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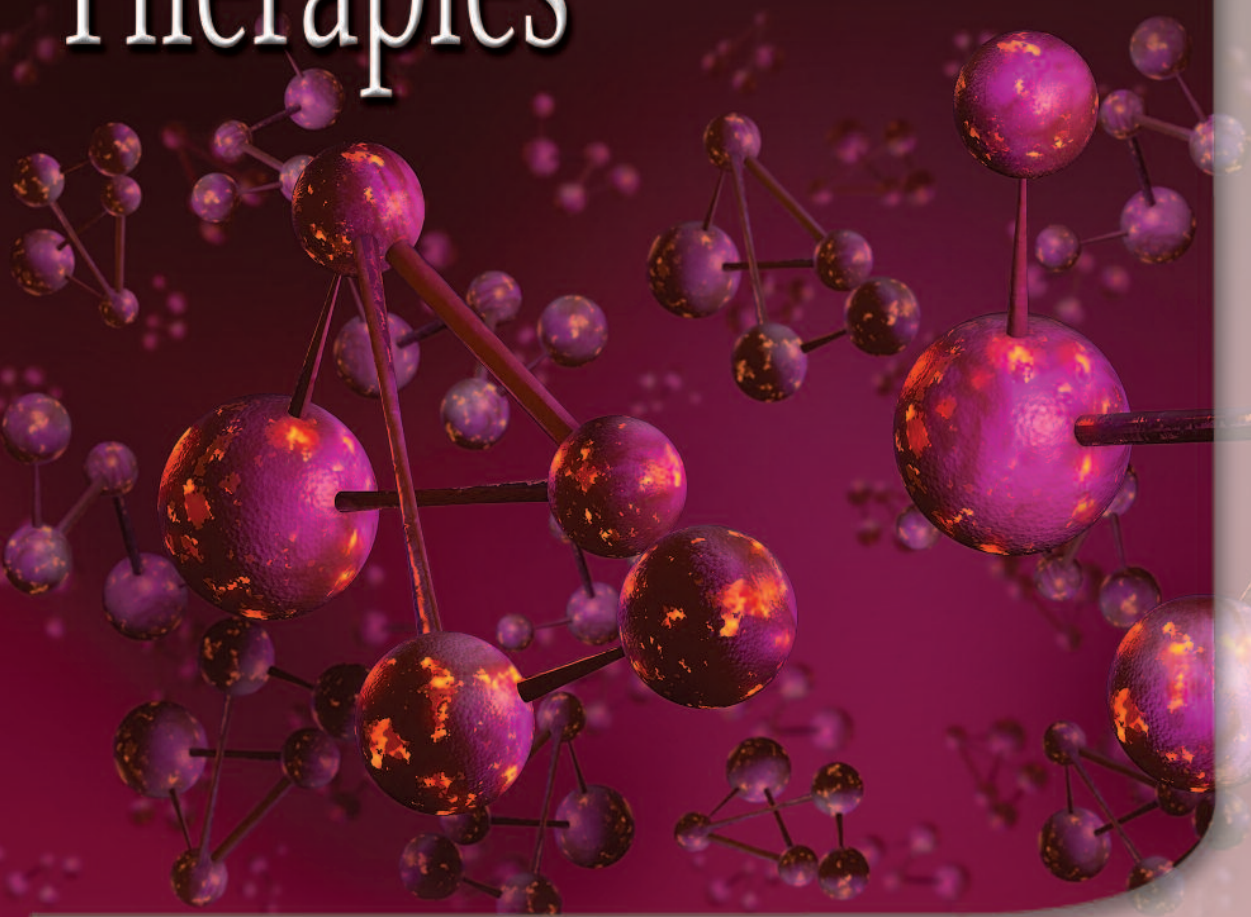
# Drug Development® & Delivery

May 2017 Vol 17 No 4 www.drug-dev.com


# Galectin-Directed Therapies



The science & business of drug development in specialty pharma, biotechnology, and drug delivery

**Peter Traber, MD**
Targeting Galectin-3 Protein in Drug Development

**Cory Berkland, PhD**
Leveraging Precision Particle Fabrication® Technology to Create Patient-Friendly Dosage Forms

**Cindy Dubin**
A Rise in Biologics & Improved Technology Give Pharma Reasons to Consider Parenteral Delivery

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INTERVIEW WITH **OASMIA PHARMACEUTICAL'S** EXECUTIVE CHAIRMAN JULIAN ALEKSOV


Commercializing an orphan drug requires designing solutions to improve the treatment journey. In-home inventory management solutions combined with sophisticated logistics expertise makes participating in a clinical trial more convenient, easing recruitment and reducing withdrawal rates. Increasing patients' access to treatment, improving adherence, reducing costly emergency visits, and enhancing the quality of life for both patients and caregivers takes high-tech solutions and high-touch patient support. It takes a committed commercialization partner. It takes AmerisourceBergen.

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CLINICAL TRIAL LOGISTICS \ MARKET ACCESS CONSULTING \ PATIENT ACCESS & ADHERENCE \ SPECIALTY RX, 3PL, GPOS \ DISTRIBUTION

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**Reference: 1.** National Safety Council. The proactive role employers can take: opioids in the workplace. http://www.nsc.org/RxDrugOverdoseDocuments/proactive-role-employers-can-take-opioids-in-the-workplace.pdf. Accessed December 20, 2016.

**Protect the pill, protect the people™**

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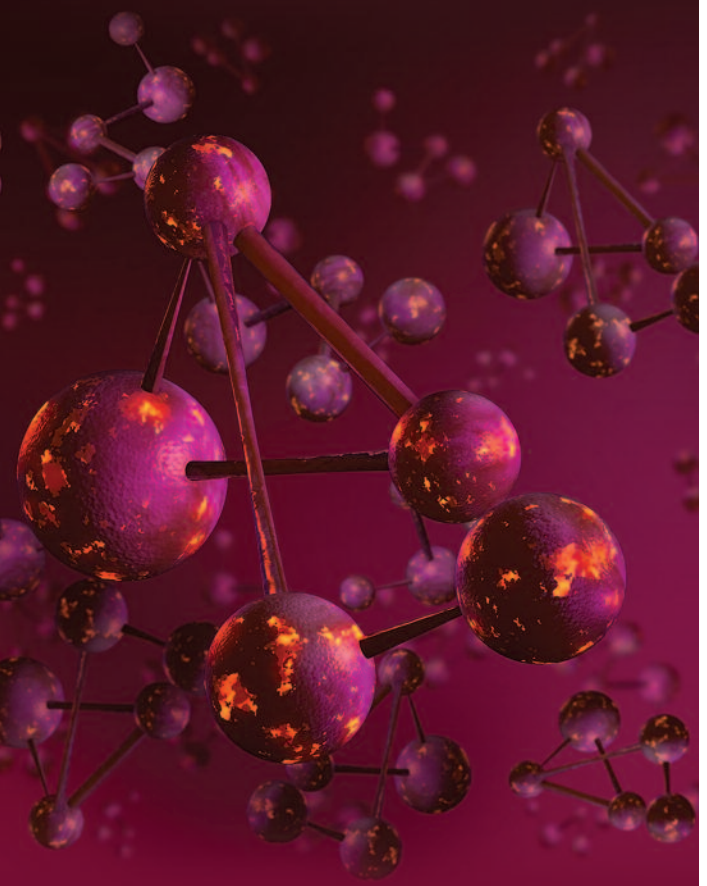
**Bio 2017 > Stand 3116**
June 19–22, San Diego, CA

**APS 2017 > Stand 7**
June 17–21, Whistler, Canada

# Galectin-Directed Therapies

"We are only at the beginning of understanding gal-3 targeted therapy and the full potential of this approach. The future likely holds additional high affinity, specific, galectin inhibitors that are bioavailable by routes other than the two currently in development, parenteral and inhaled."



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West seeks partners for its SmartDose platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company.



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#10224 0317

# Parenteral Delivery & Manufacturing

"Technical advances in the sector, rapid growth in the biologics market, and the growing preference for self-administration using autoinjectors, prefilled syringes, and pen injectors are the key factors boosting the global market for prefilled syringes. As a result, the global sales of prefilled syringes amounted to $3.5 billion in 2015 and are projected to reach $7.9 billion by 2024."

p.36

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## Departments

# Aptar Pharma
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## Megan's Relentless Rigor and Precision Delivers High Quality Biologics.

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## Metrion Biosciences & Venomtech Announce Research Collaboration

Metrion Biosciences Limited (Metrion), the specialist ion channel CRO and drug discovery company, and Venomtech Limited (Venomtech) a biotechnology company with the UK's largest venom library, recently announced a collaboration agreement that will see the two companies combine their resources and expertise to search for novel ion channel modulators for use in drug discovery research.

By combining the expertise and screening capabilities of Metrion with Venomtech's diverse venom collection, knowledge of venom-based drug discovery, hit prioritization and bio-guided fractionation capability, this partnership aims to identify, and rapidly exploit, novel tools for ion channel drug discovery research.

Venoms are well proven sources of potent and selective ion channel modulators, and have provided the foundation for many ion channel drug discovery programs to date. Metrion will screen a targeted selection of Venomtech's venom library against a panel of prioritized ion channel targets to search for, identify, and characterize new ion channel modulators and binding sites. Venomtech will use phylogenetic and geographical diversity analysis to design and build a targeted venom discovery array.

"The Metrion team is very pleased to add Venomtech to our network of collaborators. Via this partnership, we can rapidly explore the UK's largest venom collection for novel pharmacological tools for use in ion channel assay development, validation, and drug discovery research. The results of this partnership could significantly boost the chances of successful drug discovery against our prioritized ion channel targets, and Metrion is looking forward to a highly productive working relationship," said Dr Andrew Southan, Head of Commercial Operations at Metrion Biosciences.

Metrion Biosciences is a specialist ion-channel contract research organization and drug discovery business. The company provides customers with access to a range of high quality ion channel assays on a fee-for-service or collaboration basis. Metrion Biosciences' specialist ion channel expertise includes an industry leading panel of in vitro cardiac ion channel safety assays, translational native cell and phenotypic assays for neurological and cardiotoxicity testing, and a range of other ion channel screening services, such as cell line development and optimization. Metrion Biosciences is able to provide tailored assay formats, data analysis and reporting solutions, effective project management, and quality assured data packages.

Venomtech is a growing biotech company that is helping to improve human health with the power of venoms. We hold the UKs largest venomous animal library and specialize in providing solutions to drug discovery, cosmetic, and crop protection challenges, using venom-derived peptides and other molecules. Using our expertise in venomous animal husbandry and venom biochemistry, we have developed a wide range of Targeted – Venom Discovery Arrays and provide a full hit-to-lead/deconvolution service. Our approach has delivered hits, for our drug discovery clients, against many target classes, including ion channels, orphan GPCRs, and membrane transporters.

## DiFUSION Technologies Announces Breakthrough SMART Biomaterial Platform

DiFusion recently announced the completion of a series of in vitro tests and in vivo studies, carried out in part at Clemson University and the Simmons Institute at Alleghany Medical, which validate the efficacy of its new SMART polymer platform with multiple breakthrough applications. DiFusion holds six US Patents and over 80 international patents which cover new load-bearing implantable medical polymers with various applications ranging from antimicrobial, increased angiogenesis, tissue regeneration, collagen formation, and increased osteoconduction.

ZFUZE is a new load-bearing medical polymer, which has recently concluded in vivo animal studies presented at The Annual Medical PEEK Symposium on April 28th in Washington DC. http://www.medicalpeek.org/conferences.

"We are very pleased to have reached this milestone for our second medical polymer, ZFUZE which has demonstrated the ability to have bone be attracted strongly enough to its surface that it grows across a critical bone defect model in a skeletally mature rabbit," said DiFusion Founder and CEO Derrick Johns. "This is a remarkable achievement for an implantable polymer as it is difficult for skeletally mature animals to grow new bone let alone for it to jump a void."

"I am extremely excited by the recent ZFUZE study results in a critical defect animal model. The base technology underlying these polymers will clearly evolve into the realm of regenerative medicine as the ongoing R&D expands its clinical applications. I think the technology could eventually rival that of drug-eluting scaffolds given our early findings and results," added Paul Kraemer, MD, Indianapolis Spine Institute. https://vimeo.com/214500384.

ZFUZE follows CleanFuze a load bearing antimicrobial polymer which has been approved in the European Union via ISO 13485 CE Mark. In a separate in vivo study at Clemson University, CleanFuze demonstrated that it resists biofilm formation and did not allow any microbial colonization of the implant surface. Third-party in vitro antimicrobial testing revealed a 99.9999% reduction in MRSA and S.aureus colonies, compared to a competitive antimicrobial material-silicon nitride and titanium spinal implants; which showed no antimicrobial efficacy relative to CleanFuze.

DiFusion Inc. is an advanced biomaterials manufacturer located in Austin, TX. DiFusion has developed multiple patented SMART polymer technologies for antimicrobial, cellular repair, tissue regeneration, bone growth, scaffold construction, and increased angiogenesis. The company will submit the new ZFUZE polymer for FDA 510(k) clearance in 2017. For more information, visit www.difusiontech.com.

## Atara Bio Announces Collaboration With Merck

Atara Biotherapeutics, Inc. recently announced it has entered into a clinical trial collaboration agreement with Merck (known as MSD outside the United States and Canada), to evaluate Atara Bio's allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (CTL), or ATA129, in combination with Merck's anti-PD-1 (programmed death receptor-1) therapy, KEYTRUDA (pembrolizumab), in patients with platinum resistant or recurrent EBV-associated NPC. The Phase 1/2 trial will evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the combination and is planned for initiation in 2018.

Atara Bio's ATA129 is an investigational therapy in which a healthy donor's T-cells are stimulated to recognize EBV antigens, or viral proteins, expressed in the cells of certain liquid and solid tumors. ATA129 has previously been evaluated as a single agent in Phase 1 and 2 trials that enrolled patients with a variety of EBV-positive malignancies including 14 patients with chemotherapy refractory, metastatic NPC. In these trials, evidence of radiographic response was observed and EBV-CTLs were also shown to expand after administration without concomitant lymphodepleting chemotherapy. Recent studies suggest that EBV upregulates the transcription of PD-L1 in EBV-associated solid tumors, such as NPC and gastric cancer, suggesting the potential for synergy in combination with anti-PD-1 therapies, such as KEYTRUDA.

KEYTRUDA is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

"Both ATA129 and KEYTRUDA have shown evidence of objective radiographic responses in NPC, and there is a strong biologic rationale to combine these therapies as their complementary mechanisms of action may enhance the anti-tumor activity," said Chris Haqq, MD, PhD, Executive Vice President of Research and Development and Chief Scientific Officer of Atara Bio.

The collaboration agreement is between Atara Biotherapeutics, Inc. and Merck Sharp & Dohme B.V. Under the agreement, the trial will be sponsored by Atara Bio. Additional details of the collaboration were not disclosed.

EBV is associated with a wide range of hematologic malignancies and solid tumors, as well as certain autoimmune conditions, such as multiple sclerosis. T-cells are a critical component of the body's immune system and can be harnessed to counteract viral infections and some cancers. By focusing the T-cells on specific proteins involved in the cancers and infections, the power of the immune system can be employed to combat these diseases.

Atara Bio's ATA129 utilizes a technology in which T-cells are collected from the blood of third-party donors and then exposed to EBV antigens. The resulting activated T-cells are then expanded, characterized, and stored for future therapeutic use in an appropriate partially human leukocyte antigen, or HLA, matched patient, providing an allogeneic, cellular therapeutic option for patients. In the context of EBV infection, ATA129 finds the cells expressing EBV and kills them.

ATA129 is currently being studied in ongoing Phase 2 clinical trials in patients with EBV-associated cancers, including EBV-associated post-transplant lymphoproliferative disorders (EBV-PTLD) and NPC. ATA129 is also available to eligible patients with EBV-positive tumors through an ongoing multicenter expanded access protocol trial. Atara Bio is planning to initiate two Phase 3 trials of ATA129 in patients with rituximab-refractory EBV-PTLD following either hematopoietic cell transplant (HCT) or solid organ transplant (SOT).

## Intellia Therapeutics Granted CRISPR/Cas9 Genome Editing Technology Patent

Intellia Therapeutics recently announced that the European Patent Office (EPO) has decided to grant a patent broadly covering the CRISPR/Cas9 genome editing technology. The patent includes claims covering compositions of the widely adopted CRISPR single guide RNA technology for use in any non-cellular and cellular setting, including eukaryotic cells such as human or mammalian cells, as well as for use in human therapeutics.

According to the EPO, the patent will formally grant on May 10, 2017. The EPO's decision to grant this patent follows its March 24, 2017, notice of intent to issue the patent, which was not challenged by any third party. This European patent will be nationalized in, and cover, approximately forty European countries, including Germany, Italy, France, Spain, and the Netherlands. As provided by relevant European legislation, third parties will have nine months from the issue date to oppose the patent in the EPO.

In addition to the EPO decision, earlier this year, the United Kingdom's Intellectual Property Office granted national UK patents on the CRISPR/Cas9 genome editing system. The UK patents cover the single guide RNA for uses in both non-cellular and cellular settings, as well as chimeric CRISPR/Cas9 systems in which the Cas9 protein is modified to provide alternative DNA-modulating activities. The underlying international patent application is based on a US application, which was filed on May 25, 2012, by the University of California on its own behalf and on behalf of the University of Vienna and Dr. Emmanuelle Charpentier. In the US, the corresponding application has been involved in an interference proceeding with the Broad Institute, Harvard University, and the Massachusetts Institute of Technology, which was terminated without a decision on which sets of inventors were the first to discover the application of the CRISPR/Cas9 technology to eukaryotic cells.

"We are extremely pleased with this EPO outcome as it recognizes Jennifer Doudna, Emmanuelle Charpentier and their team as CRISPR/Cas9 pioneers, and also acknowledges the breadth of their original patent application," said Intellia Therapeutics CEO and Founder, Nessan Bermingham, PhD. "Intellia continues to build on the compelling preclinical data we have generated and to focus on the development of our pipeline of novel human therapeutics that will potentially transform the lives of patients with genetic diseases."

Intellia has rights to this intellectual property estate, including the European and UK patents, for human therapeutic, prophylactic, and palliative uses (including companion diagnostics), excluding anti-fungal and anti-microbial applications. Intellia obtained these rights through a 2014 license agreement with Caribou Biosciences, Inc., which is the exclusive licensee of the University of California and University of Vienna, two of the co-owners of the intellectual property.

Intellia Therapeutics is a leading genome editing company, focused on the development of proprietary, potentially curative therapeutics using the CRISPR/Cas9 system.

## Bio-Path Holdings Presents Study Results Showing Potential of BP1002

Bio-Path Holdings, Inc. recently announced results of preclinical in vitro and in vivo studies supporting the potential of BP1002 in the treatment of aggressive non-Hodgkin's lymphoma (NHL). These results were presented at the annual meeting of the American Association for Cancer Research (AACR) in Washington, DC.

The poster, titled Activity of Bcl-2 Antisense Therapeutic in Aggressive Non-Hodgkin's Lymphoma, summarizes results from two studies: an in vitro study in which 15 cell lines of aggressive NHL subtypes were incubated with BP1002; and two in vivo studies in which mice with follicular lymphoma xenografts were treated with BP1002. BP1002 was shown to have strong anti-NHL activity in each of these studies.

"Survival for patients with aggressive NHL has improved with the use of certain chemotherapy regimens, but the prognosis remains poor for the 30% of patients who relapse after treatment," said Peter Nielsen, Chief Executive Officer of Bio-Path Holdings. "Aggressive NHL is associated with high levels of Bcl-2 expression, making it an ideal candidate for treatment with BP1002, a potent and targeted inhibitor of Bcl-2. While these results are early, we believe they indicate a potential for BP1002 to provide a survival benefit to patients with aggressive NHL. We look forward to initiating a clinical study later this year to assess this candidate in patients with NHL."

In the in vitro study, cell lines of germinal center B-cell lymphoma diffuse large B-cell lymphoma (DLBCL), activated B-cell DLBCL, mantle cell lymphoma and Burkitt's lymphoma were incubated with BP1002. After 4 days, it was determined that BP1002 induced greater than 50% inhibition in 11 of the 15 cell lines tested. In the two animal studies, none of the untreated or control (empty liposome) mice survived beyond 39 days. In the BP1002 arms, a combined 87% of treated mice survived until the end of the 5-week studies.

BP1002 (Liposomal Bcl-2 antisense), Bio-Path's second product candidate, is a neutral-charge, liposome-incorporated antisense drug designed to inhibit protein synthesis of Bcl 2, a protein that promotes cellular survival and inhibits apoptosis. Bcl-2 is overexpressed in a majority of non-Hodgkin's lymphoma subtypes, including follicular lymphoma and diffuse large B cell lymphoma, as well as in a wide variety of solid tumors. Bio-Path is preparing to submit an investigational new drug (IND) application for BP1002, and is planning to initiate a Phase I clinical trial for lymphoma in 2017.

Bio-Path is a biotechnology company focused on developing therapeutic products utilizing DNAbilize, its proprietary liposomal delivery and antisense technology, to systemically distribute nucleic acid drugs throughout the human body with a simple intravenous transfusion. Bio-Path's lead product candidate, prexigebersen (Liposomal Grb2 antisense), is in a Phase II study for blood cancers and in preclinical studies for solid tumors. BP1002 is Bio-Path's second liposomal antisense drug candidate, and is ready for the clinic where it will be evaluated in lymphoma and solid tumors.

## Caris Life Sciences Announces Study Results for ADAPT Biotargeting System

Caris Life Sciences recently announced results of a study that demonstrate the ability of the company's ADAPT Biotargeting System to identify the molecular target, a cell surface regulator of MYC, for a cytotoxic aptamer that may have potential utility as an anti-cancer therapeutic.

The aptamer, C10.36, has been shown in earlier studies to selectively bind to the surface of several non-Hodgkin's Lymphoma (NHL) cell lines and cause cell death, suggesting a possible therapeutic approach. However, the targets of the aptamer were previously unknown. The ADAPT Biotargeting System uses a broad library of synthetically-manufactured molecules (aptamers) that bind to a wide range of biological targets and characterize complex biological systems in their native state, enabling them to profile biological samples at a systems-wide scale. Using the ADAPT Biotargeting System, the study identified a series of ribonucleoprotein components that co-purified with C10.36. Upon further analysis, the investigators determined that C10.36 directly and specifically bound to one of those components, heterogeneous nuclear ribonucleoprotein U (hnRNP U).

hnRNP U has been shown to increase MYC-mediated transcriptional activation. MYC is a transcription factor that regulates a number of cellular processes, including proliferation and programmed cell death. Dysregulated expression of MYC has been shown to play a key role in several cancers, including NHL. Cytotoxicity mediated by C10.36 may result from its ability to bind to hnRNP U and disrupt its ability to promote the oncogenic potential of MYC in NHL cells.

"Our ADAPT Biotargeting System has most commonly been used as a tool to identify biomarkers for drug development, diagnostics, and theranostics," said David Spetzler, MS, PhD, MBA, President and Chief Scientific Officer of Caris Life Sciences. "This study demonstrates the broad flexibility of the platform through the demonstration of an additional application: the identification of the target of a potential therapeutic agent, which itself is an aptamer."

