Drug Development & Delivery

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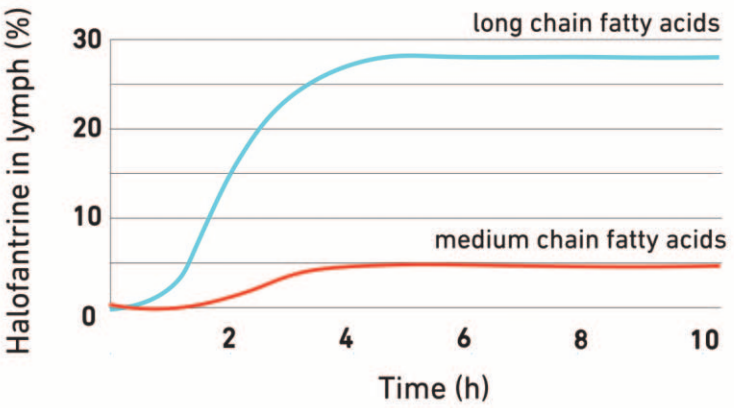

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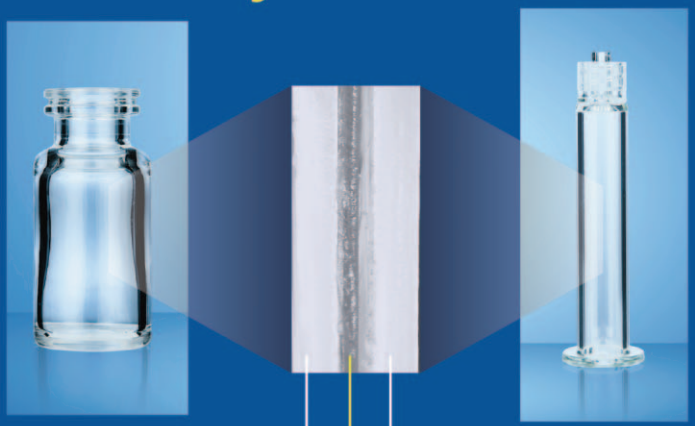

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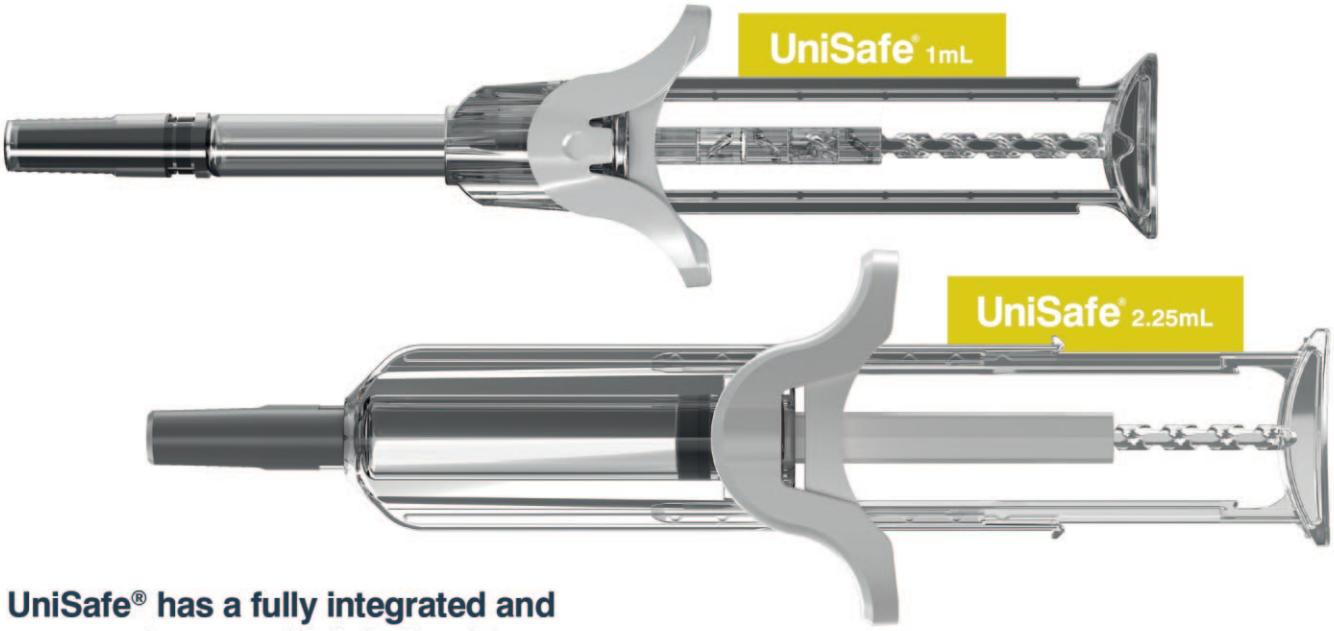

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Targeting the Upper Airways

"The Cascade Impactor studies as well as the CFPD simulations demonstrated a relatively high deposition rate in all three face mask or mouthpiece configurations with depositions in the upper respiratory tract ranging from 9.2% to 37.9% across the targeted areas, in contrast with negligible lower airway deposition ranging from 0.96% to 2.2%. Nasal airway deposition, specifically targeting the NALT region, can also be enhanced by breathing in through the mouth and subsequently exhaling via the nose, with the mouth acting as a kind of spacer."

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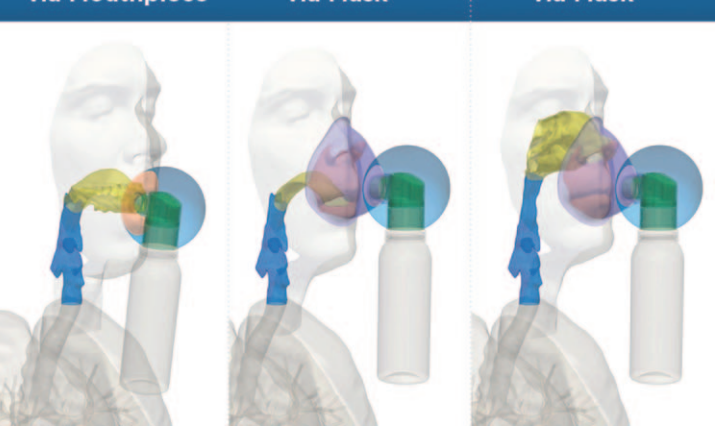

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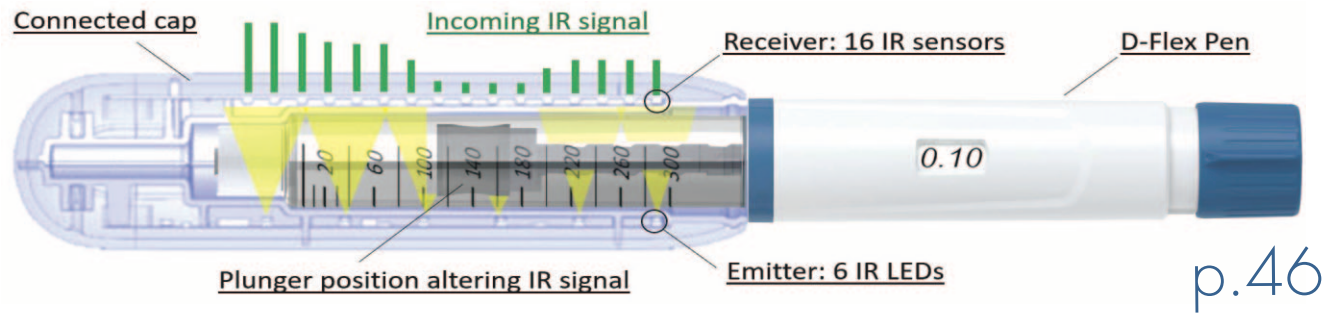

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"The global injectable drug delivery devices market is expected to show significant growth in the coming years as manufacturers introduce technological advancements and product innovation meant to improve convenience, compliance, and ease of administration of parenterals. Additionally, the increasing preference for at-home self-infection is driving the market as patients prefer to continue to avoid healthcare settings post-COVID."

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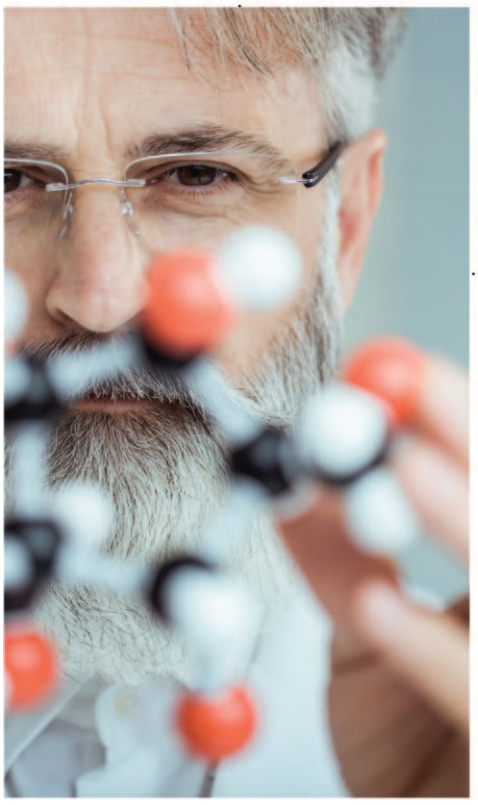

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- Packaging & Labeling
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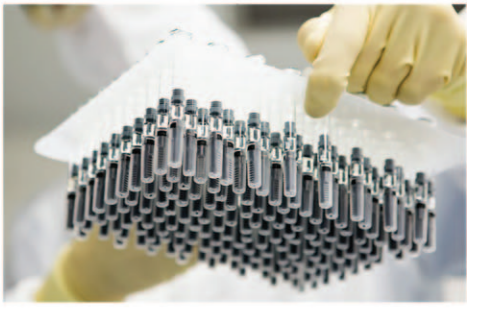
- Analytical Development



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Evonik Acquires JeNaCell to Expand Biomaterials Portfolio for New Medical Device Markets

Evonik has acquired German biotech company JeNaCell. The acquisition expands Evonik's biomaterials portfolio to provide biotechnologically derived cellulose. The nature-identical material developed by JeNaCell is used in medical technology and dermatology for the treatment of wounds and burns as well as in hydroactive skin care. The employees of JeNaCell will continue to work at the development and production site based in Jena, Germany.

Evonik recognized JeNaCell's potential in 2015 and invested in the start-up through its own venture capital arm. Following the complete takeover, JeNaCell's portfolio will be integrated into Evonik's health care business. The company accelerates the portfolio shift of its Nutrition & Care division toward system solutions and expands the division-wide technology platform of natural materials for medical technology. The share of system solutions in Nutrition & Care is to be increased from 20% today to more than 50% by 2030.

"JeNaCell has developed one of the most innovative biomaterials for medical device technologies. With the help of the creativity and expertise of JeNaCell's specialists, we will ensure that even more patients benefit from these products in the future," said Thomas Riermeier, Head of Evonik's Health Care business line. "The acquisition will help us to further strengthen our position as an innovation hub for the world's leading medical technology companies."

"The acquisition by Evonik is a quantum leap for JeNaCell to realize the full potential of our innovative technology," said Dana Kralisch, Chief Executive Officer and co-founder of JeNaCell. "We are excited to have found a strong and trusted partner to develop our technology platform and a new home for our passionate team of experts. Together, we will expand our customer base and explore new application areas."

The acquisition confirms Evonik Venture Capital's strategy of investing early in start-ups with visionary technology that are relevant to Evonik's innovation growth fields.

"JeNaCell is a great example for the innovation strength and the value that startups can bring to corporations," said Bernhard Mohr, head of Evonik Venture Capital. "We recognized the importance of the industry shift to nature-identical materials early on and are very happy to have supported the development of this technology with our investment."

JeNaCell began as a spinoff company from the Friedrich-Schiller-University of Jena in Germany. In 2017, the company launched its first product epicite, a medical wound dressing for the treatment of chronic wounds, surgical wounds and burns that is based on biotechnologically derived cellulose. It is a skin-friendly and soft biomaterial that provides a healing-promoting microclimate on the wound and can be removed painlessly. Further technologies developed by JeNaCell include soft tissue implants, transdermal delivery systems and dermatological applications.

JeNaCell's product developments are complementary to the portfolio of Evonik's Health Care business, which is a leading global solutions provider for innovative materials for medical device and pharmaceutical markets. RESOMER, now commercially available for more than 30 years, is the industry's most comprehensive GMP (Good Manufacturing Practice) portfolio of standard, custom and specialized bioresorbable polymers for use with implantable medical devices and pharmaceutical drug products.

Recipharm Launches New Laboratory to Expand Analytical Services Offering

Global contract development and manufacturing organisation (CDMO), Recipharm, has announced the completion of a new analytical laboratory at its facility in Bengaluru, India.

The new 370 m2 area is fully cGMP compliant and is equipped with state-of-the-art technology and instruments to cater for the rising demand from customers for the company's stand-alone Recipharm Analytical Solutions.

Recipharm Analytical Solutions is designed to help customers with timely, reliable outsourced support for analytical services from concept through to commercial. The new laboratory will accommodate 40 scientists and will bolster the team's capacity to support additional projects.

Ramesh Jagadeesan, PhD, Assistant Vice President, said "It's great to be able to announce the inauguration of our new analytical laboratory under Recipharm Analytical Solutions. Despite all the challenges the pandemic has presented, our team has worked diligently to complete the project and ensure the laboratory is operational, on time."

"We're confident the new laboratory will bolster our ability to support our customers and meet their method development, validation and stability studies requirements while maintaining the quality services they're accustomed to from Recipharm."

Recipharm has also appointed Mr. Manivel Thangapragasam as Associate Director to lead the new laboratory. Manivel brings 21 years of experience in the field of analytical development and stability studies. Commenting on the appointment he said "I'm delighted to join the Recipharm team. Recipharm provides high quality analytical programmes and flexible capacity to customers when they need it. Given the speed the market is moving, it is clear that the demand for such services is on the rise."

The new lab has been in full operation since August 1 2021. Recipharm is a leading Contract Development and Manufacturing Organisation (CDMO) in the pharmaceutical industry employing almost 9,000 employees. Recipharm offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies. Recipharm's annual turnover is approximately SEK 11 billion. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and is headquartered in Stockholm, Sweden. For more information, visit www.recipharm.com.

Curia to Expand US Commercial Manufacturing Capability, Investing More Than $35 Million

Curia, formerly AMRI, a leading contract research, development and manufacturing organization, recently announced plans to expand its commercial manufacturing capacity at its Rensselaer, NY, facility. The increased capability to flexibly manufacture complex Active Pharmaceutical Ingredients (APIs) will further strengthen Curia's ability to partner with customers, meeting small-scale to large-volume requirements with reliable delivery.

Curia is investing more than $35 million in these state-of-the-art expanded manufacturing and product-handling solutions for complex small molecules. The expansion will include new vessel capacities that more than double the site's batch-size scaling and product output. It will allow for the introduction of a variety of new products and enable Curia to meet growing demand for high potency API manufacturing.

The expansion will generate new technical jobs in Rensselaer. Consistent with Curia's commitment to environmental stewardship, the expansion plans include optimization of energy usage and enhanced environmental standards as integral elements.

"Our Rensselaer team's history of excellence in delivering US-based complex manufacturing solutions that enable our customers to provide vital treatments to patients is resulting in increasing demand," said Curia Chairman and CEO John Ratliff. "Some of the life-saving products produced at Rensselaer are highly complex, including critical oncology therapeutics and novel treatments addressing unmet medical needs. The engineering and technology advances we have designed for the site will enhance our flexibility, efficiency and scale, allowing us to meet our customers' current and future complex manufacturing needs."

Curia's Rensselaer facility has provided high-quality APIs to global pharmaceutical companies for more than 100 years. The site currently produces APIs to meet the development and commercial needs of more than 50 products. It was the first facility in the industry to be designated "Industry Leader" as part of its re-certification under the independent SafeBridge® program for "Potent Compound Safety Certification" in 2020.

The expansion is expected to be completed within 18 months, adding to Curia's existing breadth of API manufacturing facilities in the US, France, Spain, Italy, and India, each supporting flexible manufacturing solutions for orders ranging from grams to metric tons, to provide seamless support to customers along the R&D and manufacturing continuum.

Curia, formerly AMRI, is a leading contract research, development and manufacturing organization providing products and services from R&D through commercial manufacturing to pharmaceutical and biopharmaceutical customers. Curia's 3,400 employees at 23 locations across the US, Europe, and Asia help its customers advance from curiosity to cure. For more information, visit CuriaGlobal.com.

Aptar Pharma Granted Exclusive License Option by Pharmaxis to Develop & Promote High Payload Dry Powder Inhaler

Aptar Pharma recently announced it has entered into an agreement with Pharmaxis under which Aptar Pharma has the option to acquire the worldwide rights to Pharmaxis' proprietary high payload dry powder inhaler, Orbital. As part of the agreement, Aptar Pharma will evaluate the commercial applications for the Orbital device and further develop the prototype device to meet unmet market needs. Pharmaxis retains the rights to devices containing Orbital intellectual property used to deliver inhaled mannitol.

The Orbital technology is built on Pharmaxis patents, which allow powder payloads of up to 400 mg or more to be inhaled by patients in divided doses without the need to reload. This unique platform was originally developed as a life cycle-extending product for the Pharmaxis cystic fibrosis drug Bronchitol. However, it also meets an increasing global need to deliver high doses of other drugs, such as antibiotics, to the lungs.

Howard Burnett, Vice President Global Pulmonary Category, Aptar Pharma, commented "We are pleased to partner with Pharmaxis on this novel technology, which continues the development of Aptar Pharma's industry-leading portfolio of devices for inhalation. Coupled with our broad Aptar Pharma Services offering, we will seek to expand the range of drugs administered by inhalation."

"I am delighted with the forthcoming partnership with Aptar Pharma, who are one of the world's foremost drug delivery device companies. In their hands, we hope to fully exploit the potential of the Orbital technology in other drugs and secure a return on the work we have already completed," added Pharmaxis CEO Gary Phillips. "The Orbital Inhaler is an innovative new device that eliminates the need for manual reloading of multiple powder containing capsules needed for a single dose of drug. This can deliver improvements in the patient experience, compliance, market share and also effectively extend patent life of drugs that use the device."

