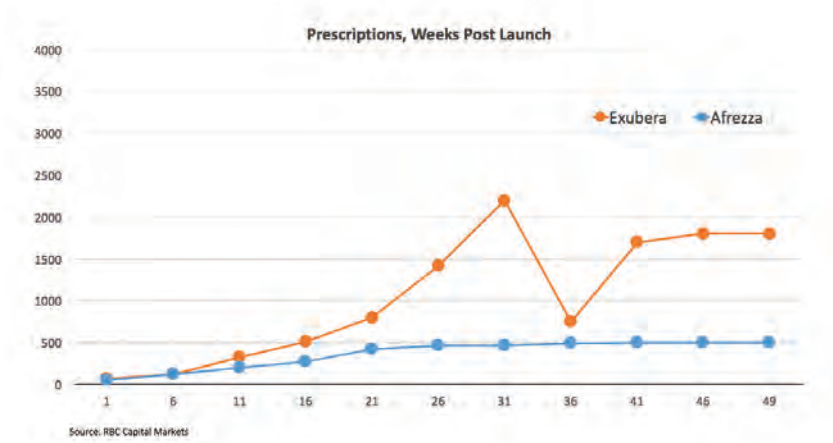
The challenges in successfully introducing an inhaled insulin product shouldn't be a surprise to anyone who follows the pharmaceutical industry. The first inhaled insulin product, Nektar and Pfizer's Exubera, was launched a decade ago with much fanfare and investment but little success. A year later, 2007, Exubera was withdrawn from the market. The general sentiment regarding its failure was that the dry powder delivery device, a large bong-shaped apparatus, was too large and unwieldy. This, combined with respiratory function testing requirements, seemed the obvious reasons for a multibillion dollar product failure. There were no quick fixes; a device redesign would take a couple of years along with several million dollars to reengineer, manufacture, and clinically validate. Easing the requirement for respiratory function testing would take even longer and require years of positive patient experience. Neither of these challenges were easy, inexpensive, or short-term. In the end, Nektar and Pfizer decided to withdraw the product, and Nektar wrapped up its inhaled insulin program, shut down its inhalation activities, and sold the assets to Novartis.

During this 2006-2007 period, Mannkind had entered Phase III testing with their dry powder insulin and were faced with a critical decision. Mannkind had by then invested almost $750 million in R&D, largely to develop their inhaled insulin, a figure that has since ballooned to about $1.8 billion. In retrospect, it seems Mannkind was confident that their product would be able to succeed largely by overcoming the most obvious shortcoming of Exubera, an unwieldy device. Unfortunately, following US approval in 2014 and first sales in 2015, the market hasn't agreed with their optimism and uptake of Afrezza, as measured by sales and prescriptions, has lagged considerably behind the corresponding performance of Exubera a decade earlier.

Mannkind has declared their intention to soldier on with Afrezza, perhaps finding a new marketing partner. They really don't have much choice if they want to succeed with Afrezza. Like Nektar and Pfizer a decade earlier, there is no quick, easy, cheap fix. Perhaps success can be found by allowing physicians and patients sufficient time to experience the benefits of Afrezza. The product may still earn enough to keep the company alive, if not pay off its development costs.

What are the lessons to be learned from the experiences of Mannkind and Nektar in the area of inhaled insulin? If we pay close attention, it seems we can sense familiar rhymes and rhythms, which if understood can provide guidance for future products targeted to treating systemic diseases using the lung

FIGURE 1



as the delivery portal. Two very capable Drug Delivery organizations, in partnership with first-class Big Pharma partners, have failed to crack the inhaled insulin opportunity. And Mannkind a decade later had the benefit of understanding the Exubera experience. Inhaled insulin is seemingly a tough challenge from a formulation, clinical, and commercialization perspective.

Afrezza seemed to have checked off all the boxes in terms of optimizing the pulmonary delivery of insulin, but still missed the mark. Will inhalation ever be a reasonable delivery option for the systemic delivery of insulin? What about any other inhaled pharmaceutical targeting a systemic indication? Is the lung even a reasonable systemic delivery portal for small molecules in an acute setting? While acute indications would seem to be the most obvious opportunity, there are no product successes to look to, even with small molecules. With the exception of Alexza's struggling Adusave for agitation, inhalation products are being used solely for locoregional pulmonary indications that range from asthma, COPD, and infectious disease to cystic fibrosis, localized cancers, and pulmonary arterial hypertension. A number of inhalation products that were intended to treat systemic conditions, such as acute pain, migraine, and erectile dysfunction, have faded away in the clinical setting.

Looking a little more closely, one can discern certain elements in the Afrezza story that seem to rhyme with previous experience and may offer some suggestions for future product development targeted to pulmonary delivery.

THE BOTTOM LINE IS SAFETY

The Hippocratic oath includes the declaration "I will utterly reject harm and mischief." That encapsulates one of the key considerations in any physician's decision. Does a new medication enhance safety, or at least not compromise safety? Is any improvement in efficacy or convenience offset by a loss in safety or tolerability? In the case of doubt, the default position for most physicians seems to be avoid the new and continue with products they know and trust. And most physicians, the classical Early and Late Adopters, are exactly the target group that any product needs to capture if it is to be successful. In the case of Afrezza, the lung is not the target organ, but it might be the one to suffer. Patients can't live without their lungs.

BALANCE RISKS WITH BENEFITS WHEN IDENTIFYING OPPORTUNITIES

Improved convenience is great if there is no compromise in efficacy or safety. Greater convenience might even improve efficacy if it improves compliance. Novel delivery approaches, especially those with any type of inherent risk, are perhaps better off initially targeting high-need indications, in which there may be a more relaxed risk/benefit threshold.

THE LUNG IS DIFFERENT

The lung is not like the skin, the nose, or even the stomach. Delivery to the skin offers a number of safety benefits. It presents a large surface area that permits delivery sites to be rotated, and it is also easily inspected for tolerability and safety issues by the health professional and the patient. In a worst-case situation, sections of skin can be removed and repaired with grafts. Delivery to the lung is a bit of a black hole. Selective delivery to distinct areas of the lung is hard to accomplish, rotating pulmonary delivery sites is hard to imagine, and assessing ongoing safety can only be performed through indirect testing. There is no simple "look-

and-see" approach to head off more serious problems.

START WITH ACUTE & MOVE TO CHRONIC

When developing applications for a novel delivery system, it's tempting to jump right in and address a chronic medical condition. Chronic treatment can lead to long-term use and commercial success. It also leads to more scrutiny and concern about long-term toxicity. Inhaled insulin has been shown to cause a slight decrease in lung function over the short-term that doesn't seem to get worse, or better, over a 2-year period. Will additional years of use further compromise lung function? Might chronic inhaled lead to other risks? Possibly not, but many issues need to be carefully considered when starting with any chronic therapy. Starting with an acute indication can often reveal and validate the usefulness of a delivery system, while building a safety database that helps support eventual chronic use.

INJECTION IS AN INCREASINGLY ATTRACTIVE OPTION

Gone are the wide bore needles and the pain, the ampoules, vials, and the need to fill a syringe. Today's options make self-injection, at least subcutaneous injection, reasonably convenient and comfortable. And with the ability to rotate injection sites, there is little concern about local tolerability. Combined with reliable systemic delivery performance, and limited concerns about significant local tissue toxicity, injection has become a very acceptable delivery route for patients once they get over the "ick" factor of self-injection.

TIME & COMPETITION DO NOT STAND STILL

Afrezza has been in development in one form or another for the better part of 2 decades. The product was in late Phase II trials in 2004, a year before the launch of Exubera. Will a compelling product opportunity in 2004 still be compelling a decade later? The challenge for any Project Team starting from scratch is not to imagine the best product today, but the best product at the time of launch. That may be as much as 10 or 15 years later. New Product Teams need to become futurists and realists with respect to development times if they have hopes of their product succeeding in the marketplace.

FIND A WAVE & RIDE IT

If necessary, create a wave to ride. Successful products are generally launched with momentum, what might be considered a wave of excitement and latent support. Riding a tall wave can generate product awareness, trial, experience, and rapid adoption. Exubera rode a wave of expectation that it would free patients from the need for daily injections. Unfortunately, that wave was either not big enough or crashed on the rocks of safety and price concerns before it could be fully exploited. This may explain why Afrezza, arguably an improvement on Exubera, has not been able to reach even the level of prescriptions and sales achieved by Exubera. There is no longer any wave of excitement and anticipation for an inhaled insulin.

Delivery to the lung is a challenge for Drug Delivery Professionals from both a device and formulation perspective, even when addressing locoregional applications. The challenges are much greater when using the lung as a portal for systemic delivery. Future success in delivering insulin via the lung, or any other pharmaceutical, will depend on managing the many technical, clinical, and regulatory challenges, while meeting physician and patient expectations. Understanding history and what has come before can provide important insights to help align reality with expectations. But even great design and execution can fall short for no apparent rhyme or reason. ◆

BIOGRAPHY

Dr. Josef Bossart is Managing Director of Pharmanumbers, a Drug Delivery and Formulation specialty group that helps clients understand, and communicate, how products and technologies can be best positioned for commercial success. He also serves as Executive Editor with PharmaCircle LLC, a trusted resource and full-service solution delivering authoritative content, global insight, and expert analysis on the pharmaceutical, biotechnology, medical device, and animal health industries. Dr. Bossart has more than 3 decades of pharmaceutical industry experience in a variety of roles ranging from sales to marketing to business development to general management. He earned his PhD from the College of Pharmacy, The Ohio State University.

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DISSOLUTION TESTING

Exploring the Link Between Particle Size & Dissolution Behavior for OINDPs

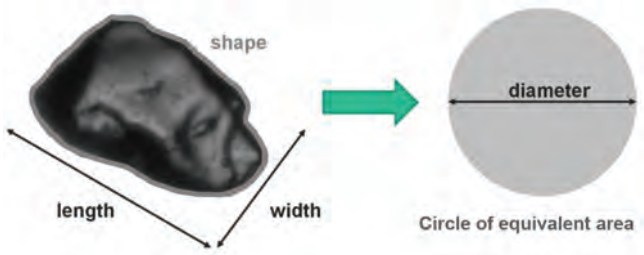
By: Paul Kippax, PhD; Deborah Huck-Jones, PhD; Julie Suman, PhD; Guenther Hochhaus, PhD; Sharvari Bhagwat, and Samiran De

INTRODUCTION

In the development of orally inhaled and nasal products (OINDPs), a primary focus is achieving deposition at the preferred site within the pulmonary system or nasal cavity. The particle size or droplet size of the delivered drug has a strong influence on this aspect of performance, explaining the reliance on particle size measurement within OINDP research. However, as OINDP performance is refined, more attention is being paid to the path of the drug molecule following deposition. The speed of drug uptake into the bloodstream directly impacts its pharmacodynamic effect and bioavailability and consequently the clinical efficacy and safety of a product. It is therefore becoming increasingly important to have a greater understanding of dissolution behavior at the site of deposition, especially when it comes to demonstrating bioequivalence, a defining element of a generic submission.

Here, we review current trends in dissolution testing within the context of understanding particle size, which impacts clinical studies and ultimately generic submissions. The experimental work we present demonstrates the correlation between active pharmaceutical ingredient (API) specific particle size information and dissolution performance and illustrates the potential value of Morphologically Directed Raman Spectroscopy (MDRS), a relatively new analytical technique. By efficiently measuring the particle size and extent of aggregation of defined components within an OINDP formulation, MDRS provides data that can be used to assess the dissolution behavior of APIs, even in the presence of particular excipients.

FIGURE 1



Morphological imaging uses advanced optics to collect images of particles. Particle dimensions are used to generate size and shape distributions for a sample.

LOOKING BEYOND DEPOSITION

The central task of OINDP development, whether innovator or generic, is to identify a formulation/device combination that will successfully deliver the required dose of active ingredient to the preferred deposition site within the lung or nasal cavity. In the case of slowly dissolving drugs, it is also important to optimize the dissolution kinetics in order to ensure that absorption occurs before the drug is cleared from the site of deposition. Principally, this relies on engineering a product that will produce particles of closely defined particle size under the conditions of clinical use. However, a lack of *in vivo* equivalence is often seen, even in cases where the particle size distribution of the formulations being developed have been shown to be very similar, indicating that other properties not captured by traditional *in vitro* assays are important.

Focusing on pulmonary delivery, an aerodynamic diameter of 5 microns is routinely taken as the upper size limit

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for deposition in the lung, although more finely sized particles may be more effective for deposition in the deep lung. In reality, the emitted aerosol particle size is a polydisperse distribution, and a full understanding of the particle size distribution and extent of aggregation of the components is critical to achieving bioequivalence. The difficulties of achieving this goal, coupled with the fact that the delivered particles are so small, has meant there has been little focus on the *in vivo* dissolution behavior of OINDPs. In addition, there is, as yet, no standard dissolution testing technique, and considerable disagreement on the approach to dissolution testing that is most relevant. However, this situation is beginning to change.

The FDA's critical path initiative, which was introduced in 2004 to ease the translation of new therapies into commercially available efficacious drugs, indicates that a complete understanding of the particle size distribution of formulation components may be a leading indicator of *in vivo* outcomes.[1] Its application to suspensions highlights some central issues with respect to demonstrating bioequivalence. One is the need for component-specific particle size information, rather than a comparison of the overall formulation, a need that underlines the specificity limitations of microscopy. Another is that a significant number of submitted comparisons between Test and Reference products are challenged on the basis of precision and accuracy. Understanding the comparability of the particle size distribution *in vitro* can prevent undesirable outcomes *in vivo* and directly expedites the commercialization of a new product - a highly valuable outcome.

This need to rigorously demonstrate bioequivalence is one of the reasons for an increased interest in OINDP dissolution testing. Because the speed of drug uptake into the bloodstream directly influences its bioavailability, understanding the impact of particle size and other particle properties on post-delivery dissolution behavior is important for demonstrating bioequivalence as part of an Abbreviated New Drug Application (ANDA). In addition, dissolution testing is becoming more of a focus in the development of innovator products. Here, controlling and meeting performance targets is an increasingly demanding task due to the desire to deliver less-soluble, larger molecule active components within OINDPs.