Caris Life Sciences is a leading innovator in molecular science focused on fulfilling the promise of precision medicine through quality and innovation. The company's ADAPT Biotargeting System is a revolutionary and unbiased profiling platform currently being utilized for drug target identification, therapeutic discovery and development, fixed tissue-based companion diagnostics, blood-based cancer screening, and biomarker identification. The ADAPT Biotargeting System is able to simultaneously measure millions of molecular interactions within complex biological systems in their natural state(s). Caris Molecular Intelligence, the company's Comprehensive Genomic Profiling Plus (CGP+) molecular testing service and the world's leading immunotherapy diagnostic provider, assesses DNA, RNA, and Proteins, including microsatellite instability (MSI), total mutational load (TML) and PD-L1, to reveal the molecular drivers of cancer and enable the delivery of personalized medicine. Headquartered in Irving, TX, Caris Life Sciences offers services throughout the US, Europe, and other international markets.

## SteadyMed Raises $30 Million

SteadyMed Ltd recently announced that it has entered into a definitive agreement to sell its ordinary shares and warrants to purchase its ordinary shares for aggregate gross proceeds of approximately $30 million in a private placement. The financing was led by Adage Capital Management, OrbiMed, Deerfield Management and Kingdon Capital Management.

"We recently achieved several significant milestones, having received a favorable ruling by the Patent Trial and Appeal Board of the U.S. Patent and Trademark Office (USPTO) in our Inter Partes Review (IPR) that invalidated all of the claims in the United Therapeutics' '393 patent and completed the clinical validation study of our lead drug product candidate Trevyent, that is in development to treat Pulmonary Arterial Hypertension (PAH)," said Jonathan Rigby, President & CEO of SteadyMed. "We are on track to submit our NDA for Trevyent in this calendar quarter and continue executing on our pre-commercialization strategy, leading to the launch of Trevyent in the U.S. in 2018, if approved by the FDA. We are delighted with the strong support of our existing investors and pleased to have several new, high quality institutional healthcare funds that support our belief that Trevyent has the potential to capture substantial share of the PAH market."

According to the terms of the definitive agreement, SteadyMed will sell approximately 5.0 million ordinary shares and warrants to purchase approximately 2.5 million ordinary shares for aggregate gross proceeds of $30.0 million in the private placement. The price to be paid for the ordinary shares, $5.90 per share ("Original Issue Price"), is equal to the consolidated closing bid price on the Nasdaq Global Market on the day of pricing, April 20, 2017. The purchase price for each whole warrant will be $0.125 per ordinary share subject to such warrants. The warrants are exercisable at a price of $6.785 per share and expire five years from the date of issuance. The transaction is expected to close on or about April 25, 2017, subject to customary closing conditions. Proceeds from the private placement will be used primarily to fund the NDA submission for Trevyent approval for sale in the U.S., as well as pre-launch commercial activities, distribution network establishment and manufacture of commercial Trevyent inventory aimed at a 2018 U.S. commercial launch subject to NDA approval, and other general corporate purposes.

SteadyMed Ltd. is a specialty pharmaceutical company focused on the development of drug products to treat orphan and high value diseases with unmet parenteral delivery needs. The company's lead drug product candidate is Trevyent, a development stage drug product that combines SteadyMed's pre-filled, sterile, single use, disposable, PatchPump infusion system, with treprostinil, a vasodilatory prostacyclin analogue to treat pulmonary arterial hypertension (PAH).

FROST & SULLIVAN

# What do you *really* know about end users of drug delivery technologies?

Drug delivery technologies are a vital component of the dynamic Life Sciences industries, but how well does your company understand the end-user's perspective on desired attributes, compliance issues and drivers of adoption/non-adoption for different drug delivery types?

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For more information on how to find growth opportunities in the drug delivery market, please contact Mireya Espinoza at mireya.espinoza@frost.com or **210-247-3870**.

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# How Polymer Science is Changing the Functional Role of Capsules

New developments in polymer science are broadening the role that capsules play in drug delivery, formulation science and medical research. Today options exist to achieve immediate, delayed, controlled, site-specific or colon-targeted release. Specialized capsules can now play a functional role in improving bioavailability, meet the clinical needs for specific plasma time-course profiles, avoid site-specific degradation in the GI tract, and improve drug efficacy for patients.

## DRUG RELEASE WITH HARD CAPSULES

Hydroxypropyl methylcellulose (HPMC) polymer capsules were developed to meet the industry need for a non-animal-derived alternative. HPMC provides greater compatibility with hygroscopic materials and avoids cross-linking that can occur with gelatin under accelerated storage conditions. The ability to withstand temperature excursions without a change in performance and meet religious and dietary requirements make HPMC an important capsule polymer.

Capsugel's introduction of an HPMC capsule manufactured through thermo-gelation provided a means of eliminating gelling agents, a cause of variable *in vitro* dissolution. This gave the new HPMC capsules pH independent disintegration, and was shown in a human biostudy to provide bioequivalence compared to a gelatin capsule.[1]

## *ACID-RESISTANT* CAPSULES

Launched in 2011, DRcaps™ capsules have delayed release properties and are designed for sufficient enteric protection or gastric resistance for nutritional market application. These capsules protect the ingredients from fully releasing in the stomach, and allow complete dissolution in the intestine – a gamma scintigraphy study showed an average of 52 minutes to first opening.[2] DRcaps were also studied using a capsule in capsule concept. Their *in vitro* dissolution and disintegration tests used a double-wall DRcaps capsule which significantly increases the acid resistance (pH1.2) and delays dissolution in the pH6.8 JP2 buffer. In the test, the double DRcaps did not exhibit any significant delay at the pH6.8 JP2 stage. The study showed that DRcaps acid resistance is not affected by the presence of up to 40 percent alcohol (ethanol) in the dissolution media, which may help prevent alcohol dose dumping in delayed-release products. The results also confirmed that these capsules can be considered an option as an extended delayed-release oral dosage form.[3]

Another study – the results of which appeared in medical journals – described how investigators at Massachusetts General Hospital used DRcaps for an unusual treatment of a serious medical problem. They used pre-screened frozen fecal material from healthy donors to treat recurrent diarrhea caused by *Clostridium difficile* (*C. difficile*) infection (CDI), a major cause of morbidity and mortality. The capsules obviated the need for invasive procedures, thereby eliminated procedure-related complications and reduced the cost of treatment. Among the 20 patients treated, 14 had clinical resolution of diarrhea after the first administration and remained symptom free at eight weeks. The six non-responders were re-treated, with five patients having a resolution of diarrhea. The overall rate of clinical resolution of diarrhea was 90 percent.[4]

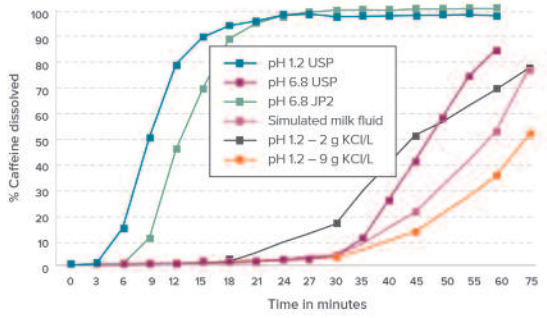
## FULL ENTERIC PROTECTION FOR PHARMACEUTICAL APPLICATIONS

In late 2016, Capsugel introduced a functional capsule that provides a viable alternative for enteric protection and delayed release without adding functional coating. The capsules, Vcaps® Enteric, use a polymer blend of HPMC and Hydroxypropyl methylcellulose acetate succinate (HPMC-AS). While the polymer blend differs from what the enTRinsic capsules use, Vcaps® Enteric offer a similar benefit: simpler enteric delivery implementation from early stage development to commercial manufacturing.

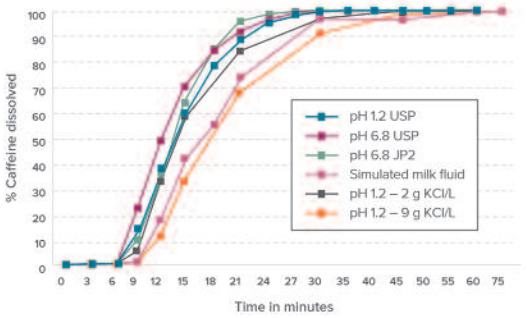
These enteric capsules comply with relevant EP, JP and US Pharmacopeia monographs and have been evaluated *in vitro* across a number of compounds. The results show they protect the stomach from aggressive APIs and delay release to provide maximum absorption. Vcaps® Enteric capsules work with all but the most sensitive APIs.

## Dissolution variations introduced by gelling systems in HPMC capsules

Influence of gelling systems on HPMC capsules in dissolution testing




*In vitro* dissolution of caffeine in Vcaps® Plus capsules




## ENTERIC PROTECTION FOR HIGHLY SENSITIVE SMALL AND LARGE MOLECULES

The enTRinsic™ drug delivery technology provides full enteric protection and targeted release of acid- and heat-sensitive active ingredients to the upper GI tract without the use of functional coatings. Examples include nucleotides and peptides, vaccines and live bio therapeutic products. The intrinsically enteric capsules, which use approved pharmaceutical polymers, have been shown to rapidly release at pH 5.5, allowing optimal absorption in the upper GI tract. The technology also enables formulators to accelerated product development of acid-labile or gastric-irritating compounds because the capsules eliminate the preparation, application, scale-up and process validation steps associated with functional coatings.

## LOOKING FORWARD WITH FUNCTIONAL CAPSULES

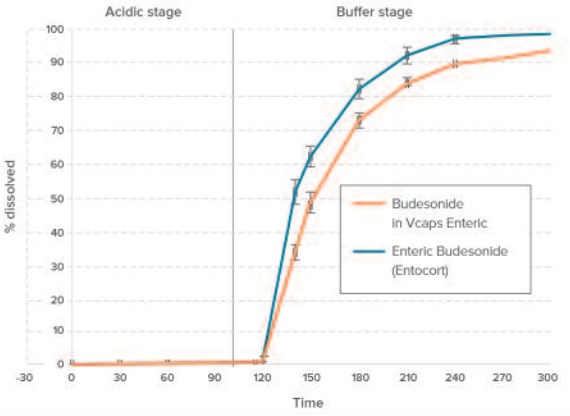
*In-vivo* tests have shown that soluble compounds are well absorbed from both HPMC-based Vcaps® Plus and gelatin capsules. In most cases, capsules of either material perform similarly, but in some applications they don't.

HPMC capsules, for example, can interact with poorly soluble APIs in a way that leads to a lower crystallization rate in the GI tract. This can be important when there are supersaturated APIs in the intestine, as can occur when dosing either a high-energy salt form or a weakly basic API. In those cases, HPMC-based capsules can help maintain super-saturation by inhibiting crystallization. The degree to which crystallization inhibition affects *in-vivo* performance will depend on a particular application, but HPMC has the potential to play a role as a functional excipient which improves bioavailability.[5] Capsugel's Bend, OR, formulators predict approximately 40 percent of molecules are weakly basic, having a basic pKa between 2 and 7, and almost all these compounds are poorly water soluble. This indicates that there are many compounds that could benefit from HPMC-based capsules.[6]

## SUMMARY

Today's HPMC capsules are more than an alternative to gelatin capsules. They offer an array of opportunities to improve drug delivery. From research to human dosing, HPMC capsules provide predictable delivery of simple, immediate-release formulations and address the complex needs of targeted release, moisture protection, and enteric delivery. The variety of HPMC capsules now available, combined with a host of innovative strategies and technologies for drug delivery, offer a means of addressing the challenges of today's APIs and provide a platform to develop patient centric formulations that incorporate the next generation of molecules in development.

## Enteric release without the need for coating with Vcaps® Enteric capsules





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Capsugel®

# GALECTIN-DIRECTED THERAPIES

## Targeting Galectin-3 Protein in Drug Development

By: Peter G. Traber, MD

### INTRODUCTION

Fibrogenesis is a major cause of morbidity and mortality, and anti-fibrotic agents have been termed a holy grail of drug development. The galectin-3 (gal-3) protein appears to be critical to the process of fibrogenesis, and targeting gal-3 could potentially treat a broad spectrum of diseases.

Two approaches have been taken to develop drugs that bind gal-3. One involves modified disaccharides (TD139), and the other uses large polysaccharides that contain galactose (GR-MD-02). Studies are being conducted on the use of GR-MD-02 in non-alcoholic steatohepatitis (NASH), chronic inflammatory skin diseases, including plaque psoriasis and atopic dermatitis, and in combination cancer immunotherapy.

### WHY GALECTIN-3 IS AN ATTRACTIVE DRUG TARGET

The galectin-3 (gal-3) protein is an intriguing new drug target to treat a variety of human disorders, a number of which represent large unmet medical needs. Gal-3 is a member of a family of lectin proteins that binds to galactose-containing glycoproteins. First discovered as a major expressed protein in macrophages, gal-3 is expressed in many cell types in the body but predominantly in immune cells. Expression of gal-3 is increased in many chronic inflammatory and fibrotic diseases, as well as in multiple types of cancer cells. Because the immune system is involved in many diseases, the targeting of gal-3 has a broad spectrum of potential disease targets, including organ fibrosis (ie, liver, lung, and kidney), skin disease, ocular disease, atherosclerosis, heart failure and arrhythmia, and diabetes. In heart failure, for example, levels of serum gal-3 correlate with poor prognosis.

Starting in 2006, interest in gal-3 significantly increased based on experiments in gal-3 null mice, which are otherwise normal but do not express the gal-3 protein. These gal-3 null mice, when insulted in various ways, were found to be resistant to the development of fibrosis in multiple organs, including liver, lung, kidney, and heart. These data suggest that gal-3 is critical to the process of fibrogenesis, a major cause of morbidity and mortality in patients and one of the most important unmet medical needs. In fact, anti-fibrotic agents have been termed a holy grail of drug development with multiple pharma and biotech companies seeking new drugs.

### DRUGS TARGETING GALECTINS

Two approaches have been taken to develop drugs that bind gal-3: Modified disaccharides (TD139; Galecto Biotech), and large polysaccharides that contain galactose (GR-MD-02; Galectin Therapeutics). Both approaches yield molecules that are not well absorbed orally and must be given parenterally, although TD139 is being delivered by the inhaled route in a Phase I study in IPF (idiopathic pulmonary fibrosis). Galectin Therapeutics has taken the approach of using a modified, naturally occurring carbohydrate polymer that contains chains of galactose as a drug that binds to gal-3 (GR-MD-02).

There are significant differences in the binding properties of these two drugs, with TD139 having higher affinity for the carbohydrate recognition domain of gal-3 but GR-MD-02 having a binding stoichiometry of ~5 molecules of gal-3 per drug molecule

and binding to a broader area of amino acids in gal-3. While it is unknown how these differences may affect ultimate effectiveness, it is notable that both molecules had a similar effect in a mouse model of lung fibrosis.

## CLINICAL STUDIES UTILIZING GR-MD-02

GR-MD-02 is being used currently in three areas of development: 1) chronic inflammation and fibrosis in non-alcoholic steatohepatitis (NASH); 2) chronic inflammatory severe skin diseases, including plaque psoriasis and atopic dermatitis, and; 3) combination immunotherapy for cancer. While the major value driver for GR-MD-02 is as a NASH drug, there are early clinical results showing efficacy in severe skin disease.

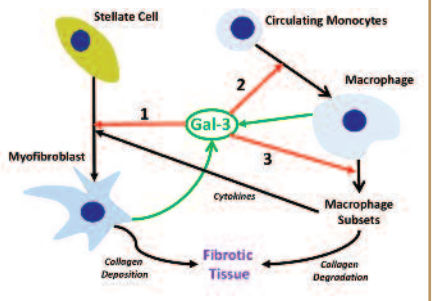
### Liver Fibrosis & NASH

Preclinical results show that GR-MD-02 has significant anti-fibrotic effects in multiple models, including liver (fatty liver and toxin induced), kidney, lung, pulmonary artery, and heart fibrosis. NASH was chosen for development of GR-MD-02 because it is one of the most common liver diseases, with 1 in 4 individuals in the world having fatty liver and about 2% of those destined to die of complications of NASH cirrhosis. There are currently no approved drugs for NASH. NASH is recognized as one of the largest potential markets for drug development today, with the global market in 2025 predicted to be as large as $40 billion.

NASH is a chronic disorder with fat accumulation in the liver resulting in inflammation, cell death, and progressive fibrosis leading over decades to the end stage of scarring, or cirrhosis. Gal-3 is markedly upregulated in liver disease and has effects on the two main liver cell types involved in fibrogenesis: macrophages and stellate cells (Figure 1). Inhibition of gal-3 may reduce the fibrogenic myofibroblasts, reduce macrophage recruitment and activation, and potentially increase the macrophage activity to reduce collagen and fibrosis.

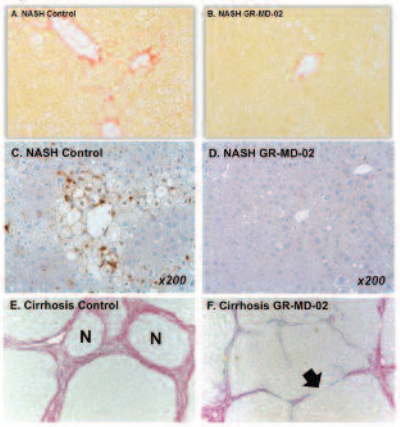
GR-MD-02 has been shown in mouse models of NASH to reduce fat, inflammation, and cell death and to both prevent and reverse fibrosis (Figure 2A and 2B).[1] In this mouse model of NASH, gal-3 is markedly increased in macrophages (Figure 2C), and this is significantly reduced with GR-MD-02 treatment (Figure 2D). Additionally, in a toxic model of rat cirrhosis, GR-MD-02 has been shown to reverse fibrosis and cirrhosis (Figure 2E and 2F), despite continuation of the toxic insult, and partially reverse the portal hypertension associated with cirrhosis.[2] Portal hypertension is the primary reason for complications in humans with NASH cirrhosis and a potentially acceptable regulatory endpoint in clinical trials.

**FIGURE 1**




**Gal-3 effects on macrophages and stellate cells in liver. Gal-3 is produced by macrophages and activated stellate cells into the microenvironment of the liver. Green lines = gal-3 production, red lines = gal-3 action, black lines = results of gal-3 action. Gal-3 has multiple effects including 1) activation of stellate cells to myofibroblasts; 2) recruitment of monocytes to the liver macrophage pool; 3) activation of macrophages into subtypes, producing cytokines and potentially macrophages that digest collagen.**

**FIGURE 2**




**Experimental effects of GR-MD-02 in two animal models of liver fibrosis. A and B show liver collagen staining (red) of mice with NASH, control and treated with GR-MD-02, respectively. C and D show liver gal-3 staining (brown) of mice with NASH, control and treated with GR-MD-02, respectively. E and F show liver of rats treated with toxin to induce cirrhosis, control and treated with GR-MD-02, respectively. N = nodules associated with cirrhosis; arrow = broken strand of collagen.**

Based on these robust preclinical findings, GR-MD-02 therapy in development is being directed at patients with NASH cirrhosis, with the goal of reducing portal pressure by reducing fibrosis and thereby improving outcomes. After obtaining an IND for NASH with advanced fibrosis and fast-track designation, two Phase I trials and an exploratory Phase II trial were completed showing good safety and a lack of drug interactions. This led to the currently underway Phase IIb clinical trial in patients with NASH cirrhosis and portal hypertension (NASH-CX).

There are a number of important elements in the NASH-CX trial. First, it is one of only three currently ongoing clinical trials in NASH cirrhosis, and the next one to

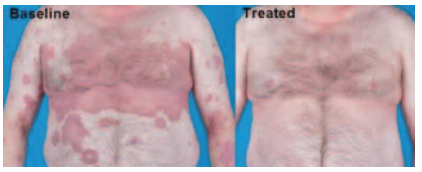
read out top line data in this calendar year. The trial has enrolled 162 patients in three treatment arms, placebo and two doses of drug, with a treatment duration of 52 weeks. The primary endpoint of the trial is the baseline adjusted reduction in portal pressure as assessed by hepatic venous pressure gradient (HVPG), which is directly related to patient outcomes and is potentially an acceptable regulatory endpoint for provisional approval with follow up outcomes data. Additionally, secondary endpoints will evaluate change in liver biopsy, serum biomarkers, complications, and several non-invasive measures of liver structure and function including FibroScan (Echosens) and 13C methacetin breath test (Exalenz). The study is powered at >80% to demonstrate a difference in HVPG of at least 2 mmHg, a change which is potentially clinically significant in these patients. More than 25% of subjects have completed the trial, and it is on track to report top line data in December 2017.

The NASH-CX trial is a significant milestone in NASH therapy as well as a proof-of-concept for therapies directed at gal-3. Most of the many current ongoing clinical trials in NASH are directed to therapy in pre-cirrhotic NASH, but the NASH-CX trial is the next trial to read out in the more advanced patients with NASH cirrhosis. Success in this area could be a breakthrough finding for liver cirrhosis and additionally open the possibilities for gal-3 targeted therapy in fibrotic disorders of other organs.

### Clinically Meaningful Effect of GR-MD-02 in Psoriasis & Atopic Dermatitis

Serendipity struck the GR-MD-02 clinical development program when a patient enrolled in a Phase I NASH trial had a remarkable remission of her psoriasis, a skin disease not known to resolve itself naturally. In addition to this clinical finding, research publications suggested the potential importance of galectin-3 in psoriasis.

**FIGURE 3**




**Photographs of patient with severe psoriasis at baseline and following treatment with 13 doses of GR-MD-02, 8 mg/kg administered every 2 weeks.**

On this basis, an exploratory, open-label, Phase IIa trial was conducted in five adult patients with moderate-to-severe plaque psoriasis [PASI (Psoriasis Area and Severity Index) ≥ 12 and BSA (Body Surface Area) ≥ 10%]. One patient had an 80% reduction in PASI 30 days after their last infusion (13th) (Figure 3), while the other four patients reached 50% reduction in PASI by their 10th infusion.

Scientific studies also show that there is a link between the galectin-3 protein and disease activity in atopic dermatitis with increased amounts in the skin of patients and reduced disease in mice with atopic dermatitis that lack the galectin-3 protein.

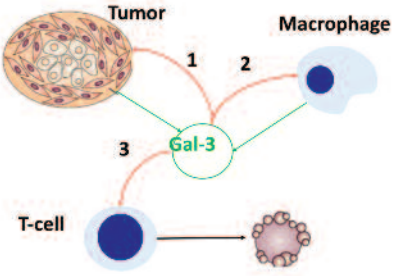
GR-MD-02 treatment of severe and refractory atopic dermatitis was also studied in three patients in an open label, investigator-initiated study. All three patients showed clinical response as determined by reduction of the Eczema Area and Severity Index (EASI) score at week 12 having received six every-other-week doses, with two patients achieving a 64% and 74% reduction in EASI, respectively, at 6 weeks after receiving only three doses of GR-MD-02.

These early clinical results demonstrate activity of GR-MD-02 in two severe skin diseases, providing some confidence that there may be clinical activity in other gal-3 dependent disorders. Importantly, there is a higher incidence of psoriasis in patients with NASH. While significantly more development work and formulation will be required to demonstrate clinical utility, these findings open up an entirely new target area for severe skin diseases, with potential market utility in the relatively underserved area of moderate-to-severe atopic dermatitis.

### Cancer Immunotherapy

Gal-3 expression is increased in most cancers and secreted into the tumor microenvironment. There are multiple effects of gal-3 in cancer (Figure 4), including the promotion of angiogenesis and metastasis and decreased apoptosis of tumor cells, macrophage M2 polarization, increased chemotaxis to recruit more macrophages, and enhanced macrophage gal-3 secretion, and T-cell apoptosis and impairment of TCR signaling reducing the ability of im-

**FIGURE 4**

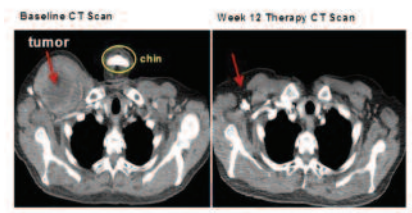



**Gal-3 effects on cancer cells, macrophages, and T-cells in the tumor microenvironment. Gal-3 is produced by both tumor cells and macrophages and has the effects of 1) promoting angiogenesis and metastasis and decreasing apoptosis of tumor cells; 2) promoting macrophage M2 polarization, increasing chemotaxis to recruit more macrophages, and enhancing gal- secretion; 3) promoting T-cell apoptosis and reducing TCR signaling thereby blocking immune effect on tumor cells.**

mune system to kill tumor cells.

The Providence Cancer Center (Portland, OR), recently reported early results of GR-MD-02 combined with pembrolizumab (KEYTRUDA®) in patients with advanced melanoma, oral/head and neck cancer (OHN), and non-small cell lung cancer (NSCLC). Six subjects, five with advanced melanoma, were enrolled in the lowest dose cohort (2 mg/kg GR-MD-02) with one partial response and one mixed response in the five melanoma patients. Figure 5 is a chest CT scan of the patient with a partial response showing a marked reduction in tumor size at week 12 of therapy, after three doses of combined GR-MD-02 and pembrolizumab.

**FIGURE 5**




**Chest CT scan of the patient with a partial response showing a marked reduction in tumor size at week 12 of therapy, after 3 doses of combined GR-MD-02 and pembrolizumab.**

The investigators were encouraged by these early safety results, and although one cannot conclude whether the one partial response was related to GR-MD-02, the response provides a clinically relevant signal to follow as GR-MD-02 doses are escalated. This study is ongoing, and a decision to progress to Phase II will be based on the response rate of the combination of pembrolizumab with GR-MD-02 as compared to historical response rates to pembrolizumab alone.

## GR-MD-02 HAS A STRONG SAFETY PROFILE

In each of the clinical trials with GR-MD-02, the drug has shown to be safe and well tolerated, with no serious adverse events ascribed to the drug. At this time, the total number of doses of GR-MD-02 administered to humans is nearly 3000. This is encouraging for the development program, given the high rate of drugs that are dropped from development based on significant toxicities. Additionally, given that GR-MD-02 is a complex carbohydrate, it is metabolized via different mechanisms than typical small molecule drugs, and a lower likelihood of toxicities based on drug metabolites is anticipated.

## THE FUTURE OF GALECTIN DRUG DEVELOPMENT

The treatment effect of GR-MD-02 on psoriasis and atopic dermatitis provides evidence for efficacy of one anti-gal-3 drug in human disease. Ongoing trials in NASH cirrhosis, with results at the end of 2017, and combination chemotherapy will add to the data. Additionally, presentation of results are awaited from the Phase I trial using TD139 in the treatment of IPF. Each of these trials should add to the foundation of information on the potential for anti-gal-3 therapeutic approaches, which could extend to multiple important diseases.

We are only at the beginning of understanding gal-3 targeted therapy and the full potential of this approach. The future likely holds additional high affinity, specific, galectin inhibitors that are bioavailable by routes other than the two currently in development, parenteral and inhaled. In this regard, Galecto Biotech has suggested it has oral inhibitors in preclinical development, and Galectin has a discovery program for identification of small molecule inhibitors of gal-3. Such oral inhibitors will likely open many possibilities for galectin-directed therapies for a broad range of human disease. ◆

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**BIOGRAPHY**

**Dr. Peter G. Traber** is President, CEO, and CMO of Galectin Therapeutics and President Emeritus of Baylor College of Medicine, where he was CEO from 2003 to 2008. From 2000 to 2003, he was Senior Vice President of Clinical Development and Medical Affairs and CMO of GlaxoSmithKline plc. He served as CEO of the University of Pennsylvania Health System and was Chair of the Department of Internal Medicine and Chief of Gastroenterology for the University of Pennsylvania School of Medicine. Dr. Traber has also managed a molecular biology research laboratory and published over 100 articles of original research, reviews, and book chapters. He earned his MD from Wayne State School of Medicine, his BS in Chemical Engineering from the University of Michigan, and a certificate in medical leadership from Wharton Business School.


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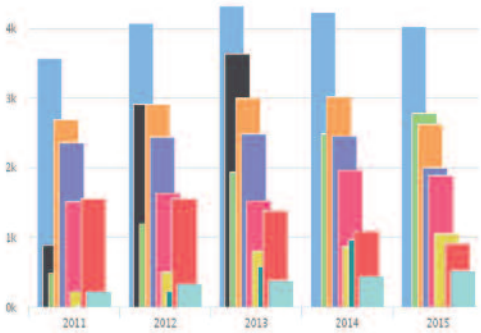


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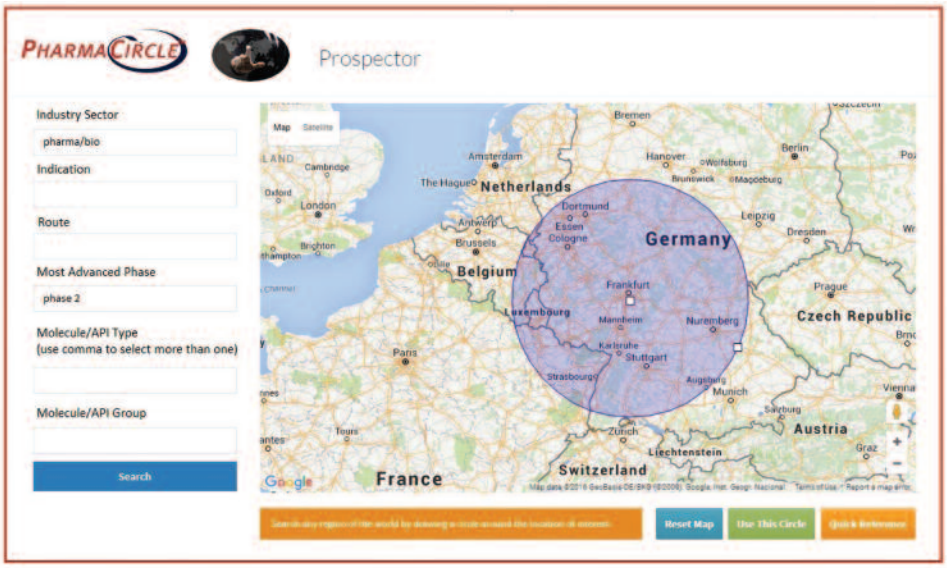


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# CONTROLLED RELEASE

## Leveraging Precision Particle Fabrication® Technology to Create Patient-Friendly Dosage Forms

By: Cory Berkland, PhD, and Nathan Dormer, PhD

### INTRODUCTION

The rising cost of healthcare and the resultant shift of policies focused on lowering costs and incentivizing better outcomes are driving increased demand for drug delivery solutions that can improve patient compliance and provide economical solutions for special patient populations, such as pediatrics and geriatrics. Controlled-release solutions play a critical role in patient-centric design, offering the ability to reduce the number of administrations required for the patient. The need for controlled release may vary for specific patient populations: getting a child through the school day or helping elderly patients better manage their multiple medication regimes. However, the evidence is clear that reducing the number of administrations is correlated to an increase in medication compliance and therefore improves patient outcomes.[1] Palatability of a drug product can also impact compliance, and therefore, taste is also an important consideration when creating patient-friendly products. Unpleasant taste has been documented as one of the biggest barriers to completing treatment in pediatric patients with more than 90% of pediatricians reporting that a drug's taste and palatability were the biggest barriers to completing treatment.[2] The ability to appropriately address both controlled release and palatability in next-generation formulations offers the opportunity to significantly improve patient outcomes. While current approaches do exist to create controlled-release and taste-masked solutions, the ability to do so in a patient-friendly format can be fraught with formulation challenges of its own.

### CONTROLLED-RELEASE CHALLENGES

Attaining controlled-release kinetics with tablets is a relatively simple process, as the size and form factor of the dosage form lends to using vigorous coating methods, oftentimes with multiple layers.[3,4] Capsules have the advantage of being moulded, extruded, or pressed with gelatin and other dissolution-enhancing excipients in a high-throughput manner, enabling delivery of large doses of medication. Tablets are simply pressed, then coated with subsequent layers of controlled-release components, which makes adaptation of specialized kinetics straightforward.[3,4] The key challenge to these techniques is that these multiple coating steps and the larger doses associated with reducing administrations often results in a large tablet or capsule size. This becomes problematic in patients for whom swallowing traditional oral solid dosage forms is a challenge. Data from current tablets and capsules indicates that the average size of a controlled-release dosage form is nearly 1.5 cm in length.[5] Physiological studies demonstrate that swallowing becomes difficult when the length of the object being swallowed is greater than half of the esophageal width, which is approximately 2.0 cm for the prototypical adult.[6] This means dosage forms over 1 cm in length, smaller than the average modified-release pill, may be too large to be swallowed easily by much of the adult population.

The scarcity of dispersible format oral products sometimes leads caregivers and compounding formularies to use alternative solutions to treat their patients that are not always backed by supporting safety, bioavailability, and stability studies. Tablets are

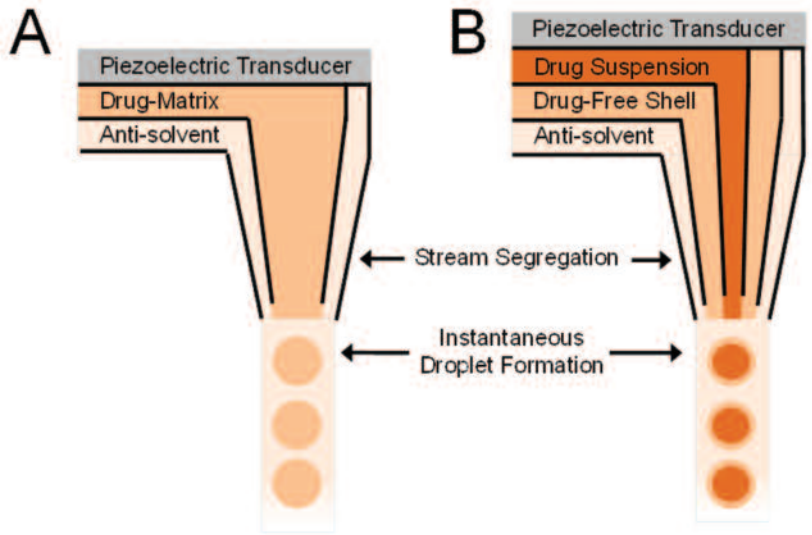
sometimes modified to ease administration challenges. Modifications can include splitting the dosage form or crushing the dosage form and mixing with food or drink. These methods may result in dosing errors and decreased efficacy, and can magnify non-adherence if the active pharmaceutical ingredients (API) is foul-tasting.[3,4] The risk associated with altering controlled-release tablets is significant as patients or caregivers may be unaware of the risk of dose dumping that this presents. This risk is highlighted by the annual publication of the "Oral Dosage Forms That Should Not Be Crushed" list published by the Institute for Safe Medication Practices.[7-16] Drugs listed in this publication are most commonly included due to their controlled-release characteristics and the risk of dose dumping associated with crushing a controlled-release product; others are selectively included for taste and exposure reasons.

The ability to provide controlled-release kinetics with format-flexible dosage forms is fundamental for serving special populations. When considering just pediatrics and geriatrics, this dosage form issue affects over half of the global population (under 18 and over 65 years of age).[3,4,17,18] However, the need extends well beyond these patient populations as there are specific therapies and indications that induce dysphagia, as well as healthy adults that suffer from dysphagia as well.

## TASTE-MASKING CHALLENGES

The demand for taste-masked product solutions will be driven primarily by pediatric markets; however, in the case of very bitter-tasting drugs, adults and children alike can benefit from palatable solutions.

**FIGURE 1**




**Optimμm® creates high-loading (A) Extended-release microspheres and (B) Modified-release microcapsules with a single-step mechanism that segregates API-containing streams from anti-solvent streams, resulting in precision layering of materials.**

While many solid oral dosage forms have techniques for masking or encapsulating bitter tastes, these methods are ineffective for many children (and some adults) because they often cannot or will not swallow pills or tablets.[2]

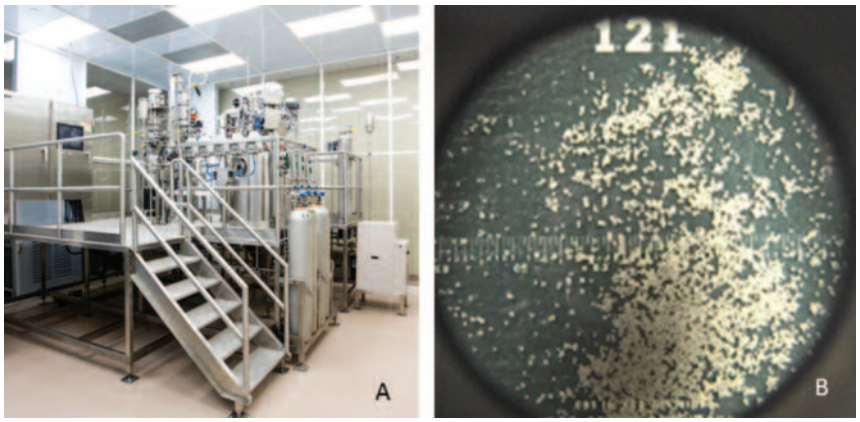
For pharmaceutics with extremely bitter taste, coating techniques can be used; however, some can result in an unpleasant mouth feel due to surface roughness. It has been estimated that nearly half of patients with organoleptic sensitivities are disinclined to take their medicine, with the majority of those reporting bad taste as a large contributor to non-compliance.[12] Artificial sweeteners and flavors are often unable to conceal the extremely unpleasant taste of many APIs in liquid formulations.[7-9] What is worse, efforts to mask foul taste using coatings or microencapsulation sometimes create poorly controlled, polydisperse particle diameters that result in a gritty consistency. In a perfect scenario, a dosage form would accomplish taste-masking with negligible texture, while maintaining controlled-release properties.

## LIQUIDS OFFER FORMAT FLEXIBILITY BUT GENERALLY NOT CONTROLLED RELEASE

The need for format flexibility has generally been attributed to pediatric patients due to their inability to swallow pills. However, this need extends well beyond pediatrics and is better characterized when including the need for dose titration as well. Patients with differing ages, weights, body surface areas, and metabolic profiles may require atypical dosing considerations.[13] Additionally, some therapeutics require titration of dose up or down when initiating or ending a prescribed course of treatment or when optimizing for best outcome. When prescribing medications in older adults, the old maxim "start low and go slow" typically applies to reduce incidence of adverse events, so titration is a key attribute of a product utilized by this population. These examples demonstrate the need for format flexibility not only for those that are unable to swallow a pill, but also for those that require dose titration.

When large oral dosage forms pres-

## FIGURE 2




**(A) Orbis has scaled the Optimμm® system to 60-nozzles to manufacture up to 30 kg of product per batch. This system resides in a class 100,000 production suite at Orbis. The current form factor can be regenerated as a larger capacity (120-, 180-, or 360-nozzle) skid depending on client need and manufacturing considerations. (B) Image of ibuprofen microspheres (~90 μm in diameter) produced on Orbis' scaled 60-nozzle manufacturing equipment.**

ent administration difficulties or titration is necessary, liquid formats, in general, succeed in providing an acceptable solution. The advantages beyond ease of dosing, however, are limited in traditional syrups with solubilized API. Liquid formats are usually not extended release, have nominal taste-masking, and can contain API particles, or encapsulated-API particles prone to aggregation and settling if not reconstituted or shaken properly prior to administration, which have resulted in risks to patient safety.[7,12,13,19-21] Due to the large size of modified-release tablets, the foul taste of traditional liquids, and the lack of controlled-release options for APIs in nearly all marketed drugs,[22,23] many pharmaceutical and contract development manufacturing organizations (CDMOs) are focusing efforts on modified-release powder formats, which combine the stability of traditional solid oral dosage forms with dose titration advantages of liquids.

## POWDERS: THE OTHER SOLID DOSAGE FORM

While the evolution of technology utilized in tablets, capsules, and pills over the past century is remarkable, the pace at which powder dosage forms are leveraging their share of the market in the past 2 decades is equally impressive. The most recent advances in controlled-release powder technology offer patient-centric solutions that have solid oral dosage form complexity and all the advantages of liquid format flexibility. However, the processes currently utilized to create controlled-release powders can involve complex processing, inclusion of materials such as polystyrene, broad particle size distributions resulting in unpredictable release kinetics, or particle size limitations that create unsatisfactory mouth feel; nearly all methods require multiple coating steps following initial particle fabrication to achieve controlled release.

The most forthright method for achieving taste-masking and controlled release with powders employs a two-step process in which a precursor particle is manufactured by a singular process, then coated with one or more layers containing modified-release excipients. Precursor particles can either be milled API crystals, API co-mixed with inert bases, or 100% inert cores without API. Particles can be manufactured by any method, which include vibratory methods, congealing/spinning disk atomization, prilling, hot-melt extrusion, spheronization, aqueous dispersions, blending/bulking, electrohydrodynamic spraying, or spray drying.[24-31] Component selection for the particle relies on manufacturing capabilities, desired target product profile, and API process stability. Desired physical properties, such as surface features, density, friability, and hardness will also dictate which manufacturing scenarios are feasible for each product. If taste-masking, controlled-release, or stability-enabling properties are required, the particle typically advances to subsequent layering steps using fluidized beds, Würster coaters, spray/pan coating, or coacervation.[20,32-35] Materials for the secondary coating steps are designated for reasons appropriate for precursor particles and patient use, such as material compatibility, controlled-release behavior, and stability. The final dosage form, typically granules in the 300-500-μm diameter range, can then be re-suspended, packaged in sprinkle packs or breakable capsules, placed in dissolving tongue strips, co-lyophilized with other materials for orally disintegrating tablets, or reconstituted in liquids.

The approach of manufacturing controlled-release powders by adding multiple coating steps to API-rich precursor particles is an accepted "way-of-life" for powder dosage forms. These techniques are, however, divergent from state-of-the art ap-

proaches that focus on chemical modification of the API and/or substrate using ion exchange resins.[36-38] The main advantages that these methods can yield are liquid stability and deterring abuse of scheduled APIs, such as opiates and amphetamines. While innovative, drug complexation employs a number of manufacturing steps and quality control aspects that far surpass that of simple bead layering and may still require a final coating step.[20,32-35] Thus, it is not surprising that pharmaceutical companies and CDMOs are investigating less complex chemistry and single-step manufacturing methods for producing controlled-release powders with pre-incorporated coatings.[39-44]

## PRECISION PARTICLE FABRICATION® TECHNOLOGY: A NEXT-GENERATION CONTROLLED-RELEASE POWDER APPROACH

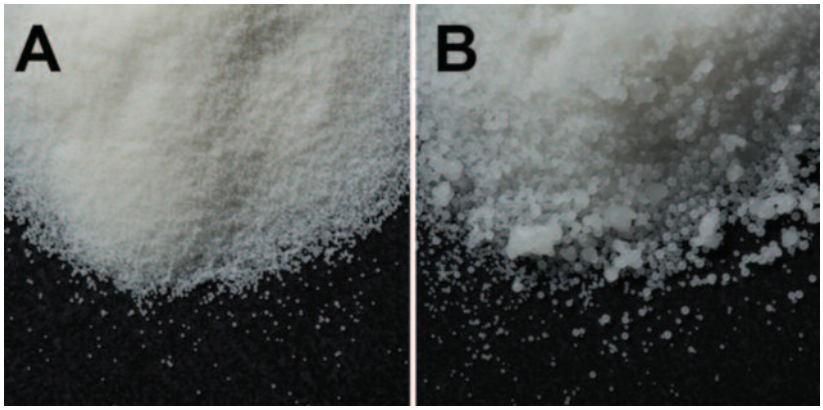
As demand grows for patient-friendly dosage forms, next-generation powder technologies offer the opportunity to provide not only operational efficiencies but speed to market by acting as a foundational building block for multiple format types. This building block approach reduces the development time associated with reformulating for multiple format types and therefore simplifies product lifecycle management for companies looking to optimize market opportunities.

Orbis' Optimμm® platform leverages its Precision Particle Fabrication® technology to deliver oral pharmaceutical products that have both controlled-release and taste-masked attributes. Unique to other commonly used processes, Orbis' controlled-release capabilities are achieved in a single manufacturing step and do not require additional coating steps to achieve taste-masking, extended release, or modified release. Figure 1 demonstrates how the Optimμm technology incorporates vibration with a scalable nozzle approach to create both microspheres and microcapsules in a single manufacturing step. The Optimμm technology produces uniform microspheres or microcapsules exhibiting a narrow size distribution offering precise control over particle morphology (e.g., porosity, coating thickness, etc.) and therefore precise control over release kinetics.[39-44] These release kinetics can include extended- or modified-release options. The flexibility of the Optimμm technology allows for the production of a wide range of particle materials, sizes, and desired characteristics in a single-step process that scales linearly by simply adding additional nozzle heads. Scale-up has been successfully validated with the commissioning of Orbis' cGMP-compliant suite (Figure 2).

Precisely controlled particle size enables key points of differentiation for those products leveraging the Optimμm technology. For example, the elimination of fines controls dose dumping and minimizes taste perception of the API improving palatability. Additionally, the consistency of the particles allows for more reliable and predictable dosage forms with batch-to-batch reproducibility for improved quality control. This consistency also creates a development workspace in which changes in attributes, such as particle size or API loading, create predictable dissolution outcomes reducing the number of iterations to reach a target product profile. This approach can be ideal for matching existing dissolution profiles for differentiated 505(b)(2) pathways. It also may serve in extending product life by limiting generic entrants as formulations leveraging Precision Particle Fabrication technology are difficult to replicate utilizing traditional technologies.

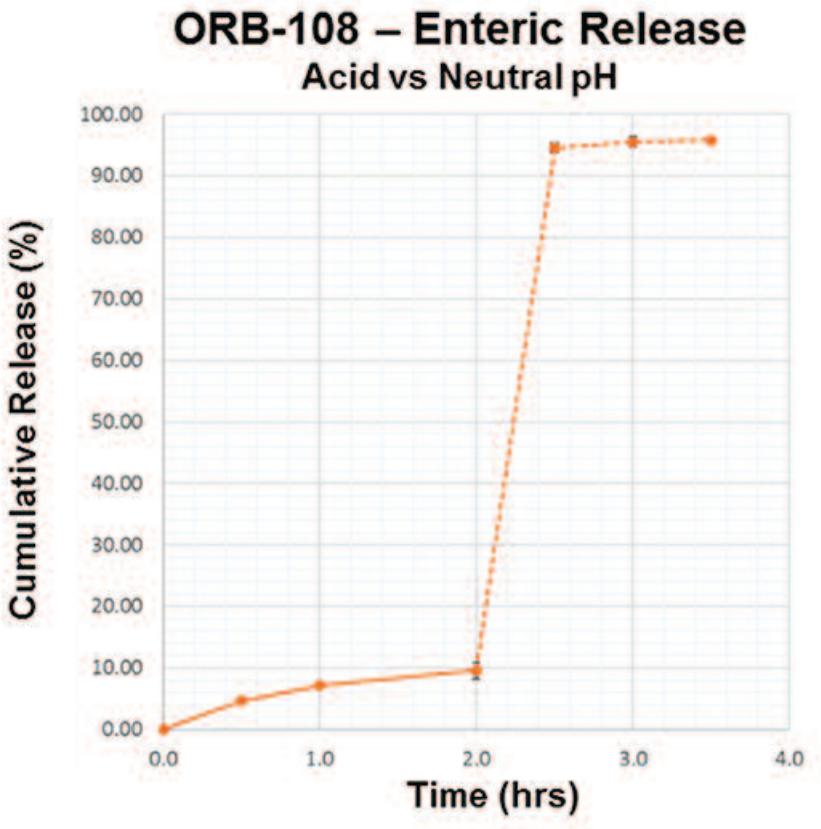
In addition to taste-masking and extended-release applications, Orbis' novel core shell technology approach enables modified-release options, such as enteric or reverse-enteric delivery in a format-flexible powder. Figure 4 highlights in vitro re-

FIGURE 3




**(A) Optimμm®-manufactured microspheres of ~200 μm in diameter, versus microspheres from a traditional prilling technique. Orbis' microspheres exhibit tight control over size and surface finish, whereas competing technologies have broad size distributions, clumping, and irregular particles; overcoming these features requires post-processing steps like sieving.**

FIGURE 4




**(A) Dissolution results for Optimμm-manufactured microcapsules with ibuprofen core and lipid shell.**

sults for an enteric release approach in which API release is limited to less than 10% for 2 hours in gastric conditions with immediate release when exposed to neutral pH similar to the small intestine. This modified-release approach is accomplished by fabricating a microcapsule with an engineered shell of uniform thickness designed for the target release specifications. Efficiencies are gained by eliminating secondary coating steps because Orbis' fabrication process requires only one step.

Not only does Orbis' technology offer a tightly controlled size distribution of its microspheres and microcapsules, it also offers a broad range of size options to address the needs of different formats. Typically, for oral applications, particle size ranges from 150 μm to 300 μm for optimal palatability. The Optimμm technology offers size ranges as low as 90 μm, eliminating the particle size limitations associated with some other powder technologies. As a melt-based process that is completely solvent-free, it also eliminates undesirable additives that can be associated with controlled- release technologies.

## CONCLUSION

Providing formulations and treatments that improve clinical outcomes, for special populations, such as pediatric and geriatric patients, has been routinely noted as an area in need of improvement for pharmaceutical companies and providers.[7-16,19-21,25,45-47] As the pharma landscape shifts from an environment of high-risk, high-reward blockbuster drugs to efficiency, economy, and ensuring patient outcomes, demand for technologies that can provide an efficient approach to product lifecycle management will increase. Controlled-release powders offer a flexible and efficient approach to addressing a multitude of patient populations, while also improving compliance. This "other solid dosage form," offers the opportunity to unlock incremental value for those seeking differentiation in an increasingly competitive marketplace. ◆

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## BIOGRAPHIES

**Dr. Cory Berkland** is the Co-founder and CSO of Orbis Biosciences. He has been developing microencapsulation and drug delivery capabilities for more than a decade. He earned his PhD in Chemical and Biomolecular Engineering from the University of Illinois, Urbana-Champaign, where he co-invented and developed the Orbis technology. Dr. Berkland is also a Professor of Pharmaceutical Chemistry and Chemical and Petroleum Engineering at The University of Kansas.

**Dr. Nathan Dormer** is Vice President of Research & Development at Orbis Biosciences. He has more than a decade of experience developing a variety of controlled-release solutions using microsphere techniques. He earned his BS in Chemical Engineering from The University of Kansas before completing his PhD in Bioengineering with Honors from The University of Kansas with NIH-sponsored training in drug delivery and protein stability. He has authored a number of publications and book chapters relating to microsphere encapsulation and has direct experience formulating dozens of active pharmaceutical ingredients.

# MARKET BRIEF

# Preferences for Targeted Therapies & Patient-Centric Approaches Drive Transformations in Oncology Drug Delivery Market

By: Piyush Bansal, Transformational Health Senior Industry Analyst, Frost & Sullivan

## INTRODUCTION

Cancer is the second leading cause of death in the US and is expected to surpass cardiovascular diseases as the primary cause of deaths over the next few years. According to estimates by the US medical research agency, the National Institutes of Health (NIH), medical expenditure for cancer in the US is expected to go above $150 billion by 2020, thereby putting even more financial pressure on an already overburdened US healthcare economy. Traditionally, surgery and radiotherapy have been the primary treatments for cancer, with anti-cancer drugs being used largely for metastatic cancers. Although chemotherapy has been successfully used for inhibiting cell growth throughout the past few decades, the side effects of chemotherapy have forced researchers to look for some alternative drugs for all types of cancer. The challenge for drug manufacturers has been how to effectively deliver the drugs to the appropriate disease site. While up until now most drugs administered have been injectables, the focus of drug manufacturers has now shifted to developing effective needle-free delivery systems in a bid to overcome this challenge, as driven by their patient-centric healthcare approach.

FIGURE 1


Source: Frost & Sullivan

**Global Oncology Drug Delivery Market Forecast, 2016–2020 ($Billions)**

## THE RISE OF THE INJECTABLES MARKET

Drug manufacturers' strong emphasis on continuous improvements in cancer treatment has resulted in the development of novel drug delivery approaches, enabling the targeted administration of drug compounds. This transformation has pushed the growth of the oncology drug delivery market, which is expected to exhibit a compound annual growth of ~11% during 2016-2020 (Figure 1). While this growth will benefit all types of drug delivery mediums, oral drugs and inhalers are expected to be among the leading gainers.

Despite strong growth in the number of oral drug prescriptions, several injectable drug companies have invested in resources to develop advanced drug delivery solutions. Although intravenous infusion drug delivery is expected to dominate the market throughout the next 5 years, subcutaneous, intra-dermal, and intramuscular modes of drug delivery are expected to gain a strong market hold, as 30-35 new products are likely to be launched by various companies.

In addition to traditional oral and inhaler methods, research

on some innovative delivery methods, including nanogels and transdermal patches, is also underway, and scientists are evaluating the bioavailability of drug compounds on target sites when a drug is delivered using these mediums. The clinical effectiveness of these mediums will largely decide the market success of these new methods.

## DO TARGETED THERAPY & NEEDLE-FREE DELIVERY MATTER?

Though significant advances have been made in the field of drug delivery, patients still have a number of unmet needs, offering ample opportunities to drug companies. Researchers have devised various strategies to effectively deliver drug concentration to the target area, but these have met with limited success in the clinical development phase. At present, there are a few clear unmet needs:

**Targeted & Controlled-Release Cancer Therapy:** Drug delivery systems capable of delivering drug compounds to targeted cells and for a specific time period with minimal or no impact on other healthy cells, thereby limiting painful side-effects.

**Needle-Free Delivery:** Supported by the home healthcare trend, patients are increasingly looking for drugs that can be easily self-administered and do not require much intervention/support from medical practitioners. Rising patient demands for painless and effective treatments (such as inhalable and transdermal mediums) have also forced companies to focus on related innovations.

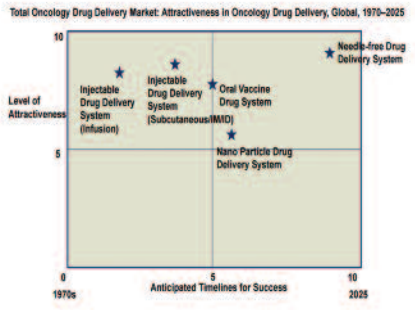
**No Targeted Cancer Therapy is Capable of Delivering More Than One Drug at Once:** In addition, bioavailability of the drug compound at the target site remains a key challenge, whatever the delivery medium.

## RACE TO SOURCING INNOVATION IS KEY GROWTH DRIVER

To overcome the existing technology limitations, a number of small biopharmaceutical companies have taken initiatives and are involved in the R&D of innovative cancer drug delivery methods. However, given several clinical hurdles and high financial costs, the rate of commercialization of the platforms developed by these companies is quite low.

Large pharmaceutical companies have traditionally relied on their innovation partners to develop such technology platforms, and they have tended to favor a strategic sourcing model rather than develop their own platforms. For example, Celgene signed a partnership agreement with Presage Bioscience to use its Arrayed Microinjections platform. Similarly, Amgen entered into a contract with Unilife to use its wearable injectable technology for its oncology drugs. As part of the deal, Amgen has secured exclusive rights to use Unilife's wearable injectors for select drug classes. Other pharmaceutical giants, including Pfizer, Novartis, and Merck, have also signed exclusive deals with such boutique research firms. A few large pharmaceutical companies are also funding academic research programs to get access to such technology innovations. Other large pharmaceutical companies have also adopted the strategy of supporting academic research projects to get access to

**FIGURE 2**




**Shift in Oncology Drug Delivery Approaches**

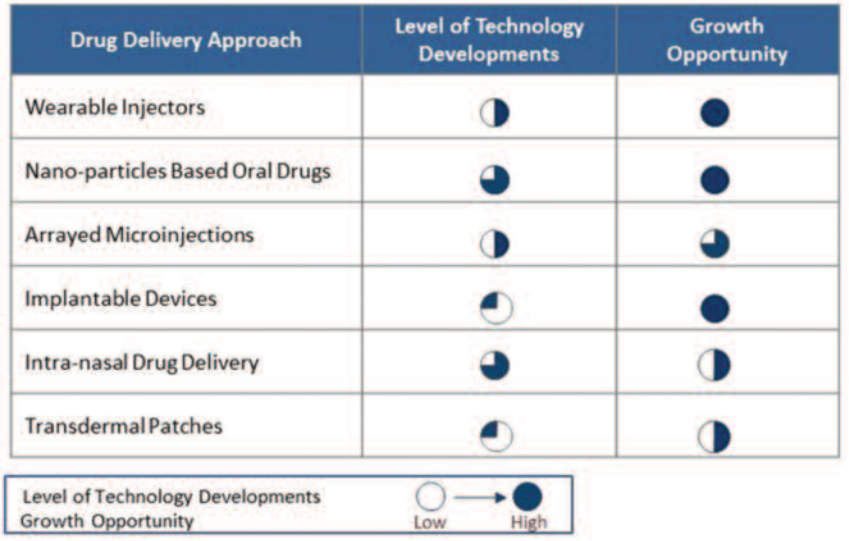
innovations. Overall, there have been relatively limited efforts from big pharmaceutical companies to invest in in-house drug delivery technology innovations.

## RANGE OF BREAKTHROUGH INNOVATIONS

A majority of technological developments are influenced by a gradual shift in cancer treatment sites – from exclusively healthcare center settings to self-administered therapy in home healthcare settings. Because of this, many researchers have focused largely on making drug administration more convenient from the patient's perspective.

While researchers have highlighted and demonstrated the use of nanoparticles to safely deliver and release the drug compound to the tumor site, the commercial application of these methods in clinical settings remains to be effectively demonstrated. Despite this challenge, nanoparticles are being considered as one of the most likely options due to their ability to enhance the drug's bioavailability. In the near future, this technology will enable physicians to apply fewer procedures to a similar site, which typically leads to chemo-resistance in cancer patients, a key reason in the failure of a majority of drug therapies.

**FIGURE 3**




**Potential Growth Opportunities in Various Oncology Drug Delivery Approaches**

From a commercial point of view, a gradual shift is expected from injectable to oral drugs in the short-term and other drug delivery mediums in the long-term. However, the adoption of and the commercial success of these drug delivery mediums will largely depend on their ability to overcome existing challenges. The following are some of the breakthrough innovations.

## WEARABLE INJECTORS

Throughout the past decade, researchers' focus has been to develop injectable products with self-administration ability, to enable anytime home healthcare. Using the same concept, wearable injectors have been developed, with the ability to deliver a large volume of a drug compound. Some drug manufacturers, such as Amgen and Roche, have started using these wearable injector solutions for their products (Neulasta Onpro and Herceptin SC, respectively).

Key companies who have made notable progress in this area include Becton Dickinson, West Pharmaceuticals, Insulet, Unilife, and Sensile Medical.

## NANOPARTICLE-BASED ORAL DRUGS

Nanogel or Nano Drug Delivery Vehicles for cancer drug carriers have been one of the most highlighted and accepted research topics because of their ability to absorb and deliver a wide variety of compounds. Although there have been significant developments on this front, the bioavailability of drugs has not been satisfactory in all cases. Hence, physicians prefer injectables for faster recovery. If nano-drug delivery is proven to be successful, oral forms of drugs can become more effective.

Furthermore, designing nanoparticles using computation modeling has shown some strong promise and is another opportunity area for innovation. A number of research activities using computation modeling are being carried out to simulate the distribution of drugs and nanomaterials. So far, there have been a few moderately successful commercialization efforts on this front. Based on commercial outcomes so far, nanomaterial-based drug delivery systems are poised for strong growth throughout the next 3 to 5 years.

Key companies to watch out for in this area are Celgene, LiPlasome, Intezyne, KeystoneNano, Leonardo Biosystems, and CytImmune Sciences.

## ARRAYED MICROINJECTIONS

Arrayed Microinjection is another interesting approach that holds significant potential in oncology treatment, on account of its ability to effectively deliver drug compounds to targeted cells. Presage Bioscience has been successful in demonstrating the use of microinjection platform technology in oncology dosing, and it has already been granted a patent for its device based on arrayed microinjection technique and quantitative analysis methodology. The platform enables the placement of multiple drug compounds directly to the tumor site. This allows doctors to directly assess the result of multiple drug compounds on tumor cells without having to worry about bioavailability, metabolism, or excretion issues. The platform is being used and tested in various clinical conditions. Early results in clinical settings from the platform have been successful, and the company has already signed strategic partnerships with Celgene and Takeda pharmaceuticals.

## IMPLANTABLE DEVICES

Another emerging approach is implantable drug-release platforms for intrav-

esical drug delivery. Although a majority of products based on this technology are still in the R&D or trial phase, considering the current challenges with other forms of drug delivery mediums, this approach holds significant potential. Key companies in this area include Taris Biomedical, Endo Pharmaceuticals, Axxia Pharmaceuticals, and Cirtec.

## INTRA-NASAL DRUG DELIVERY

Currently, breakthrough pain (BTP) or severe pain in cancer patients is targeted through the intra-nasal route of drug administration. BTP is highly prevalent in certain cancer patient populations (40% to 80% of the patients with advanced cancer). Some drugs, such as Fentanyl and Lazanda, which use intra-nasal routes, have been found to be efficacious in cancer patients. Research efforts are also focused on developing nanoparticle-based drugs to be delivered using an intra-nasal drug medium, with lung cancer and brain tumors being the key disease targets. If successful in clinical safety assessments, this method holds significant commercial potential, as lung cancer is one of the most common types of cancer identified in new cases (~17%).

## TRANSDERMAL PATCHES

Transdermal patches are another drug administration route being explored by researchers for anti-cancer drug compounds. Though the use of transdermal patches for drug delivery is not a new concept, its clinical potential and effectiveness in the case of anti-cancer agents is still being assessed. Currently, transdermal patches are being used in treating the side effects of anti-cancer drugs. There would appear to be opportunity for growth in the area of transdermal patch drug delivery in the treatment of skin cancers and in cancer vaccines.

## KEY GROWTH OPPORTUNITIES

Overall, a strong movement from injectables to other drug delivery mediums is anticipated, driven by increasing emphasis on improving efficacy of anti-cancer agents, reducing side effects, and adopting patient-centric home healthcare approaches. A strong shift is anticipated in therapy selection approaches, and ease of administration will also be considered along with effectiveness in prescription decision-making.

Short-term growth in the oncology drug delivery market can be achieved by investing in the injectable segment of the market. However, alternative forms of targeted drug delivery, such as niosomes and antibody targeted nanoparticles, are expected to be in high demand in the long-term. During 2015-2016, ~50% of the total oncology drugs approved by the FDA were oral cancer drugs. In the long-term, Frost & Sullivan expects this trend to continue. However, given the pricing pressure on drug manufacturers and HCPs, the high cost of these systems might be a limiting factor.

For the nasal route of drug delivery, Frost & Sullivan expects a high growth in the short-term for applications in cancer pain management. However, first-line therapy in pain management is still an unmet sector and is expected to remain so for the next 2 to 3 years. Also, microneedles or dermal patches are likely to make up a high market share in the more distant future, depending on their clinical success.

Furthermore, the use of informatics, computation modeling, and visualization technology is expected to increase, as companies will look to use different AI-based simulation models (for all types of drug administration methods) to limit the chances of last stage failure of their products. Frost & Sullivan expects some strong movements in this market segment throughout the next 3 to 4 years. Key companies to watch in this space are Schrodinger, Fustibal, CFDRC, and Turbine.

While this change represents a huge opportunity for small research-focused organizations, it also offers an opportunity for drug manufacturers to align themselves with this technology shift and to gain easy traction from doctors and patient groups. For contract manufacturers, early adoption of this shift in production technology will be essential. As of now, some large CMOs, such as Patheon, have already taken some initiatives on this front, and other mid-size and small CMOs are expected to follow the trend. ◆

**Piyush Bansal** is a Senior Industry Analyst for Frost & Sullivan's Life Sciences practice. He has diverse expertise within healthcare IT and life sciences with a strong focus on drug discovery, healthcare informatics, and genomics. His expertise includes market opportunity assessment, technology assessment, product launch and geographic expansion plans development, growth strategy formulation, and advanced data analytics. To supplement his expertise, he also has broad-ranging industry experience in varying sectors, where he has established long-standing working relationships with leading industry participants in areas such as pharmaceuticals, clinical trials, healthcare IT, and genomics. Mr. Bansal earned his BTech (Biotechnology) from Rajasthan University, India.

# Special Feature

## Prefilled Syringes & Parenteral Manufacturing – A Rise in Biologics & Improved Technology Give Pharma Reasons to Consider Parenteral Delivery

By: Cindy H. Dubin, Contributor

Parenteral is one of the most commonly used routes of drug administration. A steady rise in the development and availability of parenteral drugs has resulted in the increasing demand for advanced drug delivery devices that promise cost containment as well as ease of administration. Prefilled syringes are one of the most rapidly expanding segments of the injectable drug delivery devices market. There are several benefits of prefilled syringes over traditional delivery systems: improved safety, ease of administration, accurate dosing, and reduced risk of contamination. These advantages form the basic foundation for the success of prefilled syringes and are likely to continue driving the market during the forecast period.

Technical advances in the sector, rapid growth in the biologics market, and the growing preference for self-administration using autoinjectors, prefilled syringes, and pen injectors are the key factors boosting the global market for prefilled syringes. As a result, the global sales of prefilled syringes amounted to $3.5 billion in 2015 and are projected to reach $7.9 billion by 2024.[1]

In this annual report, *Drug Development & Delivery* magazine speaks with some of the leading companies in this market to find out about key trends, packaging advancements, safety improvements, and technology developments.

**Bespak's Syrina® range of assisted syringes and autoinjectors, utilizing its VapourSoft® power source.**

## Artcraft Health: Addressing the Patient Experience in Device Training

Studies show that a myriad of factors contribute to patients' adherence and compliance with their physician-prescribed treatment regimen, especially among patients who self-inject their medication. Some of the key factors for improving patients' adherence and compliance include a clear understanding of their treatment and administration technique,[2] behavior modeling, and exposure to reduce fear and anxiety related to needle injections,[3] and more active participation in their healthcare decisions overall.[4]

The findings of these studies are driving the trend toward greater investment in patient-centric educational resources and services intended to improve the patient experience and, ultimately, health outcomes, says Brett Zimmermann, Vice President, Integrated Solutions, Artcraft Health. For example, in a 2016 survey of more than 200 executives at leading pharma companies in the United States and Europe, 85% of respondents said their companies plan to increase spending on patient-centric capabilities over the next 2 years.[5]

"At Artcraft Health, we provide these patient-centric capabilities to our pharma clients, many of whom produce new and emerging therapies, including biologics, combination therapies, and medication delivery via customized prefilled syringes and on-body devices," says Marty Mason, MBA, MS, Senior Director, Business Development, Artcraft Health. "The challenge we face is that as device complexity evolves, our task becomes more difficult," he says, citing that the majority of patients do not read instructions for use,[6] and as one study found, 84% of patients use their autoinjectors improperly.[7]

In light of these challenges, clients typically express the need for clear, actionable education on the use of these products and devices for both prescribers and patients, he adds. To help patients understand and act upon educational information, such capabilities must factor in critical patient insights and unmet needs, and be pulled through using essential health literacy principles, educational design, and an understanding of the overall user experience. "We have found that the most effective solutions involve integration of health literacy into many forms of visual and tactile media—that is, education by demonstration, such as instructions for use via live video, animation, custom-molded replicas, and demonstration devices."

"Advances in innovation have allowed us to develop solutions that simulate the patient injection experience and replicate the device without the use of any fluids or other compounds," Mr. Zimmermann adds. "Our demo devices are used as training tools for healthcare providers to explain its instructions for use and model correct technique to their patients, thereby reducing their anxiety and the likelihood of errors."

As an example, in 2015, Artcraft developed a demo device of an on-body medication delivery system for one of its pharma clients. "We engineered the device to simulate its lighting and audio cues and the sensation of the automatic cannula insertion via tensile strength, cantilevers, and springs," explains Mr. Mason. "The demo device successfully simulated the 27-hour cycle that occurs in a matter of minutes, allowing patients to understand how the device works and feels on the body. In addition, as with many of our demo devices, this device was packaged as part of a comprehensive patient starter kit that featured patient-friendly education and an SMS text-back program to view an instructional video. The demo devices have been used to facilitate education among sales

**Patient starter kit designed and manufactured by Artcraft Health, featuring the on-body injection demonstration device.**

representatives, healthcare providers, and patients in an efficient and effective interaction, leading to increased treatment adherence and compliance. The client has placed its fifth reorder for these kits and has included the demo devices as part of its ex-US commercial launch strategy."


Lyophilization Center of Excellence lab in Baxter BioPharma Solutions' Bloomington, IN, facility.

## Baxter BioPharma Solutions: Remaining Flexible in Biologic Operations

The shift to biologics and customized medicine has shifted Baxter BioPharma Solutions' approach to syringe filling, explains Wendy R. Saffell-Clemmer, Director Research, BioPharma Solutions. "In the past, rotary piston pumps were the standard for precision filling. With today's molecules exhibiting a greater sensitivity to shear, peristaltic pumps is the preferred choice for many of our partner companies," she says.

Additionally, incorporating cold chain management into the formulation and aseptic filling operations has become increasingly prevalent. Here, flexibility is key. "Offering a variety of formulation options, including stainless steel tanks, disposable formulation assemblies, and low shear mixing to accommodate a range of compounded volumes is a necessity to meet our customer's expectations."

Along with biologic therapies comes the challenge of shifting the operating mindset from larger batch sizes that were common with traditional syringe therapies to the smaller batch sizes. This shift includes reducing standard line losses due to priming, purging, and filter retention, as well as optimizing the frequency and quantity of in-process testing, explains Ms. Saffell-Clemmer. "We appreciate the significant cost and time our partners have invested in these new molecules, and it is critical that we utilize Quality by Design principles during development and qualification to optimize the yields from our operations."

In addition to addressing issues in biologics, Baxter Biopharma Solutions is experiencing the impact from increasing demand in COP (and similar) syringes. "Baxter BioPharma Solutions has responded to this trend by enhancing our offering and performing preliminary stability studies in COP syringe systems and deepening our experience in manufacturing COP syringes at full commercial scale," she says.

## Bespak: Improving Patient Outcomes

The growing need for devices capable of delivering high volume, highly viscous drug formulations has resulted in several device companies developing new platform technologies. Bespak has created a proprietary injection mechanism that uses a miniaturized form of the gas canisters it uses to power its well-established inhalers. The liquefied gas in the canister provides an energy source in the form of pressurized vapor, powering delivery of the drug with low impact and a consistent delivery profile. A range of liquefied gases can be used within the container format to enable differing volumes, viscosities, and primary containers to be managed by a single device system.

When developing devices, improving patient outcomes is a key objective for Bespak. "We work closely with human factors experts internally, externally and within the biopharmaceutical companies we partner with to ensure that design, form factor, and functionality of the device suit the targeted patient group. We have incorporated easy to use features such as needle assist into our Syrina® Micro & Syrina® Mini devices, and the Syrina® autoinjectors feature manual or automatic drug delivery with passive needle safety system or even automatic needle retraction, to ensure the process is as simple as possible for patients to self-administer," says Steven Kaufman, Global Business Development Lead at Bespak.

## Credence MedSystems: Removing the Necessary Evils From Staked Needle Syringes

Since its introduction, Credence's Companion technology has materialized as an option in the industry for integrated passive needlestick safety with reuse prevention. This is in response to the industry's

# Autoinjector Trainers

## True to form and function

Noble, the leader in device training and onboarding, offers complete device training and onboarding platforms designed to reduce errors, increase device familiarity and ultimately improve patient outcomes.


*Trainers available for 1ml FNS, RNS and 2.25ml*

## Available Capabilites:

- Audio
- Tactile Feedback
- Sensors
- Error Correction
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- Ergonomics
- Packaging

## Key Features & Enhancements Pre-configured for Speed-to-Market

These training devices are custom-developed to match your device customization and also can include error correcting and smart features designed to increased memory recall and compliance.

- Plunger Speed Simulation*
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- One- and two-click audible feedback*
- Resettable Safety Systems*
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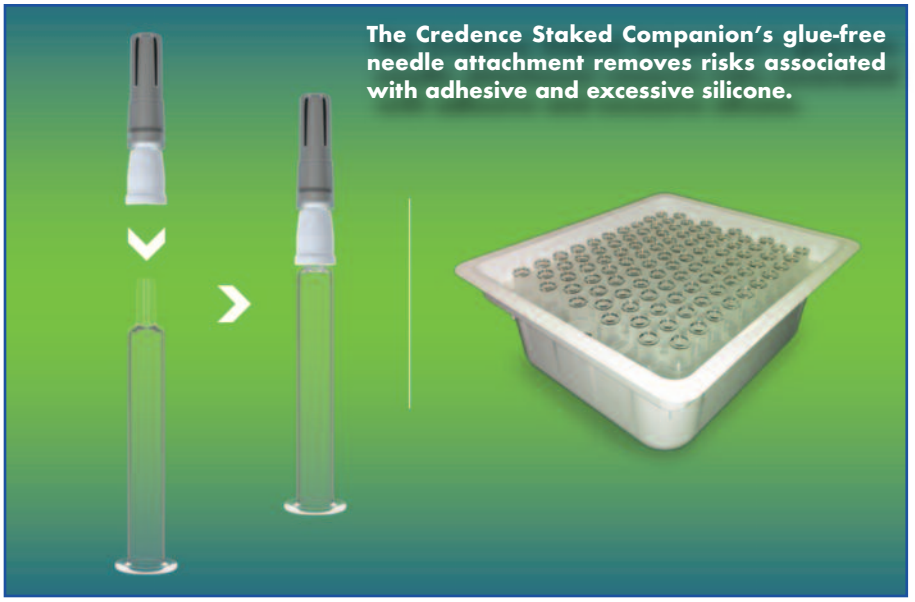
drive towards optimizing the user's delivery device experience while still minimizing risk throughout the system. Lately, however, there is an emerging appreciation from pharmaceutical manufacturers of the technology's potential to extend its impact beyond needlestick safety into a role as the future standard for a pre-attached needle, says John A. Merhige, Chief Commercial Officer, Credence MedSystems.

"This is driven by Credence's successful removal of adhesive from the mechanism of needle attachment and the downstream implications of doing so. Uncured adhesive has led to unexpected impurities found in traditional staked needle syringes and the presence of glue introduces risk of leaching into the drug product. Removing glue removes these risks. Further, it enables a finer control of silicone lubricant using techniques such as baked-on siliconization, which is not compatible with traditional adhesive-based staked-needle syringes. This mitigates the risk of excessive silicone oil, which can lead to silicone oil droplets and may cause protein aggregation in biotech applications."

By removing materials that have traditionally been viewed as 'necessary evils,' Mr. Merhige believes that Credence has provided the industry the option to define a new standard for the pre-attached needle syringe. "Along with reducing the risks associated with those materials, the Credence Companion technology enhances usability and safety, providing the user with end-of-dose cues, clear inspection of the barrel, the ability to perform common syringe procedures, passive needle retraction safety, and reuse prevention," he explains. "When a new technology provides an option with reduced risk, improved usability, and enhanced safety, all without driving significant tradeoffs, it eventually becomes negligent not to deploy it."



**The Credence Staked Companion's glue-free needle attachment removes risks associated with adhesive and excessive silicone.**

But the industry is deliberate, supply chains are entrenched, and progress takes time. To facilitate implementation, Credence is working closely with leading syringe manufacturers to make the technology available to pharmaceutical manufacturers through its preferred syringe suppliers.

## DALI Medical Devices Ltd.: Safe Auto-Needles for Biosimilars, Generics, & Novel Injectables

Market research conducted by DALI Medical Devices Ltd. regarding self-injection found that a significant percentage of patients would like to control injection speed and benefit from the ease of use of automatic needle insertion. Based on this research, DALI developed the Safe Auto-Needles (SANs) product line proposing features such as automatic needle insertion, hidden needle and passive sharps protection features from autoinjectors, reducing anxiety and perceived pain associated with needles, with manual control of injection speed, reducing pain associated with fast injections.

"Unlike conventional safety needles, the patented SAN-L is the only available hidden and automatic needle-insertion device attachable to any luer/luer-lock syringe (plastic, glass, single, and dual-chamber)," says David Daily, CEO & Co-Founder, DALI Medical Devices. "The SAN-DV and SAN-DV Pro are the only vial-based systems that utilize the SAN-L technology for use with drugs in vials."

The SAN product line has enabled DALI to compete in the growing biosimilar market. According to Mr. Daily, just five years ago, biosimilar and generic companies required an injection device that was similar to the original because the regulatory risk to develop an improved device for a biosimilar or generic drug was high. "But today, biosimilar and generic companies are seeking improved injection devices, searching for more intuitive, easier to use injectors that will increase patient compliance and adherence to therapy, and will provide a competitive advantage over the originator," he says.

DALI has initiated several SAN projects with biosimilar and generic companies. In fact, Mr. Daily explains how the company is currently customizing a SAN product for a generic pharma company, which due to the low expected annual volume and unique needle length and gauge,

**DALI's SAN-DV Pro for drugs in vials: An integrated system for easy drug reconstitution, transfer, and injection, utilizing the SAN-L automatic-needle technology.**

could not get it from the major suppliers.

Additionally, the increased need for combination therapies–and the fact that major pharma companies require exclusivity for use of the injection device they select for the drug/indication/therapeutic area–has translated into a few customization projects. Working with its autoinjectors partner, Elcam Drug Delivery Devices, DALI is developing the Flexi-Q line of autoinjectors to provide customizable options to customers.

## Datwyler: Shift Towards Fluoropolymer Coating Technologies

For coated elastomeric closures, barrier properties are no longer the only requirement that meets the ever-evolving needs of biologic and biosimilar drug packaging. The reduction or elimination of silicone oil and its subvisible particles has been recognized as a means to mitigate risks and reduce time-to-market. Pharmaceutical manufacturers opt for fluoropolymer coating technologies, providing numerous benefits, especially for sensitive biologic drugs. Global industrial supplier Datwyler is meeting this growing need with its Omni Flex coating technology for elastomeric closures.

"The packaging requirements of biologics and biosimilars are creating more specialized demands for material performance," says Susan Dounce, PhD, Senior Manager Business Development & Innovation, Datwyler. "As a consequence, market trends indicate a growth in fluoropolymer coated elastomeric closures that help to mitigate risks related to drug compatibility and stability. Omni Flex fluoropolymer coated closures not only have barrier properties that enable superior chemical compatibility, but also have the added benefit of eliminating the closure as a source of silicone-oil-based subvisible particles (SbVPs)."

For a therapeutic protein, the exact chemical make-up and three-dimensional conformation can influence the efficacy of the drug product. Interactions with leachables, including silicon oil, often used to increase the glide force of plungers in prefilled syringes, can present a risk to the safety of therapeutic proteins, says Dr. Dounce.

Datwyler's proprietary Omni Flex coating technology is a flexible fluoropolymer spray coating applied to bromobutyl vial stoppers and syringe plungers. The technology is designed to be an inert barrier to organic molecules and metal ions and imparts a low coefficient of friction, thereby eliminating the need for siliconization, explains Dr. Dounce. "The total coverage by the Omni Flex coating stands in contrast to the partial coverage of most barrier films, and therefore offers the benefit of providing a full lubricious barrier coating on the entire closure. As silicone oil from a traditional elastomeric closure can represent a significant source of subvisible particles, non-siliconized Omni Flex coated plungers' particle levels are among the lowest in the industry."

All Omni Flex coated elastomeric closures are manufactured in highly automated facilities aligned with the company's highest, First Line, quality standard. Designed to meet the evolving standards of the parenteral industry, Datwyler's First Line standard incorporates a special facility design, process flow, gowning protocols, personnel, material flow, and automation, resulting in the lowest endotoxin, bioburden, particulate and defect levels available in the industry, she says. "This innovative approach to manufacturing exceeds the most stringent quality standards of the European and US regulatory authorities and is certified to ISO 15378."

Datwyler is currently expanding its presence in the United States with the construction of a facility in Delaware that fully conforms to the First Line standard.

## Enable Injections Inc.: Large-Volume Injectors Differentiate Combination Products

Biologic drug developers/delivery device partnerships are proliferating due to two merging trends. First, pharmaceutical companies are realizing that their drugs will not alone suffice in successfully navi-

**Further ongoing development of elastomeric, plastic, and aluminum closures at Datwyler drives quality closures.**

gating new outcomes-based models health systems are adopting. Incorporating newly available wearable large-volume injectors (WLVIs) to deliver biologics in doses from 2 ml to 50 ml is widely expected to increase adherence to therapy, impact outcomes positively, and reduce health system costs. WLVIs also address the second trend, patient-centricity. Nowhere is disruptive innovation to improve the patient experience more critically needed than for delivery of the viscous biologics that now comprise approximately 70% of products in pharmaceutical development. "It's no wonder innovative, patient-focused pharmaceutical companies are partnering with LVWI developers," says Jeannie Joughin, Vice President, Corporate Development, Enable Injections Inc. "Together they are better positioned to create patient-centric, differentiated combination products."

Prefilled syringes have largely eliminated the care, skill, and work required for patients to self-inject small-molecule drugs. Ms. Joughin says Enable Injections' advanced wearable large-volume injection devices do the same for large-molecule, viscous biologics. "Enable's WLVI makes it very easy for patients to self-administer biologics without the need and expense of an IV infusion aided by a healthcare professional. And our ability to use any standard pharma industry container closure with a delivery system that is strongly preferred by users not only saves costs but also reduces development time by months."

Enable Injections' new WLVI devices are optimized to provide dosing flexibility, decrease dependence on healthcare systems, and improve compliance with therapeutic regimens. Accordingly, Ms. Joughin says Enable Injections is ready to manufacture its devices offering the customized flow and pressure control technology suited for delivery of the diversity of large-volume drugs that are in development, on the market, or in need of life cycle extension. "Our recently opened Cincinnati facility is manufacturing LVWI devices in quantities of up to 1 million, and for larger quantities, we have a manufacturing partnership with Flextronics."

Dr. Joughin wants to communicate two message to the pharma industry. First, let go of the widely held belief that only relatively small volumes, under 2 ml, can be administered to the subcutaneous space. "With the availability of wearable large-volume wearable injectors, that is no longer the case," she says.

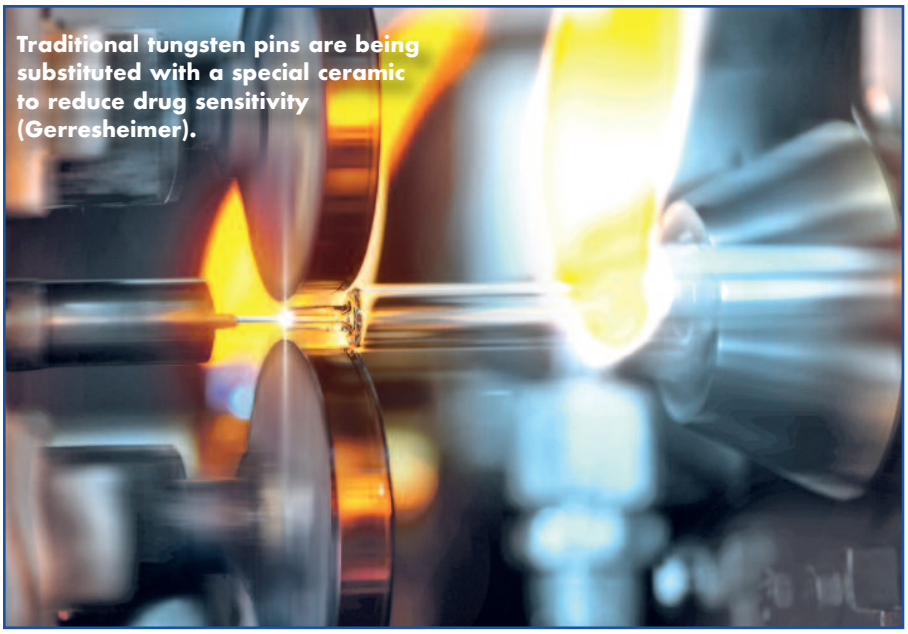
Second, be more responsive to consumer needs, quickly delivering innovative changes/customization. "This can be accomplished by partnering with companies that are addressing the major issues of patient-centricity, cost, and outcomes. Understanding patient needs and use of appropriate marketing tools will ensure pharma evolves ways to make the most of their products and services and help develop solutions, not just sell products."

## Gerresheimer Medical Systems: Metal-Free Syringe Production

An important trend with regard to prefilled syringes is the need for tungsten-free syringes, as some newly developed protein-based drug formulations are sensitive to traces of tungsten oxides. Today, glass syringes are still manufactured by means of a pin made from tungsten. Its residuals remain in the syringe bore after the forming step. Gerresheimer has solved this pending issue by substituting the tungsten pin with a special ceramic. This new material is non-cytotoxic and non-abrasive. To further this "metal-free" syringe production (currently available for luer syringes), a significant reduction of tungsten can otherwise be accomplished by a dedicated washing step, reducing the average amount of tungsten residuals below 10% of the original level.

Bernd Zeiss, Manager Technical Support Medical Systems, Business Development, Gerresheimer Medical Systems, says


**To use the Enable Injector, patients need only insert a vial, cartridge or syringe, adhere the auto-filled injector to their body, and push one button; the injector automatically warms as it fills.**



**Traditional tungsten pins are being substituted with a special ceramic to reduce drug sensitivity (Gerresheimer).**

that as drug therapies become more sophisticated, so must the prefilled syringes and vials, especially with regard to sensitive biologics. "More sophisticated syringes require a close cooperation between the syringe manufacturer and the pharma company."

And while glass may be the preferred material for syringes, COP syringes are gaining more interest and market share, says Mr. Zeiss.

## Nemera: Platforms That Address Comfort & Biologic Delivery

The Injectable drug market is the fastest growing segment within the pharmaceutical industry. In 2016, 50% of the top-10 worldwide pharmaceutical product sales were parenteral. One of the main drivers is the rise of biologic drugs, which offer high therapeutic value to patients. Biologics are large molecules (complex and sensitive) produced by cell culture, resulting viscous and/or larger filling volume drugs. To overcome biologic problems, new types of primary drug container and device technologies have emerged, such as 2.25 ml syringe-based autoinjectors or 3 ml-10 ml cartridge-based patch pumps.

For example, Nemera has developed a new generation of 2-step autoinjector for fluid and viscous injections, Safelia®. It allows tailored injections and delivers high viscosities (up to several centipoises) thanks to its patented cam-driven based mechanism. The autoinjector platforms (1ml and 2.25 ml) is suitable for subcutaneous and intramuscular injections, says Adrien Tisserand, Category Manager at Nemera.

Nemera has also developed a 2.25 ml version of Safe'n'Sound®, customizable platforms of add-on passive safety devices for prefilled syringes. "Safe'n'Sound aids in the protection from accidental needlestick injuries and facilitates the injection process through ergonomic features, such as an optional extended finger flange to improve handling, gripping, and comfort for the user," says Mr. Tisserand.

## Noble: Simulating Self-Injection Through Training Improves Patient Onboarding

Although there are many positive changes impacting self-injecting patients, there are also some challenges patients and other stakeholders face, including training decay from lengthy gaps between self-administration, forgetfulness of dosing regime, and fear of the actual injection sensation due to conditioning degradation, explains Joe Reynolds, Research Manager, Design & Engineering, Noble. "These factors could increase the risk of errors and contribute to lower adherence rates for self-injecting patient populations."

To counteract some of these challenges, Noble continues to develop prefilled syringe trainers and patient onboarding platforms to help patients with

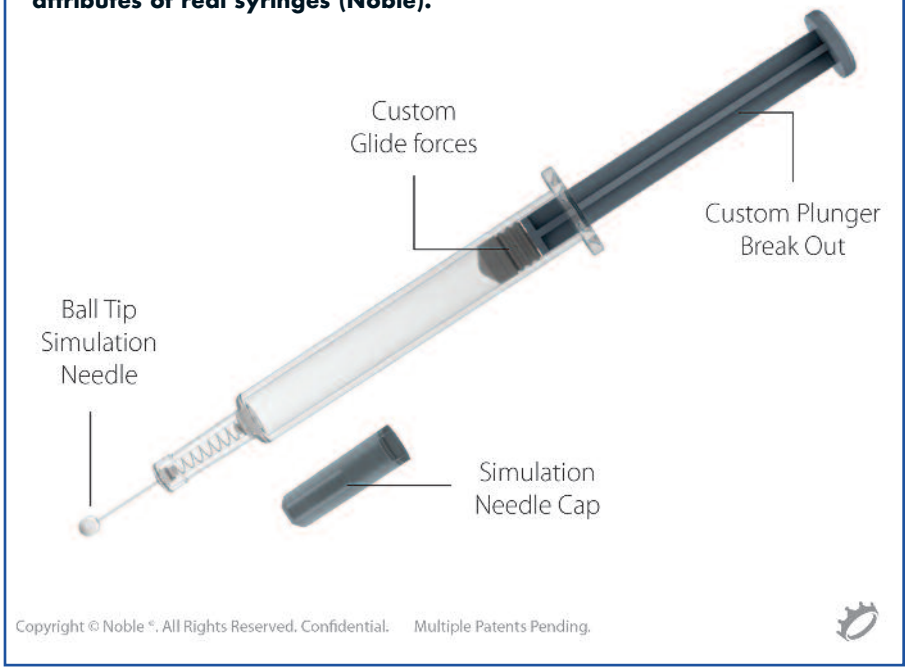
**The Safelia® 1 ml and 2.25 ml 2-step autoinjector efficiently delivers viscous biologics (Nemera).**

initial device training, continuous training, and onboarding throughout disease management to counteract self-injection training decay, and ultimately improve adherence and health outcomes.

Some of the proprietary prefilled syringe training device enhancements at Noble include plunger resistance and breakout forces that simulate the actual prefilled syringe and drug viscosity, and needle insertion technologies simulating needle sensation and force–all with the objective of enhancing the patient onboarding experience.

"As pharmaceutical companies continue to develop innovative combination therapies, Noble continues to collaborate with pharmaceutical teams to improve patient onboarding and patient outcomes through true-to-form and function platforms, including safety and standard prefilled syringe trainers, Smart Injection Pads (wirelessly connected error-correcting injection training pads used for instructing, tracking, monitoring, and collecting data to assist in improving adherence), and autoinjector trainers," he says.

**Standard training syringes and safety system training syringes simulate attributes of real syringes (Noble).**




## $SiO_2$ Medical Products: Hybrid Material Construction Improves Storage Conditions

The storage of injectable parenteral pharmaceuticals, especially biologicals, has grown increasingly difficult using traditional primary packaging materials due to reduced concentration of active ingredients and more scrutiny on package leachables. The introduction of fluropolymers solved the bulk of the issues (silicone and other organic leachables, tackiness, feeding issues, adsorption, absorption, etc.) associated with the use of elastomers, but vial and syringe container materials have not changed at the same rate as elastomeric closures. Traditional glass packaging has a plethora of well-documented problems and even the cyclic olefin polymer offerings are not without their drawbacks. What is needed is a packaging material that offers the best of both materials with the drawbacks of neither.

"$SiO_2$ Medical Products has leveraged the benefits of both plastic and glass to yield a hybrid container without their associated risks," says Dr. Christopher Weikart, Chief Scientist, $SiO_2$. He explains: The plastic injection molding technologies are used to produce primary containers with dimensional variability approaching +/- 5 microns. A chemically inert organo-glass-like coating is deposited on the inside of each container to reduce both inorganic and organic extractables and leachables, as well as unwanted drug product surface interactions. In the case of syringes, a new lubricant technology was developed to reduce particle levels approaching an order of magnitude lower than traditional silicone oil, which reduces the risk of biologic protein interactions forming agglomerates that have the potential for patient autoimmune response.

"The work we are doing is a boon to biologics due to the inert nature of our primary contact surface chemistry," says Dr. Weikart. "Biological species no longer adsorb to the vial or syringe walls so there is no loss in active ingredients to the packaging. The surface of all of our primary containers is hydrophobic, which reduces the amount of biologic solution retention on the walls of the container. Our ability to seamlessly customize the nature of the drug contact surface of our primary containers makes it attractive to drug developers that want all the benefits of glass without its deficiencies."

$SiO_2$ recently helped a client whose product shelf life failed to meet expectations with glass when packaging a multipotent neonatal stem cell for dermatological therapy. They were losing these cells due to adsorption of the side walls of the glass vial being used. The same phenomenon occurred with a cyclic olefin vial. The company evaluated the

**$SiO_2$ Medical Products incorporate a silicon-based barrier coating system that combines the durability, pH stability, and dimensional consistency of plastic with the barrier properties and low extractables of silica glass.**

$SiO_2$ vial with patented trilayer barrier coating and realized satisfactory levels of cellular activity after prolonged storage, and shelf life expectations were met. This enabled the client to proceed with further clinical investigations.

Despite the advantages of a hybrid construction, the pharmaceutical market is entrenched in certain materials of construction for its primary packaging of parenteral pharmaceuticals, says Eugene Polini, Principal Scientist, Technical Service, $SiO_2$. "There has to be a compelling need to change packaging material and that need has to be associated with a critical risk to patient health. Simple features and benefits may be advantageous, but are insufficient to change traditional packaging materials. There must be regulatory, financial, production, and patient safety motivators to convince the market."

## Vetter: Easing Self-Administration While Ensuring Drug Compatibility

Today, companies are expected to develop drugs that are highly compatible with the human body, and that can be offered in the most convenient delivery form possible. This is especially true for drugs that patients need to self-administer, and is consistent with the ever-expanding home healthcare market.

Intent on controlling and optimizing costs, health care authorities are demanding that the industry develops medicines that make it possible for patients to undertake as many procedures as possible in a private setting.

"Our service offering in this sector ranges from single-chamber bulk and presterilized syringes to our patented dual-chamber technology especially suited for sensitive compounds," says Bernd Stauss, Senior Vice President Pharmaceutical Production/ Engineering,Vetter Pharma-Fertigung GmbH & Co. KG. "In addition, we offer a novel syringe closure system called Vetter-Ject®, which applies less silicon oil than commonly used, making the system particularly suitable for silicon-sensitive drug products. Our portfolio also includes the assembly of pens and autoinjectors, both of which are especially designed for the home healthcare market."

However, as is often the case with opportunities, there are also challenges, and the manufacturing of prefilled syringes offers several. "In our experience, the creation of easy-to-apply systems often means a more complicated production process from the very start," says Mr. Stauss. "After all, a syringe system is a sophisticated and complicated tool containing a number of single components. The correct interaction between these components is critical to the syringe systems' successful operation."

In an effort to achieve success for its customers, Mr. Stauss says Vetter sees itself as a solution provider and consultant in the areas of development, manufacturing, packaging, and lifecycle management activities. "We act as an external member of the customer's team, consulting and making recommendations that help make them successful. We start by asking a variety of questions that are relevant and decisive for moving forward, and to determine what must be done prior to committing to prefilled syringes."

## West: Tackling Challenges Posed by Combination Products & Biologics

Biologics offer new promise for patients, namely less frequent dosing options and newfound freedom through the use of wearable self-injection systems that can allow more opportunities for self-care in the home setting. As more biologics and biosimilars enter the global pharmaceutical market, they present unique packaging

**The Vetter-Ject® syringe closure system.**

and containment challenges.

"Many biologics are sensitive and can interact with containers and packaging components made from glass; some biopharmaceuticals have a high pH and others require storage at extremely cold temperatures," explains Graham Reynolds, Vice President and General Manager, Global Biologics, West. "We have addressed these concerns by using materials that ensure that drug quality is not impacted."

Mr. Reynolds adds that because biologics are increasingly self-administered, West has dedicated its efforts to developing easy-to-use delivery platforms and manufacturing platforms that patients can use to effectively and safely administer therapies with simple training.

And as the transition from point-of-care out at a hospital or clinical setting to home setting continues, West offers its SmartDose® platform. In 2016, Amgen announced FDA approval for a single, monthly 420mg dose delivery option for Repatha® (evolocumab), utilizing the SmartDose technology. "We continue to work on enhancements to the SmartDose® platform, including larger dose volumes, preloaded options, and incorporating connectivity," says Mr. Reynolds. "Because combination products involve so many components—the drug, containers, electromechanical devices, connectivity to mobile devices—drug delivery technology companies like West must have a team of experts from a number of fields to support our pharma and biotech customers to deliver their combination products to the market quickly and efficiently."

West is also focused on new materials development for primary containment, such as Daikyo Crystal Zenith® cyclic olefin polymer, which offers a high-performance alternative to glass. "The design flexibility and precision of Daikyo Crystal Zenith offers significant potential to facilitate a range of containment systems for higher dose volumes, including cartridges and prefilled syringes," he says.

Also key to developing and manufacturing drug packaging components at West is its Quality by Design (QbD) approach. "The adoption of QbD principles provides an optimized drug package," explains Mr. Reynolds. New component offerings designed using QbD principles are West's NovaPure® components for prefilled syringe systems.

Mr. Reynolds says: "Building quality into the development and manufacturing process from the start helps ensure that high quality standards are met through commercialization and allows the industry to reach its ultimate goal: delivering safe, effective medications to patients."

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# PCT: Manufacturing the Future of Cell Therapies

For over 17 years, contract development and manufacturing services provider PCT has worked with a multitude of cell therapy development companies and has helped these companies and the industry itself evolve — through infrastructure, innovation, engineering, and technology. PCT helps clients overcome the fundamental challenges of cell therapy commercialization by providing a wide range of mission-critical support services, including clinical and commercial GMP manufacturing, technology, and manufacturing development, including engineering and automation services, and GTP services such as cell and tissue processing. These services are supported by PCT's capabilities in logistics, storage, and distribution. To date, PCT has worked with more than 100 clients, manufactured more than 20,000 cell therapy products, and produced treatments for more than 6,000 patients. A critical distinction between PCT and most other manufacturing partners is PCT's singular focus on cell-based therapy. Robert A. Preti, PhD, President and Founder of PCT, recently spoke with *Drug Development & Delivery* about PCT's growth and the primary challenges facing the cell therapy industry.

**Q: Can you provide some background on PCT's founding and early days? What need in the market did PCT fill?**

**A**: In the mid-1980s, I worked at a small start-up, devising a system to grow bone marrow in three-dimensions. Eventually, my colleagues and I discovered that the constructs we were using to try growing bone marrow looked more like skin than bone marrow. So we started another company, called Advanced Tissue Sciences, and created a product called Dermagraft that is still being sold today. This was my first introduction to regenerative medicine. I joined the New York Blood Center, where I had the privilege to lead its bone marrow and hematopoietic stem cell processing and research laboratories. By 1996, it became clear there was a need to create a contract provider of these services that could go beyond the manufacture and supply of bone marrow, and I became increasingly interested in other clinical aspects of cell therapy development. And so I founded PCT in 1997 with a colleague, Andrew Pecora, MD, then the Hackensack University Medical Center's (HUMC) Bone Marrow Transplant Director. We had a similar vision for the future of cell therapy and regenerative medicine, and through our synergistic and complementary skills, PCT became the first for-profit contract manufacturing organization in the cell therapy field.

We founded PCT all those years ago to meet a need that we recognized: one for high-quality manufacturing and development services in what was then a newly emerging industry. As the cell therapy field has grown, there is increasing need for the development of technological innovations to help streamline, close and automate many cell processing techniques, leading to faster scale-up, lower cost of goods, and improved robustness for the industry. PCT steps back and takes a holistic view of manufacturing processes based on our understanding of this industry.

In 2002, we took a very important step forward by assuming from Dendreon its Mountain View, CA, facility and West Coast-based clinical manufacturing activity. PCT purchased the operations, assuming Dendreon's facility, personnel, and its Mountain View-based clinical manufacturing for Provenge®. We did this with the full confidence that our ability to leverage the infrastructure among many clients and activities would provide more suitable economics and requisite skills development than for Dendreon to continue to float the entire infrastructure on the back of Provenge. We've since built out the facility significantly with the addition of more cleanrooms, QC labs, and manufacturing development space.

**Q: Can you explain how PCT's approach is different from that of other CMOs?**

**A**: That's actually quite simple. PCT is always in the act of innovating toward the future of commercial deliverability of cell-based therapies and making those innovations available to its industry colleagues. The innovations are driven by our mindset and supported by the fact that we have assembled an impressive team with expertise in cell therapy manufacturing and technology development. While many CMOs have some cell therapy experience, only PCT can bring 17 years of cell therapy-specific learning to each new project for each of our clients. Our many years of experience have uniquely positioned us to understand the challenges of delivering therapies that treat a patient with their own cells and developing new technologies and strategies to improve this process. We are driven to leverage that understanding to inform our innovation strategies.

Secondly, PCT approaches each client's project from a manufacturing perspective that we call Development by Design (DbD). The FDA has provided guidance via ICH Q8 for pharmaceutical development (where QbD principles are presented) for establishment of a Quality Target Product Profile (QTPP). The concept of DbD takes this one step further, whereby each of the critical aspects leading to viable commercial manufacturing are addressed, including not only quality, but also robustness, cost of goods (COGs), scalability, and sustainability. Together, these elements form the pillars of optimized manufacturing.

Considering DbD does not mean that a cell therapy developer needs to necessarily make a large investment much earlier on in the process, but it does mean they need to be planning ahead. Taking into account these five elements at an early stage can provide significant cost and time advantages for a cell therapy developer. Without a goal, and a road map to plot a path toward achieving that goal, developers can get lost in the moment and focus too narrowly on getting through today's important milestones while losing track of the big picture —

"In order to help a client achieve efficient manufacturing processes that can lead to a commercially viable product, PCT offers both cGMP infrastructure for the manufacturing of clients' cell therapies and a complementary suite of manufacturing and technology development services, highlighted by the work of our Center for Innovation and Engineering. We can work with clients at any point in their development to provide phase-appropriate services that are designed to facilitate and propel them to commercial success."

commercial viability.

In order to help a client achieve efficient manufacturing processes that can lead to a commercially viable product, PCT offers both cGMP infrastructure for the manufacturing of clients' cell therapies and a complementary suite of manufacturing and technology development services, highlighted by the work of our Center for Innovation and Engineering. We can work with clients at any point in their development to provide phase-appropriate services that are designed to facilitate and propel them to commercial success.

**Q: What are the drivers for the future growth of PCT?**

**A:** We believe PCT's reliability, quality, and high level of customer service are some of the primary reasons our clients tend to extend their engagements with us. Our growth is also underpinned by a general trend in the industry. In 2014, there were a reported 378 regenerative medicine trials (39 in Phase III and 206 in Phase II); in 2015, that number rose to 631 (63 in Phase III and 376 in Phase II).[1] It is expected that by 2020, there will be more than 20 FDA-approved cell therapies on the market, compared with only 11 currently.

In keeping with the growth of the industry, we strive to provide an opportunity in which clients can grow with us, moving through the clinical phases of development with our consulting and manufacturing solutions to guide them and optimize their processes. We have continued to increase the number of clinical trials we are providing manufacturing services for over the years, and our clients are progressing into Phase II and Phase III development.

Importantly, in March of this year, PCT announced a collaboration that enables us to take the next step in making our vision of becoming a global, commercial manufacturing partner a reality. By entering into a global collaboration and license agreement with Hitachi Chemical Co, Ltd. (HCC), a global conglomerate headquartered in Japan with a growing franchise in life sciences, including regenerative medicine, PCT has combined its industry-leading knowledge and infrastructure with the resources, engineering prowess, and operational excellence of a truly global powerhouse. As part of the collaboration, HCC purchased a 19.9% equity interest in PCT for $19.4 million. Caladrius, our parent company, retained the remaining 80.1% ownership of PCT. In addition, PCT licensed its cell therapy technology and know-how to HCC for cell therapy manufacturing in certain Asian territories, including Japan. PCT and HCC have also agreed to explore the establishment of a joint venture in Europe.

**Q: As PCT looks to the future, how does it plan to expand its capacity as the cell therapy industry as a whole advances and more products near commercialization?**

**A:** 2015 saw the addition of multiple long-term capacity client agreements with PCT, including Kite Pharma and ImmunoCellular Therapeutics, as well as revenues of $22.5 million. For 2016, we expect total revenue to exceed $30 million; our first half this year was $15.8 million, so we are tracking well toward that goal.

PCT has current and anticipated requests for capacity that require expansion, and we are in the process of a seamless expansion of our current capacity. We also continue to have ongoing dialogues with both existing and prospective clients as clinical trials in immuno-oncology, immune modulation, and other cell therapies continue to advance and approach commercial launch. In order to accommodate this anticipated growth, we are currently in the midst of an expansion of our infrastructure. Our ongoing expansion is planned to increase our Allendale, NJ, cleanroom capacity by 60% while developing and implementing cell therapy-specific, pharmaceutical-grade quality systems to support commercial manufacturing for the US and Europe. We intend our next moves to include further expansion to a commercial footprint in the US and Europe, including modular facilities that can be built out in stages to support our clients while allowing for technological advances of manufacturing standards over time.

**Q: How will cell therapy manufacturing processes need to evolve in the coming years to make cell therapies commercially viable?**

**A**: To achieve optimal DbD-based manufacturing, particularly for patient-specific cell therapies, the industry needs not only manufacturing processes that are vastly different from the traditional methods of manufacturing biologics, but also ones that are vastly different from even the current standard of cell therapy manufacturing. In order for the cell therapy industry as a whole to truly become commercially viable, we must envision and develop the "factory of the future." What does that look like? Ideally it is a manufacturing facility in which processes are in controlled, non-classified (CNC) spaces, with concurrent adjacent processing of patient lots. This leads to a highly mitigated risk of both human error and of cost impact due to idle capacity. An ideal facility will also have a robust, secure supply chain, a minimal set of unit operations to execute the process, and a very low failure-to-deliver-therapy rate.

Cell therapy manufacturing must move largely away from the cleanroom model and be sent to the "back of the facility," into production spaces more suited to high-volume production as described. That is not to say that cleanrooms have no place in cell therapy; they certainly do — at least for now. However, any time that automation, integration, and closed processing systems can result in steps whereby one entire cleanroom need not be dedicated to one process for one patient at a time, your bottom line will likely be in better shape for the effort.

**Q: What should cell therapy developers keep in mind as they choose a contract manufacturing partner?**

**A:** Cell therapy developers should thoroughly investigate the candidates when transferring from an in-house facility or partner (such as an academic center) to a manufacturing partner. They should look at technical expertise (Do they have experience with my specific cell type, with specific manipulations and with manufacturing development? Do they offer a broad range of technology solutions? Are they simply playing a "me too" game?); experience (What manufacturing challenges have they overcome for their clients? Do they have the experience and facilities required to meet all FDA standards?); and the process of collaboration (Are they willing to be flexible? Is there a two-way flow of communication?).

What cell therapy developers need in a partner is an organization willing to think outside the box while meeting established phase-appropriate quality standards, offer custom solutions, and find improvements which can be integrated at the right times over the course of clinical development to make their process more efficient, more cost effective, and more sustainable. A developer and its manufacturing partner should share the goal of bringing their cell-based therapy to market with a manufacturing process that best positions the product for long-term commercial success.◆

## REFERENCE

1. Alliance for Regenerative Medicine

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# Technology & Services Showcase

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# NON-CANNABIS THERAPY

## Cannabinoid Therapy Without Using Cannabis: Direct Effects™ Topical β-Caryophyllene

By: Ronald Aung-Din, MD

### THE CONTROVERSY OF MEDICAL CANNABIS

Cannabis is arguably the most controversial of known therapeutic entities. No class of compounds is associated with more controversy and stigma. While its benefits have been known for thousands of years, dating to ancient civilizations in China and Egypt; and, while it was at one point widely marketed and prescribed in traditional medical practice in the United States in the 1800s, it remains to date identified by the DEA as Controlled Substance Category 1 along with heroin: "highly addictive and of no medical use." Nonetheless, US Patent No. 6630507 was granted in 2003 to the US Department of Health and Human Services for use of cannabinoids to treat a wide range of diseases. It claims exclusive rights for using cannabis to treat Alzheimer's, Parkinson's disease, stroke, and other states of oxidative stress.[1]

In late1890, Eli Lilly and Parke-Davis joint-ventured to breed Cannabis Americana in Greenfield, IN, as alternative to Cannabis Indica. On August 2, 1937, after the lifting of alcohol prohibition, Congress made cannabis illegal.[2]

In view of many documented medical benefits of cannabinoids, but with widely persisting regulations, misinformation, and stigma associated with cannabis, it was appropriate to search for a non-cannabis-derived source of cannabinoid therapy, such as found in β-Caryophyllene.

### A COMMON NON-CANNABIS-DERIVED CANNABINOID RECEPTOR AGONIST

Caryophyllene is a natural constituent of many essential oils, especially those of clove, rosemary, hops, and Cannabis sativa. Caryophyllene is one of the chemicals responsible for spiciness of black pepper. It is considered a dietary cannabinoid.[3]

To what extent Caryophyllene modulates inflammatory and other therapeutic processes in humans via the endocannabinoid system, ECS, is not known. Caryophyllene does not bind to centrally expressed cannabinoid receptors type-1 (CB1) or exert psychoactive effects. Caryophyllene was first synthesized in1964.[4]

Of naturally occurring sources, West African black pepper (Piper guineense) has the highest concentration of caryophyllene in essential oil at 58%.Others are as follows:

- Cannabis, Hemp, Marijuana (Cannabis sativa): Up to 38% of Cannabis Flower Essential Oil
- Cloves: 20%
- Hops: 15%
- Basil: 20%
- Oregano: 16%
- Black Pepper: 7%
- Lavender: 5%
- Rosemary: 8.3%
- True Cinnamon: 11%

## CARYOPHYLLENE IN CANNABIS

Caryophyllene is the major component of the essential oil in Cannabis. Cannabis contains over 400 different secondary metabolites, including over 65 cannabinoid-like natural products. Δ9-tetrahydrocannabinol (THC), Δ8-tetrahydrocannabinol, and cannabinol are reported to activate cannabinoid receptor types 1 (CB1) and 2 (CB2). Essential oil component caryophyllene also selectively binds to CB2 receptors, thought responsible for cellular activation and for anti-inflammatory effects.[5]

Psychoactive cannabinoids from Cannabis sativa L. and arachidonic acid-derived endocannabinoids are non-selective natural ligands for the cannabinoid receptor type 1 (CB1) and CB2 receptors. The CB1 receptor is responsible for psycho-modulatory effects whereas activation of the CB2 receptor presents potential therapeutic strategy for treating inflammation, pain, atherosclerosis, osteoporosis, and other conditions.

Caryophyllene is therefore a cannabis-derived functional CB receptor ligand with a different structure from classical cannabinoids. It represents a different type of CB2 receptor-selective agonist. Cannabis extract (Sativex) was approved in Canada for treatment of neuropathic pain in multiple sclerosis. Caryophyllene, as major constituent with significant cannabi-mimetic effects, may be contributing to the observed therapeutic effects of cannabis preparations, including Sativex.

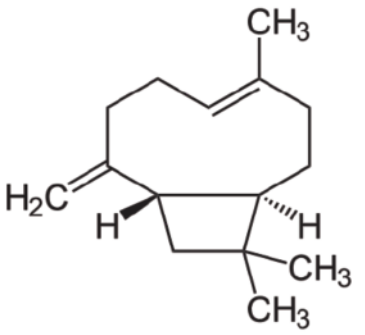
## CARYOPHYLLENE EFFECTS ON CANNABINOID RECEPTORS

Jürg Gertsch and others in 2008 reported plant-derived β-caryophyllene selectively binds to CB2 receptors and is a functional CB2 agonist. They provided evidence it exerts cannabi-mimetic effects in vivo by reducing inflammatory response in wild-type mice but not in mice lacking CB2 receptors. β-caryophyllene was identified as a functional non-psychoactive CB2 receptor ligand and as an anti-inflammatory cannabinoid in cannabis.[6]

In addition to the wide range of CB1 receptor-mediated physiological effects on the central nervous system, CNS, different cannabinoid ligands have been reported to modulate immune responses. CB2 receptor ligands have been shown to inhibit inflammation and edema, exert analgesic effects, and have a protective role in ischemia-reperfusion injury. In the gastrointestinal tract, CB2 receptor agonists have been shown to prevent colitis by reducing inflammation. The CB2 receptor has been described as a potential target for the treatment of atherosclerosis and osteoporosis. Consequently, CB2 receptor-selective agonists, being devoid of psychoactive side effects typically associated with CB1 receptor activation, are potential drug candidates for a wide range of different disease states.[7]

β-caryophyllene is commonly ingested with vegetable foods, particularly black pepper. Accordingly, adequate daily intake of caryophyllene could potentially modulate inflammatory and other pathophysiological processes via the endocannabinoid system and help maintain health. The potential of β-caryophyllene in both human and animal health needs further investigation as much of the focus of cannabinoids has been on cannabis and cannabidiol, CBD. As a selective agonist of cannabinoid receptor type-2 (CB2), caryophyllene has been shown to exert significant cannabi-mimetic anti-inflammatory effects. Anti-nociceptive, neuroprotective, anxiolytic, antidepressant, and anti-alcoholism activities have also been reported in vitro and in rodent studies.[8]

**FIGURE 1**

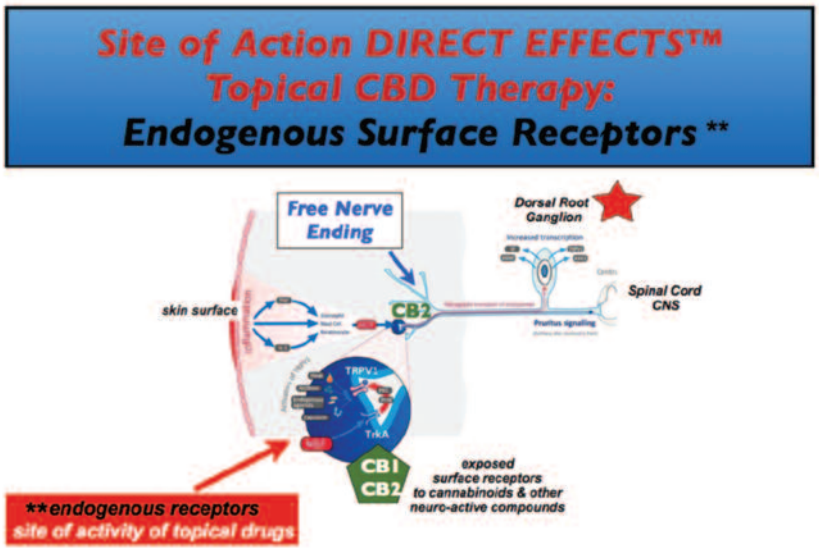



**β-Caryophyllene**

In view of its potential therapeutic effects as a cannabinoid receptor agonist, β-Caryophyllene was studied in DIRECT EFFECTS™ Topical Therapy for treating a number of neurological and neuropsychiatric conditions. The efficacy of this unique non-systemic therapeutic modality has been well established using both traditional neuro-active pharmacological compounds, such as apomorphine, sumatriptan, tizanidine, phentermine, 4-amino pyridine, and others; as well as with the therapeutic cannabinoid cannabidiol, CBD, found in cannabis and hemp.[9-12]

USPTO, EU, and Australian patents covering DIRECT EFFECTS Topical Therapy have been granted covering several compounds and associated disease states: (European Patent Office No. 1435945 and USPTO No. 12/460,966 for Topical Migraine Therapy; USPTO No. 8,592,424

## FIGURE 2




granted 11/26/2013 for topical nuchal dopamine agonist (apomorphine) therapy for Parkinson's disease, dystonia, torticollis, and tremors; USPTO No. 8,883,830 for use of topical tizanidine for migraine and tension headache, muscle sprains and spasms, spasticity, and similar conditions. Likewise, as a result of compelling clinical data, USPTO and PCT patents have also been filed for DIRECT EFFECTS topical therapy using cannabinoids.

## DIRECT EFFECTS™ TOPICAL CANNABINOID THERAPY

DIRECT EFFECTS Topical Therapy describes the drug delivery technology in which compounds and drugs are applied to skin surface as a cream or gel in an appropriate epidermal-penetrating medium to activate surface receptors on cutaneous-free nerve-endings for therapeutic benefit. Binding of therapeutic agonists to their respective endogenous receptors on the cell surface of nerve-endings causes modulation of afferent neural impulses to the central nervous system (CNS), providing therapeutic effects.

Figure 2 shows the presence of surface receptors to endogenous agonists and other neuro-active compounds on cutaneous nerve-endings under the stratum corneum. Free nerve-endings are peripheral end-components of spinal dorsal root ganglia, which function as neural relay stations between the peripheral nervous system (PNS) and CNS.[13]

Figure 3 shows various receptors that exist on the cell surface of free

nerve-endings and their respective therapeutic agonists that bind to provide therapeutic benefit.

CB1 and CB2 cannabinoid receptors are present on free nerve-endings as part of the endocannabinoid system (ECS). These can be activated by topical cannabinoid therapy to provide therapeutic benefits. DIRECT EFFECTS topical CBD has shown benefit in the following conditions in a study of 88 patients in an out-patient neurology practice (Table 1).

As β-Caryophyllene also activates cannabinoid receptors, it was formulated for use as DIRECT EFFECTS Topical Therapy. The resulting white product with slight aroma of cloves easily dissolves into skin within a few minutes of application following gentle rubbing.

## RESULTS

Topical Therapy with β-Caryophyllene, Cari-Derm, 30 mg applied to the back of neck (BOTN) or to the spinal regions elsewhere where affected, and at peripheral areas of neurological dysfunction, provided relief and benefit for the following conditions within 10 to 15 minutes of topical application:

- Anxiety Disorder
- Attention Deficit Disorder, Poor Focus
- Social Isolation, Autism-Related Symptoms
- Muscle Tension & Spasm
- Seizures & Associated Encephalopathy
- Headache

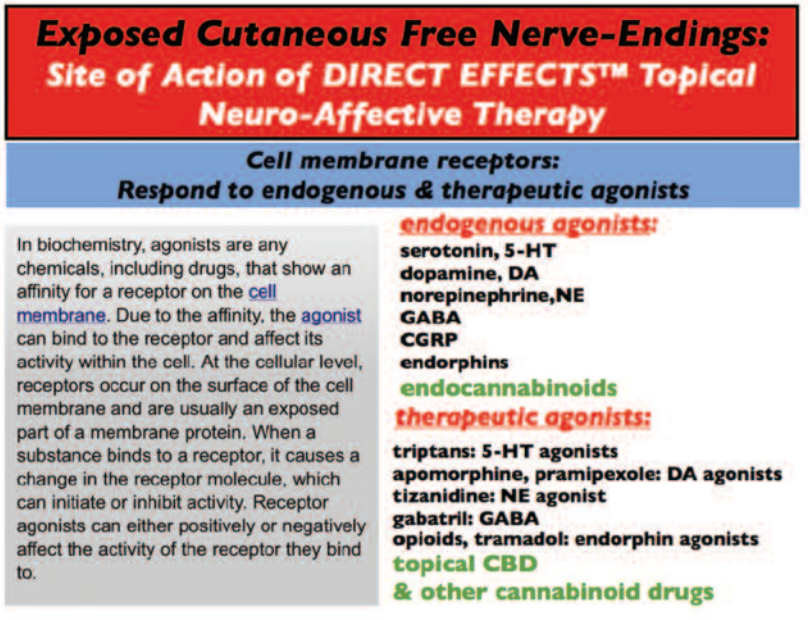
## TABLE 1

| Topical CBD-Treated Conditions in Neurology Clinical Practice |
|---|
| Seizures |
| Encephalopathy (including Lethargy, Attentional Problems & Cognition |
| Spasticity |
| Weakness |
| Pain (including Radiculopathy & Neuropathy) |
| Numbness |
| Anxiety & Other Mood Disorders |
| Hypertension |
| Parkinson's Disease |
| Insomnia |
| Bell's Palsy & Facial Nerve Dysfunction |
| Trigeminal Neuralgia |
| Hemi-Facial Spasms |
| Autism/Asperger's |
| Attention Deficit Disorder & Hyperactivity |
| Social Isolation |
| Anxiety & Mood Disorders |
| Occipital Neuralgia |
| TMJ Dysfunction-Related Symptoms |
| Cognitive Problems (including Memory Disturbance) |
| Peripheral Neuropathy |

"DIRECT EFFECTS Topical Therapy describes the drug delivery technology in which compounds and drugs are applied to skin surface as a cream or gel in an appropriate epidermal-penetrating medium to activate surface receptors on cutaneous-free nerve-endings for therapeutic benefit. Binding of therapeutic agonists to their respective endogenous receptors on the cell surface of nerve-endings causes modulation of afferent neural impulses to the central nervous system (CNS), providing therapeutic effects."

- Peripheral Neuropathic Pain & Symptoms, Including Post-Herpetic Neuralgia/Zoster
- Tinnitus/Ringing in Ears
- Sinus Congestion
- Skin Inflammatory Conditions (ie, Actinic Keratosis)
- Torticollis, Dystonia
- Arthritis-Related Pain & Decreased Range of Motion
- Dizziness & Light-Headedness
- Trigeminal Neuralgia
- Blepharospasm

**FIGURE 3**




Duration of therapeutic effect ranged from a few hours to an entire day, depending on condition treated; and its severity and duration. The only side effects expressed were occasional tingling and slight transient burning sensation following topical cream application. There was a rare headache. Rash or irritation at the site of application was experienced in less than 5% of patients treated. Many patients continue to use topical caryophyllene (Cari-Derm) on a regular long-term basis without significant problems. In particular, because of its non-systemic nature, no systemic side effects or drug-drug interactions were observed.

## CONCLUSION

Direct Effects Topical Therapy with Non-Cannabis-Derived CB2 Cannabinoid Receptor Agonist β-Caryophyllene provides therapeutic benefits similar to those observed with the cannabinoid, cannabid

iol (CBD). Sourced from other than cannabis and hemp, which remain controversial and regulated in some areas of the country and the world, caryophyllene provides means for cannabinoid therapy without restrictions or associated stigma. It uses readily available natural sources of cannabinoids in the form of caryophyllene. Further, in using Direct Effects Topical Therapy for delivery, potential systemic side effects and drug interactions are avoided, as observed with other compounds similarly used.[14]

In addition, as has also been observed with CBD, topical caryophyllene may be combined with a traditional pharmaceutical agent, such as apomorphine, milnacipran, 4-amino pyridine, tizanidine, sumatriptan, and others to capitalize on the concept of Cannabinoid Augmented Neuro-Therapeutic Effect in DIRECT EFFECTS Topical Therapy. This is a process wherein a synergistic therapeutic process occurs when a cannabinoid, such as CBD or caryopyllene, is mixed with a traditional pharmaceutical agent as a combined topical product to treat a specific medical condition. The combined therapeutic effect of the two agents is greater than that of each individually, suggesting synergism. This effect has been observed in treating neuropathic pain, headache, muscle spasm, spasticity, tremor and other movement disorders; as well as mood disorders, such as anxiety and panic attacks.◆

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## BIOGRAPHY

**Ronald Aung-Din, MD,** practices General Neurology and Neuropsychiatry in Sarasota, FL. He is one of few neurologists among the less than a hundred physicians in FL who are currently certified and actively prescribing medical cannabis for their patients through the state's Department of Health Compassionate Use Registry. In addition to active private clinical practice, Dr. Aung-Din has functioned as Principal Investigator in over 60 clinical trials through his affiliation with Lovelace Research Institute, Albuquerque, NM, helping bring to market drugs in Epilepsy, Multiple Sclerosis, Neuropathic Pain, and Parkinson's Disease. In May 2009, Dr. Aung-Din founded AfGin Pharma, LLC, a research and development biopharmaceutical company dedicated to Direct Effects Topical Neuro-Affective Therapy, a novel non-systemic delivery of neuro-active compounds useful in treating neurological and neuropsychiatric conditions. The therapy is unique in that rapid (within 10 to 30 mins) therapeutic results are achieved without usual systemic side effects and drug interactions as the bloodstream is not involved in the therapeutic process. To date, 7 patents relating to the technology have been granted by USPTO and the EU and Australian patent offices. Several other patents are filed and pending. For additional information, please contact Dr. Aung-Din at aungdinmd@afginpharma.com or visit www.aungdinmd.com or www.afginpharma.com.

Drug Development
EXECUTIVE

Julian Aleksov
Executive Chairman
Oasmia Pharmaceutical

# Oasmia Pharmaceutical: Commercializing Technologies While Pursuing the US Market

Oasmia Pharmaceutical AB develops new generations of drugs in the field of human and veterinary oncology. The company's product development aims to create and manufacture novel nanoparticle formulations and drug delivery systems based on well-established cytostatics which, in comparison with current alternatives, show improved properties, reduced side-effects, and expanded applications. The company's product development is based on its proprietary in-house research and company patents. Oasmia is listed on NASDAQ Stockholm (OASM.ST), Frankfurt Stock Exchange (OMAX.GR, ISIN SE0000722365) and NASDAQ Capital Markets (OASM.US). Julian Aleksov, Executive Chairman of Oasmia Pharmaceutical, recently spoke with Drug Development & Delivery about the company's efforts to enter the US market, its strategy to increase commercial adoption, and why it believes its underlying drug delivery system technology is significant not only within the oncology sector, but the entire pharmaceutical industry.

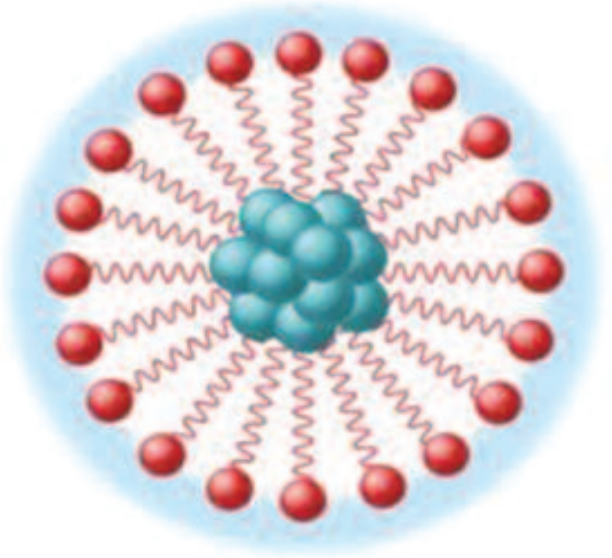
**Q: Can you please provide an overview on Oasmia Pharmaceutical?**

**A**: Headquartered in Uppsala, Sweden, Oasmia Pharmaceutical AB develops, manufactures, markets, and sells new generations of drugs in the field of human and veterinary oncology. The company's product development aims to create and manufacture novel nanoparticle formulations and drug delivery systems based on well-established cytostatics which, in comparison with current alternatives, show improved properties, reduced side-effects, and expanded applications. The company's product development is based on its proprietary in-house research and company patents. Currently, the company has multiple technologies in its pipeline spanning early stage cancer treatments as well as a commercialized product Paclical (alternatively branded Apealea) currently in use in Russia, the CIS, and other countries.

**Q: While many companies seek alternative treatments to chemotherapy, why did Oasmia choose to work on improving existing chemo technology?**

**A**: There are very few, if any, new single-treatment drugs on the market within oncology, as most new drugs are combination treatments used in concert with chemotherapy. There have also been very limited developments of widely used chemotherapy drugs, as most medical personnel have become accustomed to existing treatments, and the barriers to market approval for private and public companies remain significant. With all this considered, the sales of chemotherapy products are still a very sizable segment within the largest segment in the pharmaceutical industry, oncology.

For Oasmia, we believe in the basic fundamentals of chemotherapy. We have focused our efforts upon improving combination therapy treatments that may benefit from an improved underlying drug delivery platform, making chemotherapy more efficient, enabling higher doses and shorter treatment cycles, ultimately improving patience convenience and success



**At Oasmia, we have developed a type of nanotechnology where insoluble substances are contained within a nano-sized water soluble enclosure, a so-called micelle.**

**Q: What is Oasmia's underlying XR17 (drug delivery system) technology, and why is it applicable to all forms of pharmaceutical treatment?**

**A:** It has been reported that approximately 65% of the R&D pipeline in the pharmaceutical industry has solubility difficulties, obviously a quite common challenge. XR17 is Oasmia's proprietary excipient that transforms novel or existing un-soluble molecules into water-soluble nanoparticle formations that are instantly released in the blood stream without added solvent, resulting in shorter infusion time and no pre-medication for the patient. This innovative approach also allows for multiple cytostatics to be given in a single infusion, as opposed to a traditional process that would usually require two or more infusions. XR17 is the excipient of Oasmia's human oncology treatment compound Paclical, as well as Oasmia's formulation of doxorubicin for veterinary use, Doxophos Vet and Paccal Vet®.

While the drug delivery system poses significant potential in the oncology sector, Oasmia believes the platform's benefits can be experienced by many more forms of treatment within the broader pharmaceutical industry. The technology can be tailored for the administration of many treatments, as the greater solubility issue is not exclusive to just cancer treatment.

"While the drug delivery system poses significant potential in the oncology sector, Oasmia believes the platform's benefits can be experienced by many more forms of treatment within the broader pharmaceutical industry. The technology can be tailored for the administration of many treatments, as the greater solubility issue is not exclusive to just cancer treatment."

**Q: Oasmia is new to the US, can you explain the importance of identifying a long-term marketing and distribution partner?**

**A:** Of course, the US pharmaceutical market is widely considered the greatest in size, but the FDA approval process is considered the most stringent in terms of reaching its market. For Oasmia to achieve global adoption, the road will eventually lead to the US at some point. We believe that our efforts now make our long-term strategy even stronger.

Currently, Oasmia's main focus is on developing and producing our product pipeline, and because the company is not based in the US, we are looking to find a partner that already has the knowledge and infrastructure to execute the sales and marketing functions needed to succeed in this tremendous market.

**Q: Can you highlight the benefits and challenges to having international commercialization but seeking FDA and EMA approval?**

**A**: The Europe Medical Agency (EMA) and even more so, the Food and Drug Administration (FDA), have the highest demands for products and manufacturing in the world. Because of this, their approval is recognized by almost all other countries. While the respective processes for both the EMA and FDA are a challenge to complete, this pending approval would leave us well positioned to market our products almost everywhere, as only China and Japan have different legislations and require additional data on their native population.

With our first product Paclical/Apealea already approved in Russia and CIS countries, we have met all clinical end points that were originally requested by both the EMA and FDA. We filed with the EMA in February 2016, and anticipate filing with the FDA within the coming 6 months, at which point we will use the clinical end points as the basis for our submission.

**Q: What are the next steps for Oasmia Pharmaceutical?**

**A**: For our first product, Paclical/Apealea, the next steps are to obtain approvals and find suitable commercialization partners worldwide. While Paclical/Apealea has been proven in ovarian cancer treatments, we are also committed to extending the label to include additional cancer indications.

Our other key priority is to finalize the clinical program for our second product, Docecal, a re-formulation of docetaxel, the most active substance in the cytostatic Taxotere, marketed by the global healthcare provider Sanofi-Aventis. Prior to the patent expiration in 2010, Sanofi-Aventis executed $3 billion in Taxotere sales in 2009. Taxotere – often used in combination with other anti-cancer medicine in the treatment of prostate cancer, breast cancer, lung cancer, gastric cancer, and head and neck cancer – has continued to perform, generating sales of $350 million in 2014, clearly demonstrating market demand for the product.

As previously mentioned, we are also working with licensing our nanoparticle platform XR17 drug delivery system so other companies within both the oncology and broader pharmaceutical industry can also take benefit of using it to solve their solubility issues. ◆

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# ASSAY VALIDATION

## Biomarker Assay Validations – A Time for Change?

By: John L. Allinson, FIBMS

### INTRODUCTION

Biomarkers have been used for many years in drug development and delivery for a wide range of clinical utilities, and throughout the past decade, their use has substantially increased. To accurately assess the measurement performance and characteristics and determine the range of conditions under which the biomarker will provide reproducible and accurate data, analytical methods for biomarkers must be validated. In 1991, the Food and Drug Administration (FDA) made new guidance available for bioanalytical method validation, which informed all laboratories doing bioanalysis how they should validate their scientific methods, its central focus being on methods for the evaluation of Pharmacokinetics (PK) – [Guidance updated 2001 & 2013 (draft)]. Since that time, it has been the "holy grail" for almost all researchers working in this scientific arena. However, it has also been used by many laboratories in the same way for validating biomarker assays for drug discovery and development. Recently, there has been considerable debate within the community over whether the guidance is applicable or best scientific practice to areas outside of PK evaluation. The following explores these debates and consider whether it is time to re-evaluate the requirements for biomarker assay validation.

### WHAT IS A BIOMARKER?

The World Health Organization (WHO) defines a biomarker as, "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."[1] In practice, biomarkers include tools and technologies that ultimately help to build an understanding of the prediction, cause, diagnosis, and progression of disease and the outcome of treatment.[2]

Molecular biomarkers can take many forms and have become a pivotal tool in basic and clinical research as well as in clinical practice. In today's research environment, the use of biomarkers for many different clinical utilities in clinical trials has become widely accepted, and they are fast becoming an essential part of clinical development

### THE DRUG DISCOVERY & DEVELOPMENT LANDSCAPE

Almost 10 years ago, the pharmaceutical industry was facing a remarkably high attrition rate for drugs in clinical development. Multiple studies were reporting that clinical success rates across the drug industry could potentially be even lower than estimated previously.[3] Despite major advances in the basic science of drug discovery and development, which led to a substantial increase in the number of new drug targets, the development of novel effective therapies did not appear to be following the same upward trajectory. In 2006, it was estimated that only 8% of tested products entering Phase I trials gained regulatory approval, and many of these failures happened in late-stage clinical trials.[4] Additionally, very few drugs were making it out of the clinical research pipeline, and in 2007, the US FDA approved only 17 new molecular entities and two biologic licenses; the lowest number since 1983.[5]

The significant reduction in clinical success rates across the drug industry appeared to be caused by a gap in the industry's

ability to predict a drug candidate's early performance. To counteract the downturn in novel effective therapies, it was suggested that biomarkers, typically used to monitor therapeutic progress, disease progression, and the efficacy of interventions, could provide a solution. Biomarkers were considered attractive as they may predict drug efficacy more quickly than conventional clinical endpoints, and have the potential to substantially accelerate production development in certain disease areas. Furthermore, by identifying candidates that are likely to fail earlier in the process, biomarkers can lead to a reduction in drug development costs. As the mantra goes with drug development: if you fail early, you fail cheap.[6]

Biomarker assay requirements are designed before clinical trials commence, and a new drug would not be developed without simultaneously looking for biomarkers for efficacy, safety, and to measure the pharmacodynamics (PD) of the drug. Other utilities are also used (depending upon the mode of action of the drug for instance). The field of oncology is leading the way in the use of biomarkers in drug development, and their use as an alternative to clinical endpoints in drug development has meant that oncology has not experienced the same downturn in drug development that has been experienced by other therapeutic areas. However, many of the biomarker determinations in this arena are not performed using "wet" methods for quantitative assays in biological fluids.

## THE BIOMARKER VALIDATION CHALLENGE

Validation is the process of assessing the biomarker analytical method and its measurement performance characteristics, as well as determining the range of conditions under which the biomarker will give reproducible and accurate data.[7] The validation of biomarker analytical methods is a crucial step in the quest to deliver high-quality research data, and the criteria for validation are defined by the following:

- The nature of the question that the biomarker is designed to address
- The degree of certainty that is required for the desired answer
- The assumptions about the relationship between changes in the biomarker and clinical endpoints or other clinical utilities (eg, mechanistic, PD, etc)[8]

Although it is perfectly clear that method validation is a crucial step when using biomarkers, there is an absence of official guidelines for the validation of biomarker assays. Since the FDA 2013 Draft guidance was published, its content in relation to biomarker assays has been the subject of wide and contentious debate within the industry. This ultimately has culminated in inconsistent adaptations of related regulations in bioanalytical and clinical laboratories. It has been agreed for many years that there is a lack of standardization between laboratories. This was the original motivation behind the FDA releasing the FDA Guidance for Industry for Bioanalytical Method Validation [originally 1991, updated 2001 and 2013 (draft)], as mentioned. Essentially, these documents have driven forward improvements in the standardization of bioanalytical methods, and researchers continue to use the FDA (and other regulators) guidance(s) today.

This guidance provides assistance to

sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated drug applications (ANDAs), and supplements in developing bioanalytical method validation information used in human clinical pharmacology, bioavailability (BA), and bioequivalence (BE) studies requiring pharmacokinetic (PK) evaluation. This guidance also applies to bioanalytical methods used for non-human pharmacology/toxicology studies and preclinical studies.

However, although the guidance has undoubtedly proven beneficial, it only addresses critically the validation of assays to support PK assessments. Despite the document implying its limited scope (above) for purposes other than PK evaluation, many laboratories still continue to use the guidance verbatim, as it seems to have been interpreted that it is the only way that analytical methods should be validated. As the use of biomarkers for drug development accelerated and some researchers continued to use the FDA guidance, many clinical scientists were simultaneously questioning the extensive and confusing application of the terms "biomarker" and "validation," and whether this guidance was appropriate for biomarker analytical methods used in drug discovery and development.

## ADDRESSING THE CHALLENGES

Successful validation requires an understanding of exactly what an analytical method is doing and how it works. Once this is known, experiments can be designed to test the method and prove the performance of the assay. A further step that needs to be considered when utilizing biomarkers is the clinical validity of the results. Validation should demonstrate that a method is "reliable for the intended application." In 2000-2001, a group of scientists working under the auspices of the American Association of Pharmaceutical Scientists (AAPS) recognized that by following the FDA guidance for industry for the validation of Biomarker methods, we were often not able to answer the clinical questions being asked, nor ensure the delivery of the clinical utility of the biomarker being studied.

These scientists brought together by a Bioanalytical Focus Group of the AAPS wanted to publish a document to bring consensus as to how biomarker assays should be validated to ensure results obtained were clinically relevant. The outcome was a whitepaper titled Fit-for-Purpose Method Development and Validation for Successful Biomarker Measurement.[9] This was the first seminal document that had been published on this subject (specifically for drug development) that highlighted a number of issues that have also been recognized in other white papers published since then: the "potential need to step out of the framework of regulated bioanalysis guidelines" as it was important to: "keep in mind the intended use of the data and the attendant regulatory requirements associated with that use"

Ultimately, the whitepaper advised scientists how biomarker methods should be developed and validated when used in drug development as opposed to using them in diagnostics, to ensure that they were 'fit-for-purpose'. Many laboratories referred to this document and since Lee and colleagues published their whitepaper, the Global CRO Council (GCC) and European Bioanalysis Forum (EBF) also published papers on biomarker assay validation [10,11]. Overall, there has been a drive forward in the number of laboratories demonstrating ways in which they generate improved data, thanks to this documentation being available (GCC survey 2016 – unpublished data).

## TIME FOR A CHANGE

Despite an increase in awareness about biomarker assay validation, there are still multiple instances in which laboratories are obtaining incorrect, inaccurate, or variable results because they are following PK guidance documents for assay validation, which potentially can present a serious concern. The author has seen multiple examples in which biomarker results data has been generated that was incompatible with life, or inaccurate data has been produced that would lead to a false interpretation of the results from a clinical perspective. This is not good (nor acceptable) to the company developing the drug or the subjects participating in the clinical trials. This of course not only demonstrates the shortfalls of using a PK assay validation document for biomarker methods, but also that some bioanalytical laboratories do not have scientists with clinical knowledge that is crucial in the biomarker field. This is one of the reasons why understanding physiology and clinical biochemistry is so important to ensure that reliable and appropriate biomarker results data are generated using methods validated to appropriate standards.

By way of an example of one of the major issues from a clinical and scientific standpoint in using the PK guidance is that no weight is given to the different physiological changes seen in different biomarkers, nor the different performance characteristics of different methods when

we set acceptance criteria for QC samples used when analyzing patient samples. The degree of change seen in different biomarkers is often specific to each biomarker from a clinical significance perspective – they are not all the same. For example, of ~400 biomarkers that are well characterized and understood, intra-individual variability in normal subjects range from <1% to >90%. Using PK guidance, however, the acceptance criteria for all the biomarkers using the same technology would be the same (eg, LC-MS/MS +/- 15% to 20%, and Immunoassay +/- 20% to 25%). Not only does this not make clinical sense, but it doesn't add up statistically either because different analytical methods –even within the same technology – perform differently, and yet, the known analytical performance (from the validation experiments) is not being taken into account when setting acceptance criteria for QCs in sample batches. If acceptance criteria was primarily based on known method performance, this would prove methods are working as they should be but also give confidence limits around the results being reported, aiding statistical and clinical interpretation. In summary on this point, the concept of statistically valid Quality Control does not exist if we follow the guidance, and clinical relevance is not covered in any way in determining if the method is fit for its intended purpose.

Discussions surrounding the topic of biomarker assays and validation continue to grow, and throughout the past 12 or more months, the industry has begun to speak out on the subject of biomarker assay validation in a unified way. In September 2015, the FDA and AAPS organized Crystal City VI, called in response to the previous meeting (Crystal City V).[12] At Crystal City V, a revised version of FDA guidance published in 2013 was discussed. The document was a source of concern and disagreement from those involved in biomarker science, due to the content and also the recommendations within the paper with regard to biomarker assay validation guidance. At Crystal City VI, some very central points were raised.[13] However, the major point that was raised by several key opinion leaders was that biomarker assays differ from PK assays, meaning that they should be validated in a different way. It was agreed that when using biomarkers for drug development and delivery, several important points should be considered (Table 1).

Crystal City VI appeared to be the first time there had been a major shift in momentum. It appeared that scientists were willing to speak out in a unified voice, and a large majority were giving the same message; it was time for a change to the current guidance. Crystal City VI was followed by a number of additional meetings (WRIB April 2016, AAPS-NBC May 2016, and EBF BM workshop June 2016), featuring discussions that expanded on the points raised, and questioned how we go about moving forward. Industry key opinion leaders (KOLs) are now at a point where they have identified and are in consensus that there are numerous issues that need to be addressed, and in order to do so, it would be beneficial for a different guidance document to be considered. The significant question within the industry now is how do we move forward?

The limited scope within the existing guidance for purposes other than PK evaluation and increasing use of biomarkers for drug discovery and development means we are now at a time at which, in my opinion, a change in industry guidance for biomarker assay validation is essential.

## THE FUTURE OF BIOMARKER VALIDATION

Despite the increased use of biomarkers, it appears that many researchers are still continuing to use the FDA guidance document for validation even though it only critically addresses the validation of

**TABLE 1**

| |
|---|
| Considerations not required by PK assays in relation to physiology are important for biomarkers intended for drug development and delivery. |
| Endogenous quality controls are required to monitor the measurement of the actual biomarker rather than solely trusting recombinant/synthesized compounds. |
| Proof of how the endogenous molecule behaves in the method is required to validate its appropriateness for use. |
| Verifying the endogenous molecules properties as you would with stability is extremely important. |
| Important to study the physiology of biomarkers of interest to learn more about them at an early stage, which helps understand the method performance requirements for the methods used to quantify them. |

**Important points to consider when validating biomarkers for drug discovery & development**

assays to support PK evaluation and also has a limited scope described within the document in terms of studies where it should be used.

There have been a number of clinical studies in which the data obtained has been unrepresentative and incorrect because the bioanalytical lab has followed PK guidance to validate their bioanalytical methods. This is extremely concerning and highlights the importance of ensuring that laboratories conducting research have a real investment in terms of the right team, who understand the clinical questions being asked, and have the know-how to develop and validate methods that will answer the necessary questions.

As researchers, our aim is to follow the principles of good science, and to ensure that the results obtained are clinically robust and relevant. The use of biomarkers for drug discovery and development is a hot topic within the industry, and the FDA guidance has been questioned on many occasions in relation to its use for the validation of Biomarker assays. Now is the time to listen to the questions that have been raised and work toward an updated recommendation from industry KOLs who hopefully regulators will consider in developing revised guidance documents that will improve the reliability of biomarker results and ultimately benefit overall advances in healthcare in assisting the development of new drugs. ◆

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## BIOGRAPHY


**John L. Allinson** is the Head of Biomarker Strategy of LGC and brings over 40 years of experience in developing and working with biomarkers, including their use in drug development across all therapeutic categories and phases of development. Before joining LGC, Mr. Allinson spent 22 years in NHS Clinical Pathology services before moving into the CRO industry, where he managed Central, Bioanalytical, and Biomarker Laboratories at a number of CROs. He was part of the AAPS Ligand Binding Assay Bioanalytical Focus Group (LBABFG) Biomarker Committee, which published the first consensus white paper on biomarker assay validation requirements in Drug Development, and was also co-author of the recently published first white paper on the Validation of Multiplexed Biomarker assays. He has been an invited presenter at over 50 international conferences and continues to present an educational workshop on Biomarker Assay Method Development and Validation at the World Biomarker Congress.

# CLINICAL RESEARCH

## Behind the Wave: Clinical Research in a Digital Transformation Era

By: Kai Langel

### INTRODUCTION

Over the past few years, many well-established industries have seen rapid and disruptive innovations. Some say this transformation began with the internet, which allowed faster information sharing all over the world. Others argue that the Apple iPhone fueled this change by putting mobile connectivity into the pockets of consumers. These technologies allowed service innovations that earlier would have sounded far-fetched. Who would have guessed just 10 years ago that AirBnB would enable consumers to compete with huge hotel chains? Or that Uber drivers can now compete with taxis? Meanwhile, many traditional industries like printing, paper photography, and entertainment have had to reinvent themselves in order to survive.

While this digital transformation wave is changing the world, what has changed in the clinical trial model? Not much. Sure, some forward-thinking companies use online recruitment as a mechanism to attract more patients into trials. However, the "innovation" often ends with the interested candidate clicking on a web link where they are told to call to learn more. For the consumer accustomed to working online, this can be a disappointing user experience.

Perhaps even more discouraging is the fact that study sites often deal with the same problems they have long had. Granted, we're no longer shipping laptops to sites loaded with data capture technology, but shipping handheld devices, smartphones, and tablets to sites remains common practice. Additionally, sites still rely on several complicated systems with overlapping functionality that all have different usernames and passwords and that require the same information to be keyed in over and over again. These problems also extend to the sponsors who do not have access to real-time information, spend hundreds of hours


reconciling data streams from different systems, and have little information available to proactively manage their clinical research to avoid delays and operational issues in the study.

The remote research model and purpose-built technology offer the tools and the right process to help modernize clinical research and bring it closer to the high standard set by today's consumer technologies. The following will address key aspects of the model and technology from the perspective of the different stakeholders in a clinical trial: the patients, the sites, and the sponsors.

### PATIENT-CENTRIC VIEW

Patient-centricity is certainly one of the hottest buzzwords in the pharmaceutical industry today. Many companies are taking concrete action, and these efforts are further fueled by regulators. For example, the US Food and Drug Administration created a Patient-Focused Drug Development Program and has been vocal about patient-centricity in drug development. Many companies use patient focus groups to gain insight. Several companies have even developed patient-centricity toolkits with software and service offerings that study teams can utilize in their own programs.

However, before anyone can claim they are delivering patient-centric clinical development programs, they must truly understand the views of the patients.

Clinical research is typically conducted by highly educated people who have an in-depth understanding of the medical condition in question and the mechanism of the drug being researched. They understand the evidence that regulators expect in order for the new product to be approved. But do they understand the patient perspective? In reality, because of the way randomized clinical trials are conducted and because of patient privacy requirements, the sponsor's study teams may rarely speak with patients.

So what options does the sponsor team have to hear the patient's voice? While focus groups can be good and provide a bi-directional mechanism to discuss issues with patients to obtain qualitative input, they are limited. They often provide a small demographic sample size, are impractical for global trials, and by nature, only provide a snapshot view rather than a continuous feedback loop.

A patient-engagement technology solution can address these issues. As a trusted third-party solution, eClinicalHealth's Clinpal platform can facilitate a purpose-built patient community globally that can be continuously engaged during study design, recruitment, and conduct, ensuring that patient feedback is part of the end-to-end process. Such a platform, combined with the reach of online and social media, can be put into place quickly in a global setting to gather insights from hundreds of individuals of different cultures. Also, because potential candidates are accustomed to regular online communications (nearly three-quarters of US internet users look online for health information) new technology makes it even more easy for patients to become engaged.[1]

The patient feedback loop can be implemented in a completely remote setting, but it does not need to end there. Nearly any study can use technologies such as Clinpal to make trials more convenient and efficient for patients. Furthermore, patient recruitment is part of the consenting process, which can be supported with technology as well by using online advertising and patient- engagement technology to reach out to potential candidates. This can aid online referral processing, supported by an interactive patient dashboard with status information, study documents, and secure messaging functions. Study candidates learn about the study through remote access to the patient information sheet or even through a completely electronic informed consent, where the candidate can electronically sign the document before the first study visit. Patients and sites both benefit by:

- Avoiding unnecessary and sometimes inconvenient in-person study visits
- Enabling the patient to dedicate more time learning about the study and discussing it with family members without feeling "rushed" during a site visit
- Making study visits more efficient for all because study details are already understood by the candidate before the first visit
- Improving compliance and speeding study conduct: A remote trial conducted with Clinpal showed an 18% improvement in compliance and a 22% faster completion time[2]

Another excellent tool for improving patient engagement in clinical trials is to give patients access to their own data. In the remote VERKKO study, a Phase IV clinical trial for diabetes, patients had access to a logbook view of glucose readings they took using a smart, wireless glucose meter. The logbook indicated when readings were done at the right times and what the values were. Once they completed the required number of readings, they had access to a full report that showed their disease state at the various daily time points.[3] When patients understood the study protocol and expectations and were provided with information about how they were doing, they could manage their own compliance, which was likely a key factor in the improved compliance and faster completion time.

Patient involvement and feedback should be a process, not a milestone. Patients can be engaged at strategic points during the trial by inquiring about their satisfaction and requesting suggestions. For example, at the end of the enrollment process, patients not enrolled could be asked the key reasons they did not take part. Patients who were enrolled can be asked how they feel about the upcoming study and also asked if they have any questions.

Using a trusted third-party system, this process can involve patients directly without burdening the study sites. This process was used in the VERKKO study: Patients shared information willingly and provided meaningful insights. In this case, patients suggested improvements to patient-facing instructions as well as some things that would have made participation more convenient. Several patients also shared feedback about products and how these relate to their lives.

## THE SITES' PERSPECTIVE

Many study sites suggest that clinical trials are becoming more time consuming and cumbersome, concerned about the time spent on administration rather than on core study activities, such as working with patients and assisting with clinical procedures required by the protocol. Study resourcing can also be challenging.

Remote trial methodologies address many of these issues. While enabling patients to conduct more of the study activity remotely does not necessarily mean less work, it does mean the work can be conducted more flexibly. For example, patients with access to convenient and remote messaging tools are more likely to interact with the site than if they must rely on study visits or restricted telephone hours. These patients also will expect prompt responses. However, the work of responding to patients can be distributed to several parties as it is no longer tied to physical location or time. First-level patient communications can be delegated to a call center, for example, which can triage requests and work with sites when the issue calls for the sites' involvement. These duties can also include routine patient compliance monitoring and contacting those who need extra support.

In this way, remote trial technology can significantly reduce sites' workload, allowing them to enroll more patients with the on-site resources they have. In the aforementioned remote VERKKO study, the study nurse reported that overall patient management required only one-third the effort necessary in a previous study with a similar protocol. Dr. Vehkavaara, the VERKKO study investigator, concluded, "This study was the most convenient clinical diabetes trial I have ever participated in."

Remote clinical trial technology and processes are not a threat to traditional clinical trial sites and study coordinators. Instead, they enable sites to conduct studies more efficiently, allowing them to take part in more trials and enroll more patients with existing resources. Furthermore, study coordinators will likely find their role more meaningful as the administrative burden is decreased and they have better tools to communicate with and get direct feedback from patients.

## OPPORTUNITIES FOR STUDY SPONSORS

Clinical trial sponsors are often driven by factors involving time, cost, and quality. Let's evaluate the benefits of remote trial methods from the perspective of these three items.

### Time

Time-to-market is critical in the pre-approval stage of a clinical program. Time spent on study conduct eats into patent protection time; beating the competition to the market is essential or the whole drug approval might be at risk. There is often very little that can be done to compress the timeline defined by the protocol; however, there is much that can be done during the study design, start-up and recruitment phases to incorporate patient insights and speed up the overall trial timeline. While there is often much focus on the first-patient-in date in a clinical trial, the more important date is the last-patient-in date, which often determines the trial's end date. Remote methodologies can help get studies to this point faster by making start-up, recruitment, and communication more efficient.

In the post-approval phase when the product is already on the market, it is vital for companies to support the product launch with more data. Post-approval studies are often required, and there are market research and data demanded by payers for pricing and reimbursement. By deploying remote studies, companies can launch these time-critical post-approval studies quickly. Because they utilize flexible technology rather than manual site-based procedures, these remote post-approval studies can also be adjusted rapidly. Online advertising outreach, electronic informed consent, and remote data capture processes are key tools these remote technologies use to engage large populations quickly.

### Cost

Remote trials are cost-efficient and very scalable, making them even more attractive for large observatory, real-world trials. Many of the key aspects that remote trials address are also some of the biggest ticket items. Patient recruitment and site start-up costs can be decreased by a remote model in any phase of drug development. However, the optimal fit for the remote model is really in the population-level or registry trials that often involve tens of thousands of patients. These trials can benefit from a high degree of automation that minimize the touch points with sites; even very small process improvements can mean huge reductions in the overall study cost.

Single-platform technologies that can support the entire trial conduct can also drive costs down by minimizing data discrepancies and decreasing overall cost of ownership when compared to the typical disjointed IT infrastructure utilized in studies.

### Quality

As noted earlier, remote trials are often more patient-centric because they deploy efficient methods and technologies to support patients. Participants who are better informed and more engaged are also more likely to be compliant with the study protocol and less likely to drop out - ultimately resulting in better data quality. Moreover, utilizing a patient feedback loop and real-time metrics across the study conduct enables a completely new way of running clinical trials, one that is based on real-time information in a single database rather than offline reports based on outdated information. Remote trial methods and technologies provide access to real-time recruitment analytics, patient satisfaction metrics, study throughput flow, and protocol compliance. Any bottlenecks or issues will be identified early on, enabling the sponsor to make data-driven decisions on a daily basis to ensure successful trial conduct.

## HARNESSING THE POTENTIAL OF REMOTE TRIAL METHODOLOGY

The aforementioned technologies are readily available and proven today. Regulators are supportive of these initiatives and are actively working on programs and guidance for the industry. The sites are on board, and remote trial methods have been proven with patients. Robust technology exists to support such programs, and the benefits are clear. So why hasn't the industry seen more remote trials?

A lot has to do with change management. Sponsor companies may not have sufficient internal expertise to operationalize such innovations, and there are only a few vendors and technology solutions that support the clinical trial process end to end. eClinicalHealth and its Clinpal platform have been built from the ground up to support this need and have the in-house expertise and partner network to fully implement remote trials. The VERKKO trial was an important milestone in validating the approach and gathering satisfaction and performance metrics across the conduct of the trial. It is also important to understand that not every trial is suitable for a remote methodology, but that nearly every trial has at least some aspects that can benefit from these methods.

Similarly, it is critical to understand technology alone won't put this industry ahead of the digital wave; technology must be used only if it makes trial conduct easier. We cannot expect sites to manage whatever the latest technology platforms sponsors or contract research organizations wish to deploy. And, it is inconvenient and unwieldy for patients to lug around site-provided smartphones, tablets, or laptops and cumbersome for sites to manage. This is one reason the industry continues to seek bring-your-own-device (BYOD) solutions. For example, Clinpal enables patients to use their own devices; when the prescreening process reveals that a patient doesn't own an appropriate device, then devices are procured as necessary.

It is important to analyze each protocol and think of practical ways to apply these new methods. Our goal must be to involve patients in real ways while reducing site burden. Only when we deploy an effective, purpose-built, and single-platform technology will we truly modernize clinical research. Only then will we be able to realize the benefits of faster patient recruitment, improved patient engagement, faster time-to-market, and lower costs. ◆

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## BIOGRAPHY


**Kai Langel** is the Director, Patient Solutions and Co-Founder of eClinicalHealth. Since 2000, he has been a pioneer in patient-facing systems for clinical trials. Through his involvement in technical, operational, and scientific roles, he has gained an in-depth understanding of all aspects of the patient journey in clinical trials from recruitment and engagement through data capture. He is actively involved in providing guidance to eClinicalHealth's customers on how to best operationalize new and innovative methods for making it easier and more efficient for sites and patients to participate in clinical trials. Mr. Langel is a respected leader in the industry and frequently speaks at industry conferences. He has authored several articles targeting eClinical working practices and lessons learned.

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# External Delivery

## Fake News

By: John A. Bermingham

**John A. Bermingham** is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

We have all heard everyone complain bitterly about the fake news today's media expels at an alarming rate. One of the biggest concerns I have is how many people in this country are going to believe what they read and hear from others that is just plain wrong. Fake news leads to ignorance of facts, misconceived opinions, and negative consequences.

So what should happen when fake news raises its ugly head in your company? If it is from an external source, a good PR person, lawyer, or timely phone call to the perpetrator's management is, hopefully, enough to initiate a retraction. What about an internally generated fake news item? My first thought is it has to be dealt with quickly and decisively by the CEO.

Why the CEO? Because the employees must understand fake news is so dangerous to a company that the focus on this issue goes all the way to the top. The CEO must be very decisive. There should be no second chances and no negotiations on whether the guilty party stays or goes. As long as the company policy was made known to all employees in writing, then that employee has no defense.

The CEO must also move quickly. It is very important the faker be identified and dealt with. But the fake news still exists after the employee is dismissed for cause. What to do? In one word – Communicate. This can be accomplished through many vehicles. Here are three.

If your company has a newsletter, publish a special edition. Have the CEO and the head of HR write to the employees with HR explaining the situation via the special edition newsletter. It should address the company policy on fake news and the dangers it represents. The CEO should take the fake news information head on in the newsletter and communicate fact vs. fiction.

Another solution is to publish the same special edition newsletter with HR explaining the company policy on fake news, its dangers, and how this situation will be handled without being threatening. Then, as an option, have a full-page interview with the CEO that centers on fake news.

A third method is the suggestion box. I used this effectively at one of the companies I turned around. It was easy to figure out what was foremost on peoples' minds, but they were afraid to ask any questions because of the sensitivity of the issue.

In every company I have led, I always held monthly town hall meetings. So, I would stuff the suggestion box with requests for me to address issues I believed were extremely important. The same thing can be accomplished when addressing fake news.

You can call a special town hall meeting to address the fake news. After answering questions from the floor, open the suggestion box and read the question(s) regarding fake news that you "stuffed" it with. Don't forget the same question or request for information can be written on two or three different pieces of paper. But no matter what, speed and derisiveness are keys to this very dangerous situation. ◆

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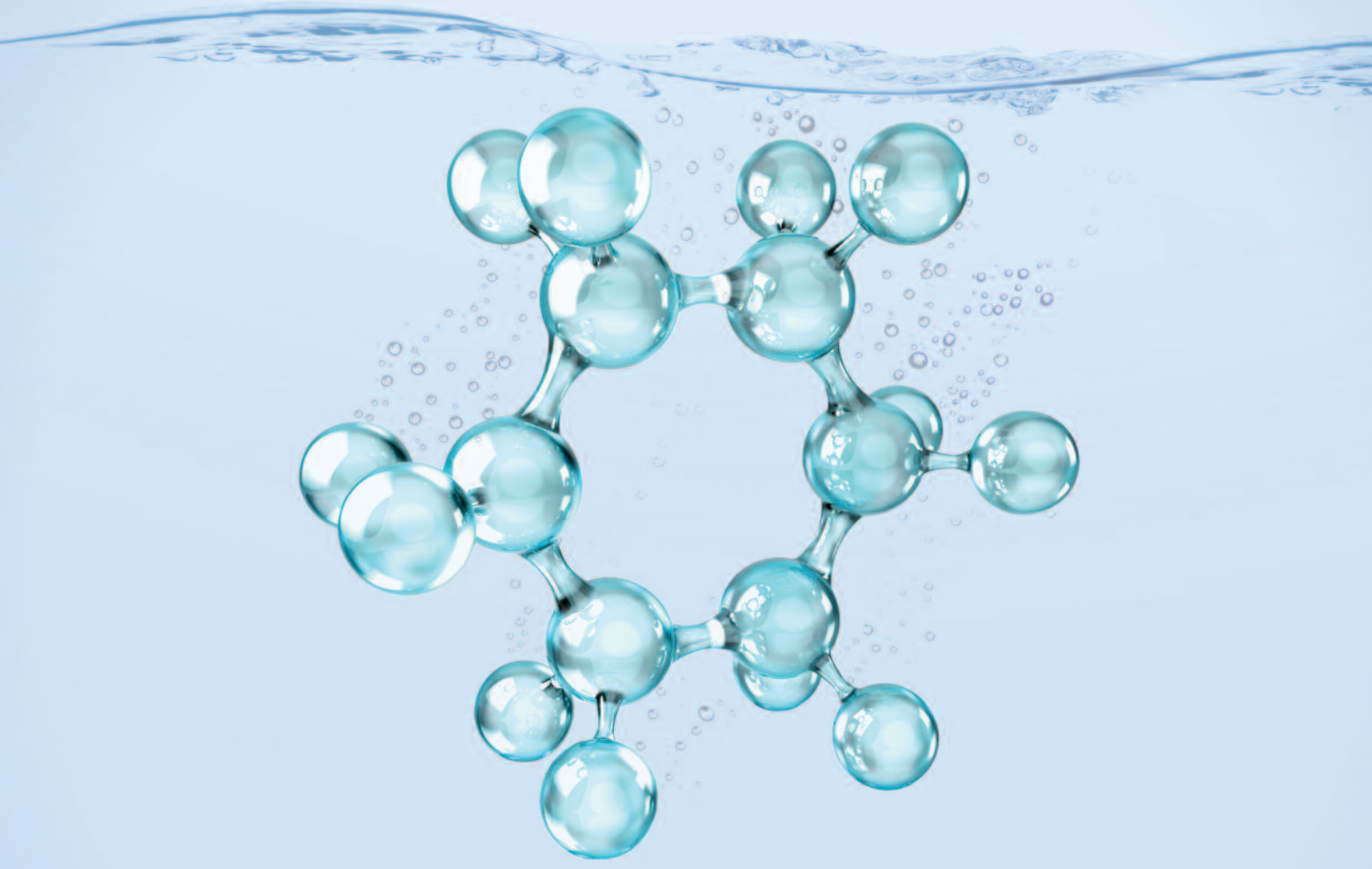

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