# Complex Drugs Require High-Quality Prefillable Solutions

**NovaPure® Components**

NovaPure® plungers are made from West's most modern, best-in-class elastomeric formulation with FluroTec® barrier film to minimize compatibility issues with the drug product.

**Daikyo Crystal Zenith® Delivery Systems**

The Daikyo Crystal Zenith® Insert Needle Syringe system was designed to maintain purity, integrity and efficacy of premium biopharmaceutical therapies.

**NovaGuard® Safety Systems**

The NovaGuard® SA Pro safety system can be deployed using a single-handed technique to shield the exposed needle, and may help prevent needlestick injuries.

An ideal choice for single-dose drugs, West Solutions for prefillable systems help to ensure a more consistent injection to help patients receive accurate dosing with their treatment regimen. Select high-quality NovaPure components to ensure consistency. Daikyo Crystal Zenith syringe systems offer an excellent option for sensitive biologics, and safety systems help to keep patients and caregivers safe from needle-stick injuries

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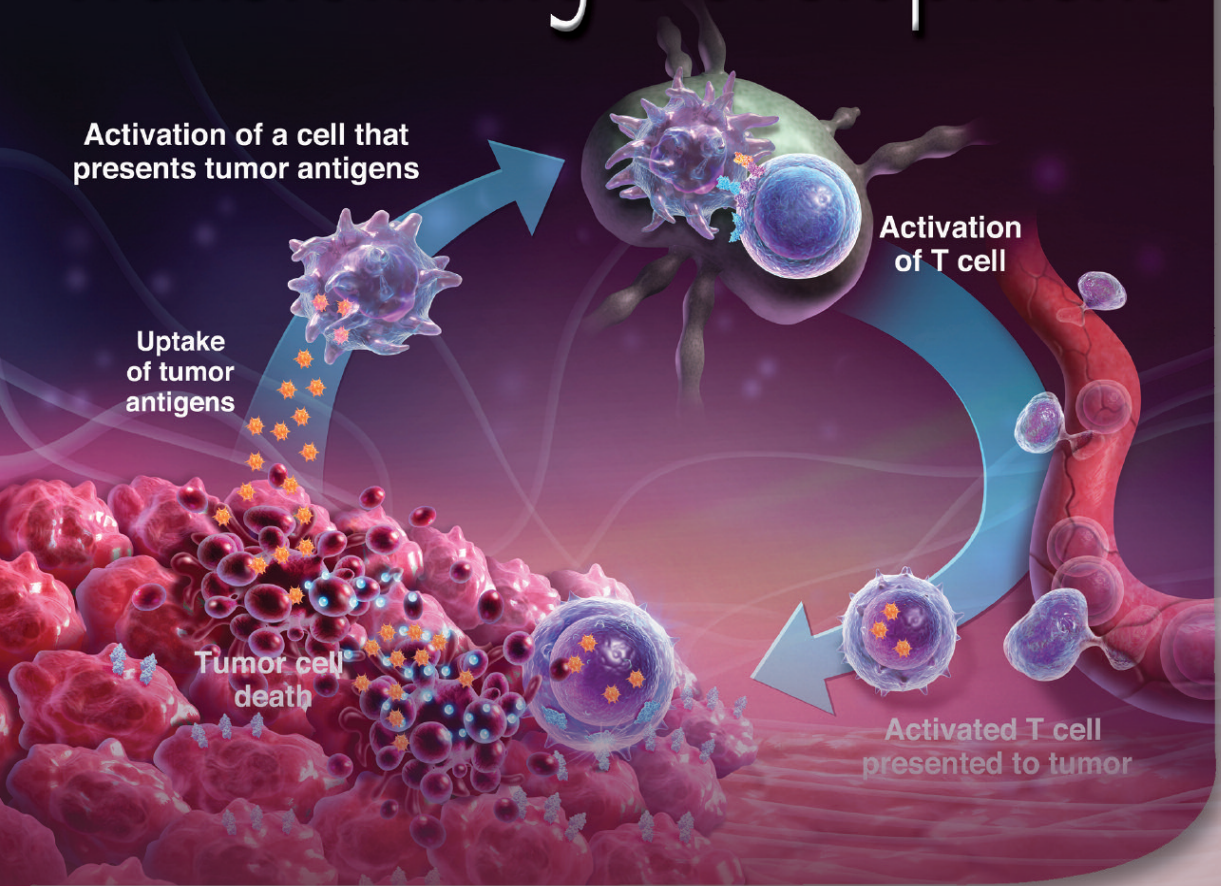
# Drug Development & Delivery

October 2017 Vol 17 No 7 www.drug-dev.com


# Platform Technologies – Transforming Development




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

**Jeff Galvin**
Gene & Cell Therapy's Growing Potential to Disrupt Drug Research & Healthcare Delivery

**Smruti Chaudhari, PhD**
Reformulation of Tablets to Resolve Sticking & Picking Issues Faced on Compression

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Are Lipid-Based Drug Delivery Systems in Your Formulation Toolbox?

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INTERVIEW WITH **APTAR PHARMA'S** PRESIDENT BAS VAN BUIJTENEN

**Formulation challenges? We can help.**

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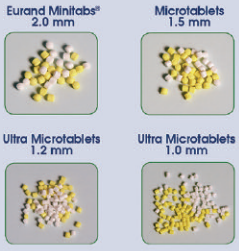


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Drug Development® & Delivery

**October 2017** Vol 17 No 7



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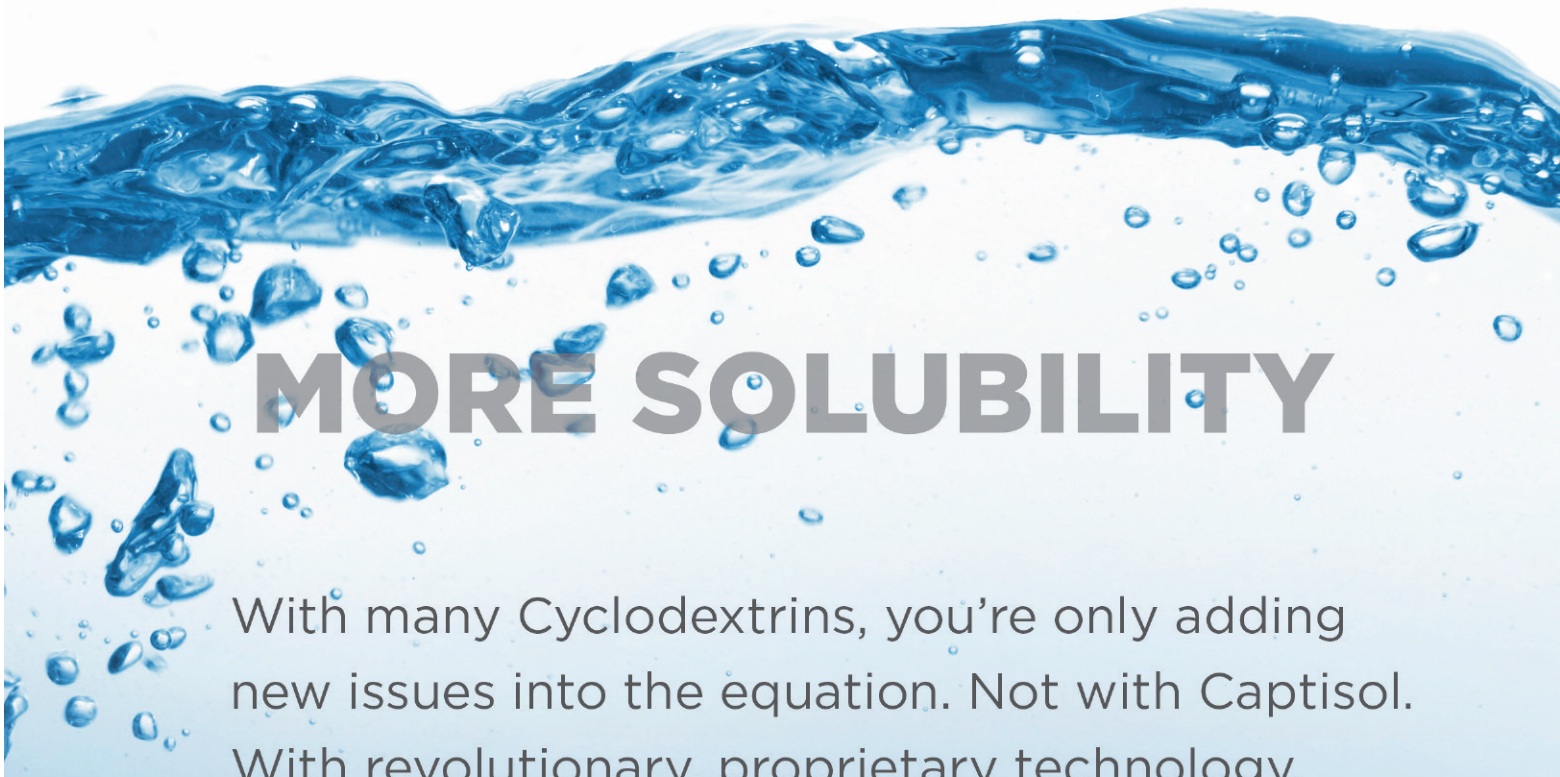
# MORE TECHNOLOGY.



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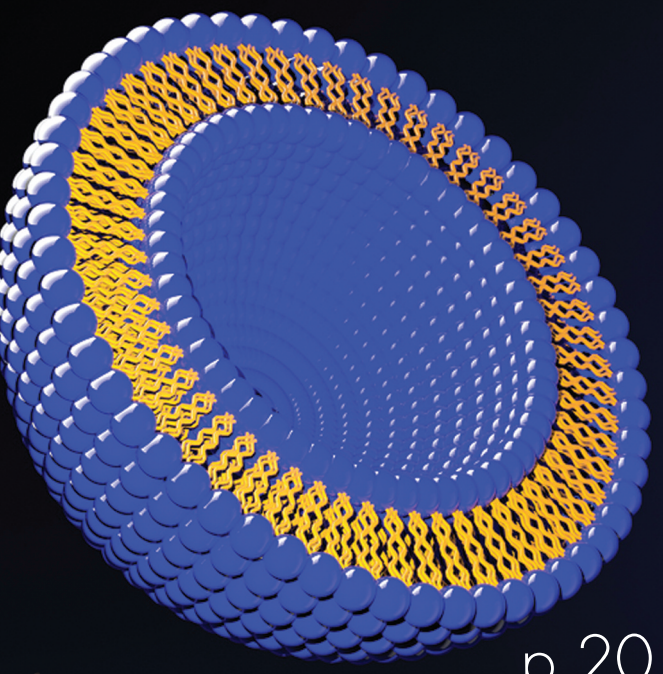
"Despite the vast array of excipients to enable development of a LBDDS in which the drug is fully solubilized, some molecules will not dissolve in lipidic excipients at their required unit dose. While suspensions in LBDDS can provide good exposure and are commercially available, for example Cipro™ Oral Suspension, typically, the best exposure from LBDDS is achieved when the drug is fully solubilized in the dosage form."



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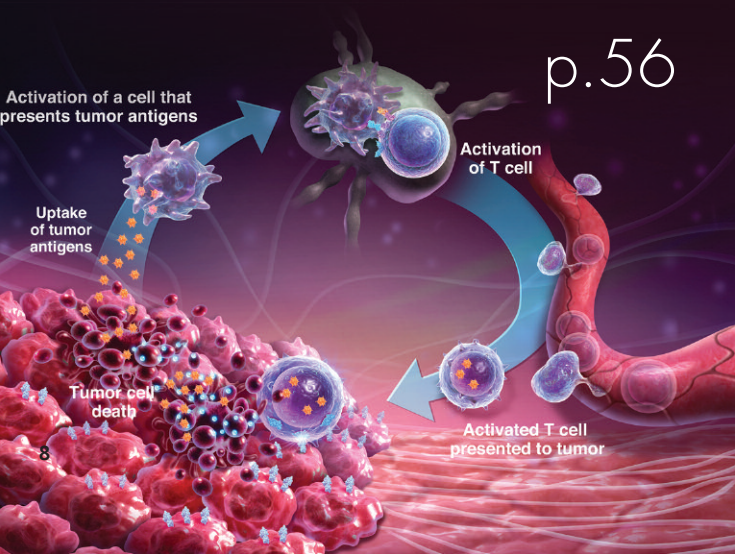
# Platform Technologies

"Platform technologies have the ability to radically improve upon current products and generate completely novel products. In this sense, they open up new arenas for drug discovery and development, potentially increasing the number of therapeutic options for patients. Once a single compound or therapeutic has been generated and demonstrates a clinical benefit in patients, it is more likely this platform technology can successfully be applied to other therapeutic areas, derisking future compounds/products."

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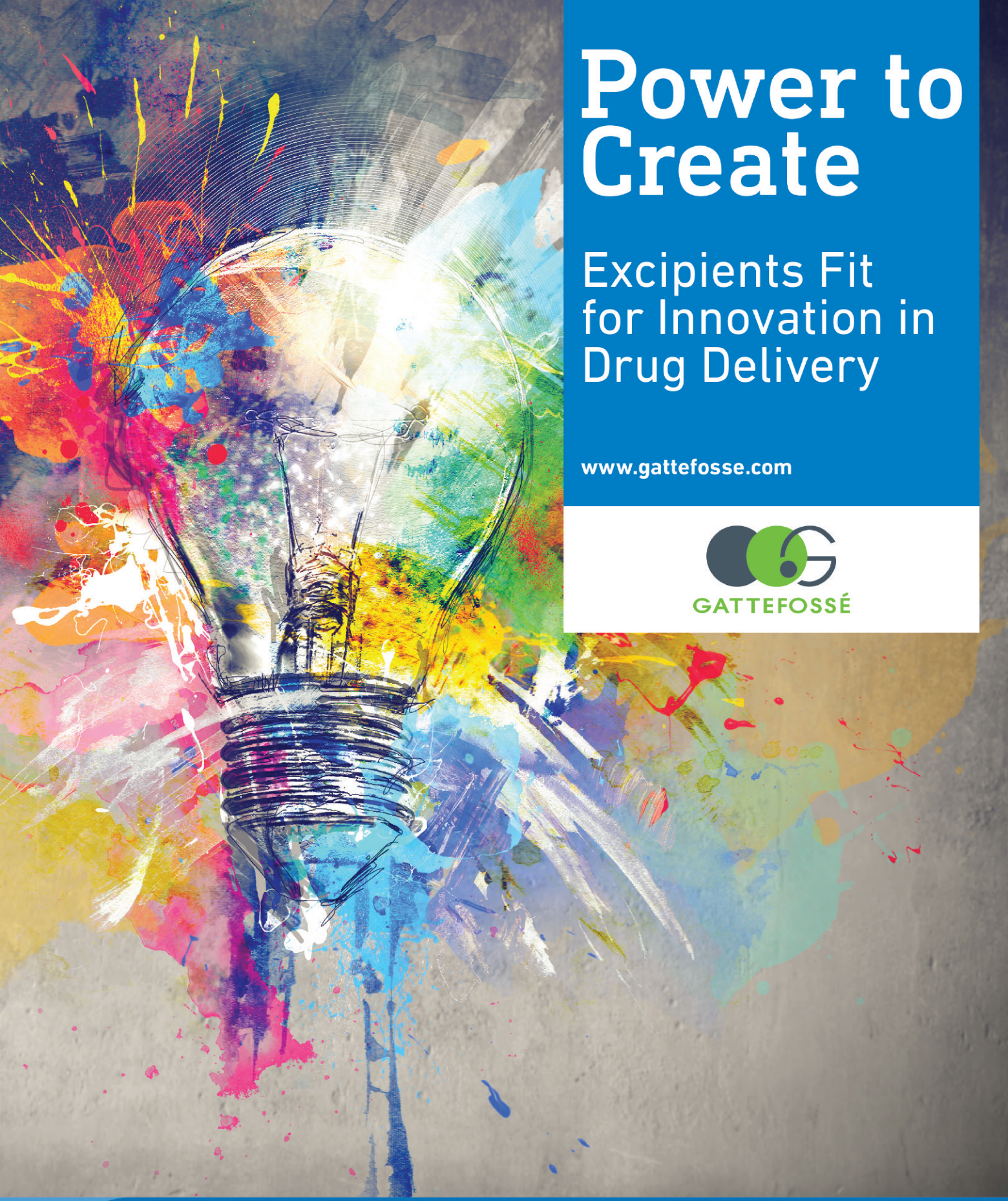

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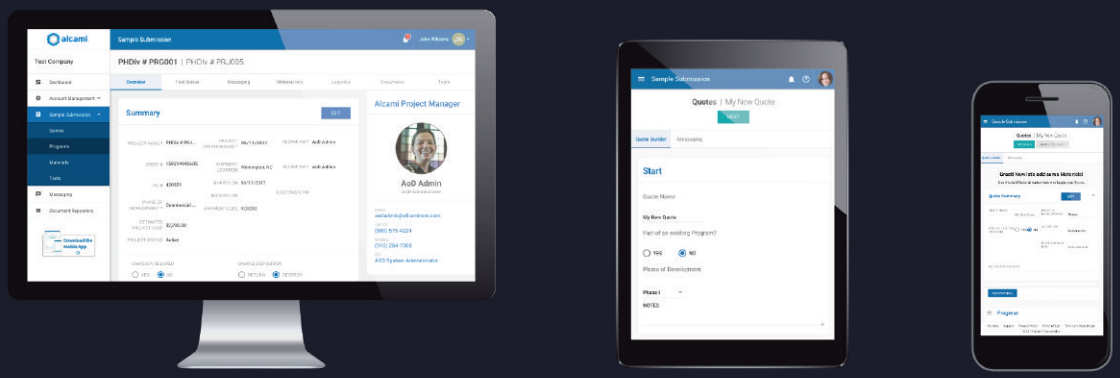
Alcami OnDemand is completely free and open for registration. Enhance your Alcami customer experience and register your account today at alcaminow.com/ondemand.

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## ERT Reduces eCOA Delivery Time for Vaccine Trials by 75%

ERT, a global data and technology company that minimizes uncertainty and risk in clinical trials, recently announced a technology platform that provides fast, regulatory compliant, and cost-effective clinical outcome assessment (COA) data capture during vaccine clinical development. The platform reduces the time needed to develop electronic diary cards by 75%, enabling vaccine researchers to benefit from the significant advantages electronic COA (eCOA) delivers without jeopardizing clinical development timelines.

"Vaccine researchers are under extreme pressure to meet critical development timelines — especially when developing seasonal treatments or responding to global pandemics," said Tim Davis, ERT's Vice President, Digital Patient. "Until now, the time required for electronic diary card development was prohibitive, leaving vaccine developers to rely on the traditional paper method that's plagued with patient compliance and data quality problems and requires significant, time-intensive manual data entry and review before regulatory submission."

ERT's platform overcomes these challenges by pre-validating the set of standard diary card questions commonly used in vaccine trials and readying them for use across different patient groups and in multiple languages. ERT's eCOA solution designers work with vaccine developers to incorporate their specific standards into the vaccines platform and to ensure the study design meets each trial's specific requirements. ERT's offering is the industry's only technology platform that enables vaccine trial sponsors to maintain study development timelines, regardless of whether the eCOA solution is deployed on provisioned devices or via patients' own devices (a Bring Your Own Device, or BYOD approach).

"By eliminating the need for custom eCOA solution design for every vaccine trial, we are enabling vaccine developers around the world to reap the same data quality benefits that so many other clinical trial sponsors have leveraged for years," continued Davis. "By providing this platform, we can help researchers meet their clinical development objectives with confidence, and quickly bring much-needed vaccines to the patients who need them."

ERT is a global data and technology company that minimizes uncertainty and risk in clinical trials so that its customers can move ahead with confidence. With more than 40 years of clinical and therapeutic experience, ERT balances knowledge of what works with a vision for what's next, so it can adapt without compromising standards. Powered by the company's EXPERT® technology platform, ERT's solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. Since 2014, more than half of all FDA drug approvals came from ERT-supported studies. Pharma companies, Biotechs and CROs have relied on ERT solutions in 9,500+ studies spanning three million patients to date. By identifying trial risks before they become problems, ERT enables customers to bring clinical treatments to patients quickly – and with confidence.

## Aclaris Therapeutics Announces Phase 2 Clinical Trial Data

Aclaris Therapeutics, Inc. recently announced that results from a Phase 2 clinical trial evaluating two concentrations (40% and 32.5%) of its drug candidate A-101 for the treatment of facial seborrheic keratosis (SK) lesions have been published in the journal Dermatologic Surgery. A-101 is an investigational, proprietary, high-concentration hydrogen peroxide-based topical solution that Aclaris is developing as a potential treatment for SK. In the trial, A-101 achieved statistical significance in clearing SK lesions on the face in a dose-related fashion. A-101 was well tolerated at both concentrations studied. The FDA's Prescription Drug User Fee Act (PDUFA) action date for the New Drug Application (NDA) is December 24, 2017. If approved, A-101 40% would be the first FDA-approved medication for SK.

In the randomized, double-blind, vehicle-controlled Phase 2 trial to evaluate A-101 topical treatment for facial SK lesions, the 40% and 32.5% concentrations were each compared to vehicle (placebo) in a total of 119 patients. Greater magnitude of effect was observed with the A-101 40% concentration than the 32.5% concentration when each was compared to vehicle. At day 106, the target lesion was clear or near clear in 68% of patients in the A-101 40% group, 62% of patients in the A-101 32.5% group, and 5% of patients in the vehicle group. Improvements compared to vehicle were seen after just one treatment, but most patients received a second treatment in accordance with the study protocol.

A-101 40% topical solution, an investigational drug, is a proprietary, high-concentration hydrogen peroxide formulation for the potential treatment of seborrheic keratosis (SK). It is being developed as a non-invasive, in-office treatment administered by physicians or other health care professionals. A 45% concentration of A-101 is also in clinical development for the treatment of verruca vulgaris (common warts).

Seborrheic keratosis (SK) is a skin condition that affects more than 83 million Americans and is characterized by non-cancerous lesions varying in color from light tan to dark brown or black. SK lesions range in size from a millimeter to a few centimeters wide and usually have a slightly elevated, waxy, scaly appearance. People with SK may be affected with just one lesion or dozens and often have a family history of SK. SK lesions can appear anywhere on the body, except the palms, soles and mucous membranes, and frequently appear in highly visible locations, such as the face or neck. Prevalence of SK increases with advancing age and the majority of patients seeking treatment from dermatologists are between 40 and 70 years of age. Fewer than 10% of people with SK receive treatment, though it is one of the most frequent diagnoses made by dermatologists. Currently, there are no FDA-approved medications for SK, and existing treatment procedures are often painful or invasive and can have undesirable outcomes like scarring or dyspigmentation.

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## Ajinomoto Althea, Inc. Opens Manufacturing Suites in New High Potency & Antibody Drug Conjugate Commercial Facility

Ajinomoto Althea, Inc. recently announced it will soon open a GMP production suite in its newly constructed High Potency Products (HPP) commercial manufacturing facility located in San Diego, CA. Althea took ownership of the new facility on May 1st, 2015 and phased construction and retrofitting commenced in January 2016. Althea is currently offering process development and analytical services to clients from the new facility and will be open for GMP bioconjugation and complex formulation in November 2017. Althea anticipates full manufacturing services including high containment fill and finish will commence in Q4 2018.

Althea has also recently secured its first manufacturing contract for the new facility located just three miles from their current operations. The new Althea facility is uniquely designed to develop, manufacture, test, and release HPPs including Antibody Drug Conjugates (ADCs), Highly Potent Active Pharmaceutical Ingredients (HPAPIs), and other complex formulations of highly potent drugs.