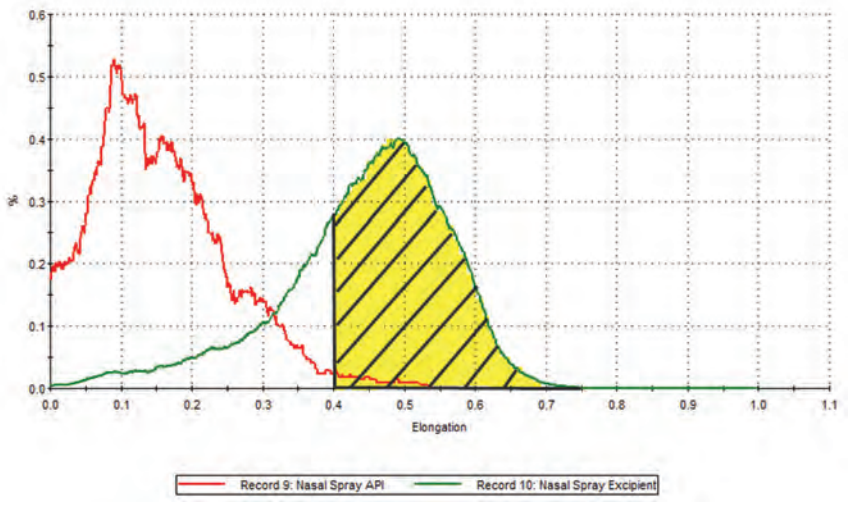
In summary there is a growing awareness of the need to consider the dissolution behavior of OINDPs and to learn how to control it by manipulating routinely measured parameters, such as particle size.

DISSOLUTION TESTING FOR OINDPS

The complexity of drug uptake within the pulmonary region presents certain unique challenges for OINDP dissolution testing. Dissolution testing for oral solid dosage is well established; however, the amount of liquid present in the stomach is substantial compared with the volume in the lung. The generation of relevant OINDP dissolution data relies on realistically recreating the saturated sink conditions that apply during pulmonary dissolution during *in vitro* testing. Furthermore, there is no consensus on the dissolution media that should be used for OINDP dissolution or how best to introduce the sample into the dissolution apparatus.

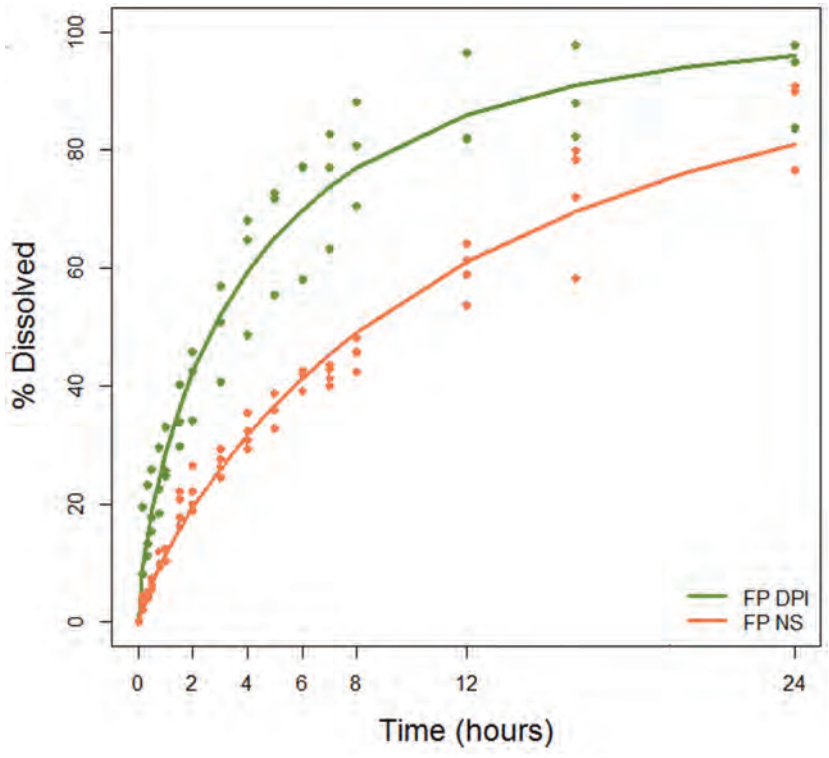
Dissolution apparatus commonly used for OINDP testing, such as paddle apparatus, custom-built flow through apparatus and diffusion controlled cell systems, are all based on the USP <711> recommendations for oral solid

FIGURE 2



Particle shape (elongation) distribution data for excipient and API in a nasal spray analyzed using MDRS show that shape descriptors can be used to identify the majority of excipient particles. Particles in the non-shaded region require chemical identification to allow them to be identified as either API or excipient.

FIGURE 3



Dissolution profiles for Fluticasone Propionate delivered by DPI and Nasal Spray. The delivery device substantially impacts the dissolution rate of the drug.

form dissolution testing.[2] However, methods are modified to realistically simulate the conditions within the pulmonary region. Dissolution apparatus customized for OINDP analysis incorporates a semi-permeable membrane, designed to mimic the wall of the lung, through which the dissolved components must pass. Dissolution profiles are then determined using high-performance liquid chromatography (HPLC), or online UV analysis, to analyze collected samples of dissolution media.

A detailed review of dissolution test methods is beyond the scope of this article, but in broad terms, methods presented in the literature vary in terms of the following:[3]

- The type of sample used – whether the bulk formulation is tested or just the size fraction likely to deposit in the region of interest
- Apparatus design
- The formulation of the dissolution medium used for testing
- Data analysis and treatment

An official compendial method for dissolution testing methodologies has yet to be agreed, and the need for one is still open to question. In the absence of a direct regulatory requirement, monograph, or standardized method for dissolution testing, it is helpful to consider whether alternative techniques can be used to reliably infer *in vivo* dissolution behavior. The establishment of a robust correlation between particle size and dissolution behavior, for example, potentially meets the need to robustly demonstrate bioequivalence while at the same time minimizing dissolution testing.

CORRELATING PARTICLE SIZE TO DISSOLUTION BEHAVIOR

The bioavailability and therapeutic action of OINDPs depend on absorption of the API rather than the bulk formulation. Therefore, the development of relevant correlations between particle size and dissolution behavior relies, in the first instance, on measuring the primary particle size distribution and extent of aggregation of the API alone. This is a complicating factor when it comes to gathering the particle size information required to assess dissolution, especially given that the current component-specific methods applied to particle size analysis of OINDP, such as cascade impaction, destroy the particles within the formulation during the analysis process, making assessments of the degree of agglomeration (or dispersion) of the API more difficult to achieve. MDRS is a proven technique for generating component-specific information and efficiently addresses this issue.

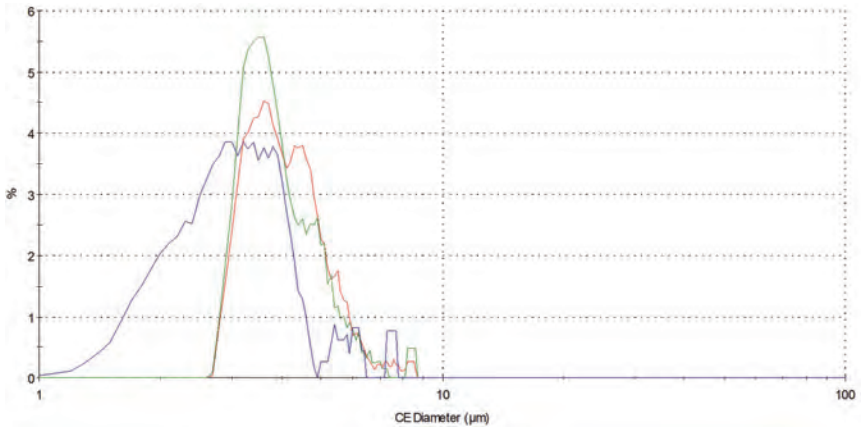
Analytical systems that combine automated imagining with Raman spectroscopy, such as the Morphologi G3-ID (Malvern Instruments, Malvern, UK) provide the chemical identification capabilities needed to deliver component-specific particle size distribution data. At the same time, such systems offer substantial improvements in accuracy and efficiency over conventional microscopy, significantly

reducing analysis times and avoiding the subjectivity associated with manual methods. Automated imaging uses advanced optics to rapidly collect two-dimensional images of a particle population that has been dispersed representatively on a plate. Smart software builds up number-based distributions of defined descriptors of particle size and shape from the measured dimensions of individual images (Figure 1).

Using automated imaging, the particles in a sample can be classified into discrete populations through the application of size and shape filters. The addition of Raman spectroscopy enables chemical identification of groups with distinct morphological features, or alternatively, the secure differentiation of particle populations that are morphologically similar. Either step enables the generation of a component-specific particle size distribution. As many API and excipient particles within OINDPs are morphologically similar, separating components with Morphologically Directed Raman Spectroscopy is often the key to achieving the specificity required for relevant analysis. Figure 2 illustrates the application of Morphologically Directed Raman Spectroscopy in a multicomponent OINDP.

Size and shape analysis reveals that the components within this product are morphologically distinct, to a significant extent. On the basis of elongation, a shape parameter derived from the ratio of particle length to width, the sample can be divided into two distinct particle populations. However, there is an overlap. Particles with an elongation ratio in excess of 0.4 can be confidently identified as excipient while those of lower elongation, though likely to be API, cannot be reliably designated as such. In this example, Raman spectroscopy enables the initial association of specific morphological features with the API and is then used to definitively differentiate particles that are morphologically similar. Using dimensions for all the particles identified as API enables the generation of an API-specific particle size distribution.

FIGURE 4



FP delivered using a DPI (blue curve) has a finer particle size compared to that observed using a NS (red and green curves).

CASE STUDY: MEASURING THE RELATIONSHIP BETWEEN PARTICLE SIZE & DISSOLUTION BEHAVIOR

In a recent collaborative project, Malvern Instruments, Next Breath (a company that specializes in OINDP research), and the University of Florida used MDRS to assess whether component-specific particle size data could be correlated directly with dissolution rates. Particle size distribution was measured for a widely used inhaled API - Fluticasone Propionate - using the Morphologi G3-ID. As the device used to aerosolize an inhaled drug influences the delivered particle size, experiments were carried out using a DPI and a Nasal Spray (NS). Particle size was measured post-actuation for each device/API formulation.

Dissolution testing was carried out using the Modified Transwell™ method at the University of Florida, courtesy of Dr. Gunther Hochhaus.[4] A glass microfiber filter was used as the dissolution membrane, and a Sodium Dodecyl Sulfate (SDS) type surfactant was incorporated within the dissolution media to promote a more representative simulation of hydrophobic drug dissolution in the lung. The dissolution data gathered were fitted to a Weibull probability distribution model, and the time required to dissolve 63% of the drug (T63) was determined for each device/formulation combination.

Figure 3 shows the dissolution profile for Fluticasone Propionate, delivered with a DPI and an NS. The dissolution profiles are substantially different, with DPI delivery being associated with more rapid dissolution

"In the case of slowly dissolving drugs, it is also important to optimize the dissolution kinetics in order to ensure that absorption occurs before the drug is cleared from the site of deposition. Principally, this relies on engineering a product that will produce particles of closely defined particle size under the conditions of clinical use. However, a lack of *in vivo* equivalence is often seen, even in the case where the particle size distribution of the formulations being developed have been shown to be very similar, indicating that other properties not captured by traditional *in vitro* assays are important."

than NS delivery.

Figure 4 compares the particle size distribution for Fluticasone Propionate delivered by DPI and by NS. The DPI-delivered samples have a finer particle size distribution than the dose delivered by NS, a finding that directly correlates with the observed dissolution data. The DPI delivers Fluticasone Propionate with a finer particle size, which dissolves more rapidly.

In addition to being able to measure the particle size of the API within each formulation, the particle size and shape data provided by the Morphologi G3-ID system can also be used to classify particles as being either primary particles or agglomerates.[5] The data obtained are provided in Table 1 and confirm that the extent of agglomeration within the NS formulation is higher than in the DPI formulation. This too may help account for the difference in dissolution rate.

The data presented here highlight a number of important aspects of OINDP dissolution testing, including the impact of delivery device on dissolution behavior and the need for repeat analysis to account for natural variations in the actuation process. The most significant finding, however, is the suggestion that MDRS can be used successfully to generate data that correlate directly to dissolution rate. This is because the technique enables the secure differentiation of API from other ingredients in the formulation, thereby providing access to particle size distribution data specifically for the component of interest.

LOOKING AHEAD

A greater understanding of the behavior of OINDP formulations post deposition is increasingly required, both to refine performance and, for generic manufacturers, to ensure bioequivalence. MDRS is a useful tool for *in vitro* OINDP testing that provides the chemical identification required to generate component-specific particle size data for APIs within a formulation. The data presented here shows how the results delivered by the technique can be correlated with dissolution data, and may therefore provide a means of assessing product bioavailability. ◆

TABLE 1

	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	% Aggregate
FP DPI	2.0	3.3	5.4	27%
FP NS	3.2	4.1	5.7	36%

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BIOGRAPHIES

Dr. Paul Kippax is Divisional Product Group Manager for Micrometrics at Malvern Instruments, and has responsibility for the company's Mastersizer, Spraytec, and Analytical Imaging product ranges. He joined the company in 1997, starting as an application scientist. Prior to this, he earned a degree in Chemistry and his PhD in Physical Chemistry, both at the University of Nottingham in the UK.

Dr. Deborah Huck-Jones is Product Manager for Malvern Instruments' Analytical Imaging range. She joined Malvern Instruments as Product Technical Specialist for Imaging Products in 2005 and later became PTS Supervisor for Imaging and Laser Diffraction. Dr. Huck-Jones earned her MChem with European study from the University of Exeter and her PhD in Chemistry jointly awarded from the University of Exeter and Université Louis Pasteur in Strasbourg, which involved the synthesis and characterization of metal-based liquid crystals.

Dr. Julie D. Suman is Co-founder and President of Next Breath, LLC, a contract research organization dedicated to the development and analytical testing of nasal and inhalation delivery systems. Dr. Suman directs the research division that supports product development and regulatory submissions for North American and International Clients in the pharmaceutical, biotechnology, and medical device markets. She earned a BS in Pharmacy from Duquesne University (1996) and a PhD in Pharmaceutical Sciences from the University of Maryland, Baltimore.

Dr. Guenther Hochhaus is Professor, College of Pharmacy, at the University of Florida. His research focuses on the clinical pharmacology of nasal and inhalation drugs with special emphasis on new methods for the bioequivalence assessment. He earned a BS in Pharmacy and a PhD in Pharmaceutical Sciences from the University of Muenster. He is Fellow of the American College of Clinical Pharmacology and the American Association of Pharmaceutical Scientists and has published over 200 manuscripts.

Sharvari Bhagwat is currently pursuing her PhD in Pharmaceutics with minors in Material Science and Engineering and in Applied Statistics at the University of Florida. Previous research projects and experience have focused on the optimization of *in vitro* analysis methods for inhaled asthma drug products as well as a pharmacokinetic/pharmacodynamic simulation model for bioequivalence of inhaled corticosteroids.

Samiran De is the Senior manager in the field of Research and Development at Lupin Pharmaceuticals.

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LYOPHILIZATION

The Key to Creating Acceptable & Effective Fast-Dissolving Oral Formulations

By: Leon Grother

INTRODUCTION

There are some patient populations for whom a fast-dissolving dosage form is extremely advantageous. If a patient has difficulty swallowing medicine, compliance with treatment regimens is going to be a challenge. This is often the case at either end of the age spectrum, with children and geriatric patients particularly likely to struggle with swallowing tablets and capsules.

Those with dysphagia, nausea, and vomiting also pose problems in terms of keeping an oral dosage form down long enough to dissolve and get to work. Tablets and capsules can pose a challenge for psychiatric patients as well. They might have difficulty in swallowing, but even if swallowing the tablet is not a problem, they may be resistant to the idea of medication and conceal it in their mouth to spit out later.

In all of these situations, a rapidly dissolving oral formulation would provide a solution. If the dosage form disperses and is absorbed extremely rapidly, it is much more likely to be administered effectively, and patient care is improved. The technique of lyophilization is important in the development of drug formats that dissolve rapidly, and offer quick dispersion while being pleasant to take.

There are other advantages in terms of product positioning. Although products such as painkillers are not difficult for otherwise healthy adults to swallow, they take time to start working. Any condition that has a rapid, unpredictable onset, such as migraine or diarrhea, would benefit from a formulation that has an effect on their symptoms more rapidly. An additional benefit is convenience, as no water is required to take them.

A dosage form that is designed to dissolve in the mouth and be absorbed rapidly needs to meet a couple of key requirements. It must indeed disperse very quickly so that it does not hang around in the mouth and cause discomfort or fail to be absorbed effectively. Furthermore, if it is going to be acceptable to the patients, it must be palatable. A product that tastes unpleasant or has a disagreeable, gritty mouthfeel is unlikely to gain widespread acceptance however effective it may otherwise be.

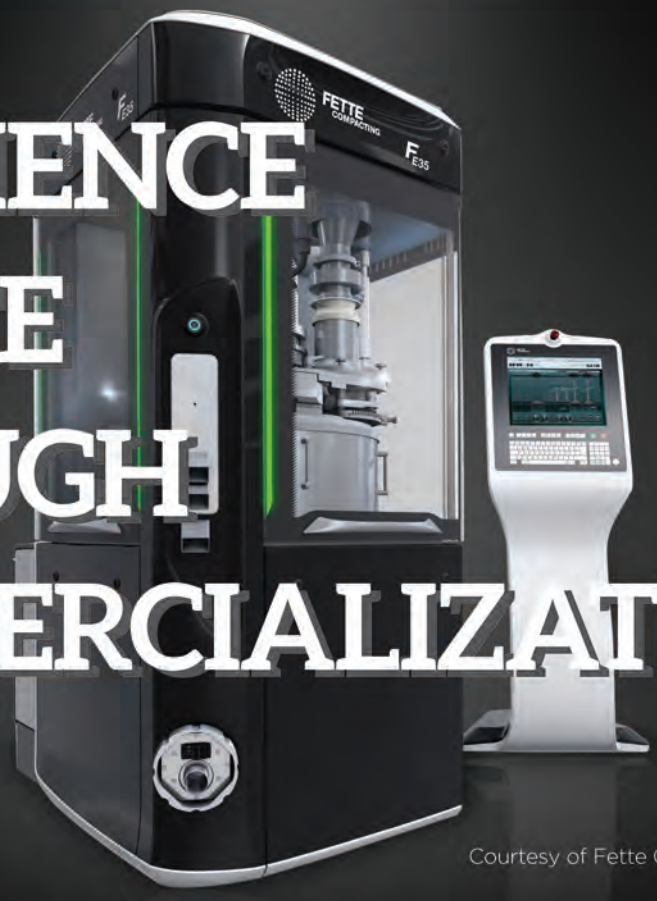
LYOPHILIZATION IN FORMULATION

Lyophilization is the key to creating acceptable and effective fast-dissolving oral formulations. The process of lyophilization, or freeze-drying, starts with an aqueous solution or dispersion being frozen. The air pressure is then reduced by applying a vacuum, and the frozen water sublimes, going directly from ice to water vapor, thus removing it from the frozen solution. The result is a highly porous solid form with only a very low amount of residual water remaining.

If the lyophilization process is very carefully controlled, it can be used to tailor the dispersion or disintegration properties of a solid drug product. It can be applied to a wide range of pharmaceutical actives, resulting in palatable, orally disintegrating tablets that disperse quickly, with good mouthfeel.

The Zydis® orally disintegrating tablet has gained widespread acceptance since it was first introduced 30 years ago, and relies on lyophilization in its manufacture. Numerous drug formulations have reached the market since then using

EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION



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In production terms, the key difference between the Zydis process and a traditional freeze-drying operation is that in the Zydis process the blisters are frozen in a liquid nitrogen tunnel ahead of placement into the freeze dryer. Normally, the freezing process takes place within the freeze-dryer. Separating the two is an important factor in the production of a tablet that disintegrates rapidly, and the material within the blisters must be completely frozen when the trays emerge from the tunnel.

this technology, including drugs to treat Parkinson's, schizophrenia, and anxiety disorders, as well as painkillers and antiemetics.

To make the tablets, the active ingredients are combined with a suitable carrier material comprising pharmaceutically compatible materials such as mannitol and gelatin. They are then either dissolved or dispersed in water using a standard mixer. The resulting liquid is dosed by weight into individual pre-formed blisters in a fully automated continuous filling process. This process requires accurate control and precision to ensure each dose contains the exact amount of active, and it is important that the suspension remains homogeneous throughout.

Once filled, the blisters are passed through a freezing tunnel cooled by liquid nitrogen. This freezes the water in the suspension ready for loading into low-temperature storage ahead of the freeze-drying process. Storing briefly in this way enables the filling to operate on a continuous basis ahead of the batch-wise freeze-drying process.

As soon as sufficient blisters have been filled and frozen, the lyophilization can begin, and they are transferred to the freeze-dryer. When the lyophilization is complete, the blisters are passed through a blister sealer, where they are sealed with aluminium foil or a suitable paper laminate. The sheets of blisters are cut to size, and the foil perforated to facilitate opening by the patient.

OPTIMAL MATERIALS & PARAMETERS

Selecting the optimal carrier materials is a crucial part of the development of a successful formulation. By selecting the correct grade of gelatin with the ideal dissolution profile, finished tablets that dissolve smoothly and rapidly in the patient's mouth can be created. The mannitol is also important, and its ease of dissolution is key in creating a product with a pleasant texture, taste, and mouthfeel. The crystallization of the mannitol during the freezing process must be controlled if the resulting tablet is going to look good and have sufficient resilience and strength to survive the rigors of handling and transportation.

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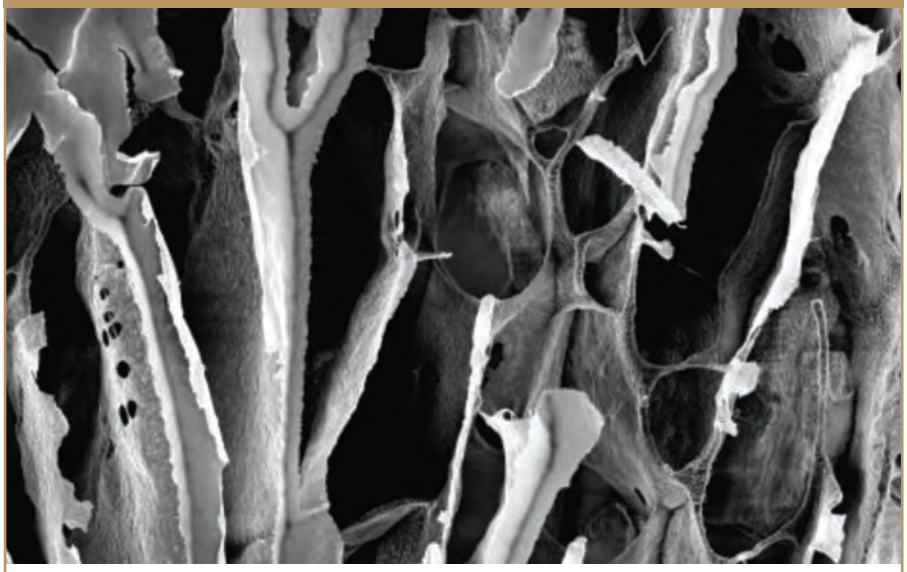
The freezing process is controlled by a combination of the temperature within the tunnel, and how long the blister pockets remain within it. These two variables can be altered to give the ideal freezing rate for an individual tablet type. The faster the rate of freezing, the smaller the ice crystals will be. The resulting tablets will be stronger, but are also likely to take longer to disperse in the mouth. Smaller crystals can also hinder the rate at which the water vapor sublimes from

FIGURE 1



A cross-section of a Zydis tablet - provides a good insight into the highly porous structure that has been created. When the tablet is placed in the mouth, saliva penetrates these pores, and it rapidly disperses.

the tablet during lyophilization, which can affect the efficiency of the drying process. Conversely, if the freezing process is slower, the ice crystals are likely to be larger. This will give tablets that disperse more quickly, but are likely to be less strong.

Creating the optimal balance between strength and speed of dispersion is the key to tuning the tablet's delivery properties. Statistical experimental design can be used to determine the ideal freezing parameters, bearing in mind the desired properties and processing efficiency. Methods such as differential scanning calorimetry can be used to garner further information about important properties, such as the solution or suspension's freezing and melting points.

When the freezing process is complete, the open blisters are stored within low-temperature cabinets to keep the contents frozen ahead of freeze drying. On the whole, the length of time over which they are stored usually has no bearing on the final product, but occasionally a specific storage period may be required. This applies to products that have high concentrations of a highly soluble drug or salts, which can inhibit the crystallization of the carrier materials, notably mannitol. Defining a minimum storage period in these cases ensures that there is sufficient time for any amorphous mannitol to become crystalline, and be less likely to shrink or crack.

CONTROL OF LYOPHILIZATION

The other crucial part of the manufacturing process is the freeze drying itself. The ice crystals formed during the controlled freezing are removed during lyophilization. This creates pores within the matrix of the freeze-dried tablet, as can be seen from the scanning electron microscope image in Figure 1.

While lyophilization is commonly used in pharmaceutical manufacture, it is more normally used to give a fixed amount of water within the product. With the Zydis process, it is crucial to control the way the ice crystals are formed and removed to create the characteristic porous structure. Instead of being stoppered or sealed during freeze-drying, in this process, they are permitted to equilibrate within a controlled environment when the lyophilization is complete. Thus, the product's final water content is determined by a combination of the freeze-drying conditions, and also the intrinsic equilibrium moisture content of the various components of the formulation, and the relative humidity of the environment in which they are manufactured. This can be monitored using dynamic vapor sorption analysis, and a moisture content testing protocol such as Karl Fischer.

To achieve a good, stable structure, the ice crystals must be removed via sublimation as rapidly and completely as possible, without melting and forming water. The two most important parameters that must be controlled are the temperature of the shelf, and the drying time. Every individual formulation has its own characteristic collapse temperature, above which, that all-important porous structure will disappear, affecting the tablet's disintegration time. It can also cause visible holes to be formed.

The temperature is controlled via heated shelves, which confer conductive, convective, and radiative heat. The more the temperature rises, the faster the drying occurs. Sublimation leads to rapid heat loss within the product, and therefore, it is much lower than that of the shelves, so the optimal temperature for the shelves may actually be higher than the tablet's collapse point.

The maximum operating shelf temperature varies from product to product. The most effective way to determine this figure is via the inspection of finished products for defects resulting from collapse or melting as the process development is carried out. This is achieved by drying test batches over multiple cycles with different primary drying temperatures, and checking for drying-related defects in the products created. Analytical techniques, such as freeze-drying microscopy and differential scanning calorimetry, can also provide an insight.

It is important that the blisters remain under vacuum within the freeze dryer for a sufficient period to ensure all the ice is removed. Product quality is not at risk if it remains in the dryer for too long, but of course, this will have an impact on process efficiency as throughput will be reduced. It is possible to assess whether the drying has reached completion using techniques such as dew point sensors and pressure rise tests. Manual inspection of the finished product can also confirm dryness.

Process development for an orally disintegrating tablet made via Zydis technology is complex. It requires detailed knowledge of the material science underpinning the tablet structure, and how this affects the overall properties of the final dosage form. If these are not optimized to produce a stable tablet that disperses quickly and evenly, the product is unlikely to be a commercial success. The process harnesses the power of freeze-drying to remove water in a controlled manner to create matrices with defined and predictable properties, when used in combination with the optimal carrier materials. In this way, the aim of manufacturing oral dosage forms that disperse within 3 seconds with a pleasant taste and mouthfeel can be achieved.

SUMMARY

Multiple products are on the market made via this controlled lyophilization process. The fast-dissolving characteristics it can impart have enabled the demands of several challenging patient populations to be met with formulations of important medicines that work well for them. Convenience and fast onset of action can be combined with ease of administration, particularly for patients who struggle to swallow conventional tablets. ◆

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BIOGRAPHY

Leon Grother is Principal Scientist at Catalent Pharma Solutions in Swindon, UK. He earned his BSc in Pharmaceutical Science from the University of Greenwich, London, and his Masters in Industrial Pharmaceutical Science from the University of Manchester, UK. He has worked within R&D for more than 15 years, primarily on Catalent's Zydis® ODT (orally disintegrating tablet) technology formulation and process development. During this time, he has gained expertise in freeze-drying and is a named inventor on several patents related to formulation of lyophilized dosage forms.


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Special Feature

Advancements in Drug Delivery Technologies Tackle Solubility & Bioavailability Challenges

By: Cindy H. Dubin, Contributor

Capsugel's commercial manufacturing facility features three commercial-scale spray dryers. Pictured here is the tank room showing a 2500L solution tank using 500L IBCs and pillar lift.

The emerging trends in the combinatorial chemistry and drug design have led to the development of drug candidates with poor water solubility. Issues associated with poor solubility can lead to low bioavailability, resulting in suboptimal drug delivery. About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble. With the advent of various insoluble drug delivery technologies, the challenge to formulate poorly water-soluble drugs can be achieved. In fact, numerous drugs associated with poor solubility and low bioavailabilities have been formulated into successful drug products, and several marketed drugs have been reformulated to improve efficacy, safety, and patient compliance. In order to gain marketing exclusivity and patent protection for such products, revitalization of poorly soluble drugs using insoluble drug delivery technologies have been successfully adopted by many pharmaceutical companies.[1]

In this annual special feature, *Drug Development & Delivery* spoke with several innovator companies to learn more about the latest advances in drug delivery to address the ever-present challenging issues of solubility and bioavailability today.

BASF—Excipients & Solubilizers Achieve Desired Solubility/Bioavailability

As the number of poorly soluble compounds continues to rise in drug discoveries, so is the interest in the pharma industry to adopt new strategies to overcome these challenges. Such strategies go beyond the traditional or conventional formulation approaches such as micro-milling or micronization, pH adjustment/salt formation, pro-drug, or complexation, and include the non-conventional innovative solid dispersion and self-emulsifying liquid dispersion technologies. "Such technologies are aimed at transforming the crystalline and high melting insoluble hydrophobic compounds to solid or liquid dispersions in pharmaceutically accepted polymers and solubilizers to achieve the desired solubility and bioavailability," says Shaukat Ali, PhD, Technical Support Manager, BASF Corporation, Pharma Ingredients & Services.

BASF offers a range of polymeric excipients and solubilizers with the desired properties compatible to formulation (and non-conventional formulation) technologies. "BASF's polymeric excipients used in solid oral dosages and surfactants/solubilizers used in liquid oral dosages could overcome the solubility challenges by maintaining the drug in supersaturation without nucleation or crystallization for an extended period," says Dr. Ali. "Highly functional excipients are versatile and can be used, and preferably switched, to meet the technological needs to yield the desired performances of a particular dosage."

Enablers such as Kollidon® VA64, Soluplus®, Kollidon®, and Kollicoat®, among others, are used in amorphous dispersion technologies, including hot-melt extrusion, spray drying, Kinetisol®, co-precipitation and/or electospraying/electrospinning. Other excipients, such as lipid-based solubilizers and surfactants, such as Kolliphor® RH40, EL, HS15, TPGS, P407, P188, PS80, are also used in the development of self-emulsifying/micro-emulsifying drug delivery systems (SEDDS/SMEDDS). "Compatibility of these excipients contributes to greater stability of APIs, and hence the development of a robust formulation," says Dr. Ali.

BASF offers a high throughput screening (SoluHTS) tool to identify excipients in the early stages of formulation development. Other approaches, such as film casting, also help expedite compound screening in a range of polymers/solubilizers, which helps identify and establish the maximum solubility or miscibility of molecules in polymers and solubilizers. "Such understanding is important for selecting an appropriate formulation technology and the excipients for an individual drug candidate," says Dr. Ali. "The SoluHTS technique provides the opportunity for formulators to rapidly

screen multiple molecules and helps establish and identify the excipients suited for the appropriate technologies involving either amorphous solid dispersions or lipid-based self-emulsifying dispersions."

Capsugel—Breadth & Depth of Technologies for Product Design to Commerical Manufacture

"As an industry, we tend to oversimplify our situation by referencing statistics about a majority of compounds in development having 'poor solubility.' The reality is, more often than not, these molecules also have additional challenges such as permeability, stability, metabolism, regional absorption, or food/pH sensitivity," comments Dan Dobry, Vice President, Bend Research, a division of Capsugel Dosage Form Solutions. "The key questions are rarely as simple as 'What's it soluble in?' or 'Can I make it amorphous?' or 'Is it physically stable?' These days, that is a low bar to set."

Capsugel Dosage Form Solutions is investing in core technologies and infrastructure that address specific industry trends, such as the growing number of highly potent compounds that are in the pipeline, partially driven by continued investments in oncology; a focus on niche areas, such as orphan drugs and pediatric applications; the 505(b)(2) regulatory pathway as an increasingly utilized route for changes in formulation, form, route of administration, and combination products, among other factors; and virtual and specialty companies, which have limited internal development and manufacturing capability, making up a larger percentage of the pharmaceutical product pipeline.

In response to these trends, Mr. Dobry points out that Capsugel Dosage Form Solutions has invested in an array of bioavailability enhancing and modified-release technologies to achieve breadth and depth, from product design to commercial manufacture of finished dosage forms. For example, Capsugel has ensured integrated product development capability from design to commercial manufacture for spray-dried dispersions (SDD), recently completing construction of a new pharmaceutical SDD commercial manufacturing facility in Bend, OR. The company has expanded its capacity and capabilities in lipid-based formulation development and manufacturing. Investments in the company's Edinburgh, Scotland facility (Encap Drug Delivery) will help increase liquid- and semi-solid-fill hard capsule manufacturing capacity, as well as add an SDD formulation and development capability. All of these investments include high containment capabilities as a critical component, says Mr. Dobry.

"Capsugel Dosage Form Solutions has also acquired Xcelience and Powdersize to further enhance our clinical trial and commercial manufacturing capability across a range of solid oral dosage forms, and the addition of clinical trial services inclusive of primary and secondary packaging," he says. "Furthermore, adding micronization and nano-milling to our toolkit allows us to support more clients at the earliest stages of product development."

Capsugel Dosage Form Solutions' technologies, including amorphous dispersions, lipid/liquid solubilized dosage forms, and micronization/particle size reduction are complemented by modified release options, and multiparticulate approaches based on fluid bed, extrusion/spheronization, mini-tablet and melt-spray-congeal processing. "We believe that our breadth in technology is critical to meeting client target product profiles and commercial objectives," says Mr. Dobry.

Gattefossé—Lipid Excipients Enhance Delivery of Challenging Molecules

Insufficient or unpredictable oral absorption is associated with poor solubility, slow dissolution and inadequate intestinal permeability. Often presented together in a single drug entity, these multiple challenges associated with an increasing number of drug entities can only be addressed by unique excipients and enabling technologies. Among the approaches that enable oral absorption of difficult molecules, lipid-based formulation strategies stand out

for their unique abilities such as concurrently addressing the physical, chemical, and biopharmaceutical challenges of a given drug. Capitalizing on lipid formulation technologies is further facilitated by significant advances in analytical, characterization, and predictive tools for successful application of lipid excipients in enhancing oral delivery of challenging molecules.

Gattefossé specializes in lipid excipients and related drug delivery technologies that aim to improve oral bioavailability. "Lipid excipients are unique because they play significant roles in the drug delivery system," says Jasmine Musakhanian, Scientific and Marketing Director at Gattefossé USA. "Depending on their physico-chemical properties, lipid excipients may influence *in vivo* processes such as biliary secretion, be subject of digestive enzymes, influence absorption barriers by for example opening of epithelial tight junctions, contribute to drug supersaturation, and even influence the route of absorption.

To simplify formulation decisions that can help minimize attrition rates and shorten the drug development path, Gattefossé created guidance documents for preclinical as well as late development stages. These documents use evaluation methods to arrive at key decisions based on API solubility in individual excipients, solubility of API in mixtures, miscibility of excipients at the desired concentrations, needed concentration of the excipient(s) to achieve the targeted dose, ability of the eventual formulation to disperse in aqueous media and more importantly to maintain API solubilization *in vivo*, and the biopharmaceutical role of the excipient(s) and their potential impact on drug absorption.

LATITUDE's PG Depot™ is a proprietary parenteral drug delivery platform for the sustained release of small molecules, peptides, and proteins over 1-7 days.

LATITUDE Pharmaceuticals, Inc.—Proprietary Platforms Establish New Intellectual Property

Experts consider approximately 90% of new chemical entities to have an aqueous solubility of less than 1 microgram per mL. LATITUDE utilizes extensive experience and proprietary technologies to solve issues of insolubility, instability, poor absorption, vein irritation, large/bulky doses, lack of IP protection, and other formulation challenges over a range of dosage forms. "LATITUDE develops its own proprietary drug formulation technologies and makes these available to its clients to improve efficacy, safety, and overall therapeutic value, and establish new intellectual property for their drug compounds," says Andrew Chen, PhD, RPh, President, LATITUDE. "In addition, LATITUDE applies its own technologies to develop improved formulations of existing drugs for out-licensing as accelerated approval 505(b)(2) NDA candidates."

Two such LATITUDE formulation platforms are Nano-E™ and PG Depot™. The Nanoemulsion Drug Delivery System (Nano-E) is a liquid formulation drug delivery platform for highly insoluble small molecule, peptide, and protein drugs. Nano-E technology is the 505(b)(2)-enabling formulation behind two NDA-stage compounds that LATITUDE has developed for its clients. One specialty pharma client needed a topical formulation to substitute for a currently marketed solvent-based topical product known to cause dry

Employees at Metrics Contract Services inspect sample taken from a processing line.

skin and eczema. LATITUDE developed an equivalent and stable solvent-free aqueous formulation using the proprietary Nano-E technology platform. The aqueous formulation was evaluated for efficacy with *in-vivo* animal models and subsequently in humans.

The Phospholipid Gel (PG) Depot technology is a versatile parenteral drug delivery platform for applications requiring the sustained release of small molecules, peptides, and proteins over 1-7 days. A pharma company requested LATITUDE develop an improved formulation for its peptide drug that was currently injected up to twice daily to control blood glucose in adults with Type 2 diabetes. To reduce the frequency of required injections, LATITUDE incorporated the peptide into its PG Depot to create a new sustained-release formulation that reduced the injection frequency to only once per week. "Reducing the injection frequency created a paradigm shift in the dosing frequency and a potential key competitive advantage over drugs in this category," explains Dr. Chen. PK studies in a diabetic rat model confirmed the no-burst, peakless, ear zero-order, and sustained-release kinetics for this peptide from the PG Depot.

Metrics Contract Services—Spray Drying & Micronization Accelerate Development

Nanoparticulate formulations can increase bioavailability in multiple ways. Due to the high surface area-to-volume ratio associated with decreased particle size, nanocrystals of poorly dissolving APIs can provide faster drug absorption and higher bioavailability by increasing the API's dissolution rate. Amorphous nanoparticle dispersions also can increase the absorption rate of drug due to the same enhancement in surface area and dissolution described above while simultaneously stabilizing the amorphous state of the API and its higher solubility. Still other forms of nanoparticles can achieve high drug loading of poorly soluble compounds (e.g. polymeric micelles and liposomes) by providing a suspending vehicle capable of transporting their drug payload across the permeable intestinal wall. On the other hand, localization to the permeable tissue may forego the need for the API to reach a higher bulk solubility in the intestinal fluid. This can be accomplished by the incorporation of adhesive excipients into the nanoparticle's composition.

To help improve solubility and bioavailability, Metrics Contract Services offers clients the ability to manufacture spray-dried material or to micronize the API received through jet milling. "Both of these technologies work well within our business model because the resulting material still will be formulated as a capsule or a tablet," says Michael DeHart, PhD, Senior Formulation Scientist at Metrics Contract Services.

In addition to technologies, Dr. DeHart says communication is the best way to accelerate the development of these challenging compounds. "It helps to know if the client has already performed some preliminary solubility studies, any kind of simple animal PK studies, or even what the critical quality attributes are (e.g., modified release, specific delivery in the small intestine). This allows us to move the project forward without having to redo, or in some cases relearn, information that may already be known."

Kyle Fugit, PhD, Formulation Developmental Scientist at Metrics, shares a case study that best

"As an industry, we tend to oversimplify our situation by referencing statistics about a majority of compounds in development having 'poor solubility.' The reality is, more often than not, these molecules also have additional challenges such as permeability, stability, metabolism, regional absorption, or food/pH sensitivity."

exemplifies how technology and communication worked together to address a client's challenge. "The client brought us a pro-drug that was susceptible to acid degradation and general hydrolysis. This meant that the drug had to be protected from stomach acid. In addition, the exposure time to the intestinal fluid of the small intestine had to be minimal. We took a combination approach to this type of drug delivery. First, we knew that an enteric coat was essential to provide acid protection. Second, we incorporated mucoadhesive polymers into the core tablet to help the tablet adhere to the walls of the small intestine. This allowed the pro-drug to permeate across the small intestine where it was then hydrolyzed to the active drug. Despite the daunting challenge of preventing hydrolysis throughout transit in the stomach and small intestine, animal studies confirmed that we were able to provide bioavailability of the molecule of interest."

Particle Sciences, Inc.—An API's Characteristics Determine the Best Approach to Improving Solubility

Solubility is one of the key physicochemical parameters a formulator needs to understand and manipulate in order to develop viable formulations. APIs are often sparingly water-soluble with a majority of New Chemical Entities belonging to the BCS Class II. "Particle Sciences, Inc. (PSI) sees its share of BCS II and IV molecules. In fact, 90% of its client's small molecules fall into these two classifications," says Robert W. Lee, PhD, Vice President, Pharmaceutical Development Services, PSI. PSI offers a number of solubilization approaches ranging from *in silico* design to nanoparticulate suspensions to solid solutions and lipid-based systems such as LyoCells® (PSI's proprietary reverse cubic and hexagonal phase nanoparticulate delivery system). For long-term delivery, PSIs drug-eluting device may also be a solution.

"It's really a question of to which technology do the API's characteristics drive one towards," states Mark Mitchnick, MD, CEO of PSI. For instance, a heat-stable, highly potent compound with a positive log P naturally drives towards hot-melt extrusion. A relatively labile molecule with good lipid solubility would warrant looking at LyoCells, says Dr. Mitchnick. Note that a classic BCS II molecule should always be evaluated for its amenability to nanoparticulate suspensions, either crystalline or stabilized amorphous.

Both gentlemen agree that a well-informed formulation effort starts with preformulation data, including extensive solubility and excipient compatibility data. PSI uses DOSE™, a proprietary solubility evaluation approach based on Hansen Solubility Parameters. "This data helps guide our selection of excipients and matrix components in the case of emulsions, solid lipid nanoparticles, polymeric micro/nanoparticles, and solid solution approaches," explains Dr. Lee. "Based on the physicochemical characteristics of the API, we assess which drug delivery approaches will

provide the biological performance and match the desired target product profile."

In all of these approaches, the excipients play a key role–whether to assist in stabilization, complexation, targeting or modifying biodistribution–and provide a pharmaceutically more acceptable or elegant dosage form.

PSI has assembled a range of technologies aimed at getting past the common bioavailability barriers of highly potent or DEA-controlled substances, to translate them from the benchtop into the clinic. And, with the acquisition of PSI by Lubrizol, clients have access to an end-to-end solution starting from polymers, through formulation development, and into commercial manufacturing on a global scale, says Dr. Lee.

"A methodical approach to increasing bioavailability through the manipulation of solubility and related addressable parameters is the path to success, especially for BCS IV molecules," says Dr. Mitchnick. "Keeping in mind that bioavailability is a multifactorial property, combining approaches in a disciplined development program is the way to go for these types of molecules. There are only a handful of unique drug delivery approaches–particle size reduction, amorphous forms, permeation enhancers, etc., but each has a different flavor and one size does not fit all. Having access to a full array of approaches ensures that the best products are developed." ◆

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NEXT-GENERATION SEQUENCING

NGS: Uniformity Across the Block

By: Andrew Birnie, PhD

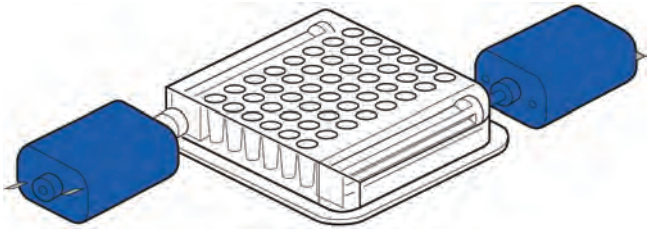
INTRODUCTION

Next-generation sequencing (NGS) allows researchers working across diverse life science disciplines to study biological systems with unprecedented throughput, scalability, and speed. From clinical diagnostics and forensics through to environmental science and now drug delivery, the application of NGS delivers a depth of genomics data that far exceeds conventional DNA sequencing techniques. However, NGS remains a high-cost pursuit. The risk of a single failed NGS run, for example, can cost in excess of $3,000. Securing complete precision and confidence at each step of the NGS workflow is therefore a critical pursuit during method development.

Quantitative Polymerase Chain Reaction (qPCR) technology is a core technique within NGS, employed for the robust quantification of library target molecules. It is essential that qPCR instrumentation deliver precise data at this point, or users risk ruining the NGS run before it even gets started. Unfortunately, many traditional qPCR systems suffer from imprecise temperature control, uniformity, and light bleed-through, which compromise the reliability of each run.

One way manufacturers are responding to these inefficiencies is to design qPCR technology that delivers complete thermal and optical uniformity across the entire sample block. This helps to guarantee that each run is completed reliably and accurately, mitigating the risk of costly NGS failure. This article explores how innovations in instruments, such as the Eco 48 real-time qPCR system (PCRmax), deliver exceptional uniformity, actively improving the reliability and productivity of the working laboratory.

FIGURE 1



Schematic of a hollow silver block for qPCR (Eco 48 PCRmax). This innovative hardware delivers more robust thermal performance and greatly expedites qPCR protocols.

NGS FOR DRUG DEVELOPMENT

Throughout the past 30 years, the development and maturation of high throughput NGS technology has transformed practically every facet of biological science. Within the clinical environment, NGS has become essential for assay development in disease detection and diagnosis. More recently, NGS has been deployed for drug development, particularly in the emerging field of personalized medicine.

NGS technology enables users to simultaneously process millions of parallel DNA sequences many orders of magnitude faster than traditional sequencing. Within drug development, NGS is increasingly used to rapidly generate genetic information to better understand the process of disease development and how patient-specific characteristics influence the response to new therapeutic treatments. NGS tests are increasingly employed across multiple disease areas, with particular success in the field of oncology. Comprehensive analysis of a tumor's genetic profile enables researchers to

study the development of a cancerous growth, its progression, and the emergence of drug resistance. In this way, NGS helps users produce pharmaceuticals with greater efficacy and performance and allows physicians to ensure patients are offered the most effective treatment available.

Today, NGS is a core technique throughout genomics research. However, despite advances in accessibility and usability, NGS remains a high-cost process. Initial capital expenditure in NGS equipment ranges from $150,000 upward to $1 million. Moreover, the cost of driving these processes is equally high. Optimizing the conditions of each run to mitigate failure is therefore an essential aspect of method development.

Target library quantitation is an area in which cost-effective technologies, such as quantitative Polymerase Chain Reaction (qPCR), are available to streamline and stabilise the NGS process, maximising returns from each run.

SAVING TIME & MONEY WITH QPCR-DRIVEN LIBRARY QUANTITATION

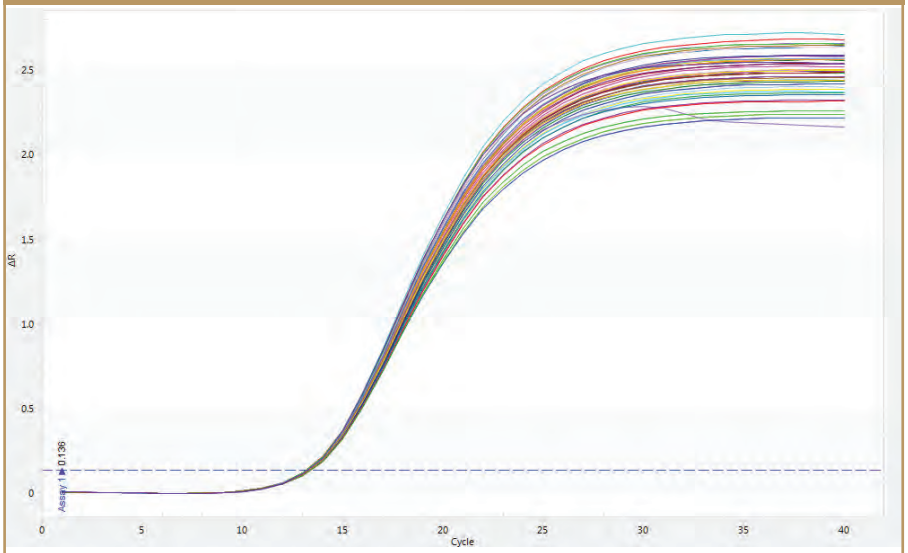
Target library quantitation is an essential step in NGS preparation, which often determines the success of the entire run. During library quantitation, fragments of target molecules are fused with adapters, followed by amplification and sequencing with polymerase chain reaction (PCR). The size of the target DNA fragments in the final library is a critical parameter for NGS library construction. If too little template is loaded onto the NGS platform, then the run will have low efficiencies. If too much is loaded, then the run not only risks low efficiency, but increased probability of complete failure. Robust and reliable library quantification is therefore critical.

Today, qPCR has become the technique of choice for NGS library quantitation, delivering precise analysis of strand amplification in real-time. During qPCR, dsDNA is amplified using primers with complementary sequences to the previously annealed NGS adapter. This results in a fluorescent signal being generated when the target strand is intercalated with DNA binding chemistry in the reaction mix. Capturing fluorescence in real-time enables precise quantification of amplification at appropriate stages of the reaction.

Real-time monitoring overcomes many of the inaccuracies associated with traditional end-point PCR, including unaccounted for variation in efficiency between samples and errors when extrapolating back to starting efficiency. Moreover, unlike end-point PCR, qPCR does not require a gel, eliminating much of the associated contamination risk. However, not all qPCR systems deliver the repeatability and accuracy required for secure NGS system loading.

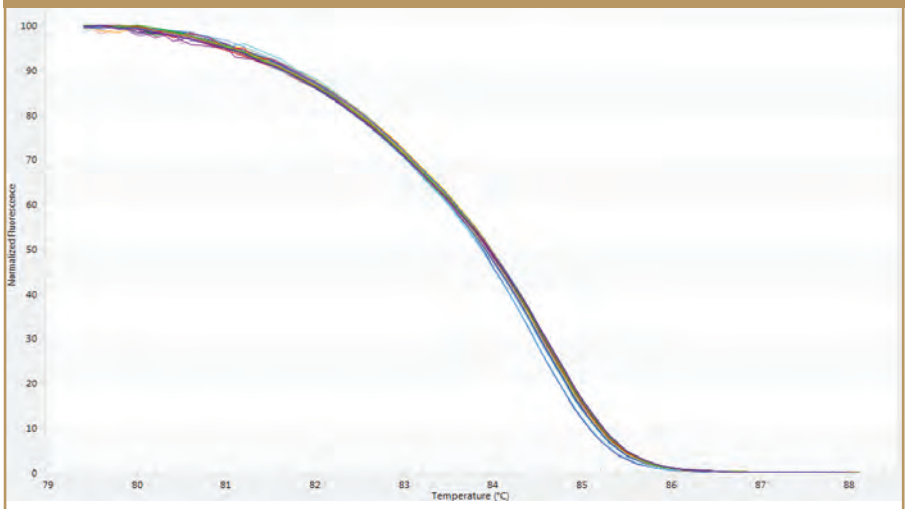
Precise temperature control is fundamental to the success of the qPCR process. Block temperature defines key features of the reaction, including primer binding and the performance of the polymerase enzyme. A qPCR thermal system must ensure that all of the samples in the well are uniformly heated so they proceed through the reaction at an equal rate. However, standard qPCR systems only have a thermal accuracy of around ±0.5°C at the 50°C to 60°C range. This is often insufficient to precisely define the cluster density, and an NGS run may risk failure if the qPCR platform under- or over-represents the true library concentration. The importance of achieving this level of precision is highlighted by stringent MIQE (Minimum Information for Publication for Quantitative Real-Time PCR Experiments) guidelines for qPCR

FIGURE 2



Baseline-corrected amplification plot showing the data from all 48 well plates. Analysis of the data showed an average C_q of 13.31 with a standard deviation of ±0.061 and a %CV across the plate of just 0.46%, indicating exemplary precision.

FIGURE 3



Normalized melt plot showing the data from all 48 well plates. The 100 bp PCR product template was melted over the range 75°C to 95°C. The Eco 48 measured the fluorescence with every 0.1°C of temperature change, the accuracy required to detect class IV SNPs with greater than 99% accuracy.

experiments, which demands increasingly sensitive qPCR technology.

With the price of high-performance qPCR instruments being outweighed by the cost of failed or low efficiency runs, employing a robust quantitative qPCR technique that delivers precise heating uniformity is possibly the simplest and most cost-effective way to guarantee consistent NGS.

ACHIEVING UNIFORMITY ACROSS THE BLOCK

Traditional qPCR systems employ solid Peltier-heated thermal blocks to drive thermal cycling. These systems are designed to heat the entire block to a temperature exceeding that of the required reaction before equilibrating to a desired plateau.

This is an energy-intensive process and the time it takes for all wells within the block to reach this point results in long run times and severely impacts the efficiency of the entire NGS run. More significantly, this method of heating contributes to high thermal non-uniformity (TNU) values of ±0.5°C and poor thermal ramp-rates. The combination of imprecision and inefficiency delivered by traditional solid-block qPCR means such systems are poorly suited to high-performance applications.

Recent advances in block heating technology overcome these issues. One significant innovation is the development of precisely uniformed hollow silver block structures through which a conductive fluid is passed to heat the sample. A single Peltier device is used to heat and cool the fluid, which is circulated evenly across all the sample wells by opposing agitators. This simple solution delivers both robust thermal performance, with TNU values below ±0.1°C at 95°C, and reduced run times. Standard 40 cycle PCR protocols take about 40 minutes to complete on these systems, while a fully optimized process can complete in only 15 minutes.

Advances in fluorescence monitoring technology have also improved the performance of qPCR techniques. High-performance optical systems enable real-time detection of up to four targets in a single reaction, and advanced detector arrays monitor the fluorescence from all wells, allowing the system to record every well, filter, and cycle without missing a single data point. Finally, the use of stable light emitting diodes (LEDs) contributes to accurate data generation and increases instrument longevity, decreasing depreciation costs. In combination, these innovations allow qPCR practitioners to meet and surpass all required MIQE guidelines, with no compromise to efficiency, cost, or speed.

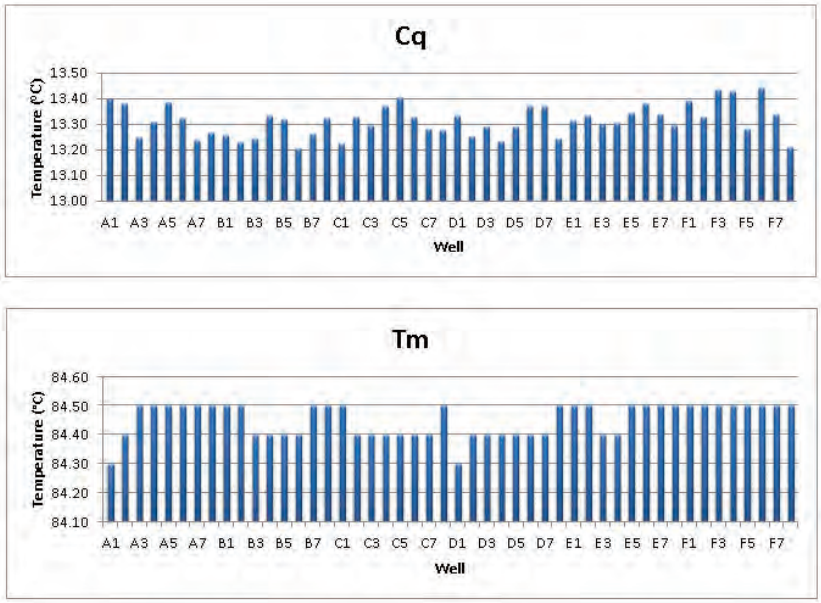
The following case study illustrates how improvements in thermal uniformity across the block deliver the sensitivity, precision, and overall efficiency required for high-performance NGS applications.

CASE STUDY: IMPROVING THE PRECISION OF QPCR

Forty-eight replicate samples were subjected to a High Resolution Melt (HRM) protocol using the PCRmax Eco 48. HRM enables precise analysis of genetic variations, such as quantifying single nucleotide polymorphs (SNPs), and is one of the most thermally demanding protocols in terms of accuracy.

Each of the 48 sample wells were filled with $1x10^8$ copies of the starting template (100bp template based on Lambda phage DNA) in a 10-microliter final volume. The plate was sealed and centrifuged for 1 minute at 12000 rpm, and the un-optimized 40-cycle PCR protocol was performed in 43 minutes total. The template was amplified for 40

FIGURE 4



Summary of C_q and T_m data from each of the 48 well plates. 0.24 cycles recorded the largest variation across all 48 samples with a maximum range in Tm of 0.2°C (84.3°C to 84.5°C) across the entire plate.

cycles (95°C, 10 secs; 60°C, 30 secs) using the GoTaq® QPCR Master Mix (2x) from Promega (part code A6001). Fluorescence data was collected at the end of the 60°C step. The results were analyzed using Eco study software to determine the quantitation cycle (C_q), the point at which fluorescence can be detected, and the melting temperature (T_m) values for each of the 48 replicates.

Figure 2 shows the baseline-corrected amplification plot for all 48 wells. The graph clearly demonstrates precision of amplification across the entire plate. Analysis of the data showed an average C_q of 13.31 with a standard deviation of ±0.061. This equates to a coefficient of variation (%CV) across the plate of just 0.46%, indicating exemplary precision.

T_m is determined by running a melting stage following the amplification of the PCR product and is one of the most effective measures of block uniformity. The amplified product melted in the 75°C to 95°C range, and the Eco 48 measured the fluorescence with every 0.1°C temperature change, the accuracy required to detect class IV SNPs with greater than 99% accuracy. Figure 3 shows the normalized melt curve.

Tm average across all 48 well plates was recorded as 84.45°C with a standard deviation of ±0.058, equating to a %CV across the plate of just 0.07%. This suggests that excellent temperature uniformity is achieved across the block. Figure 4 summarizes the results for this experiment.

DRIVING THE FUTURE OF GENOMICS

Advances in NGS technology continue to drive development across the diverse genomics arena. Within drug development in particular, NGS-driven genetically targeted therapies are delivering improved treatment pathways and greater patient care for a range of diseases. NGS data now forms the bedrock for a range of applications, and the reliability of the run is integral to the productivity of this high-cost process. The increased confidence that greater thermal control provides during NGS has made qPCR an essential feature of routine sequencing. qPCR instruments with innovative block technology, such as the PCRmax Eco 48, deliver complete heating uniformity and rapid cycles in under 40 minutes, with the sensitivity to deliver ±0.1°C uniformity across the whole block instantly after every temperature change. These leaps in efficiency allow users to achieve consistent NGS runs, helping to further their critical genomics research. ◆

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BIOGRAPHY

Dr. Andrew Birnie is an experienced molecular biology specialist. He currently works as Business Development Specialist at PCRmax (a Bibby Scientific Company); specializing in applications, technical support, and marketing. His expertise and interest in molecular biology allow him to offer significant input into product development. Prior to joining PCRmax, Dr. Birnie was a Molecular Biology Product Manager at Labtech Int. with his role involving the management of the Molecular Biology portfolio. Dr. Birnie earned his PhD in Veterinary Parasitology at The University of Glasgow, where his research focused upon the nematode caenorhabditis elegans, as a model organism for nematode parasites.

Drug Development
EXECUTIVE

David G. Watumull
President & CEO
Cardax, Inc.

Cardax Inc: Delivering Nature-Identical Astaxanthin to the Market

Headquartered in Honolulu, Hawaii, Cardax focuses on developing products utilizing astaxanthin, a naturally occurring compound demonstrated to reduce inflammation without many of the harmful side effects of current anti-inflammatory treatments, such as steroids and NSAIDs. More than 40 human clinical trials supporting the safety and efficacy of natural astaxanthin have been conducted to date. As the broader scientific community has discovered the health benefits of astaxanthin, awareness and demand for astaxanthin has increased significantly. A publicly traded company, Cardax has strategic alliances with two multinational companies: 1) BASF, the world's largest chemical company, related to the use of a proprietary, scalable, and cost-effective synthetic astaxanthin products that deliver nature-identical astaxanthin to the blood stream; and 2) Capsugel, a Pfizer spin-out and leading encapsulation, tableting, and formulation company, related to the proprietary formulation of astaxanthin for increased oral bioavailability. David G Watumull, the company's President and CEO, spoke with *Drug Development & Delivery* to discuss Cardax's plans to create a new platform for products in the consumer health and pharmaceutical markets based on the delivery of nature-identical astaxanthin.

Q: For our readers who may be unfamiliar, can you provide some company background and history on Cardax?

A: Cardax was founded in 2006 as a spin-off of Hawaii Biotech, where I had been President and CEO since 2001. However, the genesis of forming a company around astaxanthin for the mass-market came about several years earlier in the late 90s, when I was an investment banker working with Aquasearch, a firm that produced natural astaxanthin from algae on the Big Island of Hawaii. Aquasearch's original target was the salmon feed market, where astaxanthin is

used to confer salmon's distinctive pink color, but the cost of microalgal production was not competitive with the synthetic products on the market at that time. Searching for a viable business model, I noted that astaxanthin-fed salmon grew larger, healthier, and lived longer. Without astaxanthin, scientists observed, salmon were not strong enough to swim upstream. I began researching the scientific literature, and the more I looked, the more intrigued I became about the combination of astaxanthin's safety and its anti-inflammatory/anti-oxidant properties. I suggested Aquasearch develop a human dietary supplement based on microalgal or aquafarmed astaxanthin and in 2000, joined the company to help develop and launch that product. I later became convinced that large-scale, mass-market microalgal production of astaxanthin was not commercially feasible and joined Hawaii Biotech as President and CEO to develop, in addition to Hawaii Biotech's sub-unit vaccines, the natural product synthesis of a proprietary astaxanthin product for mass-market human use. To bring this vision to reality, we spun Cardax off from Hawaii Biotech in 2006 and took it public via a reverse merger in 2014.

Q: Is there a particular drug discovery methodology that Cardax adheres to?

A: We see Cardax as part of an industry trend that entails producing a category of consumer health products that have the safety of "food" and the efficacy of a drug. The Omega 3s are an example of this trend that features the convergence of pharmaceuticals and dietary supplements. To be successful, these new products must have real science behind them. As far as astaxanthin is concerned, to date, over 1,000 peer-reviewed papers exploring the compound have been published in scientific journals, including more than 40 human clinical trials. More than 50 of these peer-reviewed papers have been published by our Cardax team members, 10 of which appeared in The American Journal of Cardiology.

Our Chief Scientific Officer, Gilbert M. Rishton, PhD, terms the practice of using dietary supplements or nutraceuticals as pharmaceuticals as "disruptive therapeutics." He calls finding the new cures "disruptive drug discovery."

Sourcing natural products to treat disease seems entirely logical, but it's at odds with the current class of target-driven drug discovery methods. such as biochemical screening, which has largely failed to produce safe and efficacious drug candidates.

Rather than ending up with drugs with severe side effects, we believe it's best to start with natural products and dietary supplements that are actually safe from the get-go and (here is the key) demonstrate real efficacy through traditional human clinical trials.

Q: Can you provide more information about your products?

A: We expect our first product to be a proprietary astaxanthin consumer health (dietary supplement) product that will deliver nature-identical, pharmaceutical-grade astaxanthin to the bloodstream. This product will be manufactured via natural product synthesis by BASF, likely formulated by Capsugel, and will require GRAS (Generally Recognized as Safe) designation for marketing in the US. Once the consumer product is on the market, we plan, either directly or through other alliances, to expand usage by conducting appropriate human clinical trials and developing pharmaceutical therapies for diseases in which inflammation and oxidative stress are strongly implicated, including, but not limited to, osteoarthritis, rheumatoid arthritis, dyslipidemia, metabolic disease, diabetes, cardiovascular disease, hepatitis, cognitive decline, macular degeneration, and prostate disease.

Q: What's the rationale behind producing a synthetic astaxanthin product that delivers nature-identical astaxanthin to the bloodstream?

A: The amount of astaxanthin that can be manufactured from algae is quite limited, requiring multiple steps and copious amounts of land, water, labor, and related infrastructure. It's inherently a very expensive and time-consuming process. What's more, the "natural" product is typically only 5% to 15% astaxanthin. In contrast, we anticipate synthetic nature-identical products will be highly pure. Because you're growing algae in an outdoor setting, it's hard to keep your batch from getting adulterated – even if the contaminant is minute. In contrast, the manufacturing rigor that can be provided by a nature-identical manufacturing process can eliminate these quality constraints. Very importantly, microalgal production has not been proven to

"Rather than ending up with drugs with severe side effects, we believe it's best to start with natural products and dietary supplements that are actually safe from the get-go and (here is the key) demonstrate real efficacy through traditional human clinical trials."

scale efficiently to the quantities required for the mass-market, whereas nature-identical manufacturing should be scalable.

Q: Can you discuss your relationships with BASF and Capsugel?

A: BASF has exclusively licensed the rights to develop and commercialize consumer health products utilizing nature-identical astaxanthin and will pay us royalties on their sales. With Capsugel, our goal is to jointly develop and commercialize proprietary formulations of products utilizing nature-identical astaxanthin that will provide enhanced oral bioavailability compared with other astaxanthin products on the market.

Q: Can you talk about recent research into astaxanthin that may be of interest to readers?

A: Even though the astaxanthin market has grown considerably throughout the past few years, there is some research going on that we expect could expand the market for astaxanthin significantly. In addition to its well-established anti-inflammatory properties, it looks like astaxanthin may play a major role in aging by acting as a mimetic for caloric restriction (CR). As your readers mostly likely have heard, CR is a well-known research intervention in the biology of aging in model organisms. In fact, CR is the only non-genetic intervention that consistently has shown an extension of maximum life span in model organisms of aging.[1] Astaxanthin could provide the physiological benefit of CR without the actual need for restriction of calories. While there is not a full understanding of the biological basis of CR, our thesis is that it's linked to nutrient-sensing biological pathways that modulate growth and biological systems responsible for stress resistance, and ultimately aging.

There's another very intriguing quality to this compound. Our hypothesis is that CR induces hormesis, a low-level stress, which triggers the up-regulation of stress-resistant biological pathways. The kicker is that this includes the FOXO3 gene, which is one of only two genes that have been consistently shown to influence longevity in diverse human populations (the other gene is Apolipoprotein E). The upshot is that we believe astaxanthin is a key to triggering the FOXO3 gene's positive influence on preventing chronic diseases and ultimately improving longevity.

Q: What are the next critical steps for Cardax?

A: Clearly, we are looking forward to launching our first product(s) through our relationships with BASF and Capsugel. As part of the launch, we will work to raise scientific awareness of astaxanthin's anti-inflammatory and anti-aging qualities in the appropriate scientific forums. In addition - with additional financing or with a partner - we plan to conduct low-risk, economical human proof-of-concept clinical trials in areas of interest, including osteoarthritis, diabetes, liver disease, and cognitive decline, which may promote consumer health sales and advance our pharmaceutical development program. ◆

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Enhancing patient lifestyle I Extending product lifecycle

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Technology & Services Showcase

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CLOUD COMPUTING

Using Quantum Molecular Design & Cloud Computing to Improve the Accuracy & Success Probability of Drug Discovery

By: Ed Addison and Shahar Keinan, PhD

INTRODUCTION

Organizations that develop drugs cannot afford to stick to traditional costly and time-consuming methods of drug discovery. Nor can they remain mired in outdated thinking that focuses on the past failures of computational drug discovery. A number of newer approaches are yielding faster, more accurate, and more affordable results.

Cloud computing combined with the continued influence of Moore's Law has provided an unprecedented opportunity to apply inexpensive high-performance computing to drug discovery. This combination has now made the cloud the most promising venue for drug discovery and offers new techniques that can be combined to achieve success at a higher level.

The costs and timelines to develop effective medicines using traditional drug discovery methods are much too high, exacerbated by outrageous failure rates – resulting in very high costs that are passed onto consumers and threatening the financial stability of our healthcare system.[1,2] It's well documented that out of 10,000 discovered compounds, less than one makes it past preclinical screening and clinical trials to achieve FDA approval. This high failure rate drives up much of the cost in traditional drug discovery and development. Methods like high-throughput screening (HTS) offer some promise to reduce failure rates and improve time to market. But this process does not generate novel molecules – so we're back to high costs and staggering timelines, and challenging IP scenarios. Previous in silico methods seemed to offer the promise of a better way but have not been accurate or robust enough.

Cloud computing offers a solution by enabling more sophisticated computational chemistry coupled with rapid synthesis and optimization that helps companies identify compounds that are better suited for development from the outset. Selecting compounds with a higher probability of success then acts as a lever to reduce overall cost, which is a necessity if we're to achieve personalized medicine or "niche buster" drugs.

HOW CLOUD COMPUTING IMPROVES UPON TRADITIONAL METHODS

Deeper computational chemistry via cloud computing helps address two of the major problems with traditional drug discovery. It helps improve efficiency by picking better compounds to bind with biological targets and have good "drug-like" properties. But the goal is to not only reduce cost and improve speed. It's about producing much improved compounds for really hard-to-drug targets.

Cloud computing helps in the design of compounds for hard-to-drug targets by providing extensive computing power so that more time-consuming but atomically accurate in silico design methods can be deployed. It identifies molecules from novel chemical space – not the same screening decks that have been used before and failed. Targets that were once difficult to

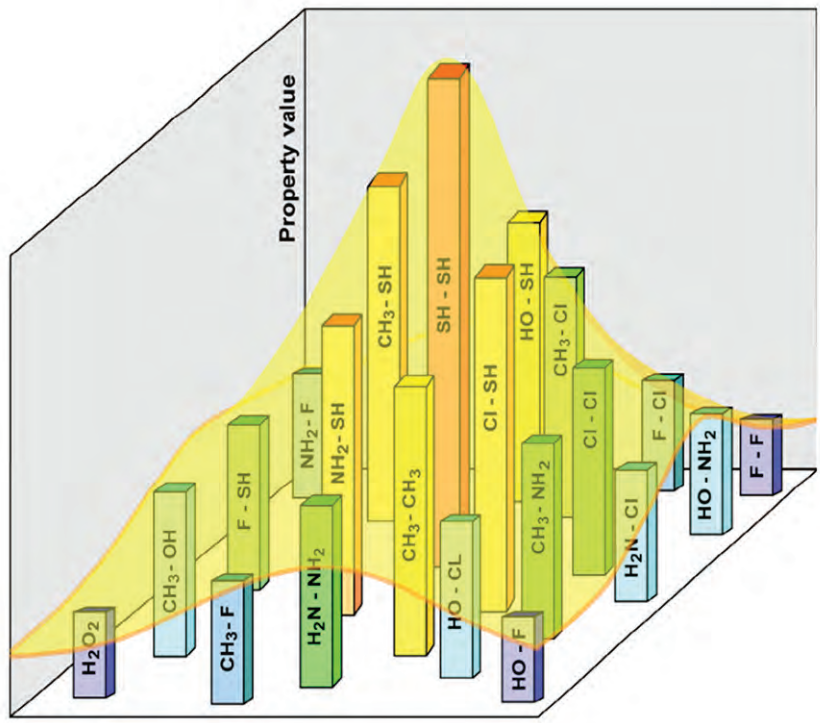
drug are showing promise through the use of more computational power via cloud computing. For example, traditional algorithms are ineffective on targets with limited structure information such as G-protein-coupled receptors (GPCRs). However, deploying sophisticated homology modeling with molecular dynamics methods helps gain structural information, that when combined with quantum chemistry in the cloud, as well as searching molecular space for novel molecules, can result in promising compounds for previously undruggable targets.[3]

A NOVEL APPROACH TO DRUG DESIGN & DISCOVERY

One approach that illustrates some of the ways the cloud is helping to improve drug design and discovery is based on pioneering work developed at Duke University. The Beratan and Yang groups at Duke University had developed novel algorithms to search chemical space. In its first implementation, the linear combination of atomic potentials (LCAP) used molecular characteristics as a function of parameters that define the contribution of a specific chemical group at a particular chemical site in a molecule (Figure 1).[4]

This method enables the construction of a potentially enormous novel space of chemical structures at a cost far below the factorial cost of individual structure evaluation. The LCAP method has been published[4-6] and experimentally tested[7] as well as shown to have several advantages, such as multiple search methods and ease of parallelization. Initially starting with the LCAP method, more sophisticated search algorithms for accessing novel chemical space have been developed by Cloud Pharmaceuticals.

FIGURE 1



A schematic representation of a molecular metric (bar heights) for discrete chemical structures and a smooth Quantum Molecular Design surface (in yellow) that allows for continuous variation among structures.

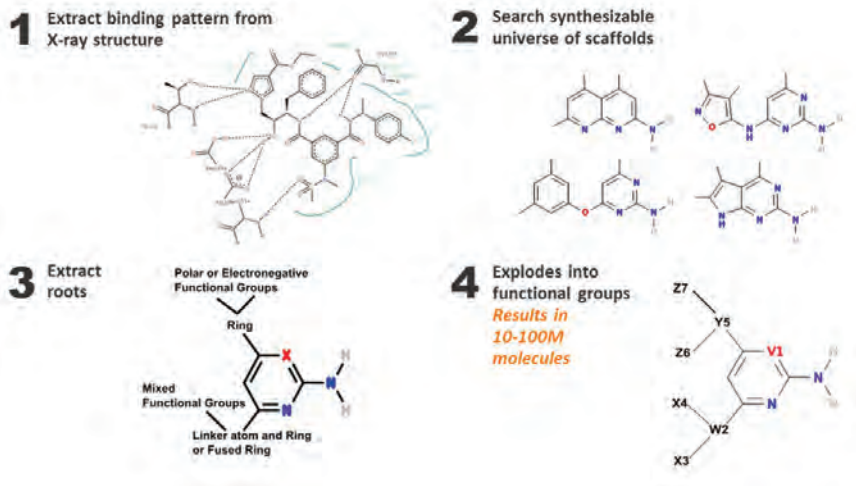
Cloud Pharmaceuticals has improved and revised Duke's original approach to allow versatile, multiple, and chemically diverse molecules with its Quantum Molecular Design process. The Quantum Molecular Design algorithm is a novel implementation that is based on a proprietary combination of transformation between chemical and vectorial space and integer-programming methods to result in better identification of totally novel compounds that result in reduced medicinal chemistry effort and greater freedom to operate. Cloud Pharmaceuticals' objective is practical drug design, as opposed to academic pursuits which often take researchers into expensive and intractable directions.

SPEEDING THE DISCOVERY OF NOVEL DRUG CANDIDATES

Quantum Molecular Design uses molecular modeling in the cloud to design drug candidates and identifies companion biomarkers through a partnership with Genomeon. Quantum Molecular Design improves upon traditional methods in three ways. First, it offers a novel way of searching for new molecules. It identifies molecules that are designed directly from the characteristics of the binding pocket of the biological target using a proprietary AI / "big data" approach.

Second, Quantum Molecular Design offers very accurate prediction of the binding affinity between a protein and a small molecule (or peptide). The process uses an optimal combination of methods adapted to the target class and molecule

FIGURE 2



Casting the net into molecular space

type, which includes one or more of: the quantum mechanics/molecular mechanics (QM/MM) method, molecular dynamics (MD), linear interaction energy (LIE), and/or free energy perturbation (FEP), with parametric adaptations. Results have repeatedly yielded correlations of 0.7–0.9.[8, 9] Specifically, it describes with atomic details the protein, molecule, and water environment. It accurately represents the role of water in solvation and in the protein active site, including a high sampling rate. It samples conformation of the protein-binding pocket as well as the small molecule and water molecules, and accurately predicts the interaction between them.

Third, Quantum Molecular Design filters molecules for chemical properties that are desirable for drugs. Results then yield only molecules that make it through all of the filters. For example, you can filter molecules based on solubility, synthetic tractability, or if the molecule crosses the blood-brain barrier. There may be molecular weight constraints for some designs that need to be filtered. Or, there may be side chains that are unstable or undesirable that you want to filter out of some designs for biological reasons. The property-filtering tools in Quantum Molecular Design help yield only "good" molecules that substantially reduce the work of the medicinal chemist during optimization.

ACCURATELY PREDICTING LIGAND BINDING

Using the methods above helps improve binding accuracies by employing a multi-scale, multi-resolution approach. This approach has a ligand solvation term calculated with implicit solvation with a high sampling rate and flexible protein, flexible ligand, explicit water model.

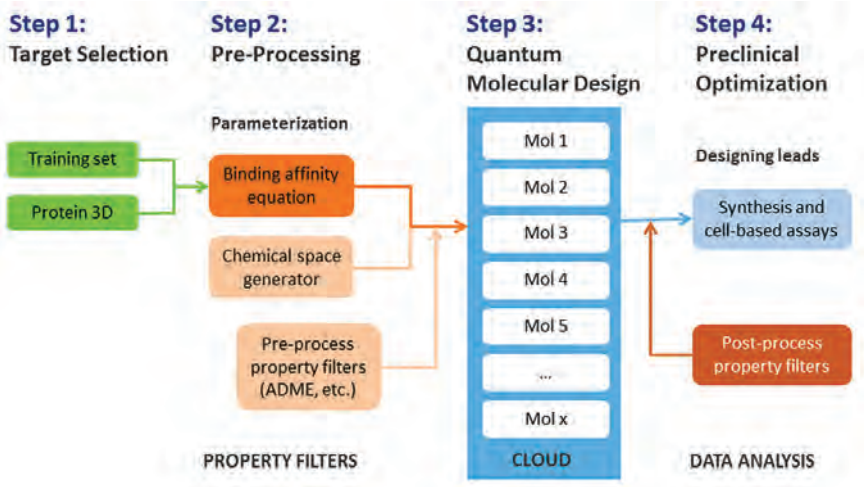
For example, this methodology was applied to the Janus family of kinases in order to discover novel inhibitors of the JAK3 enzyme that is selective against other proteins from the Janus family.[10] Due to different activities, each JAK protein is targeted toward different diseases: JAK3 for rheumatoid arthritis, immunosuppression, and inflammation; while JAK2 is targeted for cancer. Cloud Pharmaceuticals has designed inhibitors targeting JAK3 that do not target other members of the family, which produce more focused results with fewer side effects.

CASTING THE NET INTO MOLECULAR SPACE

Quantum Molecular Design searches novel space by extracting a binding pattern from an x-ray structure of the target (Figure 2). This pattern is based upon the 3-D shape of the target's binding pocket. The pattern is then queried against an enormous and growing database of scaffolds that contains all scaffolds published in literature, many theoretical scaffolds created combinatorically, and includes liberal hopping of those scaffolds to make many others. After querying that database with the binding pattern, you get a list of molecular matches. Any of those matches are scaffolds that have been stripped down to extract only the root of the scaffold.

Quantum Molecular Design then expands the scaffolds by varying the functional groups in every position of all of the scaffolds that produced a good match to create a novel chemical space, including only stable functional groups. This approach results in 10 million to a billion molecules depending upon the depth of study and the number of scaffolds or roots considered. This fast and efficient algorithm is done in the cloud and produces a novel, diverse, and relevant virtual molecular space exponentially faster.

FIGURE 3



Quantum Molecular Design process workflow

QUANTUM MOLECULAR DESIGN WORKFLOW

The way Cloud Pharmaceuticals applies this process is to first select the target and establish a 3-D model of the target from its x-ray structure or from homology. If training data is available, it is applied to help improve results (Figure 3). The next step is chemical space generation, using the method described in the previous section. The process then ventures into the cloud to identify molecules with the strongest match to the desired properties.

At each step, several thousand molecules are scored using an optimal binding affinity and solvation algorithm. Based on the calculated affinities in each step, the head node redirects the search, based on the previously explained search algorithm, and continues until achieving optimum results in rank order. The process can typically be completed in 1 week with 3,000 cloud nodes or 3 weeks with 1,000 nodes – the process is embarrassingly parallel and scales accordingly.

The next step is the beginning of the preclinical optimization process in which you take the rank-ordered hit list of matches, filtered for drug-like properties, and work with a medicinal chemist to pick the molecules to synthesize. Many of Cloud Pharmaceuticals' projects begin with synthesizing a small number of molecules – perhaps 10 or 20 with the highest scores. This preliminary experimental work includes synthesis, chemical characterization and measurements, and conducting binding assays and cell-based assays. If the results are not satisfying from the first batch, you can then analyze additional molecules systematically in rank order, accounting for diversity.

Typically, de novo design of drugs requires 500,000 CPU hours in the cloud, but this may vary based upon the depth of coverage desired. The Quantum Molecular Design process has been deployed on multiple cloud services: Amazon Web Services, ProfitBricks, Cloud & Heat, Google, and Microsoft Azure. Due to the method flexibility, it can run on almost any cloud with minimal reconfiguration.

Because Quantum Molecular Design generates novel molecules – not those from an existing screening deck – the process provides much greater freedom to operate than traditional HTS. This method has been validated by correlation with reported lab data, and by synthesizing totally new compounds and successfully conducting assays showing activity. This results in lead identification, producing compounds suitable for further optimization based on biological models.

PRECLINICAL DEVELOPMENT

Following the work completed in the cloud, the carefully screened hit list is ready for further preclinical development. Because you've eliminated many candidates that have a high probability of failure, this step should go much more efficiently. While drug designers still have to complete all of the customary preclinical development steps, they're being applied to a much more qualified list of candidates, resulting in a much higher success rate, more rapid progress, at lower cost, and on novel and hard-to-drug targets. Cloud Pharmaceuticals partners with contract research organizations (CROs) and risk-sharing partners to perform many of these steps.

The power of the cloud is that it yields novel molecules for hard targets and offers improved results that lower costs and speed time to market. Further, collaborative drug discovery and development can be securely managed among multiple partners via the cloud, which is what Cloud Pharmaceuticals does. The company integrates the efforts of its partner network to carry out a

great deal of the drug discovery, design, and development efficiently, in addition to using the cloud for computational power in design work.

DE NOVO DESIGN IN THE CLOUD

The significance of the approach detailed here is that the hit list and early lead identification steps are all performed in the cloud, until synthesis. Further, the composition of matter patents that result are more powerful because they include many compounds in the same nexus from a common process. The "hits" produced are easier for the medicinal chemist to turn into good "leads" because good drug-like properties are already built in.

In fact, Cloud Pharmaceuticals is currently working with an emerging life sciences data center in Iceland, where it expects to preemptively design inhibitor libraries for the entire druggable genome and known mutations thereof, based on data reported by the Human Proteome Project, a multi-year project expected to be disruptive to HTS.

This process has been applied to many single-target projects ranging from kinases to allosteric proteins, GPCRs, and other receptor proteins. The company is working with a long list of targets, including Aurora-A, BACE1, betaCR, DHFR, eiF4E, HDAC8, hsp90, JAK3, MetAP2, Metnase, PKCe, PKR, PLA2, ROCK2, and Serpins – to name a few. Quantum Molecular Design can be applied to any of these targets and begin with x-ray structure or with homology. ◆

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BIOGRAPHIES

Ed Addison is the CEO of Cloud Pharmaceuticals, a therapeutics company focused on cloud-based drug design and development he co-founded in 2009. Mr. Addison is a serial entrepreneur who has founded three previous ventures, two of which successfully merged with public companies in deals worth $55 million. He has a unique and strong blend of in-depth business and technical experience in biotechnology and in information technology.

Dr. Shahar Keinan is the Chief Scientific Officer and co-founder of Cloud Pharmaceuticals. She has over 20 years of extensive experience in the field of computational and theoretical chemistry. Dr. Keinan earned her PhD in Theoretical Chemistry from The Hebrew University of Jerusalem and has numerous papers and presentations in the fields of in silico drug design and discovery, as well as molecular materials design and computational methods development to her credit.

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PACKAGING SOLUTIONS

New Deep-Drawn Alufoil Container Solves Crucial Packaging Issues for Vital Pharmaceutical Products

By: Georg Buchinger and Cora Helberg

INTRODUCTION

With global demand for medical devices and pharmaceuticals at an all-time high, the risks of degradation or contamination from mold and mildew-inducing moisture in the manufacturing and transport of these critically needed items has become an increasing concern within the life sciences manufacturing sector. Both industries are highly regulated in the global marketplace and in the respective home countries of individual companies, meaning the consequences of a product package failure are quite substantial.

Furthermore, increasing globalization has had the unfortunate consequence of allowing contagious diseases to spread rapidly across borders. This requires effective and timely prevention, detection, and treatment of disease, rendering the need for safe global drug distribution and packaging even more urgent.

Packages need to meet GMP hygiene standards and be cost-effective, but also simple enough for customers of varying levels of sophistication to open and use effectively. This balance can be tricky, but alufoil containers, in use by the food industry for decades, have demonstrated both high product safety and ease of use.

We will show how the adoption of aluminum containers for pharmaceutical products is both a natural evolution of a technology used by packaging leaders since the 1990s, and an ideal prophylactic measure for the growing needs of demanding pharma customers.

ORIGINS OF ALUFOIL CONTAINERS

Multiple attempts have been made by packaging companies through the years to find a cost-effective, lightweight, and portable solution to the common problems of moisture and humidity and their attendant spoilage. Whether in storage or transit, products in nearly every industry require moisture protection because moisture frequently causes rust, mildew, mold, and an overall decrease in product efficacy, resulting in returned or unusable products. Plastics, VCI paper, and desiccant packets have been tried with varying degrees of success.

In the 1990s, an innovation was introduced for packaging meat in Europe in the form of easy-to-open alufoil containers that were retortable – composed of a laminate of flexible plastic and metal foils that offered an aseptic packaging alternative to traditional canning. Pet food manufacturers quickly adopted the packaging; for example, Mars, Inc. created a hygienic pet food container that seals completely, but is also easier to open than a can and lighter in weight.

"Constantia Flexibles developed Safemax specifically for use by a top-five pharmaceutical company. In doing so, the engineers needed to overcome multiple design challenges. Its clients, which face exacting regulatory and health standards that are inviolable, require the packaging to be sterile, with high protection against moisture ingress, as described previously; and easily opened and commercially viable in the competitive global marketplace."

By the turn of the last century, alufoil containers combining special heat-resistant seals with peelable lacquer systems became popular for desserts. This made it possible to bake a cream or cake directly into a cup, reducing labor and materials costs.

Additional applications began to emerge, demonstrating the versatility and cost effectiveness of alufoil. Containers for a variety of perishable foods, such as coffee creamer, liver pate, jam, honey, and airline catering containers were made from alufoil. In addition, the material also proved itself highly useful for non-food products, such as fuel paste, because of its cost, ease of transport, and especially, resistance to moisture and leakage.

Some of these same attributes make alufoil highly suitable for use in pharmaceutical applications. Alufoil is capable of passing muster amidst the pharmaceutical industry's stringent quality, hygienic, regulatory, and product security requirements.

One of the first pharmaceutical products to be packed in alufoil containers was an oral dose for avian influenza, which needed to be produced in large quantities after the SARs outbreak in Asia. In 2014, the first inhalation device was introduced in an alufoil container.

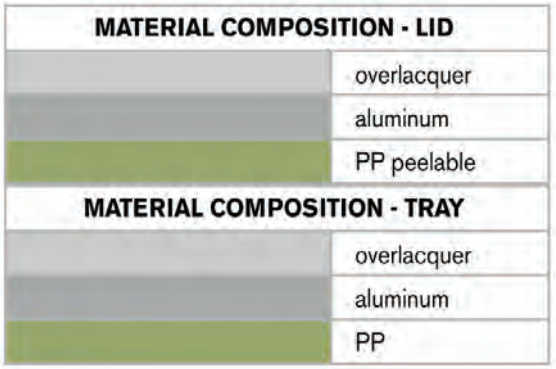
DESIGN & DEVELOPMENT OF SAFEMAX BY CONSTANTIA FLEXIBLES

Pharmaceutical devices in particular are vulnerable to outside environments; life-threatening risks of even the tiniest leak include cross contamination of blood, bacterial seeding, and insufficient or excessive medication dosages. For this reason, leak testing is commonly used in the device industry as quality standards have become increasingly stringent because product failure presents hazards to patients and healthcare professionals, and liabilities to manufacturers. The International Electrotechnical Commission (IEC)

FIGURE 1

Constantia Safemax

FIGURE 2



Material Composition of Lid & Tray

standard 60529 established and documents standard degrees of ingress protection. Titled Degrees of Protection Provided by Enclosures, it is commonly referred to as the Ingress Protection or IP Code.

Following a demanding research and development program, the pharma division of Constantia Flexibles Group in Vienna, Austria, recently introduced a breakthrough deep drawn aluminum container, dubbed Constantia Safemax, that offers a radical improvement from past technologies, providing new opportunities for containing and protecting a broad array of moisture-sensitive pharmaceuticals and medical devices.

Constantia Flexibles is a global corporation that develops, manufactures, and supplies flexible packaging solutions for the pharmaceutical, healthcare, home and personal care, and food and beverage markets. Recognized as a world market leader for die cut lids and other flexible packaging product niches, Constantia offers integrated, start-to-finish, foil-based packaging solutions to the North American pharmaceutical and nutritional industries.

Constantia Flexibles developed Safemax specifically for use by a top-five pharmaceutical company. In doing so, the engineers at Constantia Flexibles needed to overcome multiple design challenges. Its clients, which face exacting regulatory and health standards that are inviolable, require the packaging to be sterile, with high protection against moisture ingress, as described previously; and easily opened and commercially viable in the competitive global marketplace.

During this development process the dedicated team of Constantia experts relied upon its technical understanding of aluminum as an effective packaging medium, along with the firm's well-established expertise in aluminum conversion technology in previous market applications.

Taking a systematic approach, Constantia Flexibles managed to resolve the most crucial issues. In the process, the team realized a vision of a radically different pharma packaging system that, during the production process, is tailored to perfectly match clients' individual product needs.

To produce Constantia Safemax's deep-drawn tray, aluminum is laminated to polyprolypene and then combined with a highly peelable lidding foil particularly known for its consumer peelability. The result is exemplary seal integrity with easy-opening characteristics. Its exact design and format can be readily fitted to ensure the pharma device is successfully delivered to individual patients.

ALUMINUM CONTAINER TAILORED FOR INDIVIDUAL CUSTOMERS

The Safemax production process previously described differs for each customer. It begins when a potential client has an inquiry and submits its requirements for the aluminum tray with a 3D-drawing of the product and how it should be packed.

Constantia then investigates which material will be the best for this application and which features must be included in the alufoil container to meet a number of requirements. Here, typical considerations include:

- An appropriate material for the container and lidding foil to guarantee high- moisture protection of product in places as humid as the tropics.
- The design of the alufoil container interior must protect the sensitive product during transport, including the construction of ribs to secure the product or device during transport.

- The material and design of the lidding foil must guarantee a consumer-friendly opening.

- The design of the alufoil container for optimized stacking in the production process, and subsequent destacking on the packing line of the client.

All of these aspects must be taken into consideration – both with the client and the tooling maker – before any work can commence. A prototype of the container is then designed comprising a 3D print with plastic. The client first tests the 3D-container print with the device and then provides more information for optimization. Upon implementing these final alterations, the optimized alu-design is given to the client for approval.

Finally, a single head tool is produced for forming the aluminum tray. The material is die-cut, and the tray is formed out of a blank. These first samples are used from the client to make transport, stability, and shelf-life tests. Upon passing these examinations, the material is approved by the client.

BENEFITS & APPLICATIONS

Safemax is very easy to open due to its customer-convenient lidding foil and is highly transportable, but most important is that it provides the highest levels of moisture protection against ingress of liquids or moisture during global distribution. The final product meets the demanding quality, hygiene, regulatory, and product protection requirement for products in the modern healthcare market.

The radically different aluminum tray and lid are aesthetically pleasing and have high-seal integrity. Additionally, it enables market and product differentiation plus enhanced consumer valuation.

SUMMARY

Compared to alufoil, traditional containers have many limitations. Potential applications for this custom technology in the future are boundless. The packaging of syringes, for example, is now mainly done by packaging in a plastic blister. Safemax solves for this application's inherent shortcomings.

Containers, such as Constantia Safemax will certainly play a significant role in the future for pharmaceutical products because they suffer none of the risks of traditional packaging materials. Safemax would prove itself superior even when cost is not a consideration, but this breakthrough product convincingly shows how advances in materials technology are making possible better sustainability without loss of performance. And because Safemax can be manufactured at high speeds, materials availability and turn-around times are not concerns.

Constantia Safemax's exceptional benefits meet the demanding requirements of new healthcare products and, for an industry with stringent international hygienic and quality control requirements, alufoil is clearly a highly attractive choice. ◆

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

BIOGRAPHIES

Georg Buchinger is Product Manager for Constantia Flexibles, where he specializes in the design and development of high-performance packaging systems. To do so, he works in close collaboration with both partners and customers around the world.

Cora Helberg is Marketing and Innovation Manager for Constantia Flexibles's Pharma Division. She has more than a decade of experience working with flexible packaging materials that help improve product protection and efficacy.

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External Delivery

5 Topics Your Board Needs to Discuss Immediately

By: John A. Bermingham

Last week, this magazine's Executive Director, Dan Marino, asked me to comment on an article titled *5 Topics Your Board Needs to Discuss Immediately* by Patricia Lenkov that was posted on CEO.com. Ms. Lenkov serves as Chair of the Executive Search Practice at N2growth, a global leadership consultancy with practice areas in leadership development, executive search, strategy, culture transformation, organizational design, and executive coaching. The following are my comments on her 5 topics. I hope it provides some insight!

Social Media – This is the group of online channels that focus on community- based input, interaction, and collaboration. What most Boards are missing today is the critical importance of marketing and selling through social media. The days of primarily selling goods and services through radio and television spots and print advertising are over. Today, Millennials (people aged 18-34) and Generation X (people aged 35-50) are quickly moving toward social media for information on products and services. Marketers understand this and are now developing content marketing strategies to capture and retain loyal customers. If your Board is lacking the knowledge and experience in social media, strong consideration should be given to bringing in an outside director who has experience in this area.

Diversity – I have been asked on more than one occasion if I believe having diversity in my company or Board is more or less important than having the best people in the company regardless of ethnicity. My philosophy has always been that if you hire the best people regardless of ethnicity, diversity will take care of itself.

Succession Planning – This is a process that I call the "insurance syndrome." No one ever goes out on a regular basis to shop insurance policies. People price insurance only when they need it. Same for succession planning. This necessary Board activity seems to only gain attention when the CEO departs either by choice or no choice. Then the Board and the company are leaderless, and the results can be disastrous.

Board Effectiveness & Evaluations – I have never seen a Board that conducts an E & E review of themselves. Outside directors are brought on because they have certain skill sets that are valuable to the company. The problem is that the business world goes through changes and priorities and focus must change with it. Those changes often leave a Board with the wrong skill sets. As one example, take Topic 1 (Social Media). The marketing world has changed significantly over the past few years. The Board member whose expertise is in print media, although a real asset 10 years ago, is non-effective today. So the Board has to make the necessary changes to pass the Effectiveness Evaluation test.

Compensation – This is a topic that is never ending. How can a Board justify compensating a CEO millions of dollars for failure? Why is it that the CEO's compensation isn't performance based? Maybe its because the CEO has formed a Board of "good old boys" who take care of each other. One of the things that the SEC enacted in 2015 was a requirement that all companies listed on the NYSE and NASDAQ that utilize outside compensation consultants be deemed independent according to six independence criteria. It's a step in the right direction, but not a total solution.

Patricia Lenkov's full article can be read at http://www.ceo.com/business_and_government/5-topics-your-board-needs-to-discuss-immediately/. ◆

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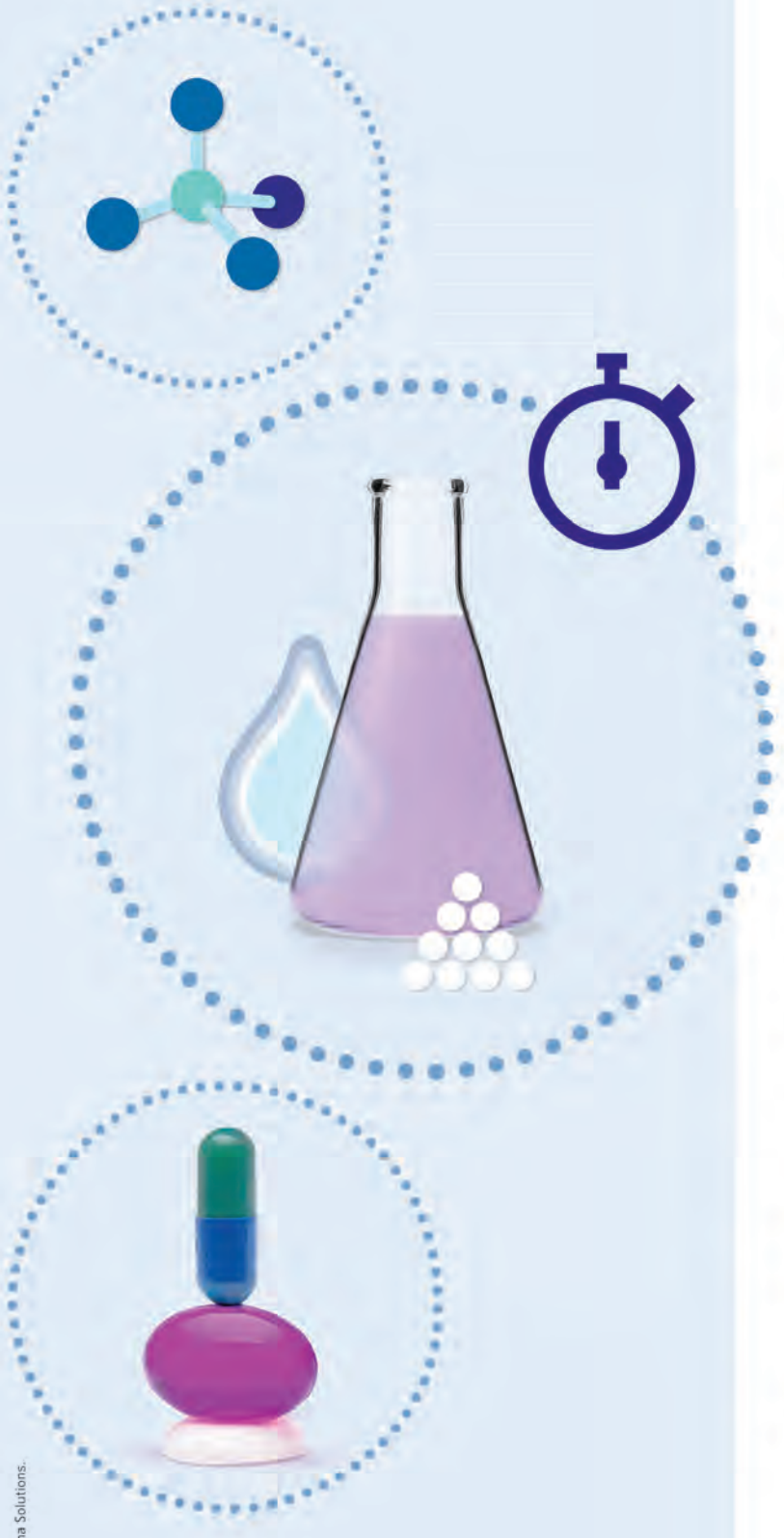

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