Pharmaxis Ltd is an Australian clinical stage drug development company developing drugs for inflammatory and fibrotic diseases, with a focus on myelofibrosis. The company has a highly productive drug discovery engine built on its expertise in the chemistry of amine oxidase inhibitors, with drug candidates in clinical trials.

Aptar Pharma is part of AptarGroup, Inc., a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions. Aptar's innovative solutions and services serve a variety of end markets including pharmaceutical, beauty, personal care, home, food and beverage. Using insights, proprietary design, engineering and science to create dispensing, dosing and protective technologies for many of the world's leading brands, Aptar in turn makes a meaningful difference in the lives, looks, health and homes of millions of patients and consumers around the world. Aptar is headquartered in Crystal Lake, Illinois and has 13,000 dedicated employees in 20 countries.

Terumo Blood & Cell Technologies & PhotonPharma Inc. Announce Collaboration to Develop Novel Cancer Immunotherapy

Terumo Blood and Cell Technologies and PhotonPharma Inc. recently announced they have established a memorandum of understanding (MOU) for collaboration to develop Innocell, a novel tumor-specific immunotherapy (a therapeutic vaccine) for solid tumors. The benefit to patients is that collaborations like this can help improve the speed to market for valuable treatments.

To help in the cancer immunotherapy development process, PhotonPharma is using Terumo's Mirasol Pathogen Reduction Technology (PRT) in the manufacturing process. The initial agreement authorizes PhotonPharma to reference the Device Master File (DMF) on record with the FDA for the Mirasol system. This DMF will then support the PhotonPharma regulatory submission for its Innocell therapeutic vaccine technology. Additionally, Terumo Blood and Cell Technologies will supply Mirasol illuminators and single-use sets for the immunotherapy preparation process used in the clinical trial.

Mirasol has been used in select markets outside the US since 2007. Terumo designed Mirasol to reduce pathogen load and inactivate residual white blood cells in whole blood and blood components. PhotonPharma's specific use of Mirasol is a further example of how Terumo's products are being used to develop treatments across the life-sciences sector to help patients gain access to medical therapies.

The American Cancer Society's 2021 forecast projects 1.9 million new cancer diagnoses and more than 600,000 cancer deaths. Each day, that's approximately 5,200 newly diagnosed cancer cases and 1,670 cancer deaths. Ninety percent of the cases diagnosed are expected to be from solid tumours.

Therapeutic cancer vaccines are developed to stimulate a patient's immune system to fight established cancer. They are different from prophylactic vaccines, which are given to healthy individuals to prevent infection and related diseases.

PhotonPharma developed its technology to be differentiated from other therapeutic cancer vaccines in its potential to preserve solid tumour antigens, cell metabolism and protein translation while also potentially achieving inactivation of cellular replication.

This MOU is the first part of a longer-term collaboration to advance PhotonPharma's Innocell. The collaboration focuses on the development, regulatory approval, and future commercialization of PhotonPharma's Innocell vaccine. PhotonPharma is currently preparing an Investigational New Drug (IND) submission related to a Phase 1 clinical trial targeting triple-negative breast cancer.

"This agreement to work together with Terumo increases the potential to advance a new therapy for patients suffering from a variety of solid tumor malignancies, including breast cancer," said Dr Gary Gordon, MD, PhD, former Divisional Vice President of Abbvie Oncology and PhotonPharma board member. "Working together will benefit patients in need of new therapeutic approaches to treat their underlying disease."

Antoinette Gawin, President and Chief Executive Officer, Terumo Blood and Cell Technologies, added "For Terumo, strategic collaborations increase the potential speed to market and decrease development costs of therapies. This will enable patients to benefit from therapies earlier. Contributing toward the development and commercialization of Innocell enables Terumo to contribute toward the next potential major medical breakthrough."

Zealand Pharma Announces First Patient Dosed in EASE-SBS 4 Phase 3b Trial Assessing Glepaglutide in Patients with Short Bowel Syndrome

Zealand Pharma A/S recently announced dose administration for the first subject in the Phase 3b trial, EASE-SBS 4, evaluating glepaglutide, the company's long-acting GLP-2 analog, which is being investigated as a potential treatment option for short bowel syndrome (SBS).

"SBS is a debilitating disease with limited current treatment options," said Adam Steensberg, Executive Vice President and Chief Medical Officer at Zealand Pharma. "We are committed to making a difference for people living with SBS and, as such, our goal with glepaglutide is to reduce the need for parenteral support so that patients can achieve nutritional goals through the course of everyday activities. This particular trial has been designed to assess the long-term direct effects of glepaglutide on intestinal fluid and energy uptake."

EASE-SBS 4 is an open-label single-center Phase 3b trial investigating the long-term effect on intestinal absorption, nutritional status and long-term safety of administration of glepaglutide in patients with short bowel syndrome (SBS.) Ten patients will receive once weekly 10 mg subcutaneous injections of glepaglutide over 26 weeks. This trial is part of Zealand's EASE-SBS Phase 3 program for glepaglutide. ClinicalTrials.gov identifier (NCT number): NCT04991311.

SBS is a complex chronic and severe condition associated with reduced or complete loss of intestinal function. Many patients have to be connected to infusion lines and pumps every day, which pose significant restrictions on their ability to engage in daily activities. In addition, they are at risk of experiencing a number of serious and life-threatening complications such as sepsis, blood clots, liver damage and renal impairment.

Glepaglutide is a long-acting GLP-2 analog in development for the treatment of short bowel syndrome (SBS). Glepaglutide is being developed as a ready-to-use liquid product in an autoinjector designed for convenient and easy subcutaneous administration. Zealand initiated the Phase 3 clinical program for Glepaglutide in October 2018. The pivotal trial Phase 3 trial, EASE-SBS 1 is a randomized, double-blind and placebo-controlled study, with both once- and twice-weekly dosing regimens. The US FDA has granted orphan drug designation for glepaglutide for the treatment of SBS.

Zealand Pharma A/S (Nasdaq: ZEAL) is a biotechnology company focused on the discovery, development, and commercialization of peptide-based medicines. More than 10 drug candidates invented by Zealand have advanced into clinical development, of which two have reached the market. Zealand's robust pipeline of investigational medicines includes three candidates in late-stage development. Zealand markets V-Go, a basal-bolus insulin delivery option for people with diabetes, and has received FDA approval for Zegalogue, (dasiglucagon), the first and only glucagon analogue for the treatment severe hypoglycemia in pediatric and adult patients with diabetes aged 6 and above. License collaborations with Boehringer Ingelheim and Alexion Pharmaceuticals create opportunity for more patients to potentially benefit from Zealand-invented peptide investigational agents currently in development.

Shape Therapeutics Enters Strategic Research Collaboration With Roche to Advance Breakthrough AAV-Based RNA Editing Technology for Neuroscience & Rare Disease Indications

Shape Therapeutics Inc. recently announced a multi-target strategic collaboration and license agreement with Roche. Through this partnership Shape will apply its proprietary RNA editing platform RNAfix and potentially leverage its AAVid technology platform for next-generation tissue-specific adeno-associated viruses (AAVs) for the development of gene therapy for certain targets in the areas of Alzheimer's disease, Parkinson's disease, and rare diseases.

During the course of the partnership, Shape will conduct preclinical research to identify and deliver development candidates discovered by its AI-powered platforms RNAfix and, potentially, AAVid. Roche will be responsible for the development and worldwide commercialization of any potential products resulting from the collaboration.

"Our mission at Shape is to unlock the next breakthrough in RNA technologies in the gene therapy space across a wide range of therapeutic areas," said Francois Vigneault, PhD, Co-founder and Chief Executive Officer of Shape. "The relationship with Roche quickly centered on a common desire to tackle some of the world's most challenging diseases by accelerating the development of breakthrough technologies towards the clinic."

"We are excited by the disruptive potential of Shape's RNA-editing approach based on nature's own mechanism for specific base editing. This new collaboration is also perfectly aligned with our broader efforts across the Roche Group to unlock the full potential of gene therapy," said James Sabry, Head of Roche Pharma Partnering. "We look forward to working with Shape to create novel treatment options for neuroscience and rare disease indications."

Under the terms of the agreement, Shape is eligible to receive an initial payment as well as development, regulatory, and sales milestone payments, potentially exceeding $3 billion in aggregate value. Shape is also eligible to receive tiered royalties on future sales of products resulting from the collaboration.

Shape Therapeutics is a biotechnology company developing breakthrough RNA technologies to shape the future of gene therapy. The Shape gene therapy platform is composed of RNAskip, RNAfix, and RNAswap payload technologies, next-generation tissue-specific AAVid delivery technology, and SquareBio, a solution for scalable gene therapy manufacturing based on industrialization of human stable cell lines. At the core of these technologies is the Shape AI engine, where data drives decisions today to enable tomorrow's gene therapies. Shape is committed to data-driven scientific advancement, passionate people, and a mission of providing lifelong cures to patients. For more information, visit shapetx.com.

DELIVERY DEVICE

Aerosol Deposition Characterization of Innovative PureHale® Technology Targeting the Upper Airways

By: Degenhard Marx, PhD, Fotos Stylianou, PhD, and Stavros Kassinos, PhD

INTRODUCTION

The nose and upper respiratory system function as a path for air to enter the body while contributing to olfactory function, conditioning the breathed-in air and removing debris. Serving as a primary contact point with the environment, they can be a route for the entry of contaminants or disease as well as a site for healing and protection using the latest targeted delivery technologies.

Moisturizing the upper airways can provide symptom relief for a variety of upper airway conditions and can also reduce the risk of viral infections because of improved mucociliary clearance (MCC). Recent studies have demonstrated the potential effectiveness of targeted administration of anti-viral or protective formulations to nasal mucosa for preventing viral infections.[1] With the ability to treat the upper airways by only using specialized inhalation delivery methods, one can deliver a targeted aerosol that simultaneously minimizes deposition levels in the lower airways.

Aptar Pharma's novel PureHale® ready-to-use nebulizer-like device was specifically developed to target the upper respiratory tract while minimizing deposition in the lower airways. PureHale provides a modern device option for the delivery of a fine mist for a variety of solutions to only the upper respiratory tract without significant deposition in the lungs and lower airways.

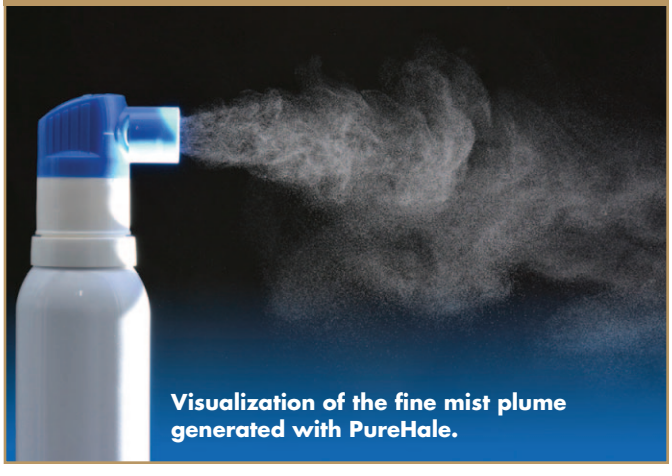
The PureHale system is based on Aptar Pharma's well-established Bag-on-Valve Technology Platform and uses an innovative actuator technology capable of producing a fine mist. The device generates a continuous fine mist with a mean droplet size of approximately 15 μm to 20 μm at a continuous output rate of ~1 ml per minute, visualized in Figure 1A. PureHale's Bag-on-Valve system requires no external power source or batteries. Inside an aluminum can, a multilayered bag serves as the reservoir for the product formulation, protected inside the bag from any environmental or propellant interaction. By turning the actuator, the unidirectional valve opens and, by means of pressurized air or any other environmentally uncritical propellant in the can, the product solution is forced at a distinct pressure through the innovative nozzle system thereby producing the desired droplet sizes and distribution.

When developing the PureHale system, Aptar Pharma performed extensive testing to demonstrate and evaluate the effectiveness of the system's ability to deliver the required fine mist to the targeted upper respiratory tract with the desired deposition pattern. Data was generated for both face mask and mouthpiece applications, using different breathing patterns, with the expectation that the combinations would show significantly different deposition of the tested formulations to specific areas of the upper respiratory tract.

Two complementary methods were combined for these studies to simulate the entire upper and lower respiratory tracts:

1. Next Generation Impactor (NGI) - differentiates deposition between upper and lower respiratory tracts.

FIGURE 1A



Visualization of the fine mist plume generated with PureHale.

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2. Computational Fluid Particle Dynamics (CFPD) - provides detailed deposition patterns and quantitative deposition fractions.

By combining NGI and CFPD technologies, a complete test method simulating the entire respiratory tract and its anatomy was created that provided data defining differential deposition patterns that PureHale achieves in the upper airways. Additionally, the designed tests could shed light on the specific deposition patterns within the entire region of interest, from the nasopharyngeal area through to the throat and larynx.

Based on the findings of the *in-vitro* and *in-silico* studies, we concluded that PureHale could effectively support targeted treatments for the prevention, protection, or cure of conditions affecting the upper respiratory tract, by moistening, cleansing, and soothing the upper airways. This could include solutions for applications such as infections or viral protection of the upper respiratory tract.

CASCADE IMPACTOR STUDIES

Several data measurement techniques were used for the Cascade Impactor Studies. Most simply, the total flow rate of the PureHale samples were determined by weighing them before and after continuous operation for 60 seconds. Initial droplet size characterization was conducted using a laser diffraction Malvern Spraytec. The Cascade Impactor model required a more complex setup to mimic the entire upper respiratory tract. For the study, a commonly available Next Generation Pharmaceutical Impactor was used, specifically designed for pharmaceutical inhaler testing with a focus on lower airway deposition. This was used in combination with an Alberta Idealized Throat (AIT) to simulate the upper airways. The Alberta Idealized Throat was specifically designed to mimic the aerosol deposition and flow in the human mouth-throat region. This two-component setup allowed the simulated measurement of the deposition of the PureHale mist when breathing through the mouth.

The experiment was conducted using the standard mouthpiece (Figure 1B), either being placed directly to the orifice of the AIT or at a distance of approximately 4 cm, simulating a spacer. Through this spacing approach, inhalation and exhalation were intended to be separated in order to achieve a higher deposition in the airways.

To complete the test system for simulation of nose breathing and the use of a face mask (Figure 1B), a special upper airway model was created. The geometry is based on a characteristic pediatric geometry of the mouth-throat and nose-throat region (developed in the Pharmaceutical Physics Laboratory of Boehringer Ingelheim Pharma GmbH & Co. KG assessed via https://www.rddonline.com). This geometry was scaled-up by a factor of 1.5 in three dimensions to better fit the size of the test equipment and the face masks, and to bring it closer to an adult geometry. The face-nose model was printed with FotoMed® LED.A at 3D-LABS GmbH.

A flow rate of 15 L/min was applied for the experiments, simulating sinusoidal breathing at 15 breaths/min (as described in USP 39 <1601> Products for Nebulization / General Information). Each experiment lasted 60 continuous seconds with at least three repetitions per simulation. For the NGI studies, the PureHale test samples were filled with fluorescein-sodium dye dissolved in deionized water (40 mg/ml fluorescein) and pressurized. The deposited formulation was retrieved for quantitation by carefully washing the different sections of the described model. Samples were photometrically analyzed at a wavelength of 487 nm to determine flu-

FIGURE 1B

The PureHale device uses Bag-on-Valve technology and offers mouth piece and face mask options for application.

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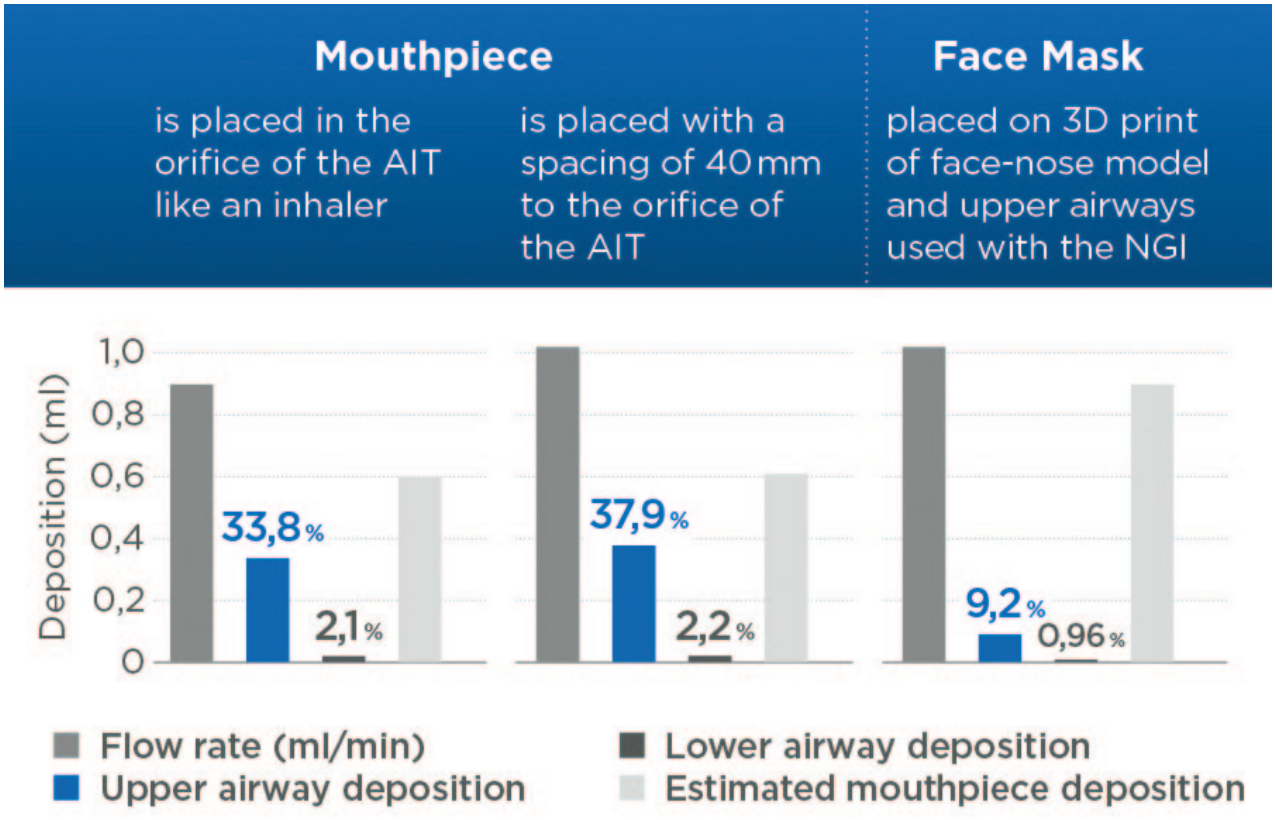
FIGURE 2



PureHale deposition measured in the NGI test setup, using an AIT or a 3D print of the face-nose model. The PureHale with mouthpiece was placed on or in front of the orifice of the AIT. PureHale with face mask was placed on the 3D print of the face-nose model.

orescein concentration. Then, with the determined fluorescein concentration deposition quantities were calculated based on the washing volumes collected from each section (Figure 2).

Deposition in the upper airway reached a high of 34% when the mouthpiece of the actuator was placed in the orifice of the AIT during oral breathing. When the mouthpiece was positioned at an additional distance of 4 cm from the orifice during breathing, the deposition measured was slightly higher at 38%. Finally, when using the facemask with PureHale during nasal breathing (not by mouth), the upper airway deposition was significantly lower at approximately 9% as expected. In all three scenarios, the data demonstrated a range of upper respiratory deposition of 9.2% to 37.9% in contrast to minor lower airway deposition ranging from 0.96% to 2.2%. This clearly demonstrates that the PureHale system provides comprehensive deposition in the upper airway but very limited deposition in the lower airway.

COMPUTATIONAL FLUID PARTICLE DYNAMICS (CFPD) SIMULATION

Some technical limitations of the modified impactor model became apparent through the studies conducted including the fact that the scaled-up face/nose model does not accurately represent an adult anatomy. We decided to apply appropriate Computational Fluid Particle Dynamics (CFPD) modeling to overcome some of these challenges and gather more definitive data. CFPD is an in-silico approach that solves conservation laws at high spatial and temporal resolution to emulate the fundamental behavior of fluids and particles in these systems. The first step in developing the CFPD model is the construction of the computational domain, which consists of the upper airways and the PureHale device with mouthpiece or face mask. The digital geometry of the inhaler was already available from the Computer-Aided Design (CAD) drawings, but the digital geometry of the upper airways had to be constructed. To generate a model, 3D face scanning technology was used in order to define the facial characteristics of a subject while inhaling with the

PureHale device. The upper airway properties were generated from medical CT/MRI images of different subjects but all with strong anatomical correlation. Nasal cavities were derived from head CT scan images, while the oral cavity and throat region were established from neck MRI images. Lastly, a partial tracheobronchial airway tree was generated from chest CT image sources. All of these data points contributed to accurately defining the upper airways in the CFPD model used in the simulations.

The second step in CFPD modeling is the generation of the grid, a process in which the computational domain is subdivided into smaller connected elements. The grid elements act as data generating points, measuring the airflow during breathing emulation. Higher grid densities lead to superior airflow resolution but with a significantly greater computational cost. Typically, a balance between resolution and cost is sought, with increased grid densities applied only to regions of important airflow and particle transport phenomena. For the purposes of this study, we have used various grids with tens of millions of elements. The largest grid size used was approximately 52 million elements, and it was simulated on 280 CPU cores with 2.4 GHz processor speed for approximately 70 days.

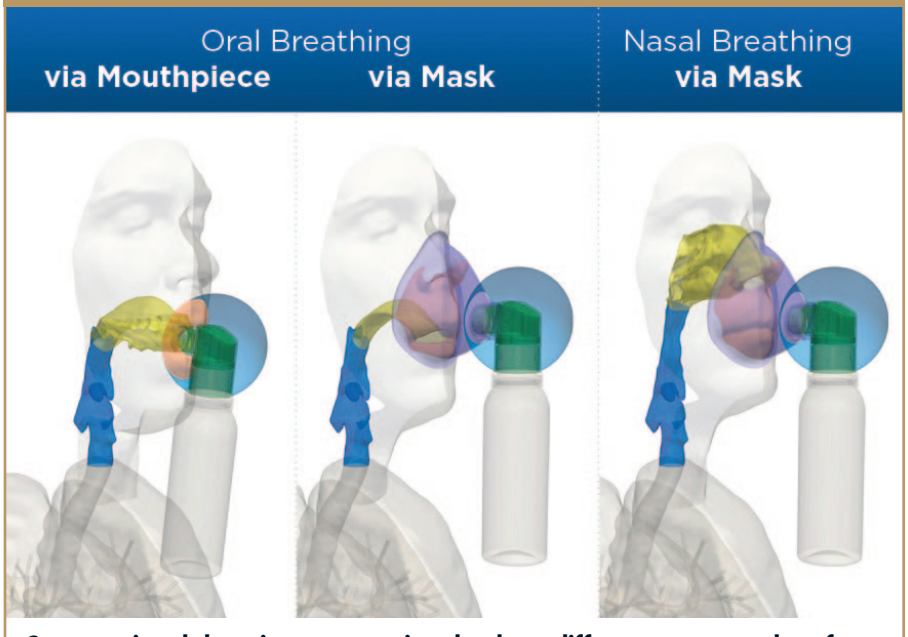
CFPD technology was used to simulate the aerosol release from the PureHale system and subsequent deposition in the extra thoracic airways. Data for a full breathing cycle with period duration of T = 2 seconds were calculated. Prior to the analyzed breathing cycle, an initialization process was simulated to subsequently emulate the aerosol deposition under a steady state breathing cycle. A sinusoidal breathing profile was applied with an average flowrate of Q = 15 L/minute corresponding to normal breathing at rest. Airflow turbulence was modeled via the Large Eddy Simulation (LES) methodology. For the fine mist with a large aerosol-to-air density ratio, only the critical forces acting on the aerosols were taken into account (ie, Drag and Gravity, and to a lesser extent the Buoyancy and Shear Lift). Accounting for the effect of aerosols on the airflow, an appropriate two-way coupling source term was applied to the airflow equations.

The simulations assumed an isotonic saline solution (0.9% w/v NaCl in water) was being injected from the 48 holes of the PureHale nozzle toward the patient. In real life, the injection process initially forms jet streams, but as they interact with the surrounding air, they become unstable and break into droplets. These interaction forces between droplets are not accounted for in the simulations. As a result, droplets were injected from the beginning of the simulation at the final expected droplet size using a consistent mass and momentum approach. In the simulations, the diameter of the droplets was set at d = 15 µm. Three different inhaler usage modes were studied (Figure 3).

One of the many simulation outputs was the deposition sites of injected droplets. The deposition locations and densities can be visualized simultaneously via the surface coverage fields. Figure 4 shows the estimated airway surface coverage fields after 15 breathing cycles for the three inhaler usage modes. These fields are estimated from single breathing computations extrapolated to represent 15 breathing cycles with the upper limit of the logarithmic scale bar reflecting the single cycle coverage. Local values above 100% indicate that the site surface would be fully covered with droplets plus a potential excess of droplets. Under this condition, the local liquid film formed could spill to the neighboring locations, but we have not accounted for this scenario as we wanted to highlight the most conservative case.

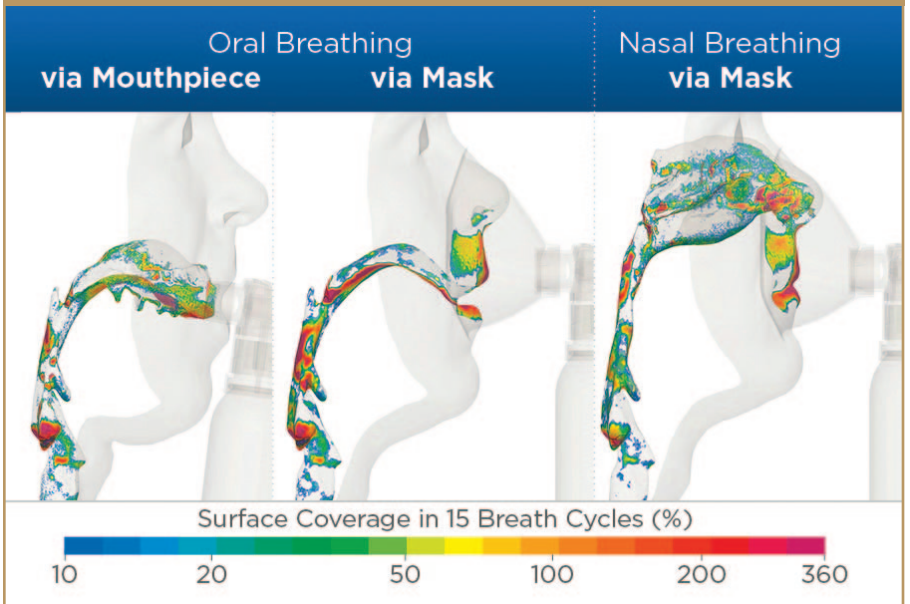
The simulation data clearly shows that airway coverage is substantial under all three breathing modes. Standard nasal

FIGURE 3



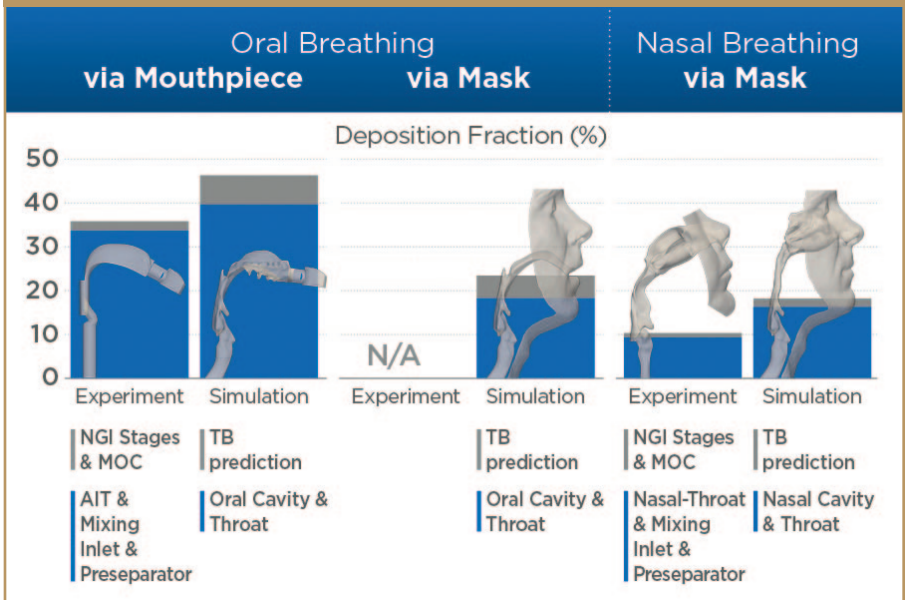
Computational domains representing the three different usage modes of the PureHale device.

FIGURE 4



Predicted deposition fields following 15 breathing cycles based on single breathing computations.

FIGURE 5



Comparison of *in-vitro* and *in-silico* deposition fractions. Oral breathing with mask was not studied experimentally.

sprays provide much more localized and concentrated nasal coverage, but the PureHale system provides more substantial coverage of the entire upper respiratory system being simulated. Furthermore, additional simulations indicate that an oral inhalation followed by a nasal exhalation provides complementary coverage of the nasopharynx-associated lymphoid tissue (NALT) region as compared to the simple nasal breathing maneuver. The NALT region, located at the rear end of the nasal breathing channel, is of particular interest because it is known to play a significant role in the development of mucosal immunity cells. Being able to deliver fine mists to this region can contribute to improved mucociliary clearance, immunology, or general nasal disinfection.

We looked at Deposition Fractions (DF) for a more quantitative measurement of these processes. Figure 5 compares the in-vitro and in-silico DFs where we separate the upper and lower airway deposition data. In general, the correlation of results between the actual experiments (where conducted) and the simulations are very strong and these variations can be attributed to the different models used between experiments and simulations. The data demonstrates that upper airway deposition is significantly higher than lower airway deposition and that unwanted tracheobronchial (TB) deposition is limited under all three breathing modes using the PureHale system.

ABOUT THE PUREHALE SYSTEM

PureHale is a novel fine mist-generating device with a high output rate of ~1 ml/min and delivers droplet sizes between 15 μm and 20 μm optimal for deposition in the upper airways. For effective use, operation of the device for at least 60 to 90 seconds per session is recommended. Addressing an unmet market need, PureHale's cordless, user-friendly system was engineered for on-the-go use anytime, anywhere. Unlike traditional nebulizers, the PureHale device requires no electrical energy source and is conveniently powered by pre-filled compressed inert gas or air in the product can for simple use wherever and whenever needed. PureHale also provides the flexibility of delivery via a mouthpiece or face mask, offering adaptable treatment options for everyone, from children to the elderly.

CONCLUSIONS

Aptar Pharma has performed a series of experiments that successfully demonstrate the ability of the PureHale technology system to reliably deliver small droplet mists to the upper respiratory tract on a targeted basis, with little deposition in the lower respiratory airways including the lungs. The Cascade Impactor studies as well as the CFPD simulations demonstrated a relatively high deposition rate in all three face mask or mouthpiece configurations with depositions in the upper respiratory tract ranging from 9.2% to 37.9% across the targeted areas, in contrast with negligible lower airway deposition ranging from 0.96% to 2.2%. Nasal airway deposition, specifically targeting the NALT region, can also be enhanced by breathing in through the mouth and subsequently exhaling via the nose, with the mouth acting as a kind of spacer.

Although the experiments and simulations utilized a simple 0.9% saline solution as a test case, the PureHale technology system may be ideal for a range of other applications that require targeted coverage of the upper respiratory tract with a fine mist, and negligible deposition in the lower airways. The self-contained, portable system is easy-to-use for both young and old and essentially unifies the delivery benefits of traditional nasal sprays with gargles for the upper airways.

A simple saline solution can be very well suited for the moistening of the upper airways in order to restore mucociliary clearance mechanisms caused by upper respiratory tract infections, allergies, colds, or other sources of nasal irritation. Viruses causing airway infections can adhere to and replicate in the upper airways, which can be specifically targeted by the PureHale technology platform and its comprehensive deposition pattern. Therefore, antiviral or antiseptic formulations applied via PureHale technology may be able to prevent or minimize the impact of an upper airway infection. Aerosols delivered by the Purehale technology system could be used to deliver a range of symptom relief or prophylactic benefits for users. Other applications for the PureHale technology platform could include aroma or halo therapies.

In summary, Aptar Pharma's PureHale technology platform combines convenient, portable ease of use with comprehensive mist deposition patterns across the targeted upper airway systems for a wide range of potential applications and solution types. ◆

REFERENCE

1. Victoria Corless, Advanced Science News, 18 June 2021: A nasal spray to prevent virus infections. https://www.advanced-sciencenews.com/a-nasal-spray-to-prevent-viral-infection/

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BIOGRAPHIES

Dr. Degenhard Marx is Director of Scientific Affairs Aptar Pharma's Consumer Health Care Division. Following his study of Veterinary Medicine, and the successful completion of his thesis at the University of Leipzig in 1992, he joined the pharmaceutical industry. During his career, he has gained extensive experience in the drug development for anti-inflammatory, respiratory and cardiovascular drugs.

Dr. Fotos Stylianou is a Postdoctoral Researcher in the Department of Mechanical and Manufacturing Engineering at the University of Cyprus, from which he earned his PhD degree in 2016. He also earned BSc and MSc degrees in Physics. In 2010, he joined the Computational Sciences Laboratory (UCY-CompSci) and has been involved in research projects funded by various pharmaceutical companies.

Dr. Stavros Kassinos is a Professor in the Department of Mechanical and Manufacturing Engineering at the University of Cyprus and the Head of the Computational Sciences Laboratory (UCY-CompSci). His works on the numerical simulation and modeling of complex physical systems include turbulent fluid-particle flows for environmental, biomedical, and technological applications. In particular, he is interested in the further development of *in-silico* methods in support of inhaled drug development.

FORMULATION DEVELOPMENT

A Quick Approach for Evaluation of Drug-Excipient Compatibility: Case of Acetylsalicylic Acid

By: Masumi Dave, PhD, and Rollie Fuller, BSc, and Jason LePree, PhD

INTRODUCTION

Drug-excipient compatibility testing is one of the early formulation screening steps that can help predict a drug product's stability. Conventional methods for compatibility testing however, are time consuming, labor intensive, require screening several excipients and eventually different formulations. For instance, HPLC analysis is often used for compatibility testing taking many weeks if not months to generate data as various blends are held at accelerated conditions.

In contrast, isothermal microcalorimetry may help reduce the timelines for evaluating drug-excipient compatibility in the early stages of formulation development. An indirect and time-efficient approach in predicting and measuring drug instability is possible by measuring interaction energies between formulation components using Thermal Activity Monitoring (TAM). The data generated by TAM may be analyzed in different ways, but for the purpose of simplicity and speed, the Gattefossé application lab uses absolute interaction energies as a singular metric to assess compatibility. This typically involves monitoring the thermal activity of a particular ratio of API: excipient at a constant temperature to that of the API and excipient individually. Any physical or chemical interaction is associated with heat production or absorption which is continuously monitored by TAM. Examples of physicochemical processes that could trigger a calorimetric response include dissolution, adsorption/desorption, evaporation, other phase transitions, crystallization, and chemical reactions. Heat signals are measured for the API and the excipient individually and are used to obtain a theoretical heat signal for the mixture of API and excipient. The theoretical heat signal of the mixture is compared to the measured heat signal. A significant difference between the two is an indication of potential incompatibility.

In this study, we monitor acetylsalicylic acid (ASA) hydrolysis in different formulations using UPLC and TAM with the objective of comparing these methods for agreement, speed, and efficiency in predicting drug stability. In parallel, we assess the impact of the excipient choices on the stability of ASA.

HYDROLYTIC DEGRADATION & ACETYLSALICYLIC ACID

Hydrolytic degradation is a frequent challenge presented by API and has remained a topic of intense review by researchers.[1] Commonly observed with some functional groups, hydrolysis occurs when a chemical bond is split (lysis) in the presence of water. The reaction is highly influenced by atmospheric humidity, pH, and the degree of the reactivity of the functional group. Hydrolysis occurs more rapidly in esters for example than in amides.[2]

Procaine is an example of an API susceptible to hydrolysis *in vivo*. Indicated as a local anesthetic, procaine, an amino ester, has short lived effects due to its inherent susceptibility to hydrolysis. Lidocaine, a similar API with local anesthetic properties, on the other hand has longer lasting effects compared to procaine due to its amide structure providing higher hydrolytic stability. Along the same vein, the active methylphenidate (Ritalin), indicated for Attention Deficit Hyperactivity Disorder, contains an ester functional group and is therefore susceptible to hydrolysis. This

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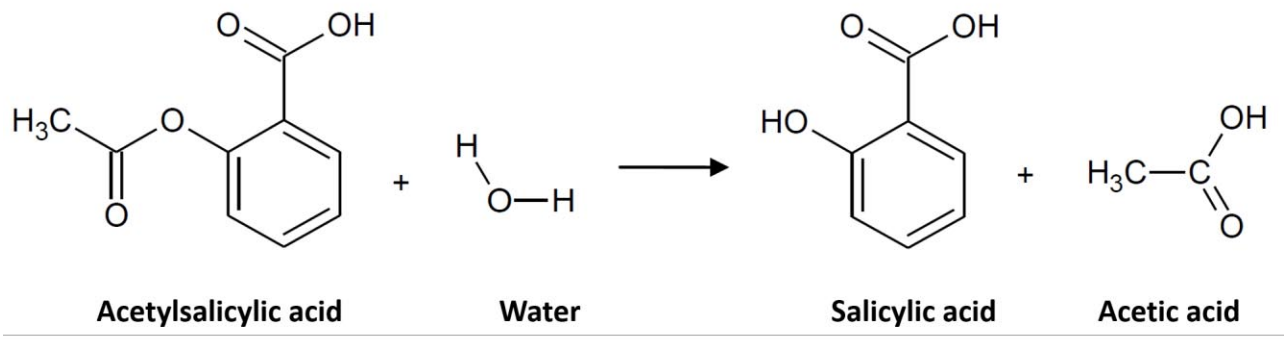
FIGURE 1



Hydrolytic breakdown of acetylsalicylic acid into salicylic and acetic acids.

leads to frequent dosing throughout the day in order to achieve and maintain therapeutic levels of the drug in the blood stream, raising concern for children attempting to comply with dosing recommendations during the day at school.[2]

Another example of a drug that is subject of hydrolytic breakdown is acetylsalicylic acid. Known for analgesic and antipyretic properties, ASA has been widely used in management of fever and arthritic pain. ASA is also known for inhibitory effect on platelet aggregation, helping reduce infarction risks in patients with cardiovascular disorders.[3]

Salicylic acid (SA) has a long history of use in the treatment of pain, fever, and inflammation. However, its side effects like severe gastric irritation, nausea, vomiting, bleeding, and ulcers led to the development of ASA.[5] In fact, ASA is an esterified pro-drug of the corrosive SA to reduce gastrointestinal irritation and the generation of ulcers.[6]

Neat ASA is quite stable but becomes susceptible to hydrolysis if exposed to humidity over time (Figure 1) leading to the formation of salicylic and acetic acids.[5] The reaction kinetics are relatively slow during storage but rise considerably depending on formulation type and processing conditions. Therefore, it is necessary to avoid hydrolytic changes that would compromise its safety.

The conversion of ASA to SA after oral intake is rapid, which may occur in the GI tract but primarily by enzymatic-mediated hydrolysis in the liver.[7] Differences exist between ASA and SA in terms of stability, therapeutic range, and elimination half-life. In pain management, ASA and SA have similar therapeutic effects. In treatment of cardiovascular disease and platelet aggregation however, it is ASA, and not SA, which has the irreversible platelet effect.[7]

Low dose ASA has been used widely to reduce cardiovascular events and deaths in patients with moderate to high risk of heart disease. However, daily use of ASA leads to increased risk of gastric irritation and serious ulcer complications, hence limiting its use and patient compliance. Lipid based formulations can provide a potential solution by ensuring the release of the API in the duodenum. B. Cryer et. al. demonstrated by a randomized clinical trial that a non-covalent complex of Aspirin-Phosphatidylcholine attenuated low-dose ASA induced ulceration.[8]

CONTROL OF HYDROLYTIC ACTIVITY

Limiting exposure to humidity during development and manufacturing, addition of buffers to control pH, and protective packaging are common strategies used for mitigating hydrolytic loss of drug activity. Additionally, polymeric coatings may be used as moisture barriers for solid dosage forms. Polymeric coating however requires the use of solvent(s) which need to be subsequently evaporated. Hygroscopic/water soluble polymers are least suited for water sensitive actives, while other polymers will require inorganic solvents which need to be recovered for health and environmental reasons.[9] Attractive alternatives to standard polymer coatings are naturally derived lipid-based matrices or coating systems. The latter involve melting of inert, solid lipid excipients before application directly onto the substrate.[10] As the lipid solidifies upon cooling, it provides a moisture-resistant barrier for the active. The solvent-free application of solid lipid-based systems can be achieved by several techniques, including hot melt coating, hot melt extrusion, and melt granulation.[11]

It has been reported that ASA on its

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own is reasonably stable given its hydrophobic nature resulting in a low level of water sorption.[12] ASA crystals tend to generate a hydrophobic field which inhibits the condensation of water from a high humidity environment thus imparting stability to neat API.[13] Mitrevej el al. demonstrated that the chemical stability of ASA cannot be improved by combination of the drug with a hydrophilic excipient. Hence, the composition of the formulation plays an important role in maintaining the formulation stability.

Lipid based formulations should be considered when formulating actives like ASA, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDS) which have the tendency to cause gastric irritation and ulceration. This was demonstrated by a randomized clinical trial conducted by Cryer B. and his team, where 42.2% of subjects treated with a traditional aspirin dosage form (tablets) developed ulcers vs 22.2% of those treated with their lipid-based formulation of ASA.[8] For these reasons, this study explores the effect of lipid-based excipients/ formulation type on the stability of ASA while comparing the stability evaluation methods.

METHODS

Lipid formulations: Three formulations containing 32.5% ASA were prepared with four lipid excipients of different phys-chem properties (Table 1).

Geloil™ SC, used in formulation A, is a thixotropic blend of three excipients uniquely developed for softgel formulations at ambient temperature when heat is to be avoided. The product facilitates dispersion of up to 50% solids (API) without loss of flow behavior for capsule filling. Geleol™ Mono and Diglycerides NF on the other hand is a solid excipient in the form of pellets with a melting point of 62°C. This excipient requires melting before mixing with the liquid Labrafac™ lipophile WL 1349 (Formulation B) and/or mixing with the liquid Maisine® CC (Formulation C) prior to dispersing the API in the mixture. Maisine® is a widely used oily vehicle, solubilizer and bioavailability enhancer in lipid-based formulations composed of long chain mono, di-, and triglycerides of linoleic acid. Labrafac consists of medium-chain triglycerides of caprylic (C8) and capric (C10) acids. It is used as an oily vehicle and solubilizer in lipid-based formulations.

Two different methods of analysis were employed to trace the ASA changes in various formulations. The first method involved assay of the ASA and its hydrolysis by-product SA using ultra-performance liquid chromatography (UPLC) on aging formulations over a 3-month period. The second method involved the indirect assay of hydrolytic activity by Thermal Activity Monitoring (TAM) over a 10-day period.

UPLC Method: The formulations listed in Table 1 were stored open dish in 250-mL glass beakers at 40°C/75%RH and assayed for SA (hydrolytic degradation product) monthly via a validated reversed-phase UPLC method for three months. As a control, neat API was also stored open dish in 20 ml scintillation vials at 40°C/75%RH and assayed for ASA and SA content monthly for 3 months.

Thermal Activity Monitoring: TAM studies were conducted under ambient humidity at 40°C for 10 days with individual components and Formulations A, B, and C in sealed glass ampoules. The expected heat flow from a mixture is made up by the contributions in heat flow from the individual components. A difference between the expected heat flow and the heat flow for a real mixture was used to determine the interaction energy and the extent of hydrolysis.

Theoretical signal = Weighted average heat flow signal of components in formulations

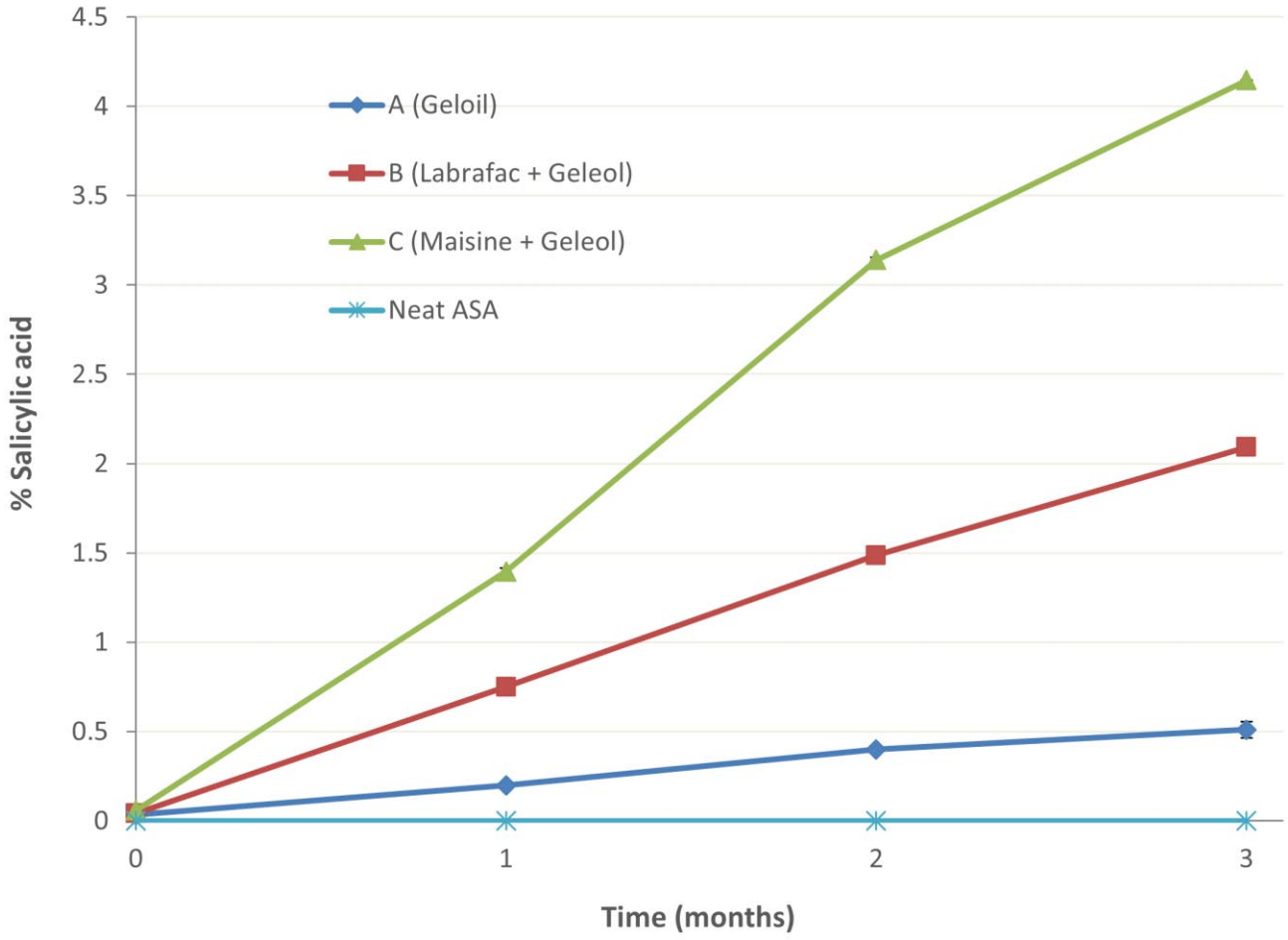
Interaction signal = Actual heat signal – Theoretic heat signal

TABLE 1

Abbreviation	Trade Name (Description per NF)	Lipid Formulations (mg)		
		A	B	C
ASA	Acetylsalicylic acid	325	325	325
Geloil	**Geloil™ SC** (Soybean oil, NF/Glyceryl distearate, NF/and polyglyceryl-3 dioleate, NF)	675		
Geleol	**Geleol™ Mono and Diglycerides NF** (Mono and diglycerides, NF)		67.5	67.5
Labrafac	**Labrafac™ lipophile WL 1349** (Medium-chain triglycerides, NF)		607.5	
Maisine	**Maisine® CC** (Glyceryl monolinoleate, NF)			607.5
Heat applied to melt excipient(s)		No	Yes	Yes

Lipid formulations assayed for hydrolytic stability of acetylsalicylic acid.

FIGURE 2



Quantitation of % salicylic acid over three months stability by UPLC.

RESULTS & DISCUSSION

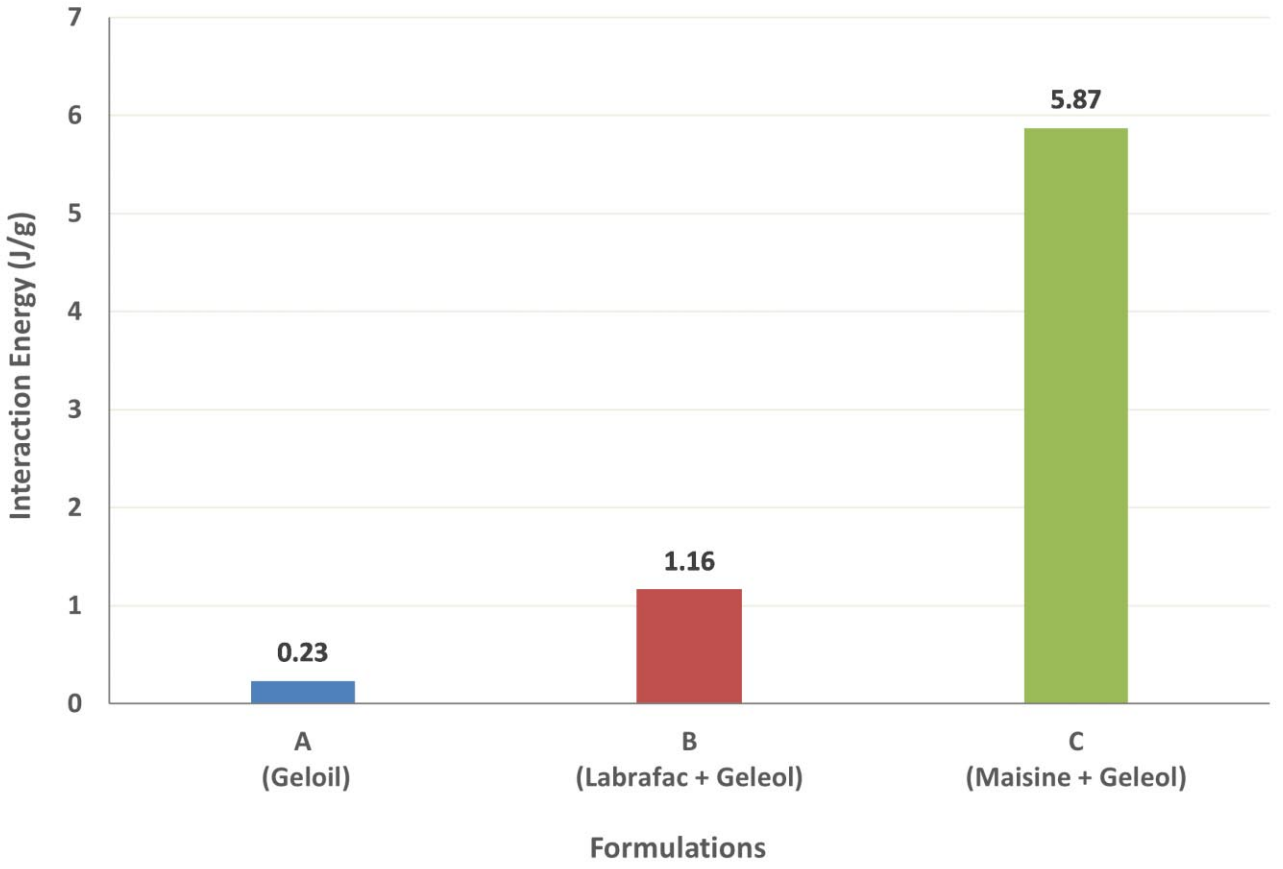
The percent assay of ASA over time (in accelerated conditions) was obtained by UPLC method. Even though some trends were evident, the high variability and standard error of the experiments suggested that a more sensitive approach would be to trace % SA, the byproduct of ASA hydrolysis. The results for the latter (Figure 2) proved to be discriminating in terms of ranking the formulations effect on hydrolytic stability.

Based on UPLC analyses, hydrolysis was lowest for formulation A (0.5% SA), given that it did not involve any heat for melting and consisted of a simple dispersion of ASA in Geloil™. Hydrolysis was evident at up to 2% SA for formulation B Labrafac™ + Geleol and even higher with formulation C Maisine® + Geleol where ASA was most hydrolyzed (4% SA) (Figure 2). For neat ASA samples stored at 40°C/75%RH conditions, no detectable levels of salicylic acid were generated in three months, confirming that neat API is quite stable as suggested by Mitrevej et al.

In parallel, the same formulations were analyzed immediately after preparation and over a 10-day period under ambient humidity at 40°C using TAM. The interaction energies for formulations A, B, and C after 10 days were 0.23, 1.16, and 5.87 J/g (Figure 3). Evidently, we were able to rank lipid formulations for API excipient compatibility. Similar to the UPLC results, formulation A was most protective of ASA hydrolysis compared to formulations B and C. Clearly, the rank order of hydrolytic breakdown indicated by TAM data is identical to the one obtained using traditional method with UPLC. For formulations which exhibited higher interaction energies, the percent SA at the end of 3 months was also higher.

The differences in the results among the formulations may be explained by the nature of the excipients and the formulation processes used. Formulation A with Geloil involved simple mixing of ASA with the excipient at ambient temperature. Formulations B and C on the other hand consist of Geleol, a solid excipient that needs melting before being mixed with other

FIGURE 3



Interaction energy measured by TAM after 10 days.

constituents of the formulation. The idea that the heat involved in formulation preparation could be a potential trigger for API degradation in both B and C is quite plausible. Meanwhile, the higher degradation of ASA in C compared to B may also be due to the nature of the liquid excipients mixed with the solids. However, additional studies to evaluate potential mechanisms are warranted. Overall, the findings are in line with the common understanding that heat should be avoided when working with a sensitive API like ASA.

We note that TAM is an indirect and yet highly sensitive method of predicting interactions in the tested formulations. Significantly less labor intensive than UPLC (validation, standard preparation, sample preparation and analysis) and with quick clues within days into the experimentation, TAM is a powerful discrimination tool in early formulation development.

CONCLUSIONS

The results suggest that the rank order of ASA decomposition C > B> A established by UPLC was further apparent with TAM analysis where the differences between the formulations were more prominent i.e., C>> B>> A. The TAM methodology was faster and less labor intensive.

As a side note, formulation A with Geloil was more promising compared to the formulations involving heat. Additional studies are needed to demonstrate the direct impact of moisture and heat on hydrolytic stability at a higher temperature and humidity level. Evaluating other API-excipient combinations for compatibility using both TAM and traditional stability testing protocols would further our understanding of the use of TAM in compatibility testing for pharmaceutical dosage forms.

Additional work with Geloil is warranted with particular attention to inclusion of antioxidant(s), reduced aeration during mixing, and addition of a desiccant to the formulation while measuring water content and acid value at each time point. Fu-

ture studies to evaluate the *in vitro* and *in vivo* performance of both the lipid-based and currently marketed formulations would provide useful insight into the potential of lipid-based excipients in enhancing the overall product performance. ◆

REFERENCES

1. LePree, et al. (2013) "Hydrolysis of Drugs". Ency Pharm Sci and Tech, 4th Ed. Taylor and Francis: NY, 1895-1900.
2. Snape et al. (2010) "Understanding the chemical basis of drug stability and degradation". Pharm J., 285:416.
3. Rosenkranz et al. (1986) "Effects of salicylic acid acetylsalicylic alone and in combination on platelet aggregation and prostanoid sysnthesis in man." Br. J. Clin. Pharmac. 21, 309-317.
4. Jannin et al. (2013) "Hot-melt coating with lipid excipients". Int J of Pharm, 457:480-487.
5. Fersht et al. (1967) "The Hydrolysis of Aspirin. Intramolecular General Base Catalysis" Am Chem Society, 89: 4857-4863.
6. Karman Rafik. (2015) From Conventional Prodrugs to Prodrugs Designed by Molecular Orbital Methods. Front in Comp Chem, 2:187-249.
7. Dressman J.B. et al. (2012) "Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Acetylsalicylic Acid." J. Pharm. Sci. 101 (8); 2653-2667.
8. Cryer et al. (2010) "Low-dose aspirin-induced ulceration is attenuated by aspirin-phosphotidylcholine: A randomized clinical trial" Am J Gasteroenterol, 106:272-277.
9. Yang et al. (2019)" An Update of Moisture Barrier Coating for Drug Delivery". Pharmaceutics, 11(9):436.
10. Jannin et al. (2013) "Hot-melt coating with lipid excipients". Int J of Pharm, 457: 480-487.
11. Becker et al. (2015) "Solvent-Free Melting Techniques for the Preparation of Lipid-Based Solid Oral Formulations." Pharm Res, 32:1519-1545.
12. El-Banna et al. (1978) "Aspirin stability in solid dispersion binary system" J. Pharm. Sci.,1631: 1633.
13. Mitrevej et al. (1983) "Influence of hydrophilic excipients on the interaction of aspirin and water". Int. J. Pharm., 243:250.

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BIOGRAPHIES

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POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
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FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
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FD&C RED NO. 40 **(Tablet/Capsule coat)**	
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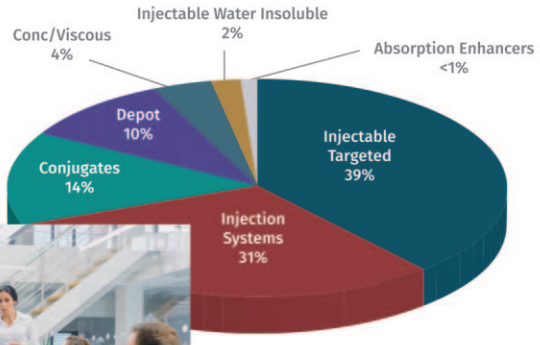

Injectable Drug Delivery Technologies

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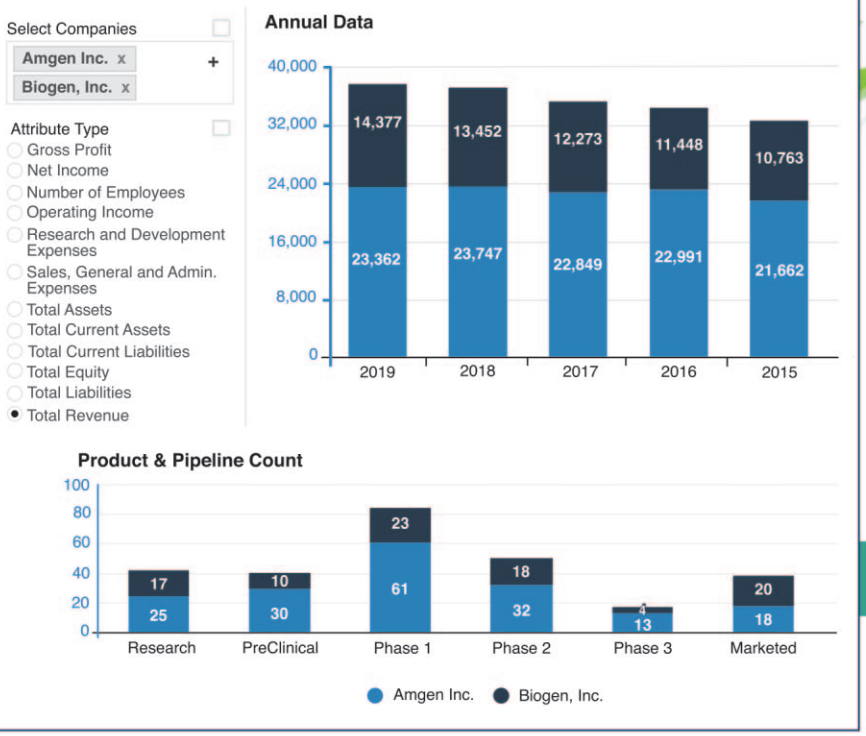

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GENE THERAPY

Solving the Puzzle: Aligning the Pieces of Gene Therapy & Creating Success for Patients

By: Sue Washer, MBA

INTRODUCTION

For a two-word phrase, the term "gene therapy" encompasses diverse and critical elements that are essential for delivering genetic material to target cells in order to treat or cure disease. Each of these elements presents challenges and opportunities for companies developing gene therapies. Each element can be a point of potential failure due to safety concerns, poor targeting of the affected cells types, or insufficient expression to achieve the desired biologic effects. On the flip side, unique and proprietary technologies that can optimize safety and efficacy may enable differentiated approaches to transgene engineering or vector development that provide clinical, regulatory, and competitive benefits. Ultimately, the seamless integration of the understanding of vector biology, genetic engineering, manufacturing, and the unmet patient needs is essential for developing transformative therapies that offer substantial clinical and commercial potential.

When embarking on the development of a novel gene therapy, it is important to keep in mind that the most direct route to the commercial marketplace may not be a straight line. While leveraging existing vectors and promoters might appear to provide an opportunity to reduce development time and risk, the reality is that effective gene therapies must be built from the ground up on a case-by-case basis, if they are to provide optimal performance in the context of a specific disease. This article will review the various elements that must come together in developing safe, effective, and commercially viable viral-based gene therapies.

VIRAL VECTORS

Viral vectors are a foundation of gene therapies because the viruses from which they are derived have evolved over millions of years to enter and deliver genetic material into human cells with high efficiency. Viruses, however, vary in the types of cells they infect, the efficiency with which they enter cells, how long they persist within an infected cell, the size of the genetic payload they can deliver, and the extent to which they activate host immune responses or even cause illness. The ease of vector manufacturing is also highly dependent on viral type.

Each vector offers unique features and benefits that must be carefully paired with the specific disease indication and the desired biologic activity for which it will be used.

For example, adenoviral vectors offer relatively large payload capacity and ease of manufacturing, but also have the potential to trigger robust immune responses that can lead to serious, and in one case, fatal inflammatory responses. The majority of adenoviral subtypes have a tropism for cells in the respiratory system, while others can efficiently transduce renal, intestinal, or ocular cells. The effect of adenoviral vectors is also short lived, which, while potentially beneficial in certain limited circumstances, would require ongoing treatment in the case of genetic or chronic indications, thus aggravating this tendency of problematic immune responses. Lentiviral vectors offer relatively large payload capacity, the ability to treat cells that rapidly turnover, and can be engineered to have tropism for a broad range of target cells. In contrast to adenovirus and adeno-associated virus (AAV) vectors, however, they can integrate into host cell DNA, resulting in potential interference with other important genes and unwanted alteration of transduced cells. Lentiviral vectors also stimulate innate and adaptive immune responses that

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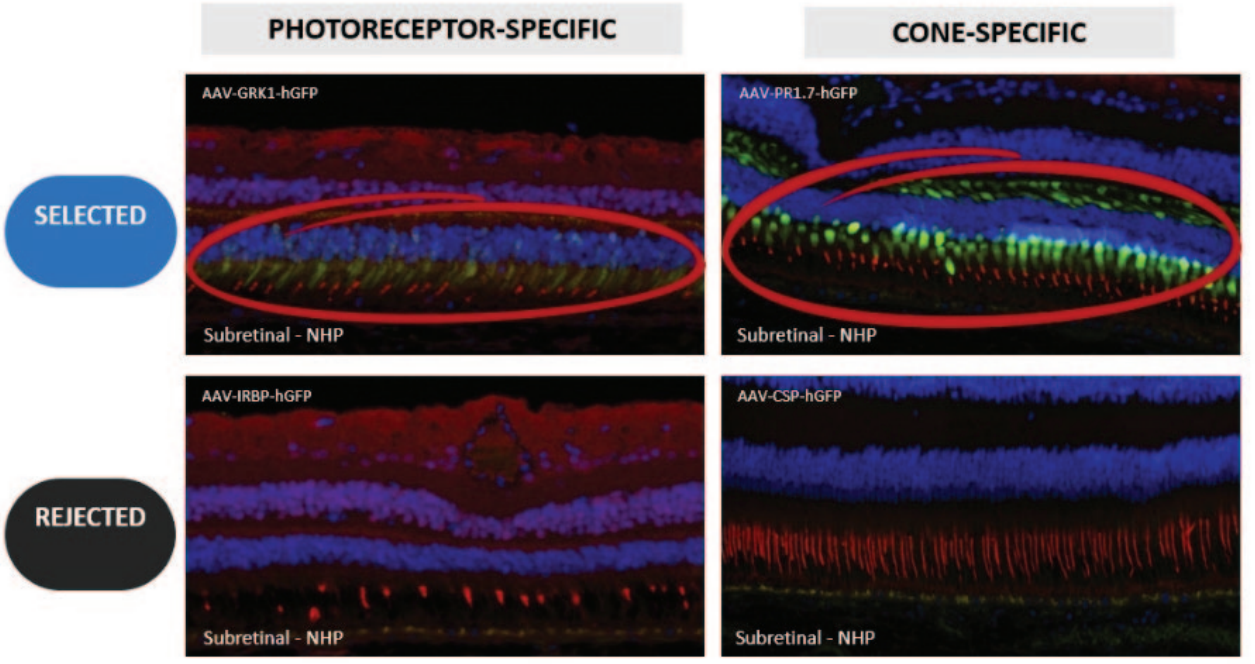
can limit efficacy and may cause inflammation. AAV vectors have somewhat more limited payload capacity and more complex manufacturing requirements, but multiple serotypes, combined with careful selection of promoters and other DNA regulatory elements, allow for targeting vectors to specific tissues. Additionally, AAV is not known to cause any human disease, which offers potential safety benefits compared with other viral vectors.

Which one, then, to choose? It depends on the therapeutic needs of the disease for which a gene therapy is being developed. For example, AGTC utilizes engineered AAV-based vectors for its inherited retinal disease (IRD) programs, because they can, in most cases, accommodate the size of the genes that need to be delivered and have reduced potential for inflammation compared with adenoviral and lentiviral vectors, which is particularly important for the treatment of ocular diseases in which inflammation may cause interference with visual function and long-term damage. There are a variety of AAV serotypes that can be used to target specific cell types with high transduction efficiency based on the biological need of a given indication, and AAV capsids can also be engineered both for increased transduction efficiency of cells for which they have native tropism, as well as to transduce additional cells types. As an example, AGTC utilizes an engineered AAV vector (AAV-TYF), which has been optimized for transduction of non-human primate photoreceptor cells, for X-linked retinitis pigmentosa (XLRP) and achromatopsia (ACHM).

PROMOTER ELEMENTS

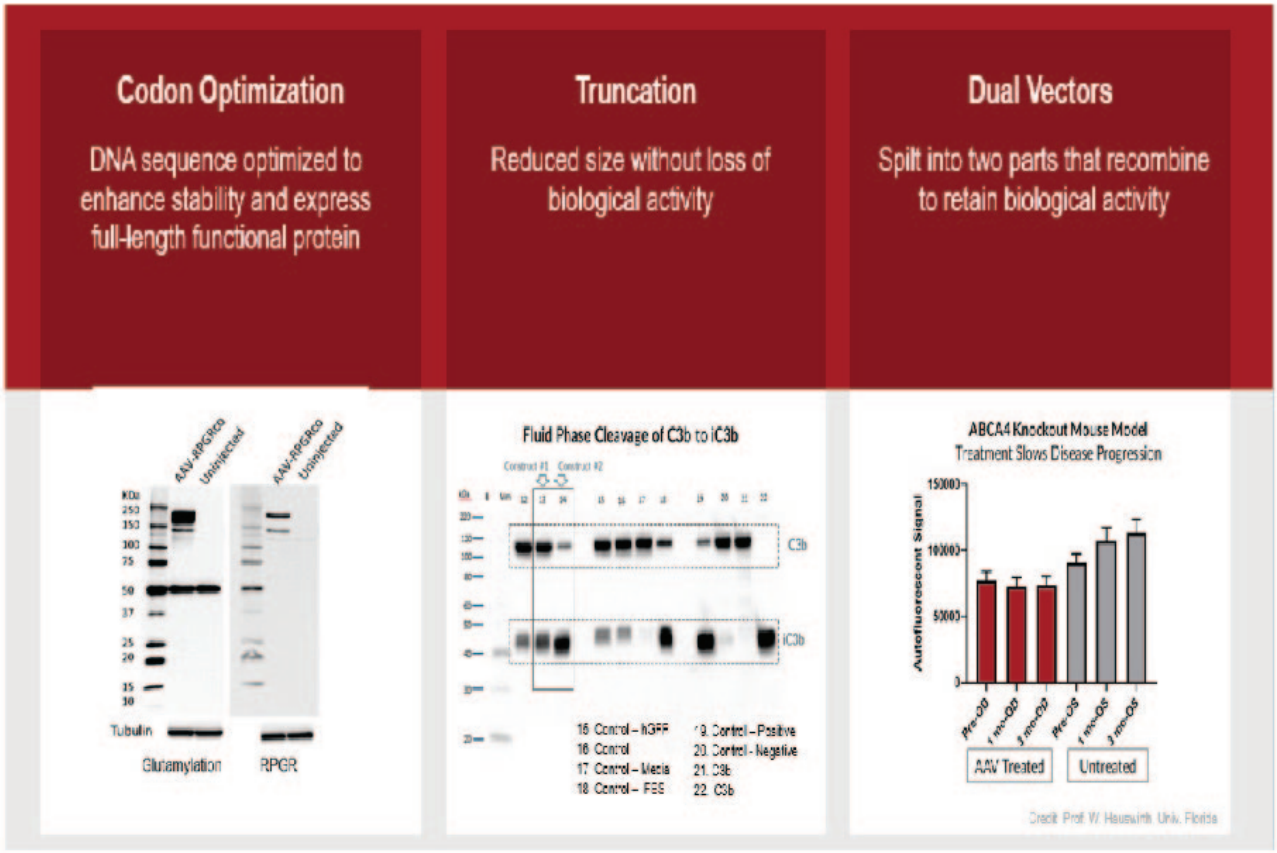
The desired therapeutic effect of a gene therapy also guides promoter selection. Promoters, which are the DNA regulatory sequences that control in which cells a gene is expressed, can be chosen based on tissue specificity, whether they are constitutively active or respond to physiologic signals, and the levels of expression that they drive. Again, the goal is to build a vector that expresses an appropriate level of protein in the target cell and minimizes expression in non-target cells. Given that a single vector may have tropism for multiple tissues, or multiple cell types within an organ system, promoter elements play a key role in targeting expression to specific cell types with greater precision. Bottom line? Capsids and promoters can be combined to maximize expression in multiple cell types or to restrict expression to spe-

FIGURE 1



Promoter selection is critical for targeting gene expression to appropriate tissues, which in turn is essential for improving safety and efficacy. The photoreceptor-specific GRK1 promoter (left) is active in both rods and cone cells, while the PR1.7 promoter is active only in cone cells (right). Based on these expression patterns, the GRK1 and PR1.7 promoters are appropriate for use in gene therapies to treat XLRP or ACHM, respectively.

FIGURE 2



Gene cassette modification can enhance expression and stability.
Left: in codon optimization, DNA sequences are optimized to enhance stability and expression of full-length protein.
Center: transgenes can be engineered to produce a protein that is smaller in size than the native protein while retaining essential biological activity.
Right: Dual vectors can be used to split a DNA sequence into two pieces that recombine in the cell to produce a protein with desired biological activity.

cific cells depending on the biology of the delivered gene and the targeted disease indication.

For example, AGTC is currently developing AAV-based gene therapies for XLRP and ACHM, both of which are IRDs. AAV-TYF efficiently transduces both rod and cone cells within the retina, but only cone cells play a role in the pathology of ACHM, and expression of the gene used for ACHM therapy in rod cells could be detrimental. Consequently, the ACHM vector utilizes a cone-specific promoter in order to restrict expression to cone cells even if the vector transduces rod cells, which should eliminate safety issues arising from off-target gene expression. In contrast, the XLRP construct uses a promoter that is active in both rod and cone cells, as both cell types contribute to the XLRP disease pathology (Figure 1).

TRANSGENE CONSIDERATIONS

In addition to optimizing delivery and expression to address the molecular basis of disease, the transgene itself plays a critical role in the safety and efficacy of gene therapies. Here again, understanding the biology of a particular indication is essential for defining the parameters that guide transgene selection and engineering. In some cases, therapeutic activity may require a transgene that produces a protein with absolute fidelity to the wild-type protein. In other cases, transgenes may benefit from codon optimization that yields a protein with enhanced expression and/or stability (Figure 2, left). Depending on the therapeutic gene and vector payload capacity, transgenes may also need to be engineered to be smaller but still produce proteins that provide therapeutic benefit (Figure 2, center).

For example, current clinical programs evaluating gene therapy for the treatment of Duchenne muscular dystrophy (DMD) encode smaller versions of the dystrophin protein. This is because the wild-type dystrophin gene, which is one of

the largest genes in the human genome, is too large for any of the currently available viral vectors. Consequently, DMD gene therapies use mini- or micro-dystrophin genes that have been engineered to retain critical functions. Although long-term data on the safety and efficacy of this approach have not yet been generated, preliminary evidence suggests that these smaller genes may provide functional benefit to patients with DMD.

Alternatively, dual vector systems may enable delivery of large, multi-domain proteins that cannot be packaged in current viral vector systems. Such systems could enable delivery of larger genes, such as the therapeutic gene for Stargardt disease, ABCA4. This can be achieved by splitting the DNA into two pieces that share an overlapping region at one end, packaging the pieces into separate vectors, and then delivering both vectors to a single cell. Once inside the cell, the overlapping regions in each gene fragment would mediate DNA recombination to create the full-length gene sequence (Figure 2, right). The efficiency of this recombination is highly influenced by the specific sequences chosen, which need to be tested and proven in appropriate animal models. Here again, vector and promoter selection will also be important for ensuring the complete protein is efficiently expressed in target cells.

VECTOR ADMINISTRATION

Other factors beyond the vector components themselves may also play a significant role in the safety, efficacy, and commercial viability of gene therapies. The route of vector administration is one such factor. Gene therapies can be administered via subretinal or intravitreal injection for the treatment of ocular diseases; through the round window of the middle ear for the treatment of otologic diseases; and via injection into the spinal cord or directly into the brain ventricles for the treatment of neurologic diseases. In each of these examples, the route of administration may have an impact on the total dose needed to achieve therapeutic benefit, the ability to target specific cell types or subtypes, and the simplicity versus complexity of administration. Additionally, more complex or invasive administration routes may pose a barrier to patients wishing to undergo therapy, although this would likely be a greater issue for indications in which other effective therapies are available, rather than for diseases in which a gene therapy would be a significant new advancement. Novel routes of administration may also require availability and testing of devices used to deliver gene therapies. Consequently, the route of administration is another important piece of the gene therapy puzzle and should be considered at the earliest stages of development in order to ensure the route and therapy have been optimized for use together.

MANUFACTURING

While the strategic selection of vectors, promoters, and transgenes is essential for the safety and efficacy of gene therapies, robust manufacturing processes are critical for commercial success and broad patient access. Scalable processes that can be performed in bioreactor systems similar to those used for decades to produce a variety of protein and antibody therapies can enable cost-effective manufacturing to meet small rare disease indications, such as IRDs, while providing capacity to support the development of gene therapies for large markets, such as age-related macular degeneration. Bioreactor-based methods also reduce the need for manual tissue culture processes that carry the risk of operator error or contamination.

A key challenge in gene therapy manufacturing is balancing the "need for speed" with the development of processes that meet regulatory requirements and will support commercial use. Many gene therapies are initially developed in academic laboratories using small-scale production methods that are appropriate for preclinical studies and may even have sufficient yield for small Phase 1 trials. These processes are not, however, sufficiently robust for late-stage clinical development or commercial manufacturing. Commercial-scale gene therapy manufacturing will require significant investment in process development, facility build-out, or contract manufacturing. Companies must strike the right balance between investing early in programs that may not warrant continued development and waiting until product candidates near approval and commercialization, which could delay the initiation of late-stage trials.

Gene therapy manufacturing processes must also be designed with high yield for vectors that have the complete gene cassette packaged within them, with limited numbers of empty vectors and with the efficient removal of the residual raw materials, such as host cell proteins and DNA. Since the initiation of its AAV manufacturing efforts, AGTC has significantly increased the productivity of its process, resulting in the current process that offers the potential for a 90-fold reduction in the cost of goods sold. Additionally, the

process results in 90% complete capsids and undetectable residual raw material. This is important for enabling optimized dosing by delivering a therapeutic dose with the lowest total viral load possible, and without impurities that could lead to side effects or toxicities.

Vector characterization is another critical element of manufacturing, as it ensures the safety, efficacy, and potency of the finished product. Regulatory agencies put as much emphasis on ensuring the safety, quality, and reproducibility of gene therapies as they do on their clinical safety and efficacy. As an illustrative example, in September 2020, the US FDA requested that Sarepta utilize an additional potency assay for release of the commercial process material prior to dosing in the company's planned Phase 3 trial of its gene therapy for DMD. This request underscores the importance of vector characterization as an intrinsic part of developing gene therapies.

ASK THE EXPERTS

The safe, effective, and successful assembly of the pieces of the gene therapy puzzle requires one other critical ingredient – disease-specific expertise. As highlighted earlier, the choice of vector, promoter, transgene, and route of administration must be done with an eye toward optimally addressing the biology of a disease that a specific gene therapy is designed to treat. This can only be achieved with insight from those who are truly expert in that disease.

For larger biopharmaceutical companies, such expertise may reside in-house and can be integrated with internal gene therapy research and development efforts. Smaller companies may achieve the same objective through strategic partnerships and collaborations that synergistically utilize complementary expertise and technologies. For AGTC, this has meant establishing collaborations with Bionic Sight and with Otonomy, to develop gene therapies for vision loss and otologic disease, respectively. In each relationship, AGTC provides expertise in gene therapy development while the partner brings expertise in optogenetics (Bionic Sight) or genetic hearing disorders. This allows development of an optimized (Otonomy) vector and administration strategy for each indication that is based on the biology of the disease and desired therapeutic outcome.

A PUZZLE WORTH SOLVING

With diverse factors and options at every step of the continuum, the path for developing gene therapies can be viewed as ridden with multiple hurdles and complexities. Yet a diligent, data-driven, and patient-focused approach to navigating this path offers unique opportunities to truly advance and transform the treatment of serious diseases that have urgent unmet need. With the potential to optimize all aspects of gene therapy development to optimize safety, efficacy, and patient outcomes, we cannot accept anything less. The patients who stand to benefit from successful gene therapy development certainly won't. ◆

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BIOGRAPHY

Sue Washer is President and CEO of AGTC and brings a decade of experience in pharmaceutical management and research with Abbott Labs and Eli Lilly & Company and more than 26 years of senior management experience with entrepreneurial firms, including three start-ups. At AGTC, she has secured private and public investments of over $290 million for AGTC, negotiated and closed two major collaborations with top Biotech companies resulting in over $150 million of cash in-flows, and led AGTC in efficiently completing critical scientific milestones. She is an appointed member of the Small Business Capital Formation Advisory Committee for the SEC, Associate Vice President of the ECSGB Board of Bio, and currently serves on the Board of Directors of BIO, and BioFlorida. She earned her undergraduate degree in Biochemistry from Michigan State University and her MBA from the University of Florida, where she was one of the first graduates from the Warrington College of Business Entrepreneurship program.

NASAL SPRAY BIOEQUIVALENCE

Between-Batch Bioequivalence (BBE): An Alternative Statistical Method to Assess *In Vitro* Bioequivalence of Nasal Product

By: Jonathan Bodin, Stéphanie Liandrat, Gabriel Kocevar, and Céline Petitcolas (Dissemination by Manuela Basso)

INTRODUCTION

In the pharmaceutical industry, we can see the development of generics is significantly growing. This trend is mainly driven by countries to give patients easier access to drugs and to define regulations accordingly.

From an industrial perspective, the success of a generic product development is based on two elements: (1) compliance with all the regulatory requirements and (2) safety for patients (ie, has the same final therapeutic effect than the brand-name product).

One way to prove the equivalence, without long and expensive clinical trials, is to conduct in vitro bioequivalence evaluation between the Innovator (Reference product) and the proposed generic (Test product).

This evaluation is generally done through average bioequivalence (ABE) , or population bioequivalence (PBE) for in vivo and in vitro testing, through statistical methods.[1-8] *In vitro* bioequivalence testing is not considered and evaluated in the same way by all instances taking part in the process.

Indeed, in the US FDA recommends the use of population bioequivalence (PBE), whereas Europe recommends using average bioequivalence (ABE).

While both ABE and PBE tests consider the device total variability, the between-batch variability, which is part of the total variability, is not considered individually in the mathematical definitions proposed by the FDA and EMA guidelines.

On one side, ABE only considers within-product variability. On the other side, the FDA guidance on Budesonide recommends

FIGURE 1

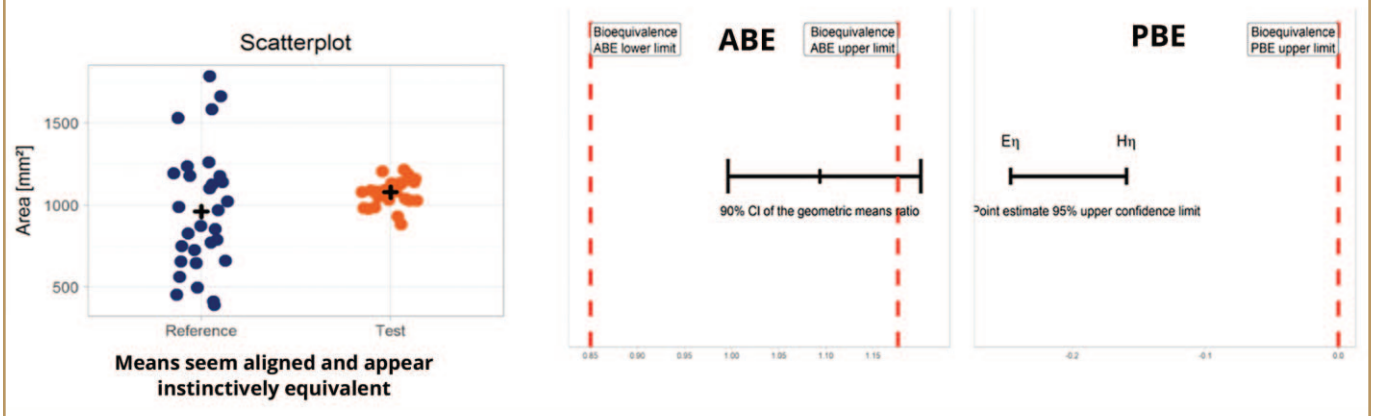

Illustration of ABE limits

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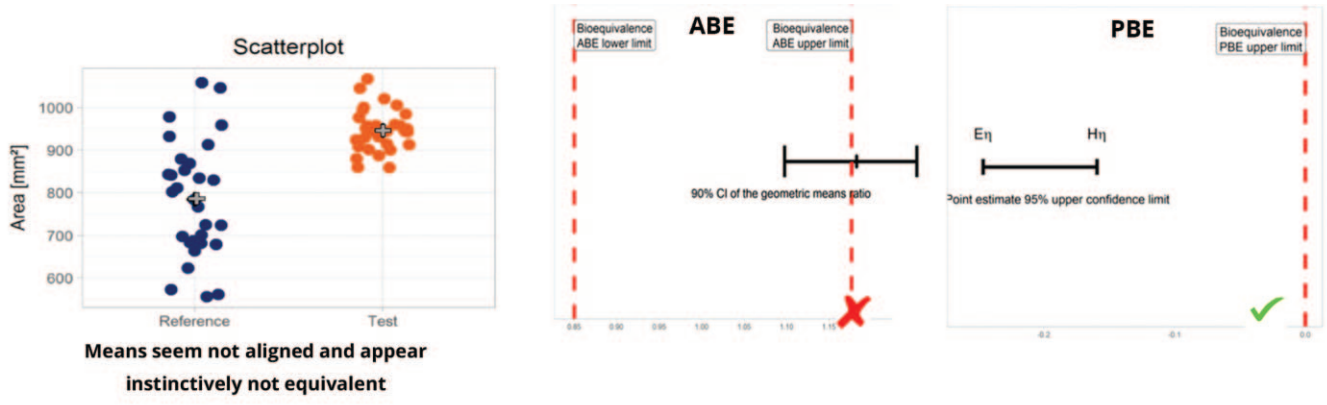
FIGURE 2



Illustrations of PBE limits

to decompose the variance as a composite of a super-batch variability (ie, after pooling all batches per product) and the within-individual variability to study the life-stages (begin, middle, and end-of-use) equivalence.[9]

These calculation methods present some limits, particularly with high variable drug products [Coefficient Variation (CV%) greater than 29,6%] but not only. In practice, some limits of the classical methods may occur from 15% for within-Product CV%, where the power tests (ABE and PBE) drop off.

PBE is less permissive than ABE, if the Reference product variability is low. Conversely, PBE is more permissive than ABE if the Reference variability is high; even more so if the Test product variability is lower than the Reference product variability.

In order to prevent the risks of erroneously accepting equivalence in cases of high variability of the Reference, it is recommended to increase the number of samples in the goal to increase the power test on PBE and ABE calculations. This increases the confidence level of the bioequivalence conclusion.

However, this solution is undesirable from an industrial point of view since it increases costs and delays by inflating the number of tests to be carried out.

This increase in cost and associated delays is not aligned with the principle goal of reduced-cost generic medicines in a short time to market.

Considering this, an alternative statistical test, named between-batch equivalence (BBE), is proposed to assess in vitro bioequivalence. This statistical approach is based on the comparison between the mean difference (Reference – Test) and the Reference between-batch variability. The main hypothesis is that considering the between-batch variability of the Reference, the BBE test will be more appropriate to demonstrate equivalence in the case of variable drug products, without needing to increase the total required sample size. This statistical method can deal with normal scale data as well as after log transformation of the raw data.

METHOD - EXPERIMENTAL: SIMULATION

As reported in several studies, neglecting non-zero between-batch variability can have a strong impact on the bioequivalence conclusions.[10,11] Thus, we developed a method that includes the Batch factor into the statistical equivalence test. In fact, the multiple measurements on a single batch induce a dependence between data and a violation of the independence assumption with the state-of-the-art methods ABE and PBE. The assumption of independence could be satisfied if the Batch factor is considered in the model.

Our methodology has been based on a comparison between the two population means (μT - μR) with the Between-Batch variability on the Reference drug product (σBBR).

As a first step, our study focused on the development of the statistical method, including an exact procedure to implement the test statistic and a confidence interval approximation to graphically illustrate the test results.[18] Then, the type II error of the BBE method, ie, the FNR (False Negative Rate), was estimated by simulations and compared with the two mainly recognized statistical methods (ABE and PBE). In a second step, the type I error of the BBE method, ie, the FPR (False Positive Rate), [18] was estimated by simulations to ensure that the BBE type I error remains of the theoretical order of 5%. In a third step, the BBE type II error was assessed and compared with the reference methods through

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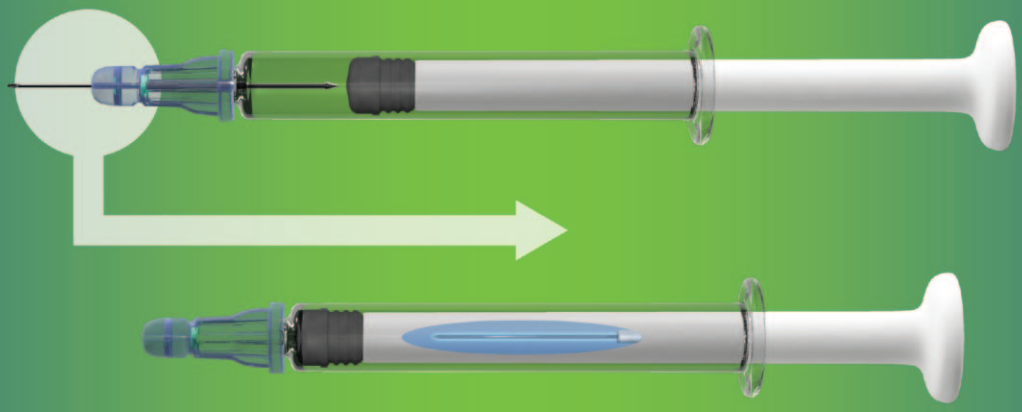

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FIGURE 3

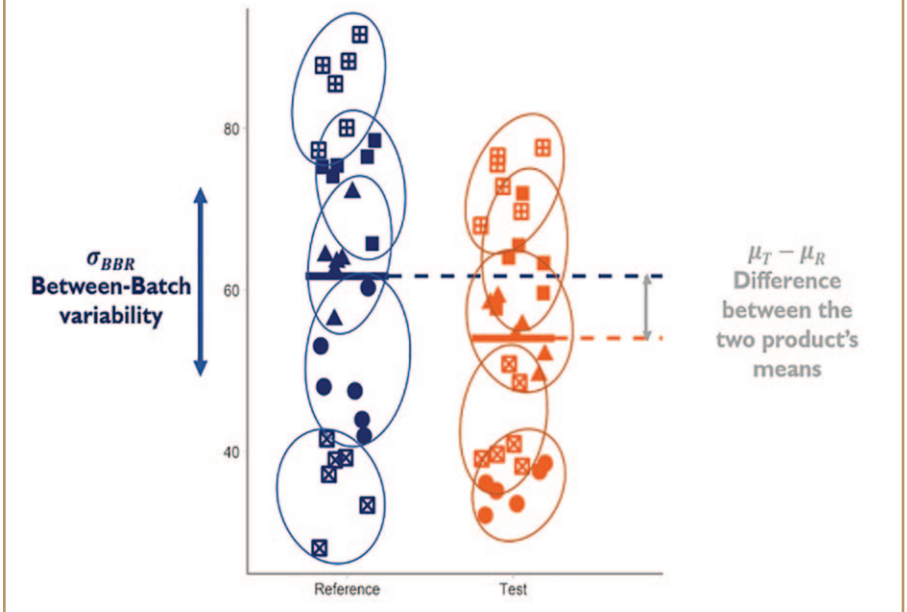


Illustration of Alternative Method Objective

a real case application on nasal spray in vitro performance that were performed on two Reference products from the market (which are by definition equivalent).

REAL CASE STUDY ON TWO NASAL SPRAY REFERENCE DRUG PRODUCTS

The BBE approach has been applied to two nasal sprays, Nasonex® (Merck) and Flonase® (GSK), which are corticosteroids used to treat nasal symptoms such as congestion, sneezing, and runny nose caused by seasonal or year-round allergies. These two products are already commercialized and considered individually as Reference products. In accordance with FDA guidance, two main parameters of in vitro spray performance were considered for the bioequivalence tests.[12-14] The control of theses parameters ensures the quality of the nasal spray product and at the end the efficacy of patient treatment.

The statistical comparison of the three methods (ABE, PBE, and BBE) was performed separately on batches of Flonase and Nasonex products.

The aim was to evaluate whether the three methods can adequately conclude in an equivalence context of each product. For that purpose, the true positive rate of each method was estimated and compared. For both criteria (D50 and area) and both products (Nasonex and Flonase), batches of each product were randomly selected to be considered as a Reference or Test for the need of the bioequivalence evaluation.

The first, Dv50 (or D50) related to droplet size distribution (DSD), was measured by laser diffraction using a Spraytec (Malvern, UK) and an automatic actuator (Proveris, USA).[15] Second, the spray pattern (area) was measured using a Sprayview system (Proveris, USA). This parameter, describing the shape of the spray is known for its high variability.[16] The study has been performed at two distances (3 cm and 6 cm) as recommended in the guidance with an actuation speed of 80 mm/s.[17]

RESULTS

The results observed in the real case application confirm those observed in the simulation results. When the total variability of the Reference is low (around 5% for the DV50 criterion) the two state-of-the-art methods reached high true positive rates, with values greater than 99%. In this situation, the BBE equivalence test reached significantly lower true positive rates, depending on the between-batch variability (69% with $\pi BB = 25\%$ and 84% with $\pi BB = 43\%$). On the other hand, with the Area parameter, exhibiting higher variability on the Reference, 27% and 18% for the Flonase and Nasonex products, the BBE method showed higher true positive rates than ABE and PBE (70% versus 14% and 60% for the Flonase and 85% versus 62 and 69% for Nasonex).

CONCLUSIONS

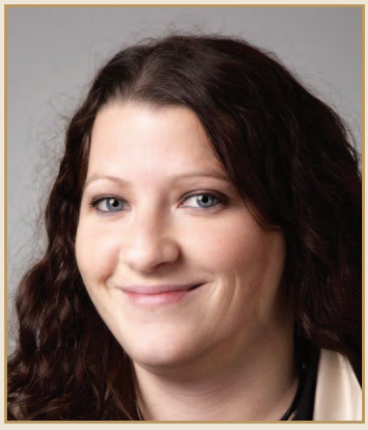
The purpose of this work was to propose the development of an alternative statistical method to evaluate in-vitro equivalence. This alternative statistical method may be more appropriate to evaluate the *in vitro* bioequivalence for a nasal spray in a batch variability context with a reduced number of samples. Thus, BBE may be of particular interest to optimize the generic development in both in vitro and *in vivo* contexts.

REFERENCES

1. European regulatory developments for orally inhaled and nasal drug products. Santos C, Marco G, Nagao L, Castro E, Chesworth T., AAPS PharmSciTech. 2018, https://pubmed.ncbi.nlm.nih.gov/30128799/.
2. Bioequivalence requirements in the European Union: Critical discussion. García-Arieta A, Gordon J., AAPS J. 2012, https://pubmed.ncbi.nlm.nih.gov/22826032/.
3. Performance of the population bioequivalence (PBE) statistical test using an IPAC-RS database of delivered dose from metered dose inhalers. Morgan B, Chen S, Christopher D, Långström G, Wiggenhorn C, Burmeister Getz E, et al. AAPS PharmSciTech. 2018, https://doi.org/10.1208/s12249-017-0941-8.
4. Draft guidance: average, population, and individual approaches to establishing bioequivalence. FDA, CDER. 1999. https://www.fda.gov/files/drugs/published/Statistical-Information-from-the-June-1999-Draft-Guidance-and-Statistical-Information-for-In-Vitro-Bioequivalence-Data-Posted-on-August-18--1999.pdf.
5. Regulatory considerations for approval of generic inhalation drug products in the US, EU, Brazil, China, and India. Lee SL, Saluja B, García-Arieta A, Santos GML, Li Y, Lu S, et al. AAPS J. 2015, Springer New York LLC, https://doi.org/10.1208/s12248-015-9787-8.
6. Draft guidance on budesonide [Internet]. US Food and Drug administration, 2016, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf.
7. Draft guidance on budesonide [Internet]. US Food and Drug administration, 2016, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf.
8. Draft guidance on mometasone furoate monohydrate. US Food and Drug Administration. 2019, https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mometasone%20furoate%20nasal%20spray%20NDA%20020762%20RV%2002-2019.pdf.
9. Method for testing bioequivalence of a distribution device. Liandrat S, Petitcolas C, Jonathan B. France. 2020, https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020053223.
10. Performance properties of the population bioequivalence approach for in vitro delivered dose for orally inhaled respiratory products. Morgan B, Strickland H. AAPS J. 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3889535/.
11. Between-batch pharmacokinetic variability inflates type I error rate in conventional bioequivalence trials: a randomized Advair Diskus clinical trial. Burmeister Getz E, Carroll KJ, Mielke J, Benet LZ, Jones B. Clin Pharmacol Ther Nature Publishing Group. 2017, https://pubmed.ncbi.nlm.nih.gov/27727445/.
12. Draft guidance on fluticasone propionate. US Food and Drug Administration. 2019, https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20propionate%20nasal%20spray%20NDA%20020121%20RV%2002-2019.pdf.
13. Draft guidance on mometasone furoate monohydrate. US Food and Drug Administration. 2019, https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mometasone%20furoate%20nasal%20spray%20NDA%20020762%20RV%2002-2019.pdf.
14. High resolution visualization and analysis of nasal spray drug delivery. Inthavong K, Fung MC, Tong X, Yang W, Tu J. Pharm Res. 2014, https://doi.org/10.1007/s11095-013-1294-y.
15. Analytical challenges of spray pattern method development for purposes of in vitro bioequivalence testing in the case of a nasal spray product. Grmas J, Rok D, Rade I. Aerosol Med Pulm Drug Deliv. 2019, https://pubmed.ncbi.nlm.nih.gov/30964389/.
16. Performance of the population bioequivalence (PBE) statistical test with impactor sized mass data. Chen S, Morgan B, Beresford H, Burmeister Getz E, Christopher D, Långström G, et al. AAPS PharmSciTech AAPS PharmSciTech; 2019, https://pubmed.ncbi.nlm.nih.gov/31444601/.
17. Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action [Internet]. US Food and Drug Administration. 2003, http://www.fda.gov/cder/guidance/index.htm.
18. Between-Batch Bioequivalence (BBE): a Statistical Test to Evaluate In Vitro Bioequivalence Considering the Between-Batch Variability. Bodin J, Liandrat S, Kocevar G, Petitcolas C. AAPS J, 2020. https://doi.org/10.1208/s12248-020-00486-5

BIOGRAPHIES

Céline Petitcolas is Customer Technical Support for nasal range at Nemera. Holding a Materials Engineering degree from the École Nationale Supérieure de Chimie et de Physique in Bordeaux, France, she joined Nemera in 2012 to develop pharmaceutical devices, focusing especially on the nasal spray area. Her role consists in helping and assisting customers from a technical point of view in their development of nasal sprays and more specifically in the area of bioequivalence. She is the preferred technical contact for customers as she interfaces with multiple Nemera teams (marketing, sales, technical) to bring customers and partners the support they need.



Manuela Basso is an experienced communications professional, with a journalism and marketing background. She holds a European Master in Management and specializes in International Marketing. After various experiences in different fields, she has been working at Nemera for 6 years, developing effective communications to support Nemera's overall vision and mission: to put patients first.

Special Feature

Injection Devices: Designing Simplicity, Safety, & Adherence Into One Delivery System

By: Cindy H. Dubin, Contributor

The global injectable drug delivery devices market is expected to show significant growth in the coming years as manufacturers introduce technological advancements and product innovation meant to improve convenience, compliance, and ease of administration of parenterals. Additionally, the increasing preference for at-home self-injection is driving the market as patients prefer to continue to avoid healthcare settings post-COVID. With all of this taken into account, one market study predicts the global market to reach almost $26 billion by 2025, up from $15 billion in 2020.[1] However, another report values the global market at $42.76 billion in 2021 and expects it to reach $50.9 billion in 2025.[2]

How the numbers will play out is yet to be determined, but the studies do highlight the focus on single-use and reusable systems. Disposable-use prefilled syringes (PFS) are increasingly used due to the prevalence of chronic diseases and the growing number of biologics best delivered by syringes. Single-use autoinjectors are also poised to experience increased demand, particularly with the growing pervasiveness of anaphylaxis disorders. Autoinjectors also provide a convenient alternative to manual syringe injections for subcutaneous administration.

Catalent Biologics can fill sterile products into vials, syringes or cartridges, including safety device and autoinjectors.

But their reusable brethren, such as pen injectors with prefilled cartridge, are also proving viable syringe alternatives. These injectors can perform hundreds of injections, with patients controlling the speed of delivery to minimize pain or discomfort during use.

"Making injection devices partially reusable is a cost-saving strategy," says William Fortina, Business Development Director, Duoject Medical Systems. "Ideally, the device's mechanism and/or electronics are the reusable parts of the system – as these are often the costliest – and the drug containers and needle are one-time use."

Another cost-saving strategy that several large pharmaceutical companies are deploying is to develop a device platform for multiple drug products in their portfolio, says Mr. Fortina. "This allows them to spend resources on a single significant development program, for one optimal injection device, which then requires minimal customization for each subsequent product line."

Despite efforts to make better, safer, simpler injection devices, patient adherence is still a challenge associated with self-administration. This has resulted in the emergence of smart devices, such as wearable injectors, which share patient data with healthcare providers to ensure compliance. And while it is expected this sector will continue to grow, some industry insiders warn against making these devices too intrusive.

"Smart devices, interconnectivity, and related technology provide real-time data to healthcare providers for analysis, but these device additions should not increase risks, including patient understanding of treatment delivery, or jeopardize compliance," says Michael Denzer, Vice President of Technical Solutions at Kymanox. "Data collection needs to be "passive" to the patient. In other words, invisible to the patient's use of the device so that the collected data provides a true benefit to the end user. If these design considerations can be implemented without impacting the patient or how they administer and receive treatment, then smart devices can provide advantages to the patient and the industry."

This annual *Drug Development & Delivery* report takes a deep dive into the myriad injectables that are either currently in development or recently introduced to the market.

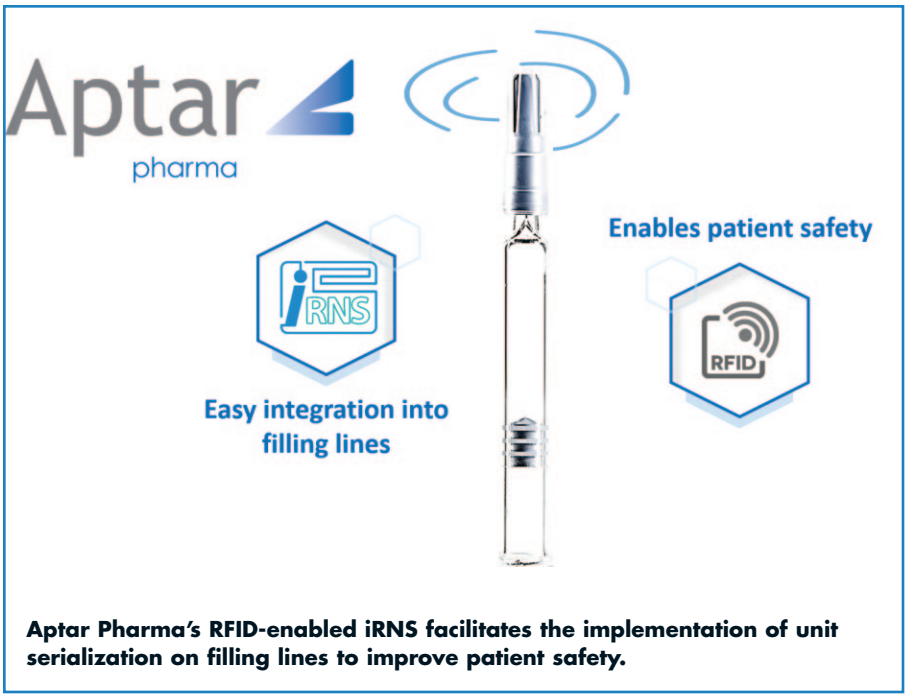
Aptar Pharma: RFID-Enabled Rigid Needle Shields for Unit Serialization & Track and Trace

Today, traceability of parenteral drug products is performed at the batch level. Health and regulatory authorities are currently looking into implementing unit serialization (Policy paper on traceability of medical products, WHO, 2021) to improve traceability from production through to patients. "Individual container traceability could dramatically improve patient safety, preventing potential mix-ups, clarifying accountability, and simplifying investigations in case of deviation during fill-finish operations," says Audrey Chardonnet, Business Director, Aptar Pharma. "Current strategies are reaching their technical limitations and new approaches must be considered to address future requirements."

Most identification strategies for injectable drugs rely on physical stickers applied onto the drug container during filling, a method that Ms. Chardonnet says is hardly applicable to unit serialization. Different technologies were considered and eventually narrowed down to two options: the engraving of a 2D-matrix on the glass container or digital chips. 2D-matrices are relatively easy to engrave on the glass, but require the installation of engraving equipment – either on the filling or glass manufacturing lines – and advanced camera systems for reading the matrix. Because it is physically engraved on the glass, the matrix cannot be read through secondary packaging and requires the container to be oriented on the filling line to allow reading. Adding a digital chip to the packaging allows individual serialization and brings further benefits. Industrial implementation requires the addition of a contactless reader to identify the dose at any point during the process – even through a secondary packaging – and the tag can be edited to attach more information on-the-go.

"The idea of unit serialization is often associated with prefilled syringes (PFS)," she says. "In addition to well-documented advantages over multi-dose or single-dose vials, including ease-of-use, safety, and reduced drug wastage, unit serialization eliminates the need for a distinct injection device, thus ensuring the patient receives the dose directly from the device that carries the tag, reducing risk of mix-ups before the injection."

Aptar Pharma's iRNS is a digitally-



Aptar Pharma's RFID-enabled iRNS facilitates the implementation of unit serialization on filling lines to improve patient safety.

enabled RNS that leverages RFID technology, miniaturizing and embedding it in the RNS plastic shell. This chip acts as a tag that can be read and edited at any time from the filling process to the time of injection. "The iRNS enables easy implementation of unit-dose "track and trace" processes on the filing lines thanks to contactless reading/editing of the RFID chip," Ms. Chardonnet explains. And, iRNS allows high-throughput unit identification without impacting the filling lines beyond the addition of a reader.

BD Medical Pharmaceutical Systems: Usability is Built into All Devices

At BD, the "smartification" of delivery devices is guided by a user-centric approach. Extensive human factors studies help to ensure that added functionalities serve to enhance, not detract, from usability. In fact, BD has conducted more than 80 human factors studies on its portfolio of products since 2010. Network security and environmental sustainability (potential pollution from electronic waste) are also critical issues every smart solution must address, says Beth DiLauri-McBride, Chronic Portfolio Marketing Director, BD Medical-Pharmaceutical Systems.

Beyond usability, new functionalities such as the ability to verify a drug's authenticity, can be achieved through smart traceability solutions. "BD is developing a traceability solution that aims to reduce manufacturing mix-ups and help to provide manufacturing to point-of-care traceability in the long term," says Marie-Liesse Le Corfec, Head of Portfolio Marketing for BD Medical-Pharmaceutical Systems. "This BD whole-system approach is based on simple, robust, and market-proven technologies and encompasses tagged and nested prefilled syringes, readers, and software as part of a fully tested and ready-to-use system."

BD also is focused on developing robust PFS solutions for the delivery of sensitive biologics while ensuring that each solution has supply availability to meet customers' demands. To achieve this, BD has developed an array of solutions for the testing and delivery of drugs or vaccines. "Most recently, we expanded our service capabilities and acquired ZebraSci," says Ms. Le Corfec. "Also, our PFS portfolio includes both coated and uncoated stoppers and bare or siliconized barrels, using, for example, baked or cross-linked silicone."

An example of BD cross-linked silicone technology is the BD Neopak™ XSi™ Glass Prefillable Syringe that helps protect against lubricant-drug interaction, while supporting the full gliding performance essential to innovative drug formulations aiming to increase payload.

BD SCF™ PremiumCoat® Plunger Stoppers for chronic drug delivery applications help protect drugs from component interaction, while aiming to improve delivery system performance.

Bespak by Recipharm: Developing Connectivity Across a Range of Autoinjectors

Digital health provides many benefits when transitioning treatments into the hands of patients. When the physical interactions between doctors and patients are reduced, smart, digitally connected devices can improve patient engagement, record compliance, and monitor clinical effectiveness. "Adding digital features to autoinjectors without adding any additional

Viscala® – VapourSoft®-powered autoinjectors from Bespak by Recipharm.

user steps is key to the adoption of such new technology," says Hans Jensen, Global Business Development Director of Bespak by Recipharm.

He says factors to consider include:

- Minimal impact on device design – ensures the device is unchanged in terms of size, shape, and how it is operated, so patients don't have to re-learn how to administer their medicine.
- Flexible interface architecture – enables integration into a connectivity suite that both patients and HCPs can use, and can be tailored to the usability needs of the target patients.
- Bluetooth® connectivity – harness wireless communication technology, so that patients can simply connect their device to their smartphones without having to spend time setting up new and unfamiliar technology.

Bespak by Recipharm is developing connectivity features that can be used across its range of autoinjectors. Its VapourSoft® autoinjector platform, including Viscala®, was designed particularly for biologics and long-acting formulations. "Viscala delivers formulations with very high viscosities – something traditional spring-powered devices are struggling to achieve," he says.

Viscala® uses the proprietary VapourSoft technology, which uses liquefied gas as the power source, rather than a traditional spring. Mr. Jensen says the benefits of VapourSoft include the ability to generate high forces within the device without damaging the syringe, delivery through patient-friendly fine needles, constant force profile throughout the delivery phase, and easy adjustment of forces by selection of gas from range of available gasses.

Catalent Biologics: Helping Pharma Partners Post-COVID

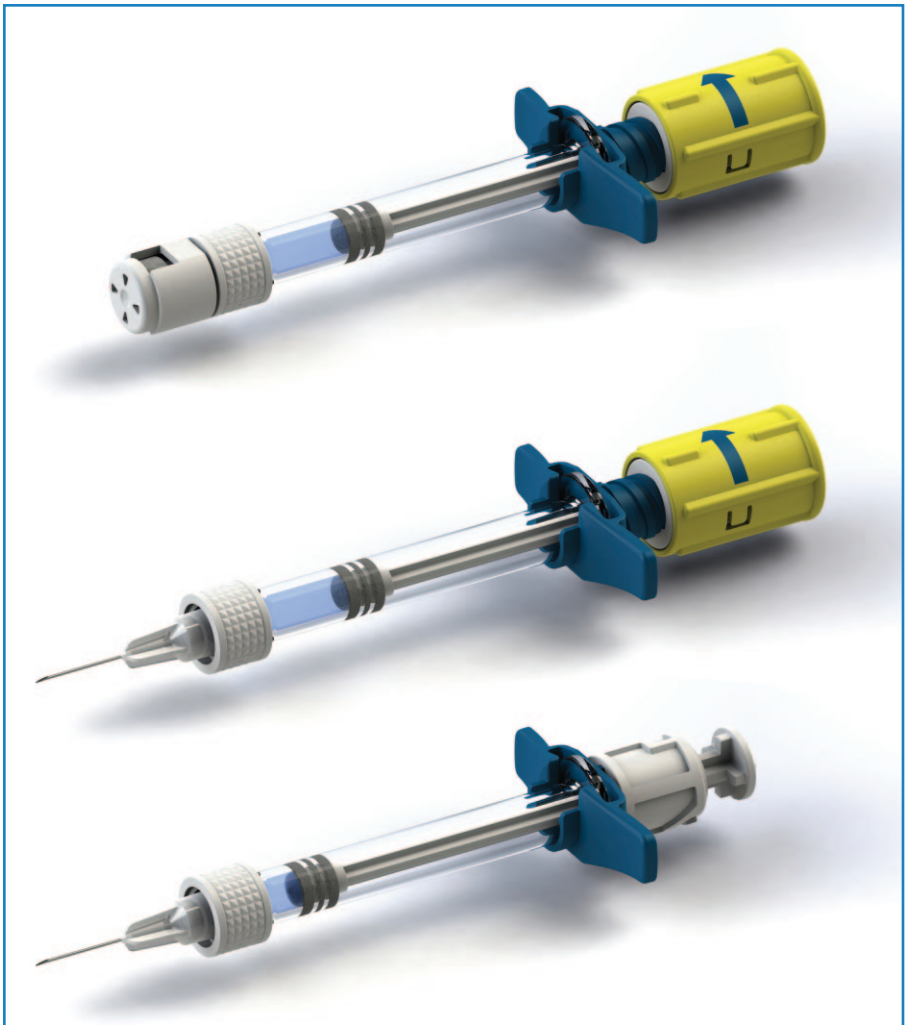
Now that COVID-19 vaccines are in production and available, Catalent has seen some of its partners shift their focus back towards non-COVID related treatments, and this includes the growing interest in "off-the-shelf" (OTS) style autoinjectors. "Historically, route of administration decisions have been made later in development, with many innovators opting for providing drugs in vials in order to reduce drug/device development complexity," says Brian Galliher, Principal Process Engineer, Catalent Biologics. "What is more apparent now is that pharma companies are working to address key end-user questions earlier, to enable a more patient-friendly experience as soon as commercial approval is achieved. This renewed focus on non-COVID indications earlier in development may lead to more self-injection options, such as OTS autoinjectors."

Over the past year, devices assembled at Catalent for customers have included anti-needlestick devices and autoinjectors for biologics used to treat autoimmune disorders.

Credence MedSystems, Inc.: Enhancing & Facilitating Intravitreal Drug Delivery

While Credence MedSystems is scaling its Companion and Dual Chamber Reconstitution Syringe Systems to meet demand from pharma customers, the company has also advanced development of its ophthalmology and gene therapy solutions. These therapeutic areas share some common requirements for drug delivery, including the requirement to deliver extremely low injection volumes with precise accuracy, the need for user-friendly solutions that do not encumber the procedure, and the need to maintain lower injection forces despite the possibility for high viscosity injectables.

Credence is developing the Micro-Dose™ Syringe System, designed to deliver a nominal dose ranging from 50µL down to below 20µL, with high accuracy. With Micro-Dose, the clinician simply presses on the plunger rod until it stops moving, explains John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc. The allowable travel length of the plunger rod determines the



The Credence Micro-Dose™ is designed for ophthalmology and gene therapy applications.

dose, providing tactile feedback and removing a source of user error. The device allows the user to control removal of the air bubble by turning the safety cover. "This helps prevent valuable drug from being wasted during conventional air bubble purging, and can allow reduction of overfill requirements, leading to economic benefits," he says.

A sister product to Micro-Dose is Multi-Site™, which allows similar precision but repeated administration of multiple doses from the same syringe in the same procedure. This product has application in certain ophthalmology applications, cosmetic applications, and dental applications.

Additionally, as pharma manufacturers develop biologics that require more viscous formulations, the ability to maintain lower injection forces becomes critical, especially with intravitreal injections. Credence is developing an adjunct technology that can be used with its Micro-Dose and Multi-Site technologies called Force-Assist™, which uses a levered advantage to reduce the force required to inject by roughly one-third of that which would be required in a traditional delivery system. Mr. Merhige says: "With the delivery of viscous fluids through very narrow/high gauge needles, this technology can enable caregivers to maintain control of the injection and avoid discomfort to the patient, while still achieving precise low-dose accuracy."

SHL Medical: Modular Platform Technology Addresses Today's Self-Injection Trends

Subcutaneous self-injections are evolving as a preferred choice owing to the advances in biologic formulations. "As self-injection technology matures, there is a compelling need for a flexible device platform that can be leveraged across a number of therapies without compromising injection experience or patient acceptance," says Magnus Fastmarken, Director of Marketing at SHL Medical.

The evolution of SHL's Molly® device technology corresponds to the growth of the autoinjector market. Introduced in 2010 as a preconfigured solution, Molly has been applied in treatments for diseases such as Rheumatoid Arthritis, migraine, osteoporosis, and atopic dermatitis, among others. Following the development of pharmacologic therapies targeting weight loss, Molly now also supports treatment for obesity.

"Molly's modularization offers cost effectiveness in device manufacturing and provides flexibility in the device designs and fill volumes, allowing for design modification according to specific combination product project needs," says Mr. Fastmarken. He adds that the modular technology in both the 1.0mL and 2.25mL standard versions of Molly autoinjectors enables design customizations in the front and rear sub-assemblies of specific device projects while keeping the core com-

The Molly® autoinjector is built upon a modular platform technology designed to support shorter development timelines.

ponents intact.

In response to the need to introduce different dosing volumes for different target markets, SHL helped a pharma company lifecycle an existing product into the Molly and Molly 2.25 devices for hypercholesterolemia. "This not only demonstrates how Molly can support pharma companies in meeting their branding requirements, but also in accommodating patient-centric device designs to support pharma's commercial strategies," Mr. Fastmarken says. "With Molly, SHL seeks to reduce the development time and resources while ensuring compatibility between a drug product and the device. By sharing commonality of a modular platform, SHL is also able to share manufacturing assets across multiple Molly device projects, contributing to the optimization of costs, development timelines, as well as the overall environmental impact from producing and operating individual machinery."

SHL has been working with Molly's platform technology to develop digital initiatives supporting connected therapeutics to address the shift from administering injections in clinical settings to homecare settings. Mr. Fastmarken says digital interventions in self-injection devices need to provide flexible and sustainable offerings to facilitate different patient behaviors and treatments. "We are in the development phase of solutions that can achieve the functionality and usability of a traditional autoinjector with additional features that allow for connected health capabilities, while mitigating the environmental impacts."

Mitsubishi Gas Chemical Co., Inc.: Staked-Needle Syringe Targeted to Biologics

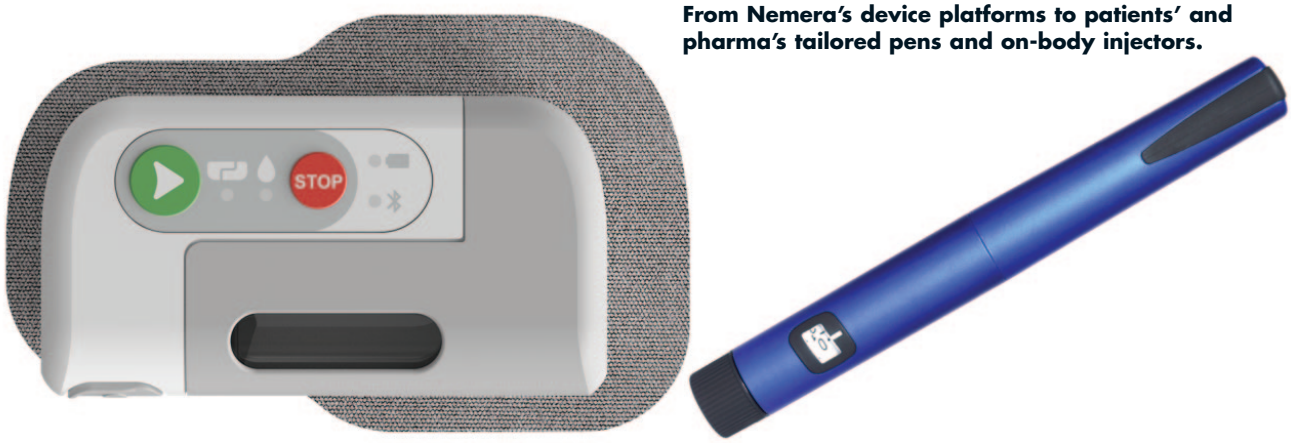
Mitsubishi Gas Chemical Co., Inc. has been focusing on developing staked-needle syringes and plans to start providing samples in 2022. The targeted therapeutic is biologics and the targeted users are biopharma and conventional drug companies.

The staked needle syringe can decrease the possibilities of needle-stick injury and eliminate the loss of time to attach a needle to syringe, according to Tomohiro Suzuki, Associate General Manager, New Business Development, Mitsubishi Gas Chemical Co., Inc. "Many customers have asked for staked needles, and we can change the needle length and gage based on requests and demands, so the syringes will handle every viscosity."

The new syringes are made of a multilayer plastic with a high oxygen and UV barrier. He says: "As there is an issue of breakage with glass containers, and COP monolayer syringes don't have sufficient oxygen or UV barrier protection, the new staked needle product avoids the risk of breakage and offers stability to oxygen- and UV-sensitive drugs."

He adds that the multilayer plastic vial and syringe, OXYCAPT™, will contribute to stabilizing every kind of drug.

OXYCAPT™ Multilayer Plastic Vial & Syringe contributes to stabilizing biologics and gene/cell therapies (Mitsubishi Gas Chemical Co.).



From Nemera's device platforms to patients' and pharma's tailored pens and on-body injectors.

Nemera: Finding a Balance Between Safety & Simplicity

For Nemera, the ultimate goal is to find this right balance between simplicity and robustness of drug delivery devices. Safety and ease-of-use are two of the crucial characteristics in advanced parenteral devices. To that end, Nemera has been focusing on developing and manufacturing safe injection devices that foster patient adherence and improve the self-administration experience as well as ease-of-use.

"Patients with chronic conditions who require lifelong medication need enhanced comfort to manage their treatment, particularly when self-administering complex, large-volume, high-value biologic drugs, such as monoclonal antibodies," says Severine Duband, Category Director, Devices, Nemera. "They need a robust, advanced drug delivery device that also offers simplicity and ease-of-use. On the other hand, patients who have specific and complex conditions – such as oncology, neurology, hematology – also need safe devices to inject their complex drugs and to avoid hospital/healthcare professional intervention. This need is increasing with the trend of switching from intravenous to subcutaneous delivery."

To address the increased trend toward self-administration of large-volume biologics, Nemera's key focus this year has been on the development of an on-body injector platform for complex, large-volume drugs (20mL) delivery, such as monoclonal antibodies with an adjustable flow rate to fit both patients' and drugs' administration profiles. And, it is sustainable thanks to its reusable electronic part and drug-containing disposable element.

As an example, the PENDURA AD is a platform dedicated to manufacturing a reusable pen injector that integrates an automatic, spring-driven feature coupled with a side activation button. Its technological solution allows the ergonomic location of the dose-release button on the side of the pen, ensuring stabilizing the hand holding the pen by resting it against the body during dosing, says Audrey Chandra, Category Project Manager, Nemera.

Owen Mumford Pharmaceutical Services: Expanding Platform to Address High-Volume Biologics

Owen Mumford Pharmaceutical Services has been focusing on its passive safety syringes this past year. These are typically used for subcutaneous administration of therapies for a variety of treatments, such as multiple sclerosis, Rheumatoid Arthritis, and Crohn's disease. The addition of a needle protection safety feature ensures patient safety and compliance with needlestick prevention regulations.

"We have expanded our UniSafe® platform with the addition of a 2.25mL device," says Michael Earl, Director of Owen Mumford Pharmaceutical Services. "Like the existing UniSafe 1mL, the product features a spring-free design that prevents preactivation during transit and provides a simple final assembly," he explains. "From a patient perspective, the absence of a spring helps with drug visualization and checking in the syringe barrel before and during administration, and also provides the same simple administration technique as a prefilled syringe. Additionally, the absence of a spring as well as preventing

UniSafe® 2.25 is the latest addition to the established UniSafe platform from Owen Mumford.

pre-activation in transit also helps with drug inspection prior to patient administration in addition to providing a longer shelf life of 3 years."

He adds that the increasing number of higher volume (>1mL) biologics coming to market has resulted in the growth of 2.25mL prefilled syringes and the need for associated safety devices. "The launch of UniSafe 2.25 makes it particularly suitable for delivery of these types of formulations."

Stevanato Group: Platform Designed for Compliance & Speed to Market

During the past year, Stevanato Group has focused on pen injectors and emergency autoinjectors. The SG Alina® is a customizable pen injector designed to target diabetes, focusing on insulin and GLP-1 therapies.

"SG Alina promotes better compliance and more effective treatment, aiding efforts to reduce costs and improve quality of care," says Adam Stops, PhD, Product Management Drug Delivery Systems, Stevanato Group.

Other advantages include: delivery forces that suit all demographics; ergonomic design of the dose dialing; labeling space for enhanced readability; cap designed for ease of use and durability; and optimized dose numbering.

The pen injector also has been designed as a platform to speed time to market for pharmaceutical companies, while also bringing the benefits of Stevanato's end-to-end solutions, such as glass products, automated assembly, and visual inspection equipment, as well as analytical services, says Dr. Stops.

A user-friendly disposable pen-injector platform for diabetes care, based on proven technology from Stevanato Group.

Vetter: Leveraging Devices for a Range of Therapies

Vetter specializes in filling, assembling, and packaging of injection systems, and is keeping a close eye on several areas where the injectable product landscape is evolving rapidly. The company has already pursued several projects to evaluate a range of different pens, autoinjectors, and wearable systems.

"We're particularly interested in how we can leverage these devices for therapeutic areas such as autoimmune diseases, growth disorders, migraine, oncology, and Type 2 diabetes," says Markus Hoerburger, Product & Service Manager at Vetter. "Patients with these conditions may derive particularly valuable benefits from treatments that are easier to self-administer at home."

This, he says, is particularly true as a result of the pandemic. "Self-

Manual loading of pen components for downstream automatic pen assembly at Vetter's Secondary Packaging Facility in Ravensburg, Germany.

injection products will play an increasingly valuable role in driving compliance, protecting high-risk patients, and reducing the need for clinic-based treatment."

ApiJect: Responding to Demand for Equity & Supply Chain Shortages

Global demand is rising for equitable access to medicine, including injectables. Self-injection is already standard for insulin, many migraine drugs, and biologics. ApiJect is developing products responsive to this demand, such as a scalable, low-cost, simple-to-use injection system that can potentially enable many patients to self-inject prescription medicines with minimal training, explains Dawn Carlson, Senior Director of Program Management at ApiJect.

"ApiJect's focus includes developing a new generation of simple, easily manufactured, prefilled syringes," says Marc Koska, ApiJect's Founder and Head of R&D. "We're seeking both to enable high-speed, high-volume drug or vaccine delivery in the urgency of the pandemic, and to help solve the problem of how to inject populations in low- and middle-income countries."