The terms of the deal are confidential, but the scope of the project will include technology transfer, analytical method implementation, process validation, and GMP Drug Product manufacture in preparation for commercial launch of the client's key therapeutic drug.

Jason Brady, PhD, Sr. Director and Business Head, states, "the opening of our first production suite and signing of our first major contract is a clear sign that our investment which addresses the high containment manufacturing needs of our clients will positively impact Althea's growing business. There is limited capacity in the marketplace and customers are eager to secure availability in a state-of-the-art facility managed by a company with an outstanding quality track record."

Althea is a fully integrated, contract development and manufacturing organization located in San Diego, CA providing clinical and commercial product development services. Althea offers cGMP drug product filling in both vials and syringes, and production of microbial-derived recombinant proteins and plasmid DNA. In conjunction with these manufacturing operations, Althea offers comprehensive development services including: upstream and downstream process development, analytical development, complex formulation, product release and ICH-compliant stability testing. Althea's formulation technology platform includes Crystalomics®, a proprietary technology that offers a formulation solution for large molecule products that must be delivered at high concentrations or as sustained release formulations. Althea also has an innovative and proven recombinant protein expression technology called Corynex® technology. For more information visit www.altheaCMO.com.

## ValGenesis Announces Strategic Partnership With VTI Life Sciences

ValGenesis Inc. recently announced the strategic partnership with VTI Life Sciences (VTI). This partnership enables VTI to provide clients with validation services using the latest technology available in the ValGenesis VLMS system. As a partner, VTI will provide clients with efficient and cost-effective validation services using ValGenesis VLMS. VTI will also be a marketing partner for the ValGenesis VLMS system.

The partnership between ValGenesis and VTI creates a fully comprehensive and innovative approach towards providing validation services using an integrated paperless validation lifecycle management platform. Life science companies will benefit greatly from VTI's validation expertise and their knowledge of the ValGenesis VLMS platform.

"We are pleased to be a strategic technology partner with VTI and look forward to enhanced efficiency, enabled compliance and reduced costs of Validation lifecycle processes through ValGenesis VLMS," said Siva Samy, CEO of ValGenesis "We share the same vision, which is providing customers with validation services through VLMS so as to satisfy their every need."

President of VTI, Herb Matheson, adds: "VTI looks forward to the partnership with ValGenesis and the team of technology experts that ValGenesis represents. Together, VTI and ValGenesis look to providing industry leading, turn-key VLMS integration and support to our customers. We look forward to better serving our clients through this partnership."

ValGenesis is a comprehensive leading paperless validation lifecycle management solution in the life science industry that allows customers to fully automate the validation process, eliminate inefficiencies found in paper based manual processes, while also reducing costs and validation cycle times. The ValGenesis Validation Lifecycle Management System (VLMS) effectively manages all types of validation activities such as equipment, instruments, computer systems, cleaning, analytical methods, and process validation. ValGenesis' VLMS covers the entire validation lifecycle thereby delivering technology solutions that are validated, fully configurable and rapidly deployable through onsite or by way of a validated secured cloud environment.

VTI Life Sciences, an ISO 9001:2008 Certified Global Company, strives to maintain and inspire professional excellence by providing Validation, Commissioning, and Qualification (C&Q) Services to Pharmaceuticals, Biotechnology, Biologics, Medical Devices and FDA/Internationally regulated industries. VTI has the experience, expertise, and demonstrated leadership that provides premier validation and compliance consulting services to life science clients.

ValGenesis, Inc. is the creator of an innovative software platform serving as the foundation for managing compliance-based validation activities in Life Sciences companies. ValGenesis, Inc. provides the first enterprise application to manage the corporate validation lifecycle process. As the only system for managing validation execution and approval 100% electronically, ValGenesis was selected by an industry peer review committee to receive the Parenteral Drug Association (PDA) New Innovative Technology Award. The solution is fully compliant with U.S. FDA 21 CFR Part 11 and Annex 11 requirements. For more information, visit http://www.valgenesis.com.

## Q BioMed Announces Development Partnership With Sphaera Pharma

Q BioMed Inc. recently announced a partnership with Sphaera Pharma to develop a new and proprietary analog of QBM-001 for pediatric developmental nonverbal disorder.

"The goal of our collaboration with Sphaera Pharma is to put the patient first, especially since QBM-001 targets a rare subset of toddlers that become non- or minimally verbal for the rest of their lives," said Denis Corin, CEO of Q BioMed.

Sphaera Pharma will employ its proprietary and patented platform to produce a novel analog that aims to reduce or eliminate potential side effects and can reduce the amount of product a toddler needs to take on a daily basis.

"Sphaera Pharma's platform has had great success by providing improved safety and efficacy profile for drugs being developed by biopharma companies," said Dr. Sundeep Dugar, CEO of Sphaera Pharma. "Being able to employ our technology to ensure a safer product that could allow these toddlers to speak is inspiring to our whole team."

Preclinical testing of the new analog is currently underway and a final product is scheduled to be ready by the middle of October, putting Q BioMed on a path to file an IND towards the end of 2017 or the beginning of 2018.

The proprietary analog will also allow Q BioMed to apply for a global composition of matter patent for QBM-001, while still ensuring Q BioMed can pursue the 505(b)2 regulatory pathway in the US to ensure toddlers can possibly benefit from QBM-001 as soon as possible. Q BioMed acquired a license to QBM-001 from ASDERA LLC in April of 2017.

There are approximately 20,000 new cases of pediatric developmental nonverbal disorder in the USA each year and a similar amount in Europe. The majority of the children are diagnosed as toddlers and fall within the autism and epilepsy spectrum disorders. Individually, the economic costs for toddlers that become non- or minimally verbal is ten million on average per person over their life. Collectively, an estimated 200 billion dollarsis spent yearly on individuals who have become nonverbal in the USA. If QBM-001 is effective, not all individuals who become nonverbal will benefit from QBM-001, but we believe that testing from a trained specialists and blood tests, coupled with genetic testing can identify a targeted population that will have a higher likelihood of responding to our treatment.

Sphaera Pharma is an integrated drug discovery and development organization led by pharma and biotech professionals. With its global presence in India, Singapore and the US, Sphaera aims to bridge innovation, resources and expertise in a collaborative model to develop novel therapies.

Q BioMed Inc. ("Q") is a biomedical acceleration and development company. We are focused on licensing and acquiring undervalued biomedical assets in the healthcare sector. Q is dedicated to providing these target assets strategic resources, developmental support, and expansion capital to ensure they meet their developmental potential, so that successful drug candidates may reach patients in need .

## Immuno-Oncology Looks Set to Become Fifth Pillar of Cancer Treatment

Immuno-Oncology (IO) looks set to become the fifth pillar of cancer treatment alongside surgery, radiotherapy, chemotherapy, and other targeted treatments according to GlobalData, a recognized leader in providing business information and analytics.

The company's health team analyzed over 4,000 clinical trials and more than 800 IO products in Phase I-III clinical trials to generate a number of unique actionable insights in their latest report Pharma Focus Visual Analysis of Immuno-Oncology Development and Opportunities. The report predominantly focuses on developments in active immunotherapy products based on their molecular targets and molecule types. The team also assessed immune checkpoint modulators (based on 21 individual targets) together with a total of 18 solid tumor types and eight blood cancers.

A large selection of treatments within immune-oncology focus on utilizing the immune system to induce an anti-tumor response, leading to tumor stabilization and potential remission from the disease. These treatments achieve their effects through the inhibition, or blockade, of immune checkpoint proteins (ICPs) such as CTLA-4 and PD-1. PD-(L)1 inhibitors are rapidly adopted in indications receiving approval due to significant survival benefit and relatively good safety profiles in comparison with other Standard Of Care (SOC) treatments. The number of regulatory designations generally correlates with the number of first-to-market indications.

Maxime Bourgognon, Senior Healthcare Analyst at GlobalData, commented "Beyond PD-(L)1 and CTLA-4, 18 other IO targets are currently being explored in Phase I–III clinical trials. However, agents targeting emerging checkpoint targets will not represent a threat to the uptake of existing PD-(L)1 checkpoint modulators, as most agents will be combined with already marketed immune checkpoint modulators."

Of the big advances in cancer care over recent years, excitement around the clinical and market potential of IO has been driven by IO's ability to harness the natural processes of the body's immune system to search for, examine, and eradicate foreign particles. IO teaches the immune system to recognize and destroy cancer cells and thereby enable the body to regain control. The future of IO looks brighter than ever, and IO drugs are now in a position to compete as monotherapies against traditional SOC chemotherapy regimens in the first line of the metastatic setting. In addition, these treatments have shown efficacy in a wide variety of indications offering a less toxic treatment alternative.

Bourgognon continued "Despite all the initial setbacks and challenges in IO, researchers and drug developers have now found innovative ways to successfully augment the immune response against cancer. In the near future, it is hoped that the combination of IO agents with other IO agents, targeted therapies, or chemotherapy regimens will lead to improved long-term survival outcomes for even more cancer patients."

Bourgognon concluded "This report consists of a highly-visual slide deck that is intended to facilitate the dissemination of aggregated data and insights. Types of graphical analyses include cumulative plots, aggregated bubble plots, pie charts, and matrix analyses."

## Aptose Biosciences & CrystalGenomics Announce Issuance of US Patent

Aptose Biosciences Inc. recently announced that the United States Patent and Trademark Office has issued US Patent No. 9,758,508 titled 2,3-DIHYDRO-ISOINDOLE-1-ON DERIVATIVE AS BTK KINASE SUPPRESSANT, AND PHARMACEUTICAL COMPOSITION INCLUDING SAME. The patent claims numerous compounds, including the CG'806 compound, pharmaceutical compositions comprising the CG'806 compound, and methods of treating various diseases. The patent is expected to provide protection until the end of 2033.

"This newly issued patent represents a major step in protecting the unique structural properties and potentially broad applications of CG'806," said Dr. William G. Rice, Chairman, President, and Chief Executive Officer of Aptose. "In addition to being developed as an orally bioavailable first-in-class multi-targeted pan-FLT3/BTK inhibitor, it has been shown to impact other relevant oncogenic targets. We look forward to bolstering the patent portfolio through additional findings and applications."

"Following the execution of the License Agreement, our two organizations have become close allies to ensure the expeditious development of CG'806, and we look forward to continuous progress towards the upcoming IND application," stated Joong Myung Cho, PhD, Chairman and Chief Executive Officer of CrystalGenomics.

CG'806 is an oral, first-in-class pan-FLT3/pan-BTK multi-kinase inhibitor. This small molecule demonstrates potent inhibition of wild type and mutant forms of FLT3 (including internal tandem duplication, or ITD, and mutations of the receptor tyrosine kinase domain and gatekeeper region), eliminates AML tumors in the absence of toxicity in murine xenograft models, and represents a potential best-in-class therapeutic for patients with FLT3-driven AML. Likewise, CG'806 demonstrates potent, non-covalent inhibition of the wild type and Cys481Ser mutant of the BTK enzyme, as well as other oncogenic kinases operative in B cell malignancies, suggesting CG'806 may be developed for various B cell malignancy patients (including CLL, MCL, DLBCL and others) that are resistant/refractory/intolerant to covalent BTK inhibitors. CG'806 is currently in pre-clinical development in partnership with CrystalGenomics.

As previously announced on June 8, 2016, Aptose and CrystalGenomics, Inc. entered into an exclusive global option and license agreement focused on the development of CG026806 (CG'806). Aptose is currently undertaking Investigational New Drug (IND) enabling studies and expects to exercise its option to develop and commercialize CG'806 under the agreement and initiate a phase 1 clinical trial by mid 2018. The potential option exercise would occur prior to submission of an IND application in the U.S and, upon exercise, Aptose would have to pay US $2.0 million in cash or in a combination of cash and common shares. Upon exercise of the option, Aptose would own global rights to develop and commercialize the program outside of Korea and China.

CrystalGenomics, Inc. is a commercial stage biopharmaceutical company focused in the structure-based drug discovery and development of novel therapeutics in unmet medical need areas of inflammation, oncology, and infectious disease. Aptose Biosciences is a clinical-stage biotechnology company committed to developing personalized therapies addressing unmet medical needs in oncology.

## Sandoz Proposed Biosimilar Accepted for Review by FDA

Sandoz, a Novartis Division, and the pioneer and global leader in biosimilars, announced today that the US FDA has accepted its Biologics License Application (BLA) under the 351 (k) pathway for a proposed biosimilar to the reference medicine, Rituxan (rituximab).

Rituxan is used to treat blood cancers including non-Hodgkin's lymphoma (follicular lymphoma and diffuse large B-cell lymphoma) and chronic lymphocytic leukemia, as well as immunological diseases such as rheumatoid arthritis.

"The cost of treating cancer in the US is a major concern for many patients and their families as well as for the healthcare system," said Mark Levick, MD PhD, Global Head of Development, Biopharmaceuticals. "With the FDA acceptance of our regulatory submission for proposed biosimilar rituximab, we plan to deliver patients a high-quality Sandoz biosimilar that, following approval, could help drive healthcare savings and increase competition, while freeing up resources for and supporting patient access in other areas of cancer care including innovative therapies."

The BLA consists of a comprehensive data package that includes analytical, preclinical and clinical data. Clinical studies included a pharmacokinetic/pharmacodynamic (PK/PD) trial in rheumatoid arthritis (ASSIST-RA), and a Phase III confirmatory safety and efficacy study in follicular lymphoma (ASSIST-FL). Sandoz believes these data provide confirmation that the proposed biosimilar matches the reference medicine in terms of safety, efficacy, and quality.

Sandoz is committed to increasing patient access to high-quality biosimilars. As the pioneer and global leader in biosimilars, Sandoz has five biosimilars marketed worldwide, as well as a leading global pipeline. We plan to launch a total of five major oncology and immunology biosimilars between 2017 and 2020. This includes biosimilar rituximab, which was approved by the European Commission for use in Europe in June 2017 (marketed as Rixathon).

Sandoz is well positioned to continue leading the biosimilars industry based on its experience and capabilities in development, manufacturing, and commercialization. As a division of Novartis, the first global healthcare company to establish a leading position in both innovative and off-patent medicines, Sandoz benefits strongly from this unique blend of experience and expertise in many different market environments.

Sandoz also continues to champion policy and legislation that enables patients and the healthcare system to benefit from biosimilars. This was demonstrated by the recent US Supreme Court unanimous positive decision related to the Notice of Commercial Marketing (NCM). The Supreme Court ruled that NCM can be provided before FDA approval, accelerating patient access to future US biosimilars by 180 days. The Court also provided additional clarity on how the "patent dance," the process by which biosimilar manufacturers may provide confidential and proprietary information to the manufacturer of the reference medicine in the patent exchange process, will function.

## GE Healthcare Advances the Delivery of Cell Therapies With New Thawing Technology

GE Healthcare recently introduced the first in its VIA Thaw series, the VIA Thaw CB1000 for thawing large volumes of cell therapies cryopreserved in cryo-bags. This range of innovative automated, dry thawing units provides users with control over the thawing of sensitive therapies, and addresses key challenges faced by cell therapy companies. Designed to overcome the multiple inconsistent elements in standard water bath thawing practice, the VIA Thaw series delivers a simple, reproducible and traceable recovery system that maintains cell viability to prevent loss of therapeutic effect.

With about 900 cell therapy clinical trials underway worldwide and a handful of products approved as treatments, the emergence of cell therapies will potentially change the landscape of healthcare. However, maintaining cell potency throughout the manufacture and cryogenic cold chain (cryochain) of these treatments is a major challenge. Cell thawing is the final and least controlled part of the cryochain. The process is often carried out in water baths across multiple sites, with inconsistencies due to subjective determination of the thaw endpoint and risk of waterborne contamination. The collection and collation of data from thaw sites, often by paper records, also impedes therapy development. In 2015, the leading UK-based cell therapy organization, the Cell and Gene Therapy Catapult, identified these barriers to the commercialization of cell therapies and approached Asymptote (now part of GE Healthcare) to apply its expertise in cryochain technology to find the solution.

Commercially available now, GE Healthcare's VIA Thaw CB1000, standardizes and streamlines the recovery of cryopreserved samples with a system that captures a complete, auditable thaw record. Combining automation with dry conduction thawing, it enables the thaw endpoint to be precisely determined, and eliminates the contamination risk associated with water baths. Thaw profiles can be customized to every cell therapy sample and transmitted to thawers across multiple sites to ensure consistent sample thawing. All VIA Thaw CB1000 units have a "lock-down" option to limit the operator to a single pre-set profile and minimize the risk of error. Electronic data logging creates a record of each step in the thawing process and enables sources of variation to be identified quickly. All VIA Thaw units integrate with the GE's digital my.Cryochain platform to standardize and audit thawing processes from any web-browser.

VIA Thaw CB1000 is available now for research use in laboratory and clinical trial settings. The VIA Thaw SC2 for thawing cell therapies contained in 2-mL screw cap vials will be commercially available soon.

The VIA Thaw series of automated thawers are intended for research use only. These are not medical devices and have not undergone medical device registration, clearance, or approval with any Regulatory Authority. The User is solely responsible for obtaining the appropriate IND/BLA/NDA, or equivalent approvals, for any clinical application.

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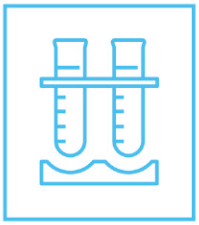
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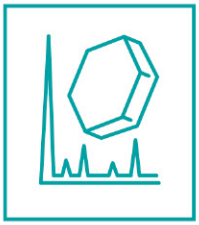
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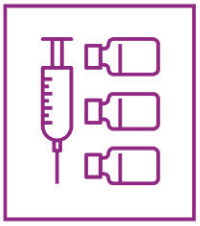
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# LIPID-BASED DELIVERY

## Are Lipid-Based Drug Delivery Systems in Your Formulation Toolbox?

By: Jason M. LePree, RPh, PhD


## ABSTRACT

This article reviews the causes of poor bioavailability for drugs. It provides an introduction to lipid-based drug delivery systems, and how the formulation approach can be used to overcome impediments to good bioavailability of therapeutic actives, including poor water solubility, low permeability, and degradation by stomach acid or enzymes *in vivo*.


## INTRODUCTION

Oral bioavailability, simply defined, is a measure of the quantity of drug absorbed into the systemic circulation following oral administration of drug. A variety of physicochemical and or physiological mechanisms can negatively impact the rate and extent of a drug's oral absorption. The unfavorable physical chemical properties of a drug may include poor aqueous solubility and low dissolution rate (frequently correlated to each other),[1-6] an octanol-water partition coefficient below 1[7] and above 3 to 5,[8] which translates into poor permeability through the gastrointestinal tract wall, and a chemical structure that renders the drug molecule prone to degradation via acid catalyzed reactions within the stomach and/or via enzymes including proteases and esterases within the gastrointestinal mucosa and blood stream.[9-11] The physiological mechanisms that can decrease bioavailability of orally administered drugs include pre-systemic elimination by digestive enzymes, P-glycoprotein mediated efflux transport of drugs back into the gastrointestinal tract lumen,[1,18-21] and/or first-pass metabolism (hepatic elimination) whereby a drug is absorbed in the intestine and is shunted to the liver via the portal circulatory system and immediately metabolized.[1,12-17]

In addition to chemical modifications to the drug molecule, there are multiple formulation approaches that can be used to overcome the aforementioned obstacles and improve the bioavailability of a poorly absorbed drug. These include alteration of solution pH and/or salt formation, enteric coating, solubilization by complexation, solid dispersions, and micronization and nanoization.[1,22-49] The focus of this article is the use of lipid-based formulations to overcome barriers to bioavailability.

## INTRODUCTION TO LIPID-BASED DOSAGE FORMS

Lipid-based drug delivery systems (LBDDS) is a wide-ranging designation for formulations containing a dissolved or suspended drug in lipidic excipients. Lipids are esters of fatty acids - lipophilic hydrocarbon chains linked to a hydrophilic group like glycerol,

**TABLE 1**

| Type | Composition | Characteristics | Examples of Approved Drug Products |
|---|---|---|---|
| I | Oils (Triglycerides, mixed mono and diglycerides.) | Non-dispersing, poor solvent capacity unless drug is highly lipophilic. Requires digestion to convert triglycerides to monoglycerides and fatty acids which combine with bile salts and lecithin to form bile salt mixed micelles. | Amitiza Rocaltrol |
| II | Oils, Low-HLB surfactants | SEDDS without water-soluble components, turbid O/W dispersion, unlikely to lose solvent capacity on dispersion. | Sandimmune Neoral |
| III | Oils, High-HLB surfactants Hydrophilic Cosolvents | SEDDS / SMEDDS with water-soluble/dispersible components, clear or bluish dispersion, possible loss of solvent capacity on dispersion, less easily digested. | Xtandi, Lipofen, Kaletra |
| IV | Low-HLB surfactants, High-HLB surfactants, Hydroalcoholic cosolvents | Micellar solutions, good solvent capacity for many drugs, loss of solvent capacity on dispersion, least digestible formulation type. | Agenerase, Norvir |

**Lipid Formulation Classification System[53]**

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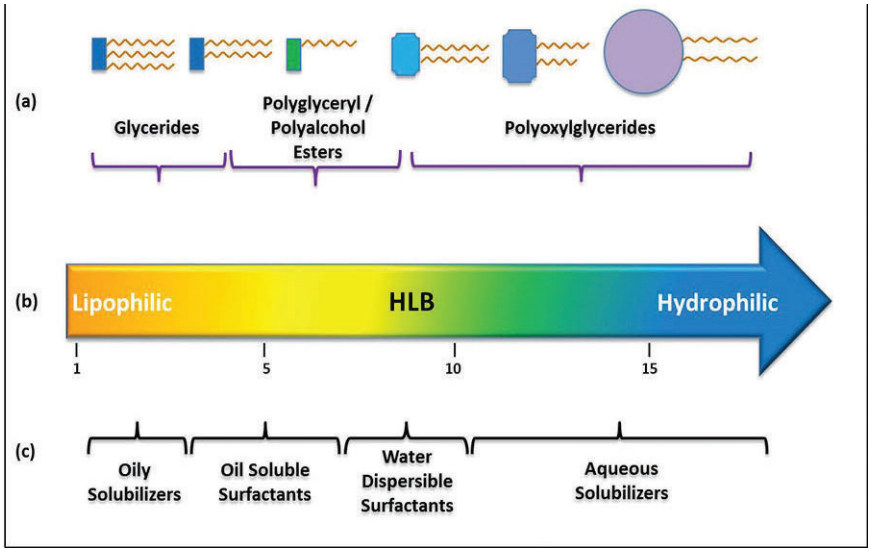
## FIGURE 1




**(A) Schematic of lipid excipient by chemistry, (B) Hydrophilic/lipophilic balance, and (C) Functionality.**

polyglycerol, or polyalcohol (Figure 1). The melting range, solubilization capacity, and miscibility properties of the excipient are defined by the fatty acid chain length and degree of unsaturation. The amphiphilicity or dual polar and non-polar nature of lipids is characterized by the Hydrophilic Lipophilic Balance (HLB), a measure of the excipient dispersibility in aqueous media (Figure 2). Briefly, the functionality of the lipid excipients is connected to its chemistry (Figure 1).

LBDDS can be as simple as a drug in oil to a more complex formulation that is designed to spontaneously emulsify upon contact with aqueous media. Such formulations are self-emulsifying drug delivery system (SEDDS) or self-microemulsifying drug delivery system (SMEDDS). Figure 3 helps visualize this spontaneous process, within seconds of introducing a small droplet of Labrafil® M 2125 CS in water, emulsification is observed. This excipient has a practical HLB of 9.

LBDDS can be used as drinking solutions, filled into hard or soft capsules, or incorporated into tablets; they maybe liquids, semi-solids, or solids at room temperature. As Savla and co-workers discussed, LBDDS provide an adaptable platform to deliver APIs that possess impediments to suitable bioavailability.[50] The versatility of the platform originates from the multitude of excipients that are available to create formulations with targeted properties, including enhanced solubility and permeability, sustained release, etc. The large selection of excipients available to the formulator, in combination with how changes in composition affect performance (solubilization, permeation, and stability) of the formulation before and after digestion can make development of a LBDDS seem complex. Fortunately, lipid-based formulations have an extensive history of development and use to enable a systematic and fast approach for their development. Excipient suppliers, like Gattefossé, offer expert assistance to formulators in the form of guidelines, technical articles, and application laboratories and will work with formulation scientists to help solve their problems.

Owing to the versatility of LBDDS in solving drug delivery issues for drugs with high formulation barriers, there are many approved and marketed lipid-based drug products. Strickley reviewed these in 2007.[51] Recently, 36 commercialized drugs consisting of LBDDS were reviewed.[50] The excipients presented in these reviews have a well-known and long-term track record for safety, and have food or generally recognized as safe (GRAS) status.

## PROBLEMS SOLVED BY LBDDS

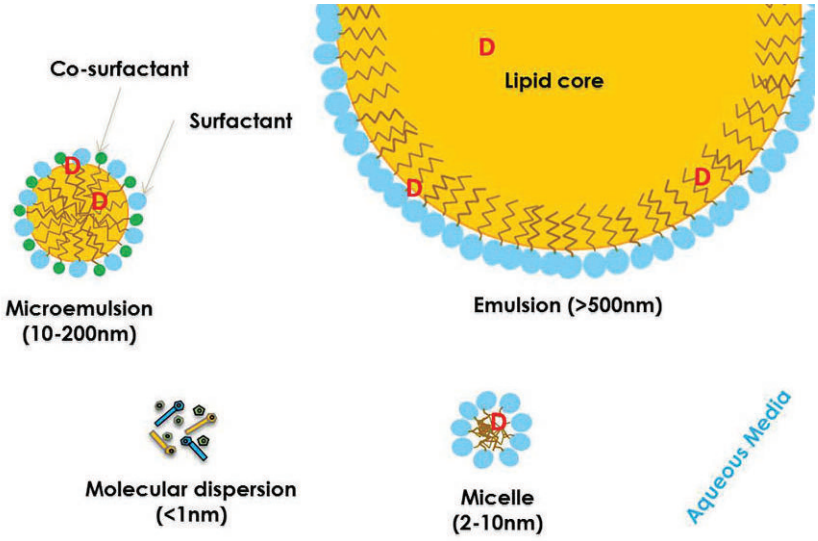
### Solubilization of Poorly Water-Soluble Drugs

Hauss has pointed out that over 70% of new drug candidates have low solubility values in water.[4] Approximately 40% of lipophilic drug candidates that demonstrate good pharmacological activity do not reach market because low aqueous solubility compromises bioavailability and leads to poor pharmacokinetic performance and low exposure.[1] The trend is likely to continue. No matter how promising the pharmacological activity of a drug, its inability to dissolve in the GI tract renders it ineffective. However, lipid-based dosage forms can be utilized to salvage good therapeutic agents that have low aqueous solubilities.

LBDDS provide the drug in a fully to partly solubilized state, and most importantly, maintain solution of the drug until it is absorbed. The drugs remain in the solubilized state because LBDDS self-emulsify (Figures 2 & 3), and/or form emulsions upon digestion. During digestion, oils in the LBDDS undergo lipolysis to form fatty acids and monoglycerides, which combine with components in the gastrointestinal fluids to form mixed micelles that can assist in maintaining the drug in solution.[52]

Lipid formulations are categorized in

## FIGURE 2




**Schematics of some lipid structures in aqueous media; localization of the drug (D).**

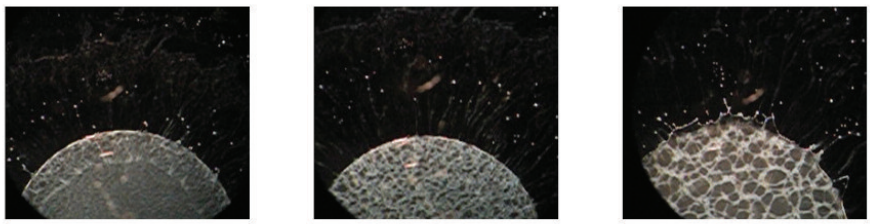
the Lipid Formulation Classification System by their formulation components, hydrophobicity, dispersibility, and digestability (Table 1).[53] A Type I formulation consists of triglycerides (oils), Type II adds water-insoluble and dispersible surfactants to the oils, Type III incorporates water-soluble surfactants and hydrophilic cosolvents (Transcutol®, ethanol, PEG), and Type IV contains no oils and is composed solely of surfactants and hydrophilic co-solvents. Type I formulations are non-water dispersible and rely on the body's natural lipid digestion processes to form mixed micelles that act as a natural detergent for the drug. Figure 4 shows an emulsion formed through digestion of alpha-tocopherol quinone in a triglyceride. Type II formulations generally form course emulsions in water and are digested to form mixed micelles. Type III formulations form spontaneously as emulsions or micro/nanoemulsions upon dispersion in water, and may rely on some digestion to assist or maintain the drug in solution. Type IV formulations form micellar solutions upon dispersion in water and are least digestible. The common feature of Type I to Type IV formulations is solubilization through micellization *in vivo*. This is in contrast to other approaches, like solubilization by dissolving a drug in an organic co-solvent in which large reductions of solubility are experienced upon dilution. The formulator must understand that categorization is not predictive of *in vivo* performance, for example Type I formulations may perform best with highly lipophilic compounds of low melting point, but such compounds will not perform well if they are formulated with Type IV formulations. Hence the choice of formulation type will depend on the molecule being delivered.

Numerous examples exist in the literature that demonstrate the solubility and bioavailability enhancement achievable with LBDDS; a non-exhaustive list of active ingredients include progesterone, halofantrine, docetaxel, carvedilol, piroxicam, nifedipine, and curcumin.[54-58]

A potential advantage of LBDDS is that the drug is delivered in solution to the gastrointestinal tract, obviating the need for dissolution. The drug remains in solution through micellar solubilization brought about by digestion and/or self-emulsification. The challenge to the formulator is to discern which excipient(s) and what proportions of them will solubilize the dose.

Alskär and co-workers analyzed solubilities of molecules in various lipidic solvents and surfactants with the goal of establishing predictive solubility relationships.[59] Some noteworthy findings from this work are: Lipophilic drugs with low melting point (< 150°C) are often soluble in oils or oily vehicles. The solubility of a drug in a mixture of lipidic excipients can be expressed as the sum of drug solubilities in the individual excipients, with each solubility value weighted by the excipient mass fraction in the formulation. Lastly, solubility values for a given molecule are similar in like solvents; for example, a

## FIGURE 3




**Dispersion of Labrafil® M 2125 CS droplet upon contact with aqueous media.**

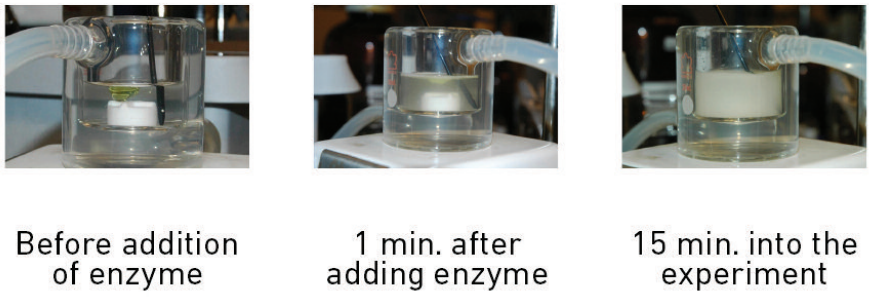
solubility value in PEG400 can be used as an estimate for solubility values in other ethoxylated solvents like Transcutol®. This research provides a framework to estimate solubilities of molecules in lipidic excipients, and eases the work of the preformulator and formulator to select excipient(s) and their proportions to enable the targeted drug load.

### Enhancement of Intestinal Permeability

To be absorbed into the systemic circulation, a drug molecule must pass through the GI wall. The resulting colloidal dispersions brought about by digestion of the LBDDS improve the drug affinity for the protective aqueous monolayer (or unstirred water layer) lining the lumen and facilitate the conditions for API permeability.[60] This effect relates to excipients such as caprylocaproyl polyoxyglycerides (Labrasol®), which improves the drug transport through intestinal cell membranes and its effect on the opening of the epithelial tight junctions.[61-65]

Earlier studies, based on the in vitro cell-based model, pointed to membrane fluidity and efflux inhibition as other potential mechanisms driving intestinal permeability. Of late however, scientists are increasingly focusing on the supersaturation of API in the GI lumen as the leading mechanism for enhancing permeability. Recent studies suggest that initially, API supersaturation (an increase in free drug fraction) results from a decrease in the solubilization capacity of the LBF following dispersion in the gastric and intestinal fluids in the small intestine, creating pressure for API absorption.[61,66-67] A subsequent imbalance created between the initial solubilized drug concentration in the GI fluids and drug solubility in the colloidal species formed post-dispersion and digestion is another factor contributing to API supersaturation. Meanwhile, the lipid metabolites are absorbed contributing to further reduction in the solubilization capacity of the remaining colloidal phases during digestion, thus promoting ongoing supersaturation.[66-67]

**FIGURE 4**




**Enzymatic digestion of a Type I lipid formulation.**

### Protection From Enzymatic/Chemical Degradation

Hetényi and co-workers recently demonstrated that therapeutic peptides, leuprorelin, insulin, and desmopressin could be paired with sodium docusate and loaded into a SEDDS formulation.[68] The researchers exposed the formulated peptides to intestinal proteases (α-chymotrypsin, trypsin, and elastase) and glutathione.They observed that no degradation of the peptides occurred in the SEDDS formulation, which was consistent with observation that the proteases and glutathione were ≤ 0.1% soluble in the oily SEDDS. This work strongly suggests that a LBDDS can protect sensitive peptide APIs from water-soluble reactants and degradation mechanisms that require an aqueous environment.

### Reduction of First-Pass Metabolism

The triglycerides in a LBDDS are digested by the natural lipolysis process in the GI tract to form fatty acids and monoglycerides. Fatty acids can be absorbed by the hepatic and/or lymphatic route, and the distribution between the routes is dependent on the hydrocarbon chain length. Fatty acids with hydrocarbon chains below 12C tend to bind to albumin, which renders them water soluble. As a result, they passively diffuse through the epithelial cells lining the intestine and are taken up by the blood stream through the portal vein before being transferred to the liver.

Fatty acids with a chain length of 14C or longer, due to their hydrophobicity, can be substrates for transporting proteins into the cells, where they can be resynthesized into lipoproteins (known as chylomicrons) for uptake by the lymphatic route.

The unsaturated long-chain fatty acids (LCFA), in particular, are known to stimulate chylomicron secretion and increase the lymphatic uptake. They have been shown to enhance the bioavailability of certain drugs, such as saquinavir, ontazolast, halofantrine, by preferential absorption through the lymphatic transport system and consequently decreased first-pass metabolism of the API in the liver.[69-71]

Because absorption by the lymph means bypassing the liver, the co-formulation with LCFAs can be a promising strategy for drug actives that are extensively metabolized in the liver. Enhanced lymphatic absorption is important in oral delivery primarily for highly lipophilic drugs (LogP > 5) with high solubility in triglycerides (Cs > 50 mg/mL), ie, APIs that are candidates for lymphatic absorption.

## NEW TRENDS IN LBDDS

### Creation of Lipophilic Salts/Ion Pairs of Drugs for Solubilization in Lipidic Excipients

Despite the vast array of excipients to enable development of a LBDDS in which the drug is fully solubilized, some molecules will not dissolve in lipidic excipients at their required unit dose. While suspensions in LBDDS can provide good exposure and are commercially available, for example Cipro™ Oral Suspension, typically, the best exposure from LBDDS is achieved when the drug is fully solubilized in the dosage form. In addition, formulation and manufacture of solutions present less challenges than suspensions that can be prone to aggregation and settling. The inability to solubilize an active agent in lipidic excipients has led formulators to rule out LBDDS as a viable technology for the drug. This unfortunate circumstance has restricted the use of this very versatile LBDDS approach to enable formulation of drugs with high formulation barriers, including poor bioavailability.

Recent work has been conducted to prepare lipophilic salts (or ion pairs) of drugs that enable increased and fully solubilized drug loads in lipidic excipients. Sahbaz and co-workers prepared docusate or decylsulfate salts of itraconazole, cinnarizine, and halofantrine to form ionic liquids or low melting point solids that were miscible or could be solubilized in SEDDS composed of long or medium chain triglycerides, surfactants, and cosolvents.[72] Itraconazole docusate or cinnarizine decylsulfate were administered to rats in SEDDS formulations in which the dose was fully solubilized. The exposure of the fully solubilized drugs in the SEDDS formulation (made possible by the synthesis of lipophilic salts of these drugs) was 2-fold higher for cinnarizine and 20-fold higher for itraconazole, relative to control formulations of the suspended free base forms of the drugs at the same dose. This study demonstrated that formation of lipophilic salts or ion pairs could enable complete solubilization of drugs in lipidic excipients and greatly improve their exposure. This important study should start a paradigm shift in which less water-soluble and more lipid-soluble salt forms or ion pairs of drugs are synthesized to permit use of the LBDDS for drug delivery.

### Use of LBDDS for Oral Delivery of Peptides & Proteins

Two recent papers focused on incorporation of large therapeutic peptides, namely leuprorelin, insulin, and desmopressin into SEDDS formulations consisting of Capryol™ 90, Labrafil® M 2125 CS, Labrasol® ALF, Peceol™, propylene glycol, tetraglycol, Transcutol® HP, and Tween 20 at various compositions.[72-73] Hydrophobic ion pairing of the peptides with anionic surfactants sodium docusate, dodecyl sulfate, and oleate was performed to enable solubilization of these highly water-soluble peptides into the oily SEDDS formulations. The hydrophobic ion pairs were evaluated by measuring the quantity of the complex formed, the n-octanol/water partition coefficient and the zeta potential of the complexes. For all three peptides, the ion pair formed with docusate gave the best combination of properties. It was observed that the docusate ion pairs of these peptides were soluble in all SEDDS formulations at greater than 10% by weight. Here, we see again, how pairing of compounds with lipophilic salts enables high loading of fully solubilized therapeutic agents into a LBDDS. As discussed in a previous section, the SEDDS protected the peptides against enzymatic degradation by intestinal proteases (α-chymotrypsin, trypsin, and elastase) and glutathione.[72] Release of the peptides from the SEDDS formulations into 50-mm Tris buffer at pH 6.8 and 37°C was studied using a dialysis membrane method. All formulations permitted release of the peptides over 6 hours. These landmark papers suggest that LBDDS can be a viable formulation approach for oral delivery of peptides.◆

## REFERENCES

Available upon request, contact Dan Marino, MSc, at dmarino@drug-dev.com.

## BIOGRAPHY

**Jason LePree** received his B.S. in Pharmacy from Rutgers University and his M.S. and Ph.D. in Pharmacy (Pharmaceutics) from the University of Wisconsin-Madison . He has over 20 years of experience in both Academia and Industry where he held leadership positions in preformulation, formulation, analytical R&D, and quality control. In parallel, Jason has served as adjunct professor at Long Island University since 1998, instructing on Physical Chemistry, Pharmacokinetics, and Pharmaceutical Analysis.Since joining Gattefossé in 2016, Jason has overseen the completion of the Gattefossé pharmaceutical application laboratories in Paramus, NJ. Equipped with the latest analytical, characterization, and processing capabilities, the laboratories' mission is to help trouble-shoot and advance customer projects to completion. Spearheading the support activity along with internal projects is the continuing mission of Dr. LePree.

# Advanced Delivery Devices

## The Staked Needle Pre-Filled Syringe: Benefits, Conventional Limitations & a New Approach

By: Horst Koller and John A. Merhige, MEM

In the world of subcutaneous and intramuscular injectable drug delivery, injection devices such as autoinjectors and wearable pumps are receiving a lot of attention. However, the importance of the Pre-Filled Syringe, both as a standalone device and as a sub-system within other injection devices, remains extremely high. Well understood benefits continue to drive the transition from vials to Pre-Filled Syringes as the preferred approach for injectable drugs. These benefits include user convenience, reduced risk of contamination, reduction on overfill requirements, and compatibility with safety devices and autoinjectors. A syringe with a pre-attached needle brings further advantages, but the current approach to forming a Staked Needle Syringe presents inherent risks stemming from the use of glue as the needle attachment mechanism. A new approach that addresses these challenges inherent in the conventional approach presents an important alternative to the current standard.

### STAKED & LUER PRE-FILLED SYRINGES

With pre-filled syringes, liquid drug formulations are commonly stored for a shelf-life of up to 3 years. Two main categories of syringes can be found; the Staked (or Pre-Attached) Needle Syringe in which the injection cannula is already pre-attached, and the Luer Cone/Luer Lock Syringes in which the user attaches a hypodermic needle at the time of injection. The Luer Lock type differs from the Luer Cone due to the presence of a groove on the neck for snap-fit components, such as Luer Lock Adapters. Each type of syringe also has various options for the proximal flange: the large and small round flange as well as the cut flange, which has the advantage of preventing the syringe from rolling during injection preparation. These syringes are described in detail in the ISO 11040-4 Standard.[1] Depending on the route of administration, certain needle geometries are typically used as seen in Table 1.

**TABLE 1**

| Type of Injection | Needle Diameter (gauge | Needle Diameter (mm OD) | Needle Length (inch) | Needle Injection Angle |
|---|---|---|---|---|
| Intradermal (ID) | 25-27 | 0.5-0.4 | 3/8-5/8 | 5°-15° |
| Subcutaneous (SC) | 23-30 | 0.6-0.3 | 3/8-5/8 | 45°-90° |
| Intramuscular (IM) | 18-25 | 1.2 -0.5 | 5/8-1.5 | 90° |

**Typical needle geometries for common routes of administration.**

An obvious but very important difference between the Staked and Luer Syringe is that the Luer Syringe requires the user to mount a needle prior to injection. This brings with it the freedom to choose the correct needle to deliver the drug to the appropriate depth for a specific patient and/or injection site. For example, a user will choose a longer needle for an IM Injection into an obese patient or for a gluteal injection, as compared to a shorter needle for a thinner patient or a deltoid injection. However, the needle-choice flexibility that a Luer Syringe provides brings with it some usability disadvantages and risk for error. The user must first choose the correct needle length and gauge and then properly attach the needle. These additional steps are inconvenient and

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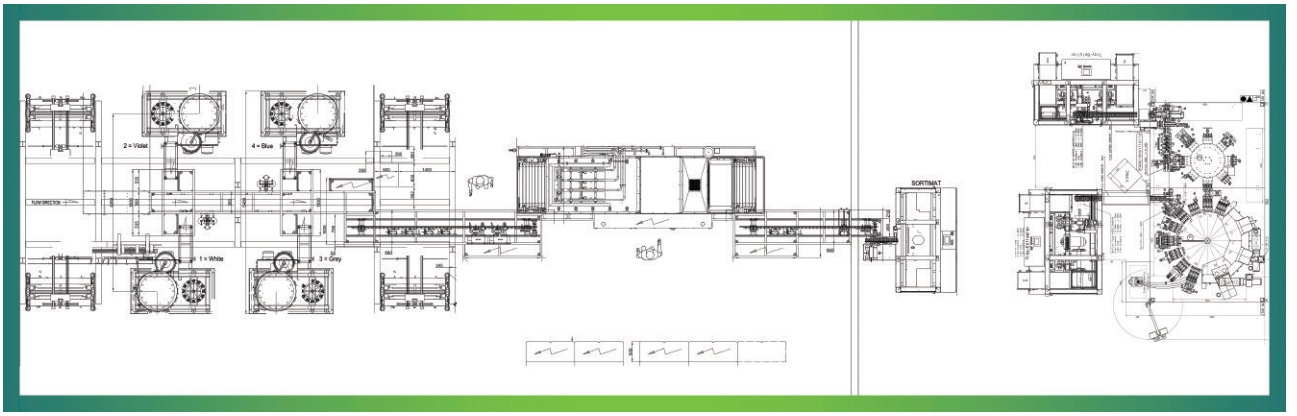
## FIGURE 1



**Staked Needle Syringe Forming and Bonding Equipment. From left to right: vertical glass converting, furnace, needle bonding station. (Picture courtesy of Nipro PharmaPackaging Germany GmbH)**

take additional time, but more importantly, they leave the user prone to impactful error; the incorrect needle can lead to a misplaced deposit of the medication, while an improperly attached needle can lead to leaking and inaccurate dosing.

## THE STAKED NEEDLE: BENEFITS & CONVENTIONAL APPROACH TO PRODUCTION

The Staked Needle emerged as an effective means of avoiding these risks by eliminating the requirement for additional user steps. While risk mitigation was the main driver, further benefits that accompanied the Staked Needle were improved handling, reduced risk of contamination, enhanced user convenience, as well as reduced time of administration. These factors have propelled the Staked Needle Syringe to cover a significant market share within the Pre-Filled Syringe industry, particularly in therapeutic areas, such as heparins, certain vaccines, and biologics.

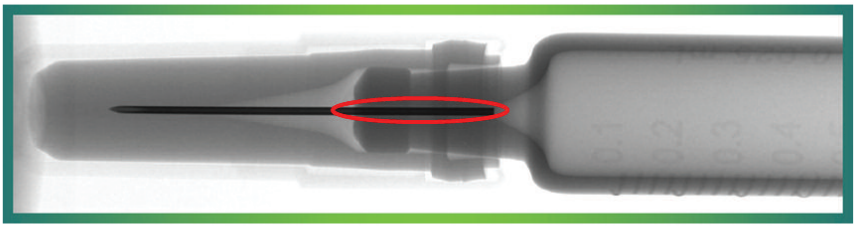
Glass Pre-Filled Syringes are manufactured from glass tubes of a predetermined inner and outer diameter. The tube is either pre-cut before forming on horizontal machines or directly formed out of the tube on vertical machines. Figure 1 shows a typical layout for vertical forming. Such lines consist of tubing loaders, hot forming units, visual inspection machines, reject stations, a furnace, and in the case of a Staked Needle Syringe, a needle bonding machine.

In the conventional approach to a Staked Needle, the stainless steel cannula is bonded into the needle channel of the syringe barrel using a UV-cured adhesive. This process occurs in the needle bonding machine depicted in Figure 1. This has been the industry's approach to pre-attaching a needle to a glass syringe for many years. The complexity and cost associated with changing and validating this needle bonding process results in a limited array of needle gauge and length offerings in a Staked Needle presentation. After bonding and curing, the syringes are washed and siliconized, closed with either a soft or rigid needle shield, nested, tubbed, bagged, and ETO sterilized. They are then shipped to the customer, ready for aseptic filling.

## LIMITATIONS OF CONVENTIONAL STAKED NEEDLE SYRINGES

Staked Needle Syringes have advantage compared to Luer Cone or Luer Lock Syringes as described previously, but they also have challenges and risks stemming from components that come into direct contact with the drug during long-term storage.

## FIGURE 2



**X-ray of the distal end of a Glass Staked Needle Syringe. Red circle added. (Picture courtesy of Nipro PharmaPackaging Germany GmbH)**

"Staked Needle Syringes have advantages compared to Luer Cone or Luer Lock Syringes as described previously, but they also have challenges and risks stemming from components that come into direct contact with the drug during long-term storage….The ideal solution, then, might be a system that preserves as many as possible of the existing components, equipment, and processes the industry trusts, while avoiding as much as possible the interaction between the drug and the unwanted components."

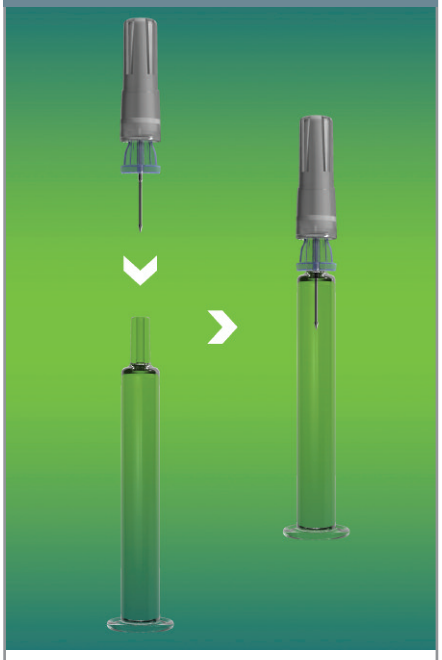
A Tungsten pin is used to form the fluid path in the cone of a glass, pre-filled syringe during syringe forming. UV-cured glue is then used to bond the needle to the glass. In the X-ray image in Figure 2 the red circle highlights the area where glue is present at the cone outlet and between the needle and the needle channel in the glass. The presence of glue introduces the risk for interaction of the drug with the adhesive and/or interaction with components of the adhesive that may be extracted. Leachables coming from the glue and/or closure system as well as residual tungsten oxides left behind from the tungsten pin can present a drug safety and efficacy risk. As an example, incomplete UV curing of the adhesive was found to cause unexpected impurities in a new staked needle Pre-filled Syringe presentation for a biological product, while this had not been previously observed in a Luer Cone presentation.[2] Additionally, tungsten residues in the glass syringe cone left behind during manufacturing have led to aggregation and particle formation in protein solutions.[3]

Knowing these phenomena exist, it is common practice to set a specification for allowed tungsten levels and limits to non-cured glue monomers to lower the risks as much as possible. Because tungsten is known to interfere with some drugs, there are two options available for risk mitigation. Either the residual tungsten is controlled to a level that does not react with the drug product or another pin material is used to avoid the presence of tungsten oxides. This second approach risks that the alternative pin material may also interfere with the drug or that the pins may be quite costly.

Another area of discussion and research related to Pre-Filled Syringes is the amount of silicone oil used to allow for syringe lubrication and easy passage of the plunger stopper down the barrel of the syringe. The silicone is applied by spraying silicone oil onto the glass or by coating the glass with a silicone emulsion that is baked onto the glass. The goal for Biotech Syringes for Biologics is to lower the amount of silicone oil inside the syringe, which is intended to address the concerns of particulates and interaction between the silicone oil and drug product. Typically, "medical-grade" silicone oils are used for the lubrication of the inner syringe barrel as well as for the needle itself.[4,5] Still, silicone can interact with proteins and lead to aggregation or silicone can be detected as particulates during particle testing. An alternative to the standard lubrication of the inner syringe barrel with pure silicone oil is a silicone emulsion that is baked at approximately 330°C for 20 to 30 mins. This process removes the water and causes a thin layer of silicone to chemically bind with the glass. The goal of this baked-on siliconization process is to reduce the chance of silicone reacting with proteins and leading to aggregation. This advanced process, however, is not compatible with standard glue-bonded Staked Syringes because the siliconization/baking process occurs after the needle-bonding process. Adhesive will not survive this baking temperature and, therefore, no baked silicone Staked Needle Syringes are commercially available on the market today. This is a significant and somewhat ironic limitation given that biologic drugs, which can benefit the most from the baked silicone process due to their sensitivity to silicone interaction, are often delivered subcutaneously and therefore lend themselves to a Staked Needle Syringe.

Staked Needle and Luer Needle Syringes each have their advantages and disadvantages and clearly play a significant role in drug delivery. Therefore, there are many new developments around Pre-

FIGURE 3



**The Credence Companion Needle Assembly is mounted to existing Luer Cone Syringe barrels via a mechanical attachment to form a new Staked Needle Syringe. No glue is used.**

Filled Syringe Systems with the goal of minimizing the limitations. For example, composite polymer Pre-Filled Syringes play an emerging role. General advantages of polymer syringes compared to glass are the higher break resistance, low leachable profiles from heavy metals, and the elimination of glue and tungsten because the needle is affixed with an "insert molding" process. Polymer syringes therefore address many of the risks inherent in glass Staked Needle Syringes, yet despite these advantages, glass Pre-Filled Syringes dominate the market. This may be because they are a known entity with a long history and a very well-known production process, from the tubing to the forming to the fill-finishing. The ideal solution, then, might be a system that preserves as many as possible of the existing components, equipment and processes the industry trusts, while avoiding as much as possible the interaction between the drug and the unwanted components. An additional element of the ideal solution would be combining this "dry needle system" with the integrated needle safety and reuse prevention elements that are required for Staked Needle Syringes in regulated environments. The Credence Companion® Staked Needle Syringe may offer such an approach.

## THE COMPANION® STAKED NEEDLE SYRINGE

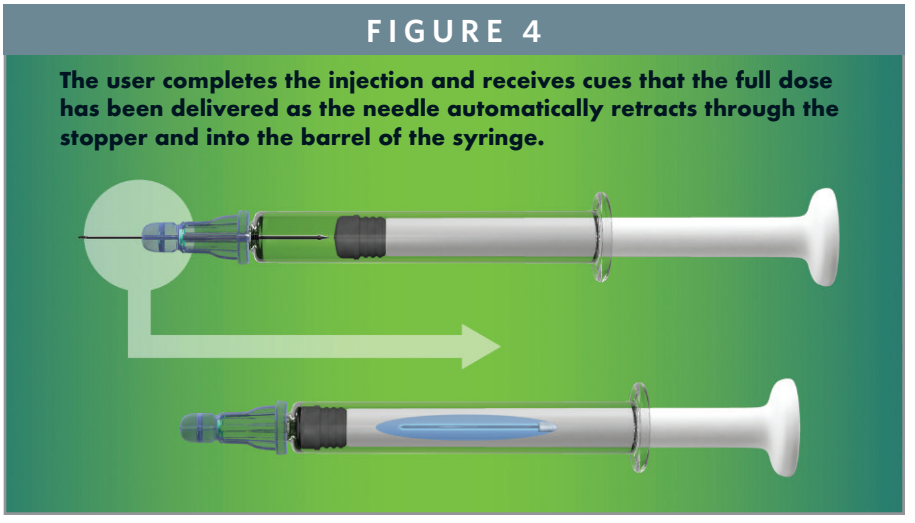
Credence MedSystems is built upon its commitment to offering the pharmaceutical industry Innovation Without Change. Credence's product design and business model are focused on maximizing the impact of its innovative drug delivery systems while minimizing the disruption to pharmaceutical manufacturers during implementation. Pharmaceutical manufacturers can drive growth, brand differentiation, and loyalty by impressing their customers with the usability and protection offered by Credence's novel injection devices, while preserving their established processes and supply chain preferences.

Credence's approach allows pharmaceutical manufacturers to choose their preferred primary syringe container and closure components from their preferred suppliers. The Companion needle and plunger rod are incorporated with the preferred components to result in a fully integrated syringe system with passive needle-retraction safety. It is the mechanism by which Credence's needle is attached to an existing syringe barrel that addresses the challenges presented by the conventional approach of gluing in a staked needle (Figure 3).

The Companion needle assembly includes a polymer hub that incorporates the following components: a needle and needle shield; piercing elements used for Credence's needle retraction technology; and a seal that is integral to maintaining container closure. A standard Needle Shield is used to cover the needle. The manufacturing process that assembles the needle system allows flexibility to incorporate a wide variety of needle gauges and lengths, offering pharmaceutical manufacturers the ability to bring Staked Needle Syringes to a larger number of drug products. The Credence needle assembly is secured to a standard, commercially available Luer Cone Syringe barrel by mechanically attaching to the groove typically used for Luer Lock Adapters, tip caps, and other closure devices. This process

FIGURE 4

**The user completes the injection and receives cues that the full dose has been delivered as the needle automatically retracts through the stopper and into the barrel of the syringe.**



occurs at the syringe manufacturer during syringe assembly so that the syringes are delivered to the filling lines pre-sterilized in the standard nest and tub configuration. The result is a system with the potential to set a new standard for Staked Needle Syringes. It preserves the use of existing syringe barrels, components, and processes, and has all the benefits of a pre-attached needle, but it eliminates the glue and thereby solves a challenge that has plagued the industry.

These significant advantages protect the safety of the patient by maintaining the integrity of the drug product. Removing the glue eliminates risk of unwanted interaction with the drug product, removes the requirement for specifications on the limit of non-cured monomers, and enables baked-on siliconization for a Staked Needle Syringe. Additionally, the system provides many important benefits to usability and user safety. The syringe has the familiar look and feel of conventional syringes, providing the user a level of comfort and allowing standard syringe operations, such as aspiration and air bubble removal. Drug product inspection is now simplified due to the unencumbered barrel. The user completes the injection and receives audible, visual, and tactile cues that the full dose has been delivered. Simultaneously, the needle automatically retracts through the stopper and into the barrel of the syringe, rendering the syringe needle-free and preventing reuse (Figure 4). These features help promote the successful delivery of the drug and drive compliance, while safeguarding the healthcare professionals, patients, and self-injectors using it.

## FINAL THOUGHTS

The advantages of a Staked Needle Pre-Filled Syringe are clear and well documented, but significant risks remain due to the glued-in mechanism of needle attachment. Human nature can prevent us from addressing a problem until a potential solution is within reach, and therefore, the industry has coped with what was available. A new alternative is now available that not only addresses the known challenges, but adds critical usability and safety features while preserving existing components and processes. When new technology eliminates "necessary evils," the technology should be explored for its potential to emerge as a new standard of care. ◆

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## BIOGRAPHIES

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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.

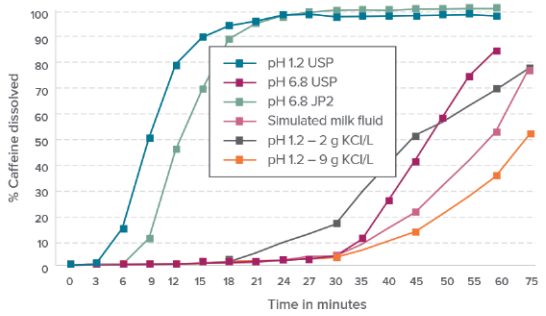
These enteric capsules comply with relevant EP, JP and US Pharmacopeia monographs and have been evaluated *in vitro* across a number of compounds. The results show they protect the stomach from aggressive APIs and delay release to provide maximum absorption. Vcaps® Enteric capsules work with all but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

Capsugel®

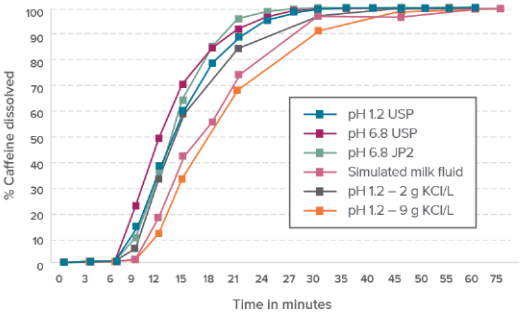
Now a **Lonza** Company

## Dissolution variations introduced by gelling systems in HPMC capsules

Influence of gelling systems on HPMC capsules in dissolution testing



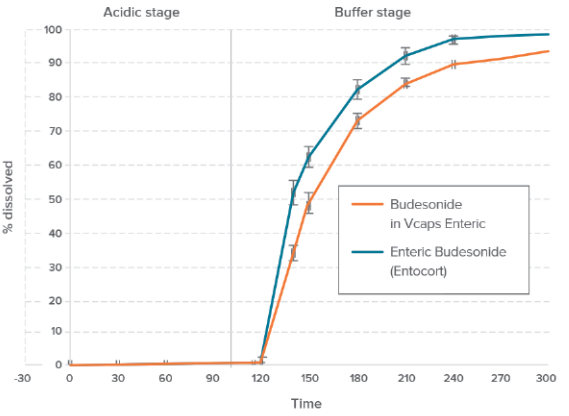

*In vitro* dissolution of caffeine in Vcaps® Plus capsules




## 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.

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




## 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.

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# GENE & CELL THERAPY

## Its Growing Potential to Disrupt Drug Research & Healthcare Delivery

By: Jeff Galvin

### INTRODUCTION

Gene therapy has been emerging for 30 years with the promise of more effectively treating and curing diseases. The basic technology initially used an engineered virus or viral vector to deliver a normal gene to overcome loss of function due to an inherited dysfunctional gene. Vector constructs did not result in sufficient functional gene expression, were not durable, and in some cases, resulted in serious adverse events. With the convergence of an increased understanding of molecular biology catalyzed by the Human Genome Project, new research tools, investments by companies in the industry (American Gene Technologies™, Bluebird Bio, Kite Pharma, Juno Therapeutics and more), a pipeline of promising product candidates are in development and, recently, some commercial products are available in the clinic. Consequently, "modern gene therapy" is maturing and becoming a powerful and practical drug development modality.

Today's advances in gene and cell therapy are not only about creating new treatment options, but also about discovering durable cures. Curing diseases differentiates modern gene therapy from many treatments available today that primarily help manage diseases. A large portion of today's healthcare delivery system is devoted to managing chronic diseases, such as cardiovascular disease, diabetes, autoimmune diseases, and cancer. With gene therapy advances, the entire industry will undergo a profound change as a growing number of chronic diseases are cured.

Today's gene therapy involves delivering genetic constructs that may include regulators of gene expression (either increasing or decreasing gene expression as required), genes encoding natural or non-natural proteins, and functions that modify micro-environmental conditions. The rich and expanding variety of well-understood genetic "tools" allow scientists and researchers to provide solutions to an increasing range of complex diseases, such as infectious diseases and cancers.

At the heart of gene technologies is the precision and power to correct expression of genes that underlie human disease. Ultimately, gene technologies will create a revolution in medicine that may surpass the impact of antibiotics and vaccines. American Gene Technologies (AGT), an emerging genetic medicine company with a proprietary lentiviral platform capable of broad applications, include large and orphan indications, immuno-oncology, and monogenic disorders, as well as other companies in this biotech sector, is at the forefront of a wave of innovation that will bring positive change throughout the healthcare system and relief to millions of patients that currently suffer from untreatable or incurable diseases.

### THE GROWTH OF GENE & CELL THERAPY

Although gene therapy was first envisioned in the 70s and attempted in the 80s, the first success was in the early 90s. The early successes in gene therapies, however, often had limited duration or unexpected and dangerous side effects. In the 90s, treating ADA-SCID (sometimes commonly called "bubble boy" disease) worked, but sometimes result in a serious side-effect: although a European experiment to treat ADA-SCID disease result in a cure, it appeared to cause leukemia for 2 out of 10 treated children.

In another gene therapy experiment in the late 90s, a death identified as being caused by a massive immune response to the treatment, temporarily put the brakes on further viral vector re-

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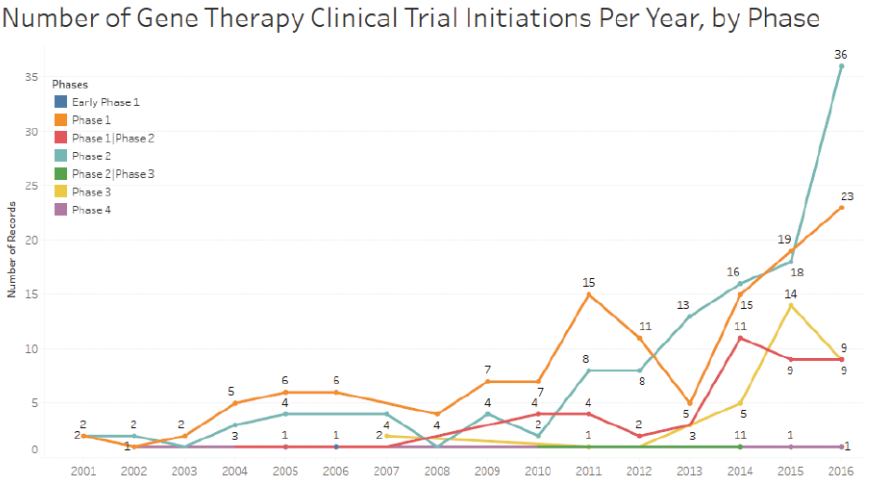
search and development in the US.

Nevertheless, gene therapy continued to evolve. Innovations continued in oncology and monogenic disorders. Mechanisms for better control of the delivery of the genetic materials and greater protection from unintended immune responses emerged. Medical research continued to gain insights into the sub-molecular functioning of genetic and biological drivers of diseases that in turn helped scientists develop gene therapies to more narrowly target and more safely treat diseases.

As the industry recovered from early missteps and failures, gene and cell therapy progressed in a manner that will fundamentally change healthcare. GlaxoSmithKline continued development on the ACA-SCID therapeutic removing elements of the viral vector that were thought to be at the root of the leukemia side-effect. Their successful "debugging" of the previous clinical attempt resulted in their year's approval of Strimvelis™ in Europe. Strimvelis is also expected to be approved in the US. The FDA has granted fast-track designations to a range of gene technology clinical trials, such as Novartis' CTL019 (tisagenlecleucel) for childhood leukemia and Kite Pharma's axicabtagene ciloleucel for non-Hodgkin's lymphoma. The Novartis drug not only received fast-track FDA review, it was unanimously recommended for approval by the FDA advisory committee on July 12, 2017 and is likely to receive FDA approval in September.

Although the number of approved drugs is still small, the number of gene therapy clinical trials is growing fast. According to clinicaltrials.gov, there were 49, 61, and 78 trials initiated in 2014, 2015, and 2016, respectively; 99 of these trials were in Phases 2 or 3 (see Figure 1). By comparison, prior to 2010, there were never more than 11 such trials initiated. These metrics demonstrate the growing body of evidence that many treatments are fundamentally safe, having moved beyond Phase 1. Many companies are also advancing in the clinic, including Sangamo Therapeutics, AveXis, and Bluebird Bio. Other gene and cell therapy companies, including American Gene Technologies are entering the clinical stage. This breadth of activity underscores the growing momentum of this promising technology.

**FIGURE 1**




**The industry-wide gene therapy pipeline shows exponential growth.**

Why are biotech scientists and key opinion leaders in biotech convinced that modern gene therapy will have a transformative impact on healthcare? The answer can be understood through parallels between computer coding and genetic coding. Human DNA is made up of nucleotides that are composed of four nucleobases (Cytosine, Guanine, Adenine, and Thymine or C,G,A, and T). These combine to form the DNA strands that specify the intricate ways genetic makeup governs how the human body functions. Gene and cell therapy uses this coding, with the growing understanding of the human genome to correct malfunctions (diseases) in the human body in a similar way to "updating" software on a computer. In fact, one could look at the bodies' coding of our "software" in C,G,A, and T as just a base-four version of computer code that is coded in base-two (0s and 1s). The "software" of the DNA is more complex than computer software, but it has much of the deterministic nature, power, and "rational design" aspects common to the programming of digital computers. The nature of this type of "coding" makes gene technologies a direct connection to the operation of the cell that is both powerful and accurate. The order of the C,G,A, and Ts in genes that make up "commands" to one's cells largely determine how those cells operate. This is highly similar to the way the order of the 0s and 1s form commands to a computer and determine what the computer executes.

The increasing ability to "hollow out" the malicious viral code inside viruses that have been infecting human bodies, now allows us the repurposing of a viruses' innate ability to deliver benevolent (update) code that improves the reliability of the programming. In fact, these new "updates" have the potential to eradicate viruses the way that updates on computers can repair viruses

"What has begun as a trickle of highly effective gene and cell therapeutics will soon become a steady stream. Eventually, a tidal-wave of cures and treatments will benefit patients and profoundly change healthcare outcomes forever. CAR-T immunotherapy and monogenic gene therapies using a range of viral vectors are at the forefront of this growing tide, and there are many other gene technology companies lining up to lead, follow, or support this field."

on a PC, Mac, or other computer device. Now there is have a swiftly growing ability to deliver DNA "updates" to specific cells in the body that can target disease much more accurately than traditional pharmaceuticals, and that act on those cells in highly specific ways. The result is a new class of drugs that powerfully change the root drivers of disease exactly where it resides, and highly limits treatment (and side effects) to non-diseased cells.

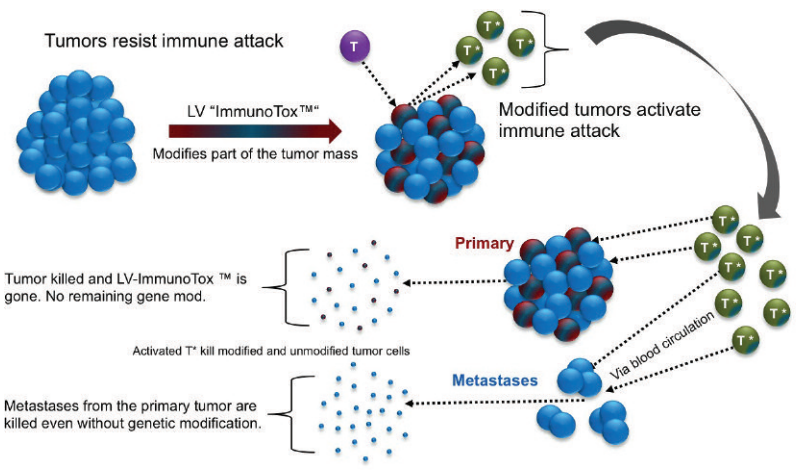
The confluence of the increased ability to deliver new "code" to cells, coupled with medical researchers' in depth understanding of the intricate workings of genes that determine cellular functions is presenting an opportunity to create a huge number of therapeutics that can substantially grow the ability to effectively (and efficiently) treat and cure disease.

The clinical application of this technology can span a broad set of serious diseases. AGT believes that immune-oncology can be significantly improved and expanded into solid tumors (which include most terminal cancers). AGT, has taken an alternative and innovative approach that "reprograms" cancer cells by lowering their defenses and secretory factors. This allows specialized cancer-surveillance T cells to greatly increase their activity against the tumor mass (up to 600 times of normal). AGT's therapeutics use the power of immuno-oncology without modifying the immune system itself. This is a critical innovation that can reduce the possibility of long-term side effects that have been a challenge to moving CAR-T forward into a wider variety of cancers.

Monogenic diseases are also an obvious target for gene therapy cures. They tend to be the result of single gene mutations or dysfunctions that can lend themselves to viral vector-delivered gene replacement. For example, AGT has a strategy to "reprogram" a set of cells in phenylketonuria (PKU) patients to permanently supply sufficient quantities of phenylalanine hydroxylate to mitigate the disease. This could result in a lifetime cure of this debilitating disease by restoring a critical biological pathway that would prevent the toxic buildup of phenylalanine in the blood of PKU patients while providing essential tyrosine downstream to maintain healthy development of nerves in the brain.

Another gene therapy class of targets

**FIGURE 2**




**The AGT therapeutic for cancer is anticipated to be broadly applicable and safe.**

is infectious diseases. Serious viral infections, including Hepatitis B and C, Tuberculosis, and HIV can be inhibited or blocked through a range of gene therapy approaches. AGT's first clinical trial will be an HIV functional cure in the first quarter of 2018. AGT's therapeutic strategy uses gene modulation both to reduce the levels of CCR5 (which can prevent cells from being penetrated by HIV thus preventing HIV from "planting" itself in healthy cells) and shut down the HIV gene expression in infected cells (thus restoring normal function to the infected cells and preventing the virus from producing new virions that attempt to infect neighboring cells). AGT's therapeutic lentivirus and cell therapy treatment is expected to restore natural immunity to HIV in HIV-infected persons; mitigating the effects of the disease and even preventing reinfection over the remainder of an individual's lifetime.

## THE TRANSFORMATION HAS BEGUN

What has begun as a trickle of highly effective gene and cell therapeutics will soon become a steady stream. Eventually, a tidal-wave of cures and treatments will benefit patients and profoundly change healthcare outcomes forever. CAR-T immunotherapy and monogenic gene therapies using a range of viral vectors are at the forefront of this growing tide. There are many other gene technology companies lining up to lead, follow, or support this field.

The coming revolution in disease therapies will not only change health treatments and outcomes, it will fundamentally change care delivery. Today's medical products and treatments are created and delivered around an economic model that substantially depends on chronic or sustained treatment of non-acute illness. Many core components of the healthcare system are on the fault line of gene therapy disruption, including non-curative blockbuster drugs based on older drug technologies; devices that diagnose, monitor, and manage illness; care delivery; medical staffing; and standards of care that specify periodic visits, tests, and the modifications of chronic care treatments. Sustained, long-term cures will greatly reduce or eliminate the need for many of these services and the products used to manage the diseases.

## CONCLUSION

Across the industry, biotech companies are making significant progress in driving the shift from disease management to cures. This transition will result in the profound disruption of the healthcare industry as many current treatments are replaced by more effective genetic treatments and even cures. As gene and cell therapy become established therapeutic modalities, a portion of pharma companies will adapt to these changes by incorporating the technologies into their own therapeutic discovery efforts, as well as aggressively in-licensing new gene therapeutics at increasingly earlier development stages.

As the pace of gene and cell therapies accelerates over this next decade, potential cures for chronic diseases (diabetes, RA, hypertension, Alzheimer's, Parkinson's etc.), cancer cures, and autosomal (inherited) defect cures will result. The efficacy of new therapeutics may move as much as $500 billion (per year in revenue) from traditional pharmaceuticals to gene technologies. Overall, treatment costs are likely to go down, not only because the cost and payment models will be different, but also because cures for diseases will be less costly overall than the long-term expense of traditional chronic care and palliative treatment of serious human disorders.

While pharmaceutical and healthcare delivery companies retool themselves to adapt to (and even survive) the sea-change in medicine, the patient and the public will benefit with increased solutions to traditionally evasive health disorders; solutions that raise the efficacy bar while lowering overall costs – providing a significantly more economically efficient healthcare system.◆

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## BIOGRAPHY

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# OPHTHALMIC SQUEEZE DISPENSER

## Eliminating the Need for Additives in Multidose Preservative-Free Eyecare Formulations

By: Degenhard Marx, PhD, and Matthias Birkhoff

### INTRODUCTION

In 1892, Dr. Rudolf Rempel patented a clever system for food conservation that did not require any additives or chemicals, such as salt, acids, ethanol, or sugar, be added to food for this purpose. This method quickly became famous around the world when it was successfully commercialized by Johann Weck, as in the Weck jars with the typical rubber rings.[1] Chances are great that a simple and reliable system for eye drops will become as successful in the world of ophthalmology as the Weck jar was in the food arena.

The wider use of eye drops started in the 1960s with thiomersal-preserved drops out of small glass vials. Thiomersal is an organomercury compound with antiseptic and antifungal properties. It was very effective, but quickly caused a number of severe side effects attributed to this preservative, and multidose droppers were switched to benzalkonium chloride (BAC).[2] BAC is much better tolerated; however, recent scientific evidence makes it obsolete, in particular for treatment of chronic ocular diseases.[3] This generated a demand for cost-effective multidose eye drop delivery systems that allow preservative-free formulations for long-term treatments, such as chronic dry eye and glaucoma. There are a few systems on the market, which claim to work without any preservatives, but not all systems are as pure and innovative as the Weck jar. Therefore, the following will serve to review the current available systems. One of these is Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD), a multidose dropper that relies solely on mechanical measures to prevent microbial contamination of the bottle content. It is widely available in Europe and around the world for OTC products, and was recently approved for use with Allergan's Restasis MultiDose™ eye drops in the US. This system has also been approved by regulatory bodies worldwide for other prescription products, such as for the treatment of increased intraocular pressure.

### TYPES OF EYE DROP PACKAGING FOR PRESERVATIVE-FREE FORMULATIONS

As of today, the most widely-used technology for unpreserved eye drops are blow-fill-seal (BFS) single-dose droppers. BFS is the filling technology used for liquid products during which the polymer containers are manufactured, filled, and sealed in a single

**FIGURE 1**

**Blow-Fill-Seal Single-Dose Units**

cycle. This very simple packaging is a variation of the Rommelag bottlepack system and became established in the field of eye drops in the 1970s. It is used for ophthalmic medications and allows for single doses with a volume between approximately 0.3 ml and 1.0 ml. The process requires substantial overfill, which make the single dose much more expensive compared to multidose dispensers. Depending on the shape and size, such droppers are not always easy to handle for people with limited dexterity and/or visual impairment. A more recently raised concern is the considerable amount of plastic waste generated by this kind of single-use packaging.

In the early 1990s, AeroPump's Comod® multidose pump for eye drops emerged in Europe.[4] There is a similar nasal spray pump (3K®-System) on the market that applies the same measures to prevent microbial contamination. Although claimed to be "preservative-free," the liquid resting at the outlet orifice is protected from microbial contamination by a silver wire placed in the proximity of the outlet tip. The formulation is filled in a special container with a collapsing bag, which protects it from contact with ambient air. The actuation force of ~25-28 N for eye drops containing hyaluronic acid (tested on commercially available HyloComod® and HyloGel® drops) is quite high compared to standard 3-piece squeeze bottles, which are in the range of 7-10 N. The actuation maneuver is similar to nasal spray pumps and requires some movement directed toward the eyes. This mode of actuation is not appreciated by all patients.[5]

In 1989, Thea Laboratories introduced the first generation of its ABAK® system.[6] A preserved formulation was filtered through a microporous pad, which removed the preservative before the drop

**FIGURE 2**


**Preservative-Free Multidose Containers Based on Pump Systems**

reached the eye. The early systems also contained some silver mesh around the dosing orifice. The system was improved step-by-step, and the current version relies on the sterile filtration of the eye drops via a special microporous pad and a hydrophilic membrane. Thus, in the current version, the formulation must not contain any preservatives. The porous pad and the hydrophilic membrane cause substantial resistance in the product flow path, which results in actuation forces in the range of 17-20 N (tested with Hyabak® 0.15% hyaluronic acid from Thea Laboratories). In addition, the design of the pad and the membrane limit the use of this technology to formulations with low viscosity.

The first product using Aptar Pharma's Ophthalmic Squeeze Dispenser was introduced into the market in 2011 with TRB Chemedica's new VISMED® MULTI eye drops. This preservative-free system follows a purely mechanical approach. The key feature is the spring-loaded tip seal. This spring-loaded valve is located directly below the opening of the tip orifice and does not allow any microbes to migrate from any surfaces or from contacted liquids into the system. The tip seal keeps the system closed until a defined pressure is reached by actuation, then the formulation is forced through the orifice. When the pressure drops at the end of the actuation, the tip seal will immediately close the orifice with an outward movement. No backflow of potentially contaminated medication or other liquid is possible. As opposed to alternative systems for unpreserved ophthalmic medications, the liquid is not filtered, nor does it get in contact with metal parts at any time. Only the venting air required to equilibrate the container after dispensing is sterile filtered using a small filter element, preventing microbial contamination via this route. The mode of actuation is a simple squeezing of the container, which is no different from millions of bottles used for preserved medications. The Ophthalmic Squeeze Dispenser has been well received by the market. As of today, more than 125 marketed products worldwide are equipped with OSD technology, both for prescription medications and consumer products, such as artificial

FIGURE 3

**Multidose Preservative-Free Squeeze Bottles**

tears. In 2016, the US FDA approved Allergan's Restasis MultiDose™ as the first prescription medication using a preservative-free multidose eye dropper.

In 2010, Rexam (now Nemera) introduced their Novelia® system. It uses a similar technology as the Ophthalmic Squeeze Dispenser but with some important differences: it features a silicone tube-based valve mechanism named PureFlow™ Technology, and the container is vented via air diffusion through a silicone membrane. To ensure microbial integrity, silver is added to the plastic material of the actuator, protection cap, and silicone valve for the design currently available. Consequently, the patient information leaflets of recently approved prescription products contain a warning "If you have a history of contact hypersensitivity to silver, you should not use this product."[7] In April 2017, Nemera announced the availability of a special vented cap for the Novelia® dropper to address the challenges of particularly sticky formulations. Current publicly available information does not make clear yet if the silver additives might become obsolete with the use of this new cap.

FIGURE 4


**Restasis MultiDose™ with Aptar Pharma's Ophthalmic Squeeze Dispenser**

## ANTI-MICROBIAL ADDITIVES IN PACKAGING MATERIAL FOR OPHTHALMIC FORMULATIONS

Quite a few elements are available and used for their oligodynamic, or antimicrobial, properties in packaging materials, but among these, silver is certainly the dominant additive. Silver is widely used for its antiseptic properties as it is effective and considered safe. In the healthcare industry, silver is used to sanitize water, as wound dressing, or to prevent biofilm formation on catheters. To exert its biocidal effects, silver ions must be released into the formulation or body fluid, so they can then interact with bacteria cell walls following accidental contamination. Therefore, when used in packaging material, it must be taken into consideration that the silver ions will be released and also react with the formulation. Before adding some silver master batches into packaging material, one should consider the consequences for the development of the container closure system. Such an additive should have no impact on the suitability, compatibility, or safety of the construction materials nor compromise the efficacy, stability, or quality of the drug product.

Silver is not listed in the USP chapter <232> Elemental Impurities, but is covered within the ICH Guidance for Industry Q3D on Elemental impurities published in 2015. The ICH guidance classifies silver as a Class 2B element, which means they have a reduced probability of occurrence in a drug product. Therefore, under normal conditions, silver can be excluded from the risk assessment unless it is intentionally added during the manufacturing of drug substances, excipients, or other drug product components. Thus, a risk assessment and mitigation strategy is required when silver is used as an antimicrobial in the container closure material. In addition, it must be assumed that the silver interacts with the drug product to exert its protective properties. As a consequence, it is imperative to "evaluate the presence of a particular elemental impurity in the drug product

by determining the observed or predicted level of the impurity and comparing with the established PDE" (permitted daily exposure). Based on the recommended dosing regimen for the drug product (dose frequency and dose volume) the likely exposure can be calculated. For silver exposure via the oral route the PDE is 167 µg/day, for parenteral administration 14 µg/day, and for inhalation 7 µg/day, but no value is provided for topical administration (ICH Q3D Guideline). In general, if the calculated exposure values for an element are below the published limits, the container closure system may be used for this particular medication. On the other hand, it should be pointed out that this is not a one-size-fits-all approach, as there are many influencing factors, including formulation properties and dose regimen.

Recently, another additive called PyClear from Pylote SA in France emerged in the public domain. The key to this technology are mineral microspheres, which are incorporated into the packaging material and which are generally agreed to be responsible for the « Pylote effect ». An abstract was published showing antimicrobial efficacy of PyClear in some multidose eye droppers in a challenge study.[8] Unfortunately, the paper provided no clear explanation for the antimicrobial action mechanism nor for its potential interaction with the formulation. Also, data from real in-use studies and from after longer storage are missing. It is fair to assume that more scientific work is required before this technology finds its way into pharmaceutical product dispensing systems. Regulatory authorities, for good reason, are quite formal regarding data requirements and it is likely that a PDE for the "Pylote effect" needs to be established.

It is important to understand that when incorporating an antimicrobial into a medical device or packaging material, data needs to be generated to justify its use and its efficacy. In July 2007, the US FDA released a draft guidance document titled Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents.[9] Even 10 years later, a final guidance document has not been issued, but this 2007 draft version provides some guidance on critical information that would be required for a submission:

- Detailed description of antimicrobial chemistry and any ancillary components, such as lubricious coatings used as the carrier for the antimicrobial additive
- Detailed description of the action mechanism, spectrum of activity of the antimicrobial agent, and minimum effective concentration
- Release kinetics and description of the release mechanism
- Detailed description of the distribution kinetics, toxicity, metabolites, and degradation products in the human body

As such, adding an antimicrobial into the packaging material will certainly increase the complexity of the development process. Evaluating potential leachable as well as degradation products resulting from a sterilization process and its interactions with the formulation may become cumbersome. This is one reason why Aptar Pharma recommends and follows the aforementioned purely mechanical approach for its Ophthalmic Squeeze Dispenser.

## CONTINUOUS IMPROVEMENT OF THE OPHTHALMIC SQUEEZE DISPENSER

Given the importance of vision to one's quality of life, it is difficult to establish a new packaging concept on the market intended for such a critical product as ophthalmic remedies, regardless of whether these are consumer products or prescription medications. The system must be safe and easy-to-use as no one should risk an eye. In addition, regulatory authorities and notified bodies need to be convinced that the new product is safe.

When developing the Ophthalmic Squeeze Dispenser, Aptar Pharma focused primarily on the microbial integrity and robustness of the new packaging system. Keeping this in mind, it is easier to understand that initial versions of the Ophthalmic Squeeze Dispenser required a squeeze force, or actuation force, that was comparably high, in the range of 30 N for a 10-ml bottle containing only 2 ml of liquid. This was due to the high tip seal opening pressure, considered necessary to ensure microbial integrity even under heavy microbial challenge conditions.

Based on feedback from the market, authorities and further research, the Ophthalmic Squeeze Dispenser, with its microbial barriers, was optimized without any compromise in terms of microbiological integrity and patient safety. In addition, the container, which is an integral part of the device, was improved. A limited offering back when the technology was originally launched in 2011, today a full range of containers is available that can be used for the Ophthalmic Squeeze Dispenser. These containers vary with respect to volume, geometry, and material (eg, polyethylene and COC) and as such offer various op-

## FIGURE 5

**Versatility of the Ophthalmic Squeeze Dispenser Technology Platform**

portunities for both developers and marketers. With the "next-generation" containers available today, the actuation force is notably reduced and is now in the range of 10-20 N without compromising microbial barrier functions.

Other additional features have been developed. For example, even though the membrane utilized to filter the incoming air is hydrophobic, some formulations tend to impair the ventilation properties of that membrane. To prevent this, a feature is available to permanently protect the filter from contact with the formulation. For liquids that tend to crystalize, a cap version with a special liner pad is available that reliably maintains the proper function of the Ophthalmic Squeeze Dispenser. The demand for additional protection prior to first use that are requested from certain regulatory bodies are addressed with a range of different options for the cap design.

Aptar Pharma recently partnered with Kali Care to combine the Ophthalmic Squeeze Dispenser with the world's first digital monitoring system for ophthalmic medications. This revolutionary technology will replace assumptions currently made in clinical trials by the collection of objective data, and will likely improve the poor adherence rates of only 43%-78% among patients receiving treatment for chronic eye conditions.[10]

The Ophthalmic Squeeze Dispenser is not a simple dropper but a versatile and flexible technology platform that can be adapted to a wide range of formulations. The process to identify the optimal configuration is well established. Lastly, its purely mechanical approach avoids the hassle associated with the extensive characterization of debatable additives. ◆

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## BIOGRAPHIES

**Dr. Degenhard Marx** is Director, Scientific Affairs at Aptar Pharma. Following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig in 1992, he joined the pharmaceutical industry. There, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he became Business Development Manager within Aptar Pharma.

**Matthias Birkhoff** is Vice President Business Development at Aptar Pharma. In this role he is responsible for Aptar Pharma's Eye Care program and coordinates research and development activities, microbiological assessment and commercial strategies. Matthias started his career in pharmaceutical sales at a major multinational pharmaco before joining Aptar Pharma nineteen years ago. Prior to his involvement in Business Development and Marketing, Matthias was in charge of sales in the AsiaPacific region. He studied medicine at the University of Dusseldorf, Germany and holds a nursing degree. Matthias has recently spoken at international events, such as NDD (Nasal Drug Delivery), London/UK, PMP (Pharmaceutical Plastics), Copenhagen/Denmark, Interphex, Tokyo/Japan, CPHI, Pharmapack, AAPS, or the IPA conference in Mumbai/India

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# TABLET FORMULATION

## Reformulation of Tablets to Resolve Sticking and Picking Issues Faced on Compression: A Case Study

By: Smruti P. Chaudhari, PhD, and Anshul Gupte, PhD

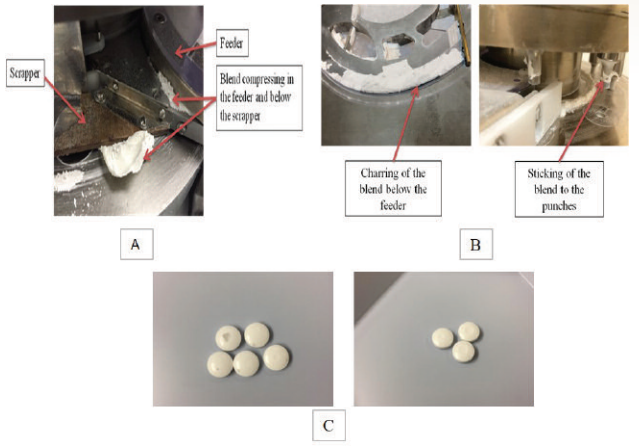
### PURPOSE

In this study, Metrics Contract Services was tasked with a complex re-formulation project. Briefly, the free-acid form of an API, Compound XY, was previously manufactured as 5-mg, 10-mg, and 25-mg strength tablets using direct compression process. But the free-acid form of the compound proved to be poorly soluble in aqueous media. Hence, to increase the solubility of Compound XY, a salt form of the drug was explored.[1] Out of all the salt forms investigated, potassium-salt was found to be the least sticky and least hygroscopic; therefore, it was selected for further study.

Metrics scientists were tasked with manufacturing the potassium-salt form tablets of Compound XY at all of the above strengths using the same tablet composition used to produce the free-acid form tablets. While manufacturing the potassium-salt form tablets, Metrics scientists observed various problematic issues described further. The blend flow from the hopper to die cavity was very poor, resulting in undesired weight variation. Additionally, the tablet surface showed discoloration, an effect that worsened with increasing tablet strength.

As a result of the study presented here, the potassium-salt form of Compound XY was reformulated to yield tablets of acceptable dissolution, weight, properties, and appearance without adding any new excipients to the formulation.

**FIGURE 1**




**A: Sticking of the Compound XY tablet blend in the feeder and below the scrapper.**
**B: Charring of the blend below the feeder and sticking to the punches.**
**C: Tablets show discoloration on tablet surface and picking in center.**

### BACKGROUND

The tablet weight of both the 5-mg and 10-mg formulations was 64 mg; the tablet weight of the 25-mg formulation was 160 mg. In order to expedite the reformulation development, it was decided to follow the same formulation process originally used to manufacture the free-form of Compound XY. Diverting from the previous formulation process would have affected the analytical methods.

During the manufacturing of 10-mg strength of Compound XY, scientists observed weight variation, so the tablet press was adjusted to accommodate the tablet weight. At this point, discoloration was observed on the tablet surface. Hence, the tablet

press was disassembled, and the feed frame was inspected. It was discovered that the powder blend itself was discoloring as a part of the compression event. Additionally, the blend was sticking to the feed frame and the die table. Figure 1A shows the sticking of the blend to the die table and the scrapper.

To avoid discoloration and resulting tablet weight variation, scientists stopped the tablet press every 5 minutes to remove and clean the scrapper. They conducted an all-process test to inspect issues such as hardness, thickness, and disintegration; everything met project specifications. Hence, compression was continued and yielded tablets with acceptable properties.

Similar compression issues were seen while manufacturing the 25-mg strength tablets of Compound XY. Indeed, due to the fact that the 25-mg strength contained the highest amount of API, those tablets delivered the worst results in terms of surface discoloration, sticking, picking, and chipping. The blend was sticking beneath the feeding and getting charred. It is seen in Figure 1B. The blend also was sticking to upper and lower tooling.

The tablet surface showed discoloration and picking in the center of the tablet, shown in Figure 1C. Scientists observed that some of the tablets were capped as they came off the press, but no capping was seen in friability. In order to circumvent these issues, scientists compressed the blend at a very slow speed of 5 rpm. Despite reducing speed, the same issues were observed. Scientists thus concluded that the compression problems were caused not by the compression process but, rather, by the inherently sticky nature of the blend. In order to resolve this issue, scientists studied the formulation composition of these tablets to identify the root causes of the stickiness.

**TABLE 1**

| Testing | | Original Formulation | Reformulation |
|---|---|---|---|
| Impurity (RRT 1.87) | Initial | 0 | 0.16 |
| | 1 month | 0 | 0.16 |
| | 3 month | 0 | 0.16 |
| | 6 month | 0.18 | - |
| Assay | Initial | 103.8 | 99.4 |
| | 1 month | 102.5 | 101.4 |
| | 3 month | 103 | 99.6 |
| | 6 month | 100 | - |
| Moisture | Initial | 2.8 | 5.1 |
| | 1 month | 2.9 | 5.4 |
| | 3 month | 3.2 | 5.9 |
| | 6 month | 3.6 | - |

**Analysis of stability samples of Compound XY tablets, 25 mg.**

A direct compression process had been employed to manufacture tablets of Compound XY. Direct compression is a well-known and popular choice for manufacturing tablets given its speed and efficiency and because it is the least complex way to manufacture tablets. In this process, the API was blended with excipients and lubricated and then followed by compression. A wide variety of APIs that are heat and moisture-sensitive can be used in this type of process. However, one must be cautious when selecting excipients during this process compared to other processes, such as granulation. Excipients used in this process must demonstrate good flowability and compression for successful operation.[2]

The original formulation of the tablets contained silicified microcrystalline cellulose (Prosolv SMCC 90), mannitol, and Avicel HFE as inactive excipients. They were primarily used as a diluent; crospovidone was used as a disintegrating agent, and magnesium stearate was used as lubricant. The drug loading was 17 w/w in the original formulation.

Silicified microcrystalline cellulose is a pre-mixed blend of colloidal silicon dioxide and microcrystalline cellulose. Avicel HFE is a mixture of mannitol and microcrystalline cellulose; it contains 8% to 12% mannitol. In all, this formulation was made up of more than 45% mannitol.

Mannitol is known within the pharmaceutical industry to cause stickiness during compression, a problem exacerbated by the potassium-salt form of Compound XY, which is sticky in nature.[3]

Also, formulations containing mannitol require lubricants because they are less flowable. The study conducted by Hutchins et al shows that as the percentage of lubricant in mannitol-containing formulation is increased, the sticking of the powder blend to the punch surface decreases.[3] Hence, it was concluded that mannitol had a relatively high affinity for the metal punch surface, which is reduced by addition of the lubricant.

The effect of mannitol grade on sticking was also evaluated. Powdered mannitol shows higher sticking propensity as compared to granular mannitol. It was shown that diluting the mannitol blend with microcrystalline cellulose and 1% magne-

"A direct compression process had been employed to manufacture tablets of Compound XY. Direct compression is a well-known and popular choice for manufacturing tablets given its speed and efficiency and because it is the least complex way to manufacture tablets. In this process, the API was blended with excipients and lubricated and then followed by compression. A wide variety of APIs that are heat and moisture-sensitive can be used in this type of process. However, one must be cautious when selecting excipients during this process compared to other processes, such as granulation."

sium stearate decreased the sticking propensity of the blend. Based on the literature, it was concluded that to resolve the sticking and flowability issue, scientists needed to replace or reduce the amount of mannitol from the original formulation of Compound XY.

Inactive excipients can be removed from formulations without adversely affecting analytical methods. It is when scientists add new inactive excipients that they could detrimentally affect analytical methods for the product or at the least would cause methods to be re-evaluated.

## METHOD

The direct compression process was used to formulate tablets of Compound XY using common blend approach. Trials consisted of screening three commonly used diluents: Prosolv SMCC90, Avicel PH102, and Avicel PH200. The percentages of excipients crospovidone and magnesium stearate used in the original formulation were kept the same in all reformulations.

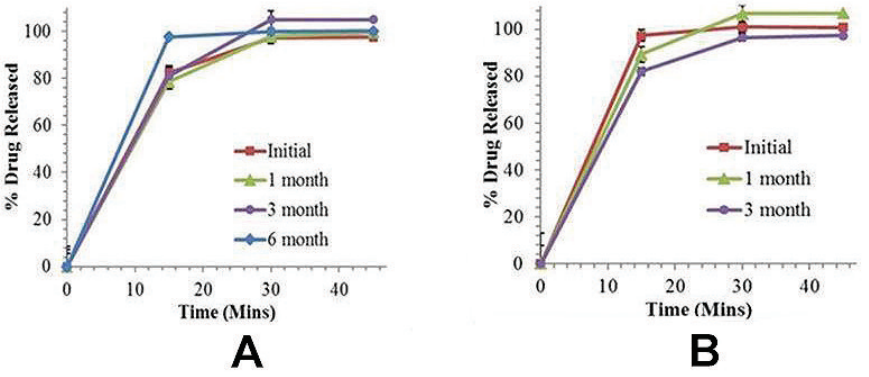
Powder properties such as bulk density, tap density, and Flodex were studied. Selected formulations were scaled up, and tablets were compressed using rotary tablet press. Tablet physical properties, such as friability, thickness, and disintegration, were studied, and a stability study was conducted. Tablets were packaged in 30-count in 60 cc bottles fitted with 33-mm cap with induction seal for stability study at 40°C and 75% RH, an industry standard.

## RESULTS & DISCUSSION

In order to replace or reduce the amount of mannitol, scientists conducted several formulation trials to identify appropriate diluents. The goal was to use direct compression process and have the blend show good flowability because this was expected to resolve the challenge of weight variation. Inactive excipients, such as Prosolv SMCC90, Avicel PH102, and Avicel PH200, were used in order to investigate improving the flow property of the blend.

A common blend approach was chosen to manufacture 5-mg, 10-mg, and 25-mg tablets. In order to use common blend approach, tablet weight of the 25-mg formulation was increased to 300 mg. The percentage of crospovidone and magne-

**FIGURE 2**




**A: Dissolution profile of Compound XY tablets, 25 mg, original formulation stored at 40ºC/75% RH.**
**B: Dissolution profile of Compound XY tablets, 25 mg, reformulation stored at 40ºC/75% RH.**

sium stearate was kept the same. The tablet blends were manufactured using diluents like Prosolv SMCC 90, Avicel PH102, Avicel PH200, and a combination of Prosolv SMCC 90 and mannitol.

The flow property of the blend was measured using the Flodex powder analyzer. The Flodex of the Prosolv SMCC 90 blend was found to be 16 mm; the Flodex of Avicel PH 102 blend was 20 mm; the Avicel PH 200 blend did not flow in Flodex, and the Flodex of Prosolv SMCC 90 and mannitol blend was found to be 20 mm.

Out of all diluents studied, the blend manufactured using Prosolv SMCC 90 had the best flow compared to other diluents. To improve flow further, scientists added 1% colloidal silicon dioxide to the blend. Addition of 1% colloidal silicon dioxide improved the flow property to 12-mm Flodex. The reformulated tablets had lower drug loading as compared to original formulation, and the percentage of Prosolv SMCC 90 was increased from 25.94% to 84.36% in the reformulated tablets. All percentages of all other excipients like crospovidone and magnesium stearate were kept the same. Compression of this blend showed acceptable physical and dissolution properties with no discoloration on tablet surface and no sticking or picking.

A stability study of original formulation and reformulation batches of Compound XY was carried out in 40°C/75% RH. The 3-month and 6-month stability samples of the original formulation of Compound XY revealed tan spots on the tablet surface. In addition, the 6-month analysis of Compound XY tablets, 25 mg, revealed a split tablet. These issues were also observed during compression of Compound XY Tablets, 25 mg. The stress relaxation in the tablets was one of the probable causes of the tablets splitting during stability study.

The dissolution profile of the original Compound XY tablets, 25 mg, and reformulated tablets of Compound XY, 25 mg, and its stability samples is shown in Figure 2A and 2B, respectively. Scientists observed that accelerated stability conditions had no effect on the dissolution profiles of either the original or reformulated batches of Compound XY tablets, 25 mg.

Table 1 shows the analysis and impurity profiles on the stability samples of the Compound XY tablets, 25 mg. The original formulation shows the impurity at RRT 1.87 at the 6-month time point, whereas the reformulated batch shows the impurity at RRT 1.87 in initial testing which remained constant over time.

## CONCLUSION

Metrics scientists successfully reformulated tablets using the potassium-salt form of Compound XY without adding any new excipient. Through the reformulation, scientists also resolved earlier issues faced during tablet compression, namely sticking, picking, poor flow, weight variation, and discoloration.◆

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## BIOGRAPHIES


**Dr. Smruti P. Chaudhari** is Development Scientist I at Metrics Contract Services, where she is responsible for preformulation, formulation, and process development, and clinical manufacturing for projects from pre-IND phase through Phase III. She also manages scale-up and technology transfers for solid oral dosage forms. She earned her PhD in Pharmaceutics and Drug Design from Long Island University, from which she previously earned her MSc in Industrial Pharmacy.



**Dr. Anshul Gupte** manages all aspects of operations related to formulation and manufacturing of a client's clinical trial materials. As Associate Director, he supervises a team of formulation scientists, specialists, and technicians who develop solid dose formulations for Phase I-III clinical trials — and who scale-up and validate those materials as needed. He oversees clinical trial batch manufacturing and packaging under cGMP guidelines, supervises technology transfers, and documents clinical trial material batch records.

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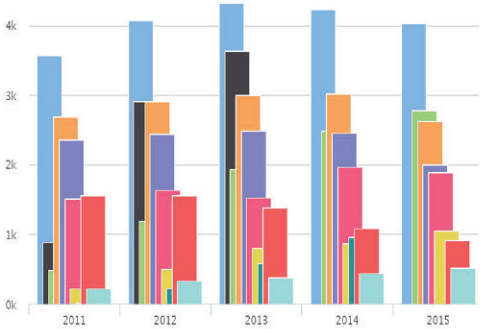


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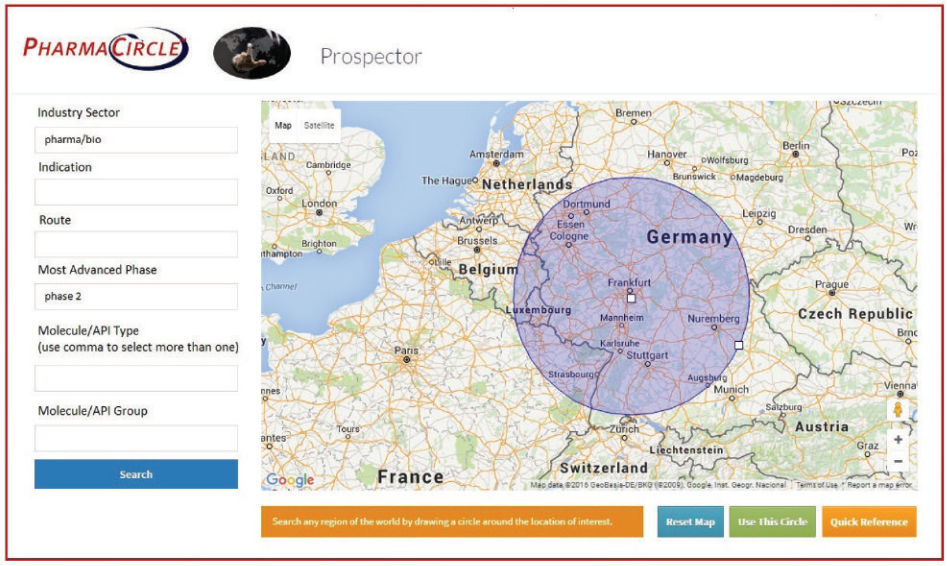


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# Particle Sciences: Experts in Development & Manufacturing of Complex Dosage Forms

As insoluble drugs are now the norm, and targeted, niche therapies are often the strategy of choice, pharmaceutical companies are continuously searching for partners who can address the unique set of needs these complex products present. Particle Sciences has established themselves as the partner of choice for the development and manufacturing of complex dosage forms, and throughout the past 25 years, has built a leading portfolio of capabilities in this area. The Lubrizol Corporation, a Berkshire Hathaway company, recognized this value and acquired Particle Sciences in 2015. Particle Sciences is currently part of their LifeSciences business unit. Since that time, the company has been investing heavily in both technologies and facilities to meet the demand of this growing sector. Staffed by industry experts, the company focuses on complex products providing formulation and a comprehensive suite of supporting services, including analytic, bioanalytic, physical characterization, and manufacturing. An array of standard and proprietary technologies, as well as the ability to deal with poorly soluble and highly potent compounds under GxPs in both sterile and non-sterile environments, distinguishes Particle Sciences from others. Drug Development & Delivery recently spoke with Dr. Mark Mitchnick, CEO of Particle Sciences and CMO of Lubrizol, to discuss the rise of complex drug products, the capabilities needed to develop and manufacture these products, and the company's expansion in this area.

**Q: What are considered Complex Drug Products?**

**A**: The term "complex" when used to describe drug products, used to be synonymous with uncommon. However, with the rise of insoluble APIs, biologics, and 505(b)2 applications, complex dosage forms are now a first-line approach. And with this trend, the definition of complex drug products has been broadened to dosage forms that for one reason or another present an atypical challenge in either manufacturing and/or administration.

While it is clear that complex products are gaining popularity, and there are literally hundreds of advanced delivery platforms in development, only a handful of technologies are of practical use at this time. Product technology examples in this sector include nanoparticles, drug-eluting devices, liposomes, polymeric microparticles, and so forth. Complex processing challenges include, among others, aseptic manufacturing, the inclusion of highly potent compounds, milling, spray drying, extrusion, and microfluidization. Our team has purpose-built our capabilities around these technologies and processes to meet the needs of our clients tackling complex drug products.

**Q: Why has there been such an increase in the use of complex approaches?**

**A**: There are two main drivers for this. First, newer therapeutics are frequently not amenable to simple approaches, such as traditional solid oral dosage forms. For small molecules, this is usually related to bioavailability – the API is not soluble and/or has low permeability. For large molecules, bioavailability (oral) is also a common concern, and in addition, stability issues are often present. In all of these cases, various complex approaches can help. For example, a typical BCSII small molecule's oral bioavailability can usually be substantially increased by reducing particle size.

The second driver for the increased interest in complex approach forms is the trend toward 505(b)2 products. These approaches can greatly improve convenience, economics, and even efficacy. In addition, intellectual property can be gained or circumvented using this approach. As an example, long-acting depots have been developed for indications ranging from antivirals to CNS indications to contraception. These long-acting products significantly improve compliance, and thus outcomes, and provide additional economic opportunities for their sponsors.

**Q: How does one develop a product based on complex approaches?**

**A:** Generally speaking, the development process is the same as any other dosage form. For success, the developer needs to assess an array of approaches and should, from the beginning, take into account the characteristics unique to the particular dosage form. We believe it is our extensive experience in a wide range of technologies that make us uniquely capable. Highly specialized unit operations, working with controlled substances and aseptic manufacturing are all well within our capabilities at Particle Sciences. In 2015 alone, we ran nearly 50 cGMP batches for clinical trials on products ranging from vaginal rings to depot injections to microparticle-based tablets to solution and particulate-based eye drops. During preformulation, it is especially important to understand the implications of the downstream processing. For example, drug/excipient compatibility should be performed under conditions similar to that which might be experienced during production. Extrusion and wet milling present very different kinds of stresses to the product components, and simulating those early on can save significant time and money down the road.

Another area of focus is physical characterization. Though we encourage thorough physical analysis of all applicable dosage forms, this is especially true in the case of some complex forms. For example, analytic methods for particulates can be quite distinct from other forms, especially in the case of dissolution testing. Physical characterization of complex dosage forms is the backbone of our developmental process at Particle Sciences and is something that our clients recognize as differentiating as it is a skillset not widely available in the industry today.

"There are a couple of things to keep in mind in selecting a contract development and manufacturing organization (CDMO) partner. First, no single technology addresses everyone's needs. In fact, no single technology addresses even the majority of needs. Therefore, partnering with a group that is not limited to a specific platform is key. In today's environment, a CDMO should have multiple approaches that span the range of commonly encountered problems."

**Q: What are the main challenges facing Biopharma when looking to find a CDMO for the development of a complex product?**

**A:** There are a couple of things to keep in mind in selecting a contract development and manufacturing organization (CDMO) partner. First, no single technology addresses everyone's needs. In fact, no single technology addresses even the majority of needs. Therefore, partnering with a group that is not limited to a specific platform is key. In today's environment, a CDMO should have multiple approaches that span the range of commonly encountered problems.

Second, adequate chemical and physical characterization of the drug product is as important as the formulation itself. This requires not only a great deal of instrumentation and a knowledgeable staff but also the experience to know what is important both from a scientific and regulatory perspective. Something as seemingly straight forward as measuring particle size distribution requires an understanding of how the instrument makes the measurements and the underlying algorithms used in data analysis. Here, as an example, most of the algorithms assume a perfectly spherical particle, and this is rarely the case. Knowing how to translate the development data into a viable QC method is a skill only learned through experience.

There are many things to look for in a development partner, but a third capability worth mentioning is the ability to bring the product into the clinic and preferably through to commercial production. Transferring a complex product from a preclinical developer to a separate clinical material manufacture is both costly and time-consuming. CDMOs that have cGMP manufacturing capability tied directly to the development group are much more attuned to the need to develop products that are amenable to scale-up and production.

**Q: How has the expansion of Particle Sciences grown your ability to meet the complex dosage market?**

**A**: We have invested heavily into acquiring an unparalleled array of technologies and capabilities ranging from drug-eluting devices to polymeric particulates to aseptic nano-milling to lyophilization. Our cGMP suites include ISO5 areas, isolators, dedicated high-potency compound rooms, and a wide variety of unit operations. This broad capability has been key to our success and to our returning customer base. We place great value on the client relationship, and our high-touch approach has resulted in many repeat customers across a variety of projects.

Clients look to us to stay current on the emerging trends in the complex market place, and they are willing to support this knowledge-base and expertise. In fact, the continued growth of the company has allowed us to in-license new technologies to offer our customers who are seeking proprietary protection via formulation approaches. We pride ourselves on our ability to

absorb new technologies while maintaining state-of-the-art facilities and QA programs.

It is the recognition of our differentiated approach that has allowed us to expand, and in late 2017, we will be bringing our new commercial facility on line. This facility will service both products we have developed for clients and those that are being transferred to us after development by our biopharma customers.

**Q: With such broad formulation capabilities, how did you decide what products to accommodate in your Commercial Manufacturing Facility?**

**A**: As highlighted earlier, while the CDMO market for finished dosage forms is substantial and generally well served, there is a lack of manufacturing capacity for complex drug products. Such a facility requires not only purpose-built infrastructure but a specialized staff. For our commercial facility, we focus on products that can leverage our expertise and where there is the most demand.

Designed to produce both sterile and non-sterile dosage forms, the modular manufacturing space is compliant with existing and anticipated international regulatory requirements and built with flexibility and adaptability in mind. The processing suites are built with a "plug-and-play" skid design from industry-leading equipment manufacturers, allowing GMP processing technologies to be assembled, installed, and qualified rapidly. Pre-sterilized, single-use equipment is employed when possible to reduce cleaning validation time and costs. Isolator technology allows for the processing of highly potent compounds and organic solvents, and also supports compounding, processing, and aseptic/sterile filling.

The automated, aseptic filling equipment is designed to accommodate a variety of the most used primary packaging configurations allowing for maximum flexibility. We have sterile lyophilization, milling, and microfluidics capability that can process a variety of batch sizes. We employ a transparent fish bowl design to allow both clients and regulators to view the processes in order to facilitate understanding and audits. We also have room to expand, so if you are pursuing manufacturing of a complex product, chances are we can accommodate your needs.

**Q: Where will Particle Sciences be focusing in the next 5 years, and how will you continue to differentiate yourselves in the crowded CDMO space?**

**A**: In the future, we plan to bring in new formulation approaches and expand our footprint both organically and, likely, through acquisition. Through this growth, we will continue to do what we have done throughout the past 25 years – maintain our expertise while looking for new, innovative, and creative approaches to solve the problems of the future. There is tremendous innovation amongst the small-to-midsize companies, and while we will always nurture our relationships and services to our large clients, we will also continue to serve companies of all sizes. It is this flexibility and willingness to take on the toughest and most unique products that have differentiated us.

With the Lubrizol team and the backing of Berkshire Hathaway, we have even more bandwidth to tackle the challenges in the pharma community. We now have access to polymer scientists and can pair our formulation knowledge with new innovative delivery systems. We look forward to continued growth in the complex pharma market and encourage you to reach out if you are in need of a quality driven CDMO.◆

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# Special Feature

## Platform Technology – Derisking & Transforming Drug Development

By: Cindy H. Dubin, Contributor

Platform technologies have the ability to radically improve upon current products and generate completely novel products. In this sense, they open up new arenas for drug discovery and development, potentially increasing the number of therapeutic options for patients, says Brian Atwood, CEO of Cell Design Labs.

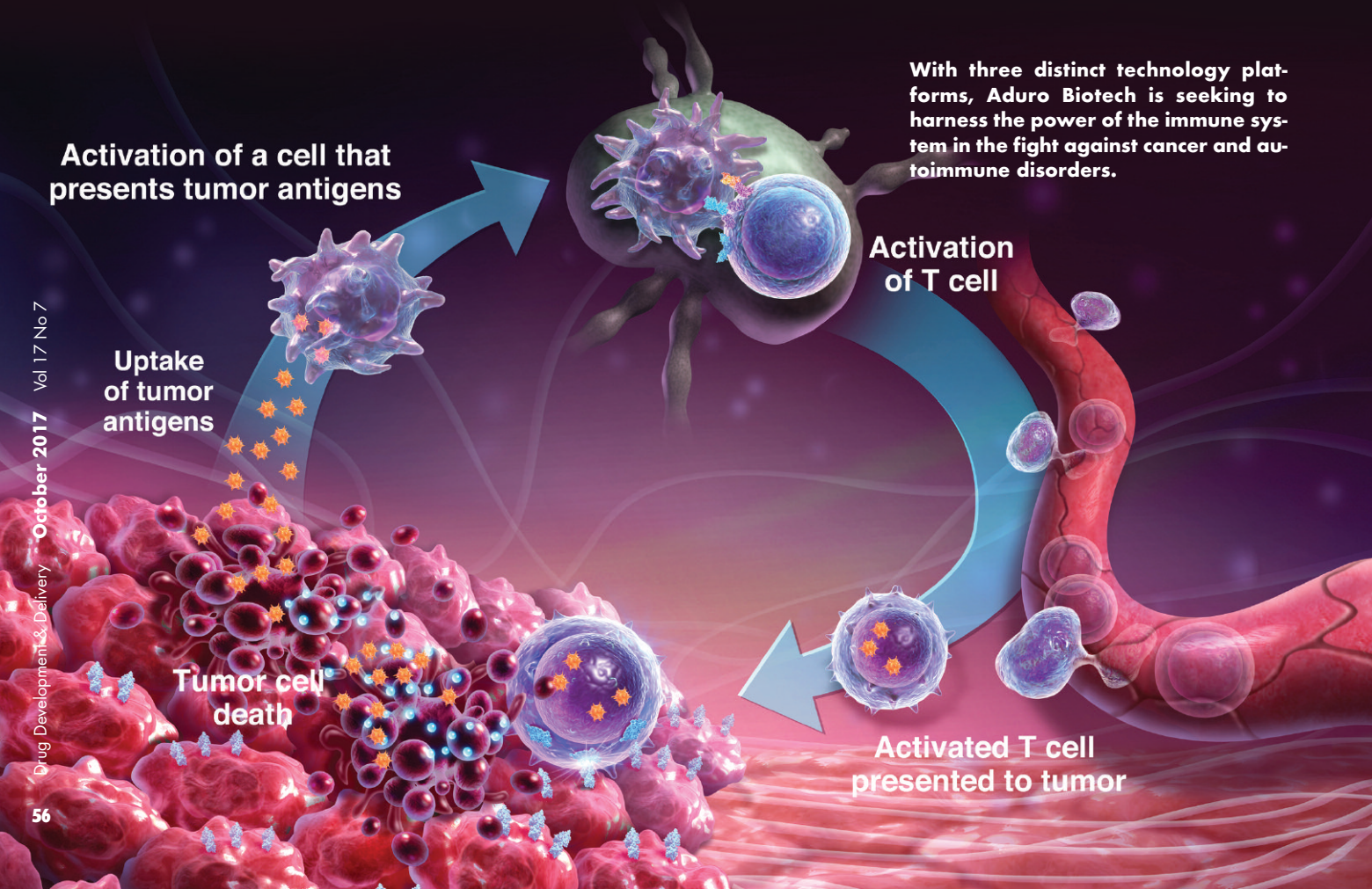
"Once a single compound or therapeutic has been generated and demonstrates a clinical benefit in patients, it is more likely this platform technology can successfully be applied to other therapeutic areas, derisking future compounds/products," says Mr. Atwood.

Complex drugs by their very nature are challenging and costly to manufacture. This, in turn, translates into higher costs for patients and other payers, explains Ross Macdonald, PhD, Managing Director and Chief Executive Officer of Cynata Therapeutics. He says: "In order to provide safe and effective therapies at a reasonable price, it is necessary for the industry to develop manufacturing technologies that reduce costs and provide a consistent product."

"While the initial investment may be larger, manufacturing costs will be lower over time as the manufacturing process is solidified," agrees Mr. Atwood.

Despite the initial upfront costs, Dr. Macdonald says that platform technologies inevitably provide pragmatic solutions to production challenges, while yielding safer and more effective therapeutic products.

*Drug Development & Delivery's* second annual report on platform technologies highlights some of these novel discoveries and describes how they are transforming drug development.



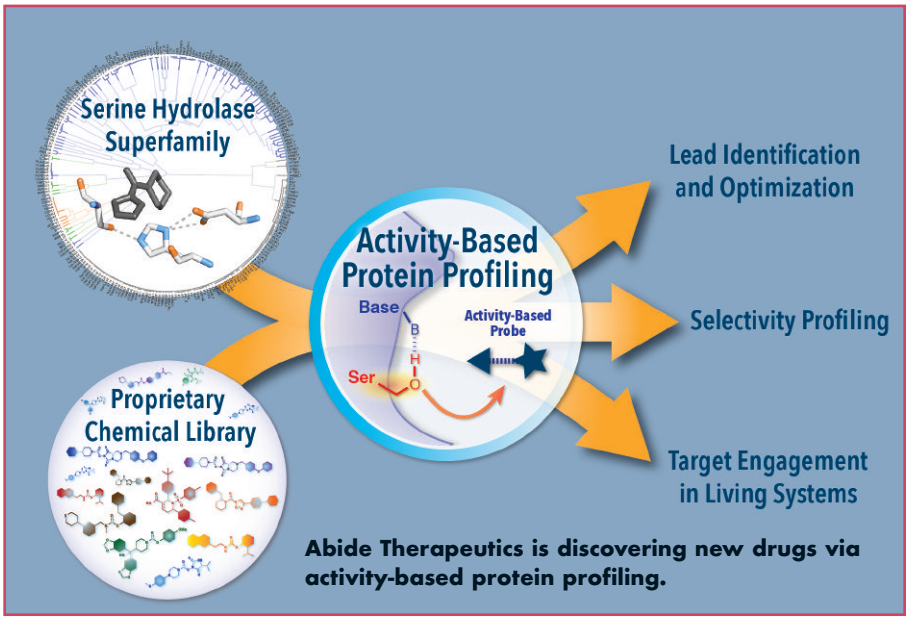

**With three distinct technology platforms, Aduro Biotech is seeking to harness the power of the immune system in the fight against cancer and autoimmune disorders.**

## Abide Therapeutics: A Transformative Platform for Serine Hydrolase Drug Discovery

Abide Therapeutics integrates a powerful chemoproteomic technique called activity-based protein profiling (ABPP) with innovative chemistry to develop first-in-class medicines targeting a large family of enzymes – the serine hydrolases – that plays key roles in physiology and disease, explains Alan Ezekowitz, MBCHB, D.PHIL., FAAP, President and CEO of Abide.

"The serine hydrolase superfamily is one of the largest known enzyme classes, comprising approximately 250 enzymes," he says. "These enzymes are involved in a range of physiological processes, including CNS signaling, digestion, inflammation, and metabolism. Several approved drugs (Xenical®, Januvia®, Aricept®) have shown that the enzyme superfamily is a potentially rich source of first-in-class medicines, yet the value of serine hydrolases remains largely untapped. Abide's unique platform can fulfill this promise."

Today, most serine hydrolases are poorly characterized, but their roles in disease are under active investigation with Abide's chemical library, which is tailored to selectively target these enzymes in live cells and animals, providing a means to concurrently validate new drug targets and discover new inhibitors. Abide's ABPP technology enables precise measurement of enzyme activity through the use of broad-spectrum chemical probes that covalently react with the active sites of serine hydrolases, all of which rely on a shared catalytic mechanism. New drugs can be discovered via ABPP by allowing small molecules from Abide's library to compete with activity-based probes for binding to enzyme active sites, thereby inhibiting probe labeling, explains Dr. Ezekowitz.



**Abide Therapeutics is discovering new drugs via activity-based protein profiling.**

"This technique has several advantages over classical approaches for measuring drug activity," he says. First, enzymes can be screened in their native context, within cells and tissues, without requiring recombinant expression or purification of each target. Second, the activity-based probe serves as a "universal" assay for its enzyme targets, meaning that inhibitors can be developed for enzymes that have no known substrates or biomarkers. Third, inhibitors are screened against many enzymes in parallel, enabling concurrent optimization of inhibitor potency and selectivity.

"Abide's unique approach provides a deep understanding of inhibitor action in living systems before moving to human testing, assuring drug candidates reach their intended targets in the physiologically relevant tissue while sparing off-targets that could lead to detrimental side effects," says Dr. Ezekowitz.

Using this transformative platform, Abide brought its first drug candidate from the lab to the clinic in less than three years. ABX-1431 is a first-in-class inhibitor of the serine hydrolase monoacylglycerol lipase (MGLL) designed to treat nervous system disorders by tuning brain signaling networks in an unprecedented way. A study of ABX-1431 in patients with Tourette Syndrome is ongoing, and other CNS disorders, such as multiple sclerosis, are being investigated.

## Aduro Biotech: Harnessing the Power of the Immune System Through Three Diverse Technology Platforms

With three proprietary immunotherapy platforms — Live, Attenuated Double-Deleted Listeria (LADD); STING Pathway Activators; and B-select monoclonal antibodies — Aduro Biotech is positioned to transform the treatment of challenging diseases, including cancer, says Andrea van Elsas, Chief Scientific Officer of Aduro Biotech.

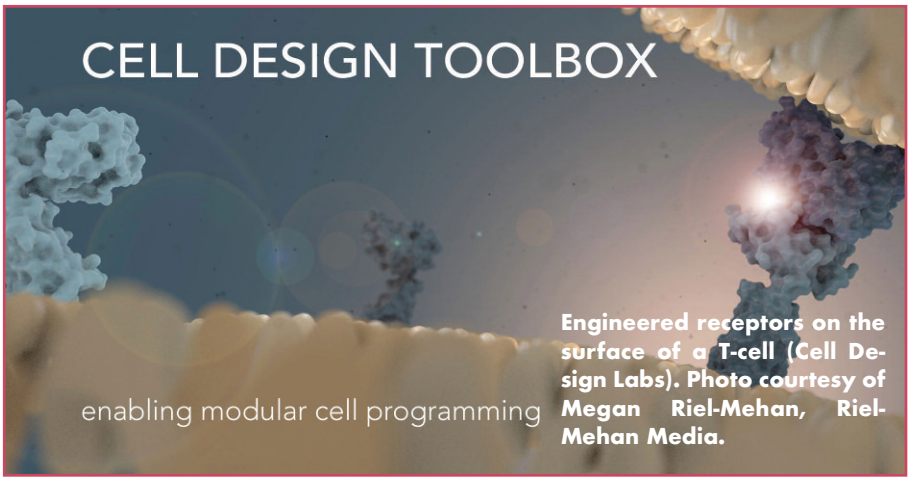
Aduro's LADD platform harnesses the power of bacteria to direct the immune response against cancer. The platform is based on proprietary attenuated strains (strains in which two virulence genes have been deleted) of *Listeria monocytogenes* that have been genetically engineered to express specific tumor antigens. Aduro is

also leveraging this technology to develop a personalized approach to cancer treatment, which uses tumor markers from a patient's own tumor cells. To date, LADD product candidates have been administered to more than 350 patients and have been generally well-tolerated, says Dr. van Elsas.

Aduro's STING Pathway Activators platform seeks to use a patient's own tumor composition to activate an anti-cancer immune response. This approach is based on the activation of the STING (Stimulator of Interferon Genes) receptor, which is generally expressed at high levels on immune cells. "The company's proprietary STING pathway activator product candidates, including ADU-S100 (MIW815), are synthetic small-molecule immune modulators designed to target and activate human STING, thereby initiating a profound innate immune response through multiple pathways," Dr. van Elsas says. These synthetic STING Pathway Activators are being developed for direct injection into tumors to stimulate an immune response against antigens present in the tumor.

"The process is expected to use the tumor itself as a vaccine, enabling the induction of a tumor-specific immune response that is unique to the treated individual — an off-the-shelf small molecule approach to personalized immunotherapy," he says.

Aduro's B-select antibody platform seeks to modulate cancer immunity. The company's propriety, ultra-selective screening process is designed to identify antibodies with unique binding properties against a broad repertoire of targets. Through this process, Aduro has developed a deep pipeline of proprietary monoclonal antibodies (mAbs) that hold the potential to regulate the immune system in the fight against cancer. Two investigational mAb product candidates in Aduro's pipeline include BION-1301, a novel anti-APRIL antibody, and an anti-CD27 antibody being developed in partnership with Merck.



**Engineered receptors on the surface of a T-cell (Cell Design Labs). Photo courtesy of Megan Riel-Mehan, Riel-Mehan Media.**

## Cell Design Labs: Disruptive Biology Platform for Cell-Based Oncology Therapies

Cell Design Labs is a biotherapeutics company leveraging the power of the body's immune system to develop smart living therapies for patients with cancer. "Currently, modified immune cells – CAR T-cells – are poised to revolutionize the field of cancer therapy," says Brian Atwood, CEO and Co-founder of Cell Design Labs. The most commonly used approaches to generating engineered immune cells are modifying T-cells with chimeric antigen receptors (CAR-Ts) or with tumor antigen specific T-cell receptors (TCR-Ts). However, Mr. Atwood points out that excitement for these new therapeutics is tempered by three primary challenges: safety, including off-target toxicity; development of resistance; and a lack of clinical efficacy in solid tumors. Cell Design Labs' customized molecular modules, THROTTLE Switch™ and synNotch™ engineered modules, enable design of next-generation CAR-Ts and TCR-Ts to overcome these challenges.

**synNotch modules:** By modifying the external and internal portions of the naturally occurring Notch receptor, and placing these unique constructs into a patient's immune cells, the patient's body can be instructed to detect new molecular targets and to turn on new genes. In addition, further modifications of the synNotch scaffold can enable diverse sensing and response behaviors. By expressing synNotch receptors in T-cells, it is possible to create a programmable immune cell. When this reprogrammed cell binds to its sole intended target (i.e., a cancer cell), it triggers one or more specific molecular activities: locally producing and modulating tumor defense mechanisms such as a specific CAR, delivering drugs such as checkpoint inhibitors, inducing a customized cytokine profile to supercharge the immune system, or encouraging T-cells to differentiate into specific subtypes to convey long-term protection against cancer recurrence. "With this approach, the synNotch receptor confers extremely versatile sense-and-response functionality to T-cells, which already have the ability to migrate throughout the body to find targets," Peter Emtage, PhD, Chief Scientific Officer of Cell Design Labs, says.

**THROTTLE Switch modules:** The company's proprietary THROTTLE Switch technology allows CAR-T cells to be turned on and off, enabling them to be better tolerated and more effective, says Dr. Emtage.

"Once a single compound or therapeutic has been generated and demonstrates a clinical benefit in patients, it is more likely this platform technology can successfully be applied to other therapeutic areas, derisking future compounds/products." – Brian Atwood, CEO of Cell Design Labs.

This is achieved by constructing two separate and inactive receptor components into the cell membrane of a CAR-T cell, meaning the natural state of the CAR-T cell is "off."

"Only in the presence of an FDA-approved small molecule compound will the two come together – closing the "switch" – into an active state, seeking out and eliminating cancer cells," says Dr. Emtage. "With this type of control-switch CAR-T cells, physicians can rapidly and precisely control the activity and safety of CAR-T cells."

Mr. Atwood adds: "Cell Design Labs is operating at the edge of scientific discovery to harness fresh insights about cell behavior and computer-based modeling to create a new generation of medicines. While currently focused on cancer, this platform may have broad applicability to a number of serious diseases."

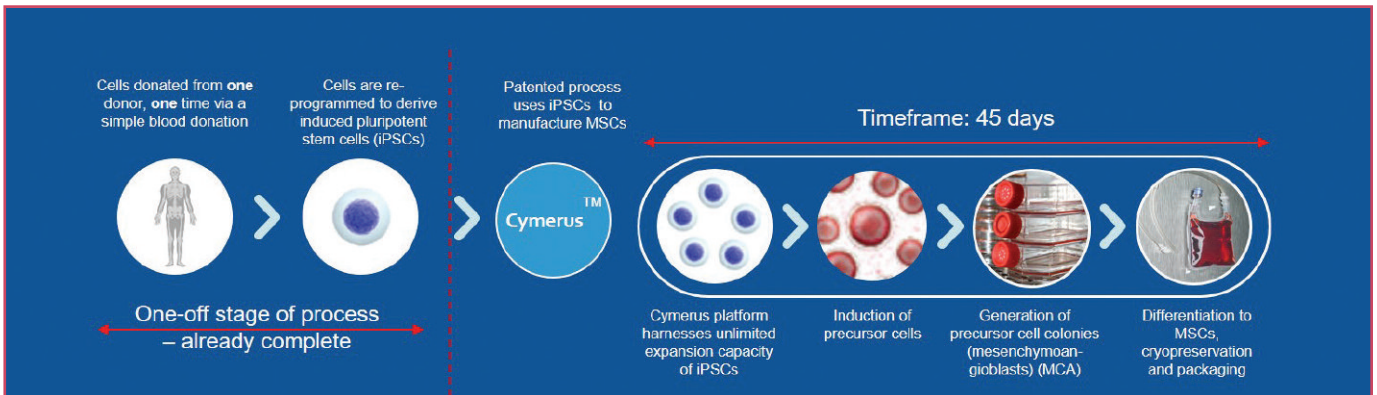
## Cynata Therapeutics: Technology Platform Could Revolutionize Regenerative Medicine

"Cynata Therapeutics' proprietary Cymerus™ technology platform has the potential to revolutionize the regenerative medicine industry and overcome one of its biggest obstacles: the economical manufacture at commercial-scale of mesenchymal stem cells (MSCs) for therapeutic use," says Ross Macdonald, PhD, Managing Director and Chief Executive Officer of Cynata Therapeutics.

MSCs are multipotent cells found in a variety of human tissues. Dr. Macdonald says there is significant interest in MSCs' therapeutic potential across many diseases, due to their immunoregulatory and tissue regeneration properties. "In fact, MSCs are often called medicine-secreting cells because of their impressive production of bioactive molecules."

There are more than 600 trials worldwide investigating the potential clinical utility of MSCs in conditions like cardiovascular disorders, stroke, and autoimmune diseases. Product for these trials is obtained using first-generation production techniques that require repeat donor-derived materials and massive expansion of MSCs in culture to derive sufficient quantities. "These production techniques have significant limitations, most notably, the small number of MSCs recovered from each donation and limits on MSC expansion," says Dr. Macdonald.

Cynata's Cymerus technology may overcome these issues by generating large-scale MSCs based on a single blood donation from one adult donor. Cynata's novel approach involves using induced pluripotent stem cells (iPSCs) as starting material. iPSCs are derived by reprogramming the donor's cells from a single donation. iPSCs can reproduce indefinitely without losing their pluripotent characteristics, thereby providing an essentially limitless and consistent source for the manufacture of the finished product, the MSCs, via a unique intermediate cell type




**Cynata's Cymerus platform enables MSCs to be manufactured effectively and efficiently by eliminating the need to use multiple donors, multiple times.**

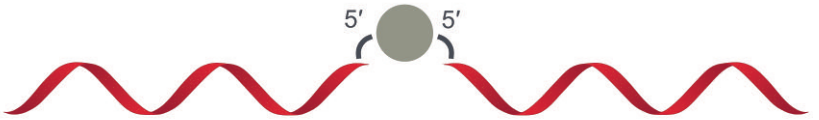
called mesenchymoangioblasts (MCAs).

Cymerus mitigates concerns associated with batch-to-batch variability and excessive expansion in culture, and eliminates the need to repeatedly identify new donors. A typical bone marrow donation yields 10,000–20,000 MSCs[1,2], though clinical doses are usually 35–350 million.[3] Therefore, first-generation methods may require hundreds, if not thousands, of donations each year to meet commercial demand. In addition, switching donors requires robust comparability testing to ensure a consistent clinical outcome is derived from the different donations. Dr. Macdonald points out that it cannot be assumed that MSCs expanded at a large scale will retain the same functional properties. It has been suggested that MSCs expanded to produce 10,000 doses per donation may have limited efficacy versus modestly expanded MSCs.[4]

"The Cymerus process produces an essentially unlimited number of new MSCs," says Dr. Macdonald. "Moreover, Cymerus MSCs originate from one donor and are identical to one another, limiting the risk of contaminating non-target cells and eliminating the need for donor-to-donor comparability."

Cynata is conducting the world's first clinical trial of allogenic iPSCs-derived MSCs. The ongoing trial of CYP-001 in graft vs. host disease (GvHD) is enrolling in the UK and Australia, and is expected to be completed by early 2018. Cynata's positive pre-IND meeting with the FDA in May 2017 cleared the path for a U.S. clinical program. In addition, preclinical data generated by Cynata's academic partnerships support expansion into diseases like asthma[5], heart attack[6], and glioblastoma.

**Schematic of 3GA Structure: red strands represent oligonucleotide arms; grey circle represents glycerol linker (Idera Pharma).**




## Heat Biologics: Making an Impact on Immunotherapy

Heat Biologics is a biopharmaceutical company developing immunotherapies designed to activate a patient's CD8+ "Killer" T-cells against cancer. "We believe the future of cancer immunotherapy will be focused on drug combinations, and will lead to the success of finding effective and lasting treatments for patients with cancer," says Jeff Hutchins, PhD, Chief Scientific Officer, Heat Biologics.

Heat uses its Immune Pan-antigen Cytotoxic Therapy (ImPACT®) platform to develop product candidates that consist of live, allogeneic "off-the-shelf" genetically-modified, irradiated human cancer cells. These cells are intended to secrete a broad spectrum of Cancer Testis Antigens (CTA), classified as tumor antigens, together with the "heat shock" gp96 protein.

Through ImPACT, Heat developed HS-110 as a potential treatment for patients with non-small cell lung cancer (NSCLC). It is the company's first biologic product candidate in a series of proprietary ImPACT-based immunotherapies designed to stimulate a patient's own T-cells to attack cancer. HS-110 is made of a cancer cell line that has been genetically modified, and is designed to secrete a range of lung cancer-associated antigens bound to gp96 proteins, to activate and expand a broad, T-cell mediated immune response against the patient's cancer, explains Dr. Hutchins.

The T-Cell Activation Platform (TCAP) approach produces therapies designed to turn immunologically "cold" tumors "hot," and be administered in combination with checkpoint inhibitor therapies and other immuno-modulators to increase their effectiveness. This approach can also be used to combine with existing T-cell checkpoint inhibitors and co-stimulators in a single treatment. This offers the potential benefit of combination immunotherapy without the need for multiple, independent biologic products.

"Unlike autologous or "personalized" therapeutic, monotherapy approaches that either require the extraction of blood or tumor tissue from each patient or the creation of an individualized treatment, the product candidates are fully allogeneic, and do not require extraction of individual patient's material or custom manufacturing," he says. "As a result, the products can be mass-produced and readily available for immediate patient use. Because each patient receives the same treatment, Heat's immunotherapy approach offers logistical, manufacturing, and other cost benefits, compared to patient-specific or precision medicine approaches."

## Idera Pharmaceuticals: Improving the Safety & Efficacy Profile of Proprietary Oligonucleotide Therapeutics

Antisense oligonucleotides hold the promise for targeting diseases caused by aberrant RNA that are considered "undruggable" by traditional therapeutic plat-

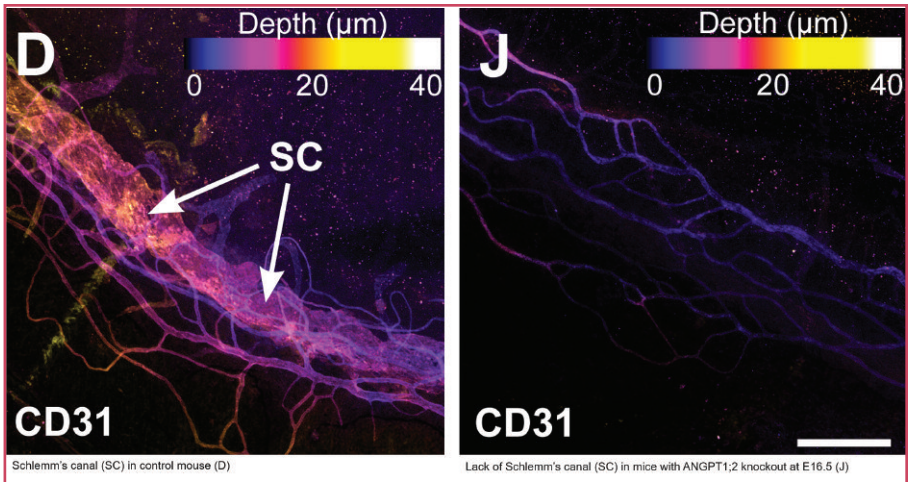
forms. This technology has been in development for a few decades, with tremendous progress made in the pharmacokinetic and pharmacodynamics properties of oligonucleotides. Recent regulatory approvals bring the hope that the technology is nearing maturity. Nevertheless, broad applicability of antisense therapeutics has been hampered by factors such as pro-inflammatory effects, tissue build-up leading to toxicities, and off-target effects, explains Jonathan Yingling, PhD, Idera's Head of Early Development.

Idera Pharmaceuticals is a clinical-stage biopharmaceutical company developing nucleic acid therapeutics for the treatment of certain cancers and rare diseases. Idera has focused its research efforts on understanding not only gene silencing technology, but also the interaction of oligonucleotides with the host immune system. "The latter provides critical insight for addressing factors that continue to limit the therapeutic index of gene silencing oligonucleotides," says Dr. Yingling. "Based on our knowledge and expertise in nucleic acid therapeutics and Toll-like receptor biology, we have designed novel gene silencing oligonucleotides, called third generation antisense oligonucleotides (3GA)."

3GAs are composed of two short oligonucleotides complementary to target RNA, linked via their 5'-ends with a glycerol linker. "The elimination of free 5'-ends mitigates immune activation while the resulting exposure of the 3'-ends facilitates nuclease degradation, thereby reducing tissue build-up," explains Dr. Yingling. "This design can also lead to improved gene silencing potency."

In parallel, Idera has created a proprietary algorithm for optimized target sequence selection. This algorithm, combined with the unique 3GA structure and the flexibility to introduce positional modifications to optimize individual 3GA assets, provides the foundation for applying the platform across various targets and diseases.

Early mechanistic studies have shown that the central region of the 3GA is critical for target engagement. "Indeed, incorporation of a single nucleotide mismatch at the central region of the 3GA leads to reduction in gene silencing activity, suggesting that 3GAs can be highly specific," Dr. Yingling says. "We are currently leveraging this cleavage site specificity to design 3GAs that can selectively target point mutations. More detailed mechanistic studies are underway to further understand how 3GAs work at the molecular level. These studies, as well as other research efforts, inform our strategy and design as we continually work to improve the safety and efficacy profile of proprietary oligonucleotide therapeutics."



Schlemm's canal (SC) in control mouse (D)

Lack of Schlemm's canal (SC) in mice with ANGPT1;2 knockout at E16.5 (J)

**Mice develop glaucoma due to defects in ocular drainage, illustrating the relationship between the ANGPT/TIE2 pathway and glaucoma (Mannin Research).**

## Mannin Research Inc. & Q Biomed Inc.: Small Molecule That Activates the Angiopoietin-TIE2 Signalling Pathway

Mannin Research is a biotechnology company focused on the discovery, development, and commercialization of first-in-class therapeutics for vascular diseases, utilizing the angiopoietin/TIE2 signaling pathway. Mannin Research partnered with Q BioMed Inc., a biotech acceleration company, that provides strategic resources to accelerate the development of biotech assets.

TIE2 is a transmembrane receptor tyrosine kinase. The primary ligands for the receptor are angiopoietin-1 (ANGPT1) and angiopoietin-2 (ANGPT2); two protein growth factors that promote angiogenesis and the formation of blood vessels. TIE2 is expressed almost exclusively in endothelial cells in mice and humans. The angiopoietin/TIE2 (ANGPT/TIE2) signaling pathway is a major regulator of vascular development and homeostasis, and altered expression of ANGPT ligands or activity of the TIE2 receptor is linked to a variety of vascular diseases and adverse outcomes in patients.

Mannin is currently developing small

molecules targeting the ANGPT/TIE2 pathway designed to reduce intraocular pressure (IOP) and treat primary open-angle glaucoma. In an article in the *Journal of Clinical Investigations*, Dr. Susan Quaggin, Mannin Research's Chief Scientific Officer, and Director of the Feinberg Cardiovascular Research Institute and Chief of Nephrology and Hypertension in the Department of Medicine, demonstrated that genetic disruption of the angiopoietin/TIE2 signaling pathway results in high IOP, buphthalmos, and classic features of glaucoma, including retinal ganglion degeneration and vision loss.

Dr. Quaggin explains that the angiopoietin/TIE2 signaling pathway is a key signaling pathway that is essential for proper drainage and maintenance of intraocular pressure, and is needed for proper growth and function of the drainage apparatus in the front of the eye. A specialized blood vessel, known as Schlemm's canal, is the major drainage pathway for fluid to escape from the eye. Blockage of this canal or a birth defect resulting in a small or absent Schlemm's canal, leads to glaucoma in patients. The loss of angiopoietins 1 and 2 also results in deterioration or absence of the Schlemm's canal.

She says that to treat glaucoma, it is necessary to increase the drainage of fluid from the front of the eye, preferably by way of a novel eye-drop treatment. This can be accomplished by increasing the flow of fluid through Schlemm's canal. "To that end, Mannin is in lead optimization of a small-molecule therapeutic that will activate the Angiopietin-TIE2 pathway. Mannin's goal is to develop a painless and simple eye drop therapeutic for patients with glaucoma," says Dr. Quaggin.

Although Mannin Research is currently focused on developing a therapeutic for glaucoma with technology partner Q BioMed as its first indication, Mannin and Q BioMed believe the technology can be applied to treat various vascular-related diseases, such as cystic kidney disease, Ebola, cardiorenal syndrome, congestive heart failure, and more.

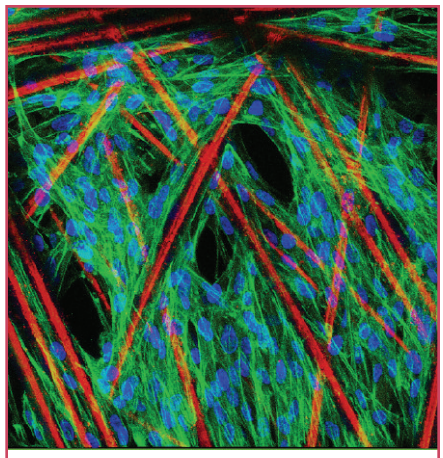
## Maxcyte: Chimeric Antigen Receptor Uses Messenger RNA to Engineer Immune Cells

MaxCyte has developed a novel and proprietary platform for next-generation chimeric antigen receptor (CAR)-engineered T/NK-cell therapies (CAR-T). CARMA, as a CAR platform, provides several unique attributes over existing CAR-T products and platforms, according to Doug Doerfler, President and CEO of MaxCyte.

First, CARMA is differentiated from traditional CAR-T therapy by its use of messenger RNA (mRNA) to engineer the immune cells that are delivered back into a patient, without the need for a viral component. CARMA provides for transient expression, as shown in preclinical studies, to control the adverse side effects seen in first-generation, viral-based CAR therapies. This allows for CAR-T immunotherapies to address a broader range of cancers, including solid cancers, than traditional CAR approaches.

Second, CARMA offers the potential to deliver therapy to the patient in a fraction of the time of other autologous CAR-T products, says Mr. Doerfler. This is due to a more streamlined manufacturing process without the complexity of virus-based products.

MaxCyte's first CARMA drug candidate is moving towards clinical development in a solid tumor indication, where CAR-based treatments have been less successful. This product candidate, MCY-M11, employs repeat infusions of



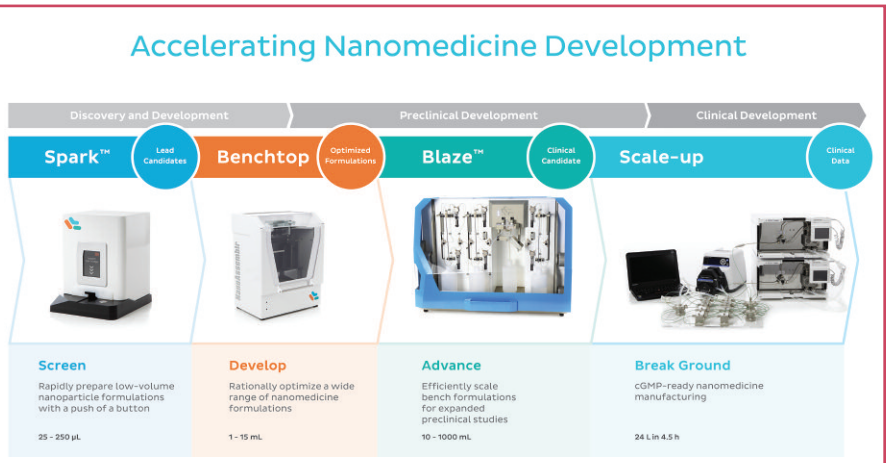
**PLX cells create a three-dimensional environment between the fibers that make up the unique macrocarriers by depositing extracellular matrix components between the carriers fibers (Blue: Cell nucleus; Green: actin fibers; Red: carrier fibers); Pluristem.**

mesothelin-specific mRNA CAR-transfected into PBMCs (peripheral blood mononuclear cells) to permit controlled persistence, which other CAR-T therapies are seeking, says Mr. Doerfler. Early non-clinical testing has provided preliminary evidence of the safety and anti-tumor activity of this platform. MaxCyte and its collaborators at the Johns Hopkins Kimmel Cancer Center explored the various attributes of MCY-M11. The studies found that cryopreserved MCY-M11 expressed CAR in >95% of cells, and recognized and lysed tumor cells in an antigen-specific manner. In addition, expression of CAR was detectable for 5 to 7 days *in vitro*, with a progressive decline of CAR expression related to *in vitro* cell expansion, Mr. Doerfler explains.

In a murine ovarian cancer model, a single intra-peritoneal (IP) injection of CARMA product resulted in the dose-dependent inhibition of tumor growth and prolonged the overall survival (OS) of the mice. Weekly IP injections of the optimized MCY-M11 dose boosted disease control and further prolonged OS, both of which

improved with an increasing number of injections. No significant off-tumor toxicities were observed.[7]

"The data provide a strong scientific foundation for clinical development of our novel and proprietary CARMA platform providing 'controlled persistence' in tumor-targeted immunotherapies using peripheral blood lymphocytes," says Mr. Doerfler. "We can control 'on-target, off-tumor' toxicities, while reducing manufacturing complexity for therapies targeting a wide variety of malignancies."




**The NanoAssemblr™ Platform: Solutions for every stage of nanomedicine development (Precision NanoSystems).**

## Pluristem: 3D Macrocarrier Bioreactor Technology Overcomes Limitations of 2D Microcarriers

Pluristem's products are placenta-derived adherent stromal cells. Placenta-derived cell therapies are allogeneic in nature and are intended to be manufactured in commercial quantities for off-the-shelf use. To fully harness the potential for commercial manufacturing of allogeneic cells, process scalability should involve scale-up and scale-out aspects.

"Most of today's cell therapy production platforms are based on 2D technologies, such as cell factories or cell stacks," says Lior Raviv, Vice President Development, Pluristem. "The major drawbacks of these technologies are limits in the total number of cells that can ultimately be produced, significant increases in cost of production, and poor control over culture parameters, which can lead to batch-to-batch variability. Due to the limitations of the standard 2D technologies, some companies use microcarrier-based bioreactor systems to grow their product."

Microcarrier platforms are considered more like 2D rather than 3D platforms due to the substantial difference between the cell size and the carrier curvature. Although this system is more controlled than common 2D systems, the real manufacturing challenge consists of the shear forces acting on the cells during culturing and harvesting, which compromise cell yield and quality, explains Mr. Raviv.

Pluristem developed a bioreactor platform that uses macrocarriers (Fibra-cel Discs) in a packed bed configuration. The Fibra-Cell discs are composed of non-woven polyester fibers creating a 3D web-like environment, enabling a fast cell attachment (more than 90% in less than 1 hour). During the seeding of cells onto carriers, cells attach to the fibers and start secreting Extra Cellular Matrix components between the fibers, increasing the surface area available for cell growth and creating a 3D environment that is more like these cells' natural environment.

The combination of the unique growth environment in a packed bed with a specially designed impeller provides shielding from shear forces during growth, protecting the cell quality. Furthermore, in order to have a complete manufacturing solution, Pluristem developed an automated bioreactor harvesting device that controls harvesting parameters and can adjust them to different products. "Our system provides high cell recovery while maintaining cell quality," says Mr. Raviv. "Our bioreactors also enable automated monitoring and adjustments of physical and chemical factors that can affect cell growth, such as pH, dissolved oxygen, and temperature, thereby reducing batch-to-batch variation to levels not achievable by traditional platforms."

## Precision NanoSystems: Controlled, Tuned & Fully Scalable Manufacturing of Nanomedicines

Nanoparticle encapsulation is gaining momentum as an effective drug delivery system, but traditional manufacturing methods are labor intensive, hard to reproduce, and difficult to scale up. Precision NanoSystems Inc. has developed a proprietary technology – the NanoAssemblr™ platform – for the rapid development of nanoparticles and seamless scale-up for clinical studies and commercial production. This cartridge-based microfluidic system takes advantage of the highly predictable, time-invariant mixing offered by laminar flow to ensure rapid, controlled production of a variety of nanoparticles for the delivery of drugs or biological molecules.

"This standardization of processing allows the manufacture of nanoparticles with

carefully defined characteristics, including chemical compositions, concentrations and drug/excipient ratios," says James Taylor, CEO and Co-founder.

Parallelization is at the core of the NanoAssemblr technology, enabling throughput to be increased to meet the requirements of each phase of the drug development workflow without changing the reaction conditions. Precision NanoSystems offers four small footprint systems based on the same underlying microfluidic technology to match the various needs of the market. The smallest system in the family – the NanoAssemblr Spark™ – is designed for early-stage research and development activities, using disposable microfluidic cartridges to provide controlled and reproducible formulation of 25-250µl nanoparticle suspensions in less than 10 seconds. Once screening is complete, the NanoAssemblr Benchtop™ enables process development and optimization in 1-15ml volumes. A simple, semi-disposable microfluidic cartridge offers flow rates up to 18 ml/min, and most nanoparticle formulations are completed in just 15-20 seconds, allowing more than 40 formulations to be prepared in one day, explains Mr. Taylor.

"The NanoAssemblr Blaze is designed to seamlessly scale NanoAssemblr Benchtop formulations up to one liter volumes. Using the same microfluidic mixer as the NanoAssemblr Benchtop, it employs continuous flow and parallelization to increase volumes and throughput, greatly reducing the need for process development compared to traditional methods," says Mr. Taylor.

Finally, the largest system in the family – the NanoAssemblr Scale-Up – has been developed specifically for manufacturing clinical grade materials in the cGMP environment. Designed to be run in a clean room and customizable to meet customers' specific requirements, it offers a completely flexible solution from early-stage clinical trial manufacturing to commercial production. Mr. Taylor says: "This powerful technology is transforming the development and manufacturing of a range of nanoparticle formulations from a hit-and-miss affair to a standardized process, accelerating novel nanomedicines from the bench to the clinic." ◆

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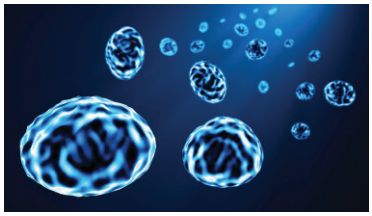
## Nanoparticle Formulations



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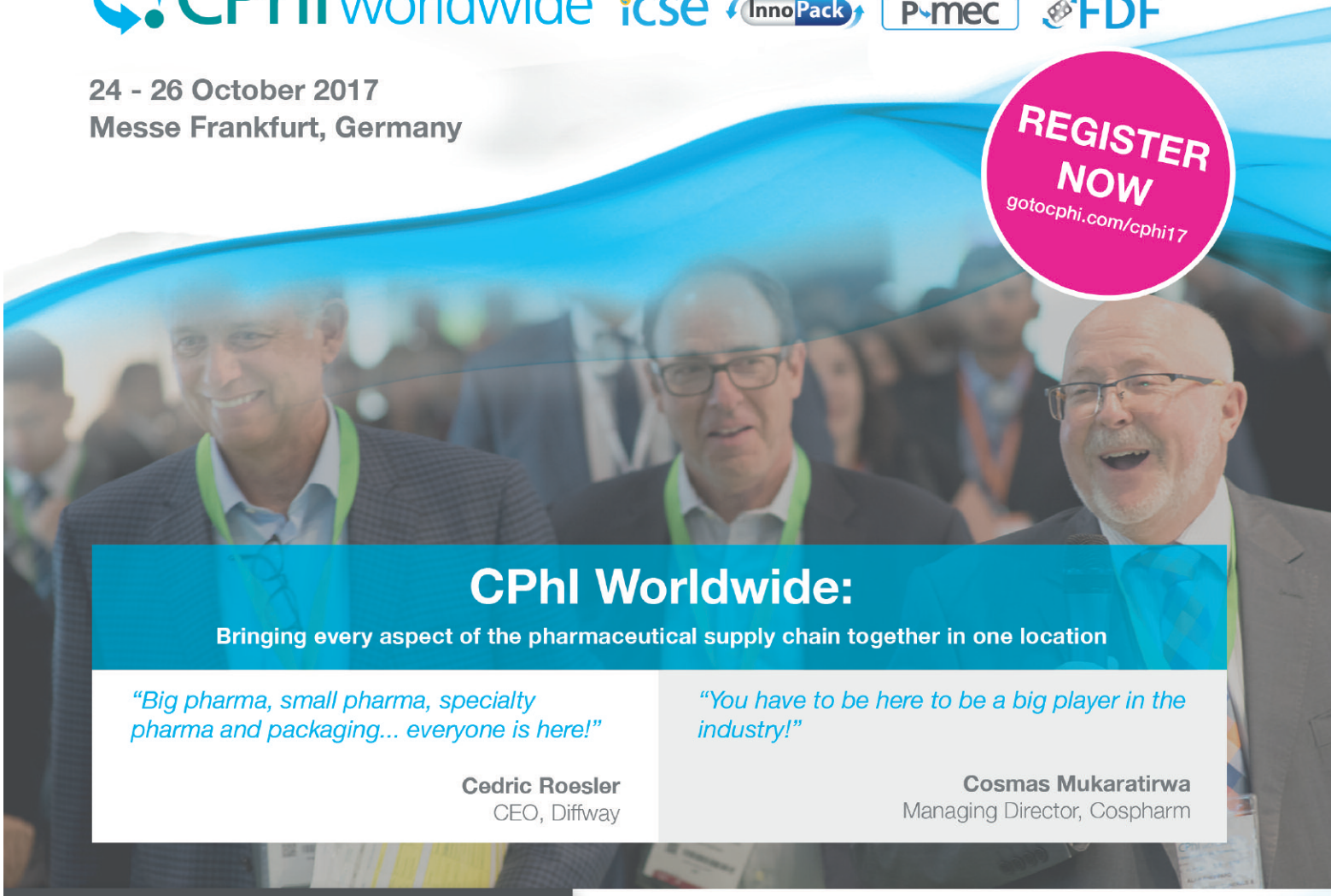

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Injectable Division

Aptar pharma

# Aptar Pharma: Quality Will Inject Real Growth Into the Injectables Market

Aptar Pharma provides drug delivery systems, components, and services across a wide range of therapy areas, including Nasal, Pulmonary, Eye Care, Dermal, and Injectable. Overall, 6 billion systems are produced annually across 12 manufacturing sites and are accessed by 1.6 billion patients; $50 billion worth of pharmaceutical products depend on its systems. The injectable division is recognized as a global leader and a trusted partner, working with 9 of the top 10 pharmaceutical companies that utilize injectable systems. Overall, the company serves 700+ customers in more than 70 countries. Throughout the past 50 years, its injectable specialists have led the way in developing innovative elastomer closure solutions for injectable drug delivery systems. This commitment to continuous improvement, coupled with its expertise and track record of customer collaboration, enables Aptar Pharma to take on the challenges others fear, so that it remains at the forefront of injectable development. *Drug Development & Delivery* recently spoke with Bas van Buijtenen, President of the Aptar Pharma Injectable Division, who reviews the past 12 months and assesses what will drive the market in the future.

**Q: What do you see as the market drivers for injectables right now?**

**A**: The focus for the past 12 months and the months ahead can be summarized in just one word: Quality. Quality in R&D, quality in customer insight, and quality in product solutions. We recognize that both our Pharma and Biotech customers are facing many complex challenges, from increased regulatory requirements to their own internal developments of extremely sensitive drug formulations. To support these needs, we have challenged ourselves to deliver the highest standard of cleanliness in elastomer components. We acknowledge there is an obligation to ensure that the stopper protects the drug throughout its life, and that continues to be the foundation of our business. We are excited to be able to provide a robust solution to our customers' growing requirements for high-quality medicines.

Here at Aptar Pharma, we are proud of our heritage in pioneering innovative elastomer solutions. Indeed, we were the first company to provide a DMF for the Ready-To-Sterilize (RTS) process. There, we set the quality standard that the market universally adopted. We were also the first company to provide Ready-To-Use (RTU) stoppers to the market – a quality standard that is now seen as the norm.

We know that our past glories do not necessarily mean future success. Our future will be in quality, pushing the boundaries, and taking on complex challenges. The development of our Premium portfolio of injectable components is just one example of this commitment.

Due to over 50 years of R&D investment, we already offer the market elastomer formulations, which feature best-in-class extractable and leachable profiles. Our Premium family offering takes that commitment on improving quality to even greater levels of reassurance for our customers.

**Q: Can you tell our readers more about the Premium offer?**

**A**: There are three components to our Premium offer:

- **PremiumFill®:** A guaranteed specification to our highest quality of production, resulting in lower embedded particles, improved particulate cleanliness, and an overall reduction in defects.

- **PremiumCoat™**: Sets the standard for film-coated stoppers with an unrivalled reduction in particulates. The 1.3 PCI (Particulate Count Index) achieved today is market-leading compared to the historic standard of 2.9.

- **PremiumVision™** – A guaranteed quality commitment using an in-line, automated vision inspection system designed to further validate against critical defects for PremiumFill®.

PremiumCoat provides the highest standard level of guaranteed specification for film-coated stoppers in the market today. PremiumCoat are coated stoppers featuring a Fluorinated (ETFE) film that is applied during the manufacturing process. This approach delivers a homogenized coating, which is the established best practice method to create the most robust and effective barrier between the drug and the stopper.

Currently, PremiumCoat is offered on 13-mm and 20-mm stoppers, which cover the majority of global market demand. We can provide RTS and RTU options. Our RTU option features leading-edge gamma irradiation sterilization, which provides demonstrable benefits over the traditional method of steam sterilization.

**Q: That sounds like quite some investment – does that mean you are just investing in PremiumCoat?**

**A:** Not at all. Although, we do plan to extend the range of sizes available with PremiumCoat very soon. We have invested heavily in both of our manufacturing plants in France, with the Brecey facility featuring what we believe to be the most modern pharmaceutical-grade mixing facility in the world.

Perhaps more notably for our US customers, we have recently announced the expansion of our Congers facility in New York. This investment reinforces our commitment to the US market, which we see as our Number one regional growth opportunity.

The Congers manufacturing facility is state-of-the-art. The injectable area is dedicated to the exclusive provision of elastomeric stoppers for the US market and features semi-automated processes and 100% vision inspection, designed to identify and prevent the release of components with critical defects. To reach the highest specification, PremiumVision can easily be added to any product out of the Congers facility, which again is a guaranteed quality commitment using the in-line, automated vision inspection system to further validate against critical defects for PremiumFill components.

**Q: Do you see automation as a critical component for future success?**

**A:** Absolutely! We are able to drive higher quality standards through automation, and as I have already mentioned, quality will be the main driver for our future success. We have already automated many aspects of our manufacturing process, including the charging and discharging of molds, trimming of components, and of course PremiumVision.

At every stage of the process, we are looking to reduce human contact and therefore mitigate against risks of errors or entrance of particulates into the facility. This isn't to say humans aren't important. Quite the opposite, it is simply about using automation to improve the quality and cleanliness of the end product. Our people are at our core, we count on them to improve the quality of our thinking, our designs, and our customer interactions. That's why 10% of our employees are engaged in R&D.

**Q: How else can you improve quality?**

**A**: We have invested heavily in our PremiumFill offering, which provides a guaranteed specification to our highest quality of production, resulting in lower embedded particles, improved particulate cleanliness, and an overall reduction in defects. We can accomplish this specification by placing more of the manufacturing process into a cleanroom environment.

Conventionally, manufacturing is segmented into several different production units, each with their own requirements in terms of contamination control. Receipt, weighing, and mixing of the masterbatch rubber is conducted in an ambient air environment; molding and trimming processes are delivered in a protected area; with finishing and packaging completed in a controlled area, that being ISO 6.

To achieve the PremiumFill specification today, the manufacturing differs from the conventional process in two critical ways. First, the manufacturing is in-line, which reduces the risk of contamination during transport around the plant. Second, the more important differentiator, is that the molding, trimming, and finishing/packaging process are all conducted within cleanroom conditions. Molding, trimming, and washing are conducted in an ISO 7 environment, and finishing/packing is conducted in an ISO 6 environment.

Another key offer in the provision of quality is our RTU product, which is sterilized with gamma irradiation to provide customers with better quality, real flexibility, and convenience. First, the RTU offering reduces the number of human product interactions. Second, our customers' manufacturing productivity is improved, as the stoppers may be used immediately upon receipt and be directly introduced into RABS or isolators. Our RTU offer also allows the product to be introduced to the manufacturing line at the point of use. Lastly, there are significant economic advantages with reduced capital investment for sterilization equipment, negated maintenance costs, and reduced stock levels.

In addition, gamma sterilization is proven to be a more effective means of pre-sterilizing stoppers than steam sterilization. Steam sterilization works well when run in line in a drug manufacturing site. When the stoppers are supplied RTU, pre-sterilized, gamma radiation has the advantage of sterilizing the vial stoppers while they remain in their packaging; limiting contamination risks during transfer, eradicating moisture, improving productivity, and controlling exposure. Our special RTU packaging allows customers to verify the integrity of the packaging and therefore of the sterility of the product – something that is impossible with stoppers pre-sterilized with steam.

**Q: So, quality is important, but surely price is a factor. Aren't you worried about low-cost competition?**

**A**: Historically, Aptar Pharma has focused on complex challenges that require intelligent solutions. In fact, 90% of our business is in high-value products in which the integrity and quality of the elastomeric components are fundamental to the performance of the drug. We believe true experts love a challenge. Our experience, expertise, and ongoing commitment to quality enable us to take on the injectable challenges others may fear.

**Q: What do you foresee in the next year for Aptar Pharma?**

**A**: To some extent, more of the same. We will be enhancing the PremiumCoat offering with more available sizes and introducing pre-filled syringe components to the family. We are investing further in capacity and the deployment of vision systems in all three of our manufacturing facilities.

The injectables market as a sector has a strong pipeline for growth. We will be at the forefront of that growth agenda by delivering on quality, agility, and accepting injectable challenges others may not.◆

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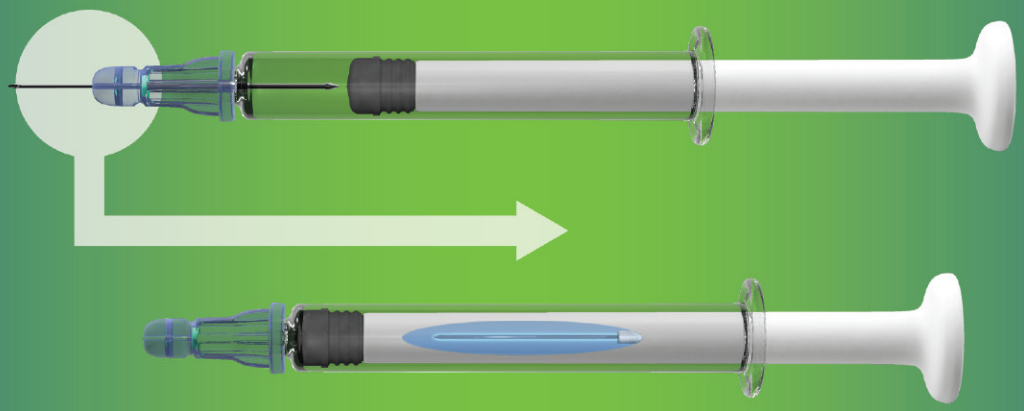

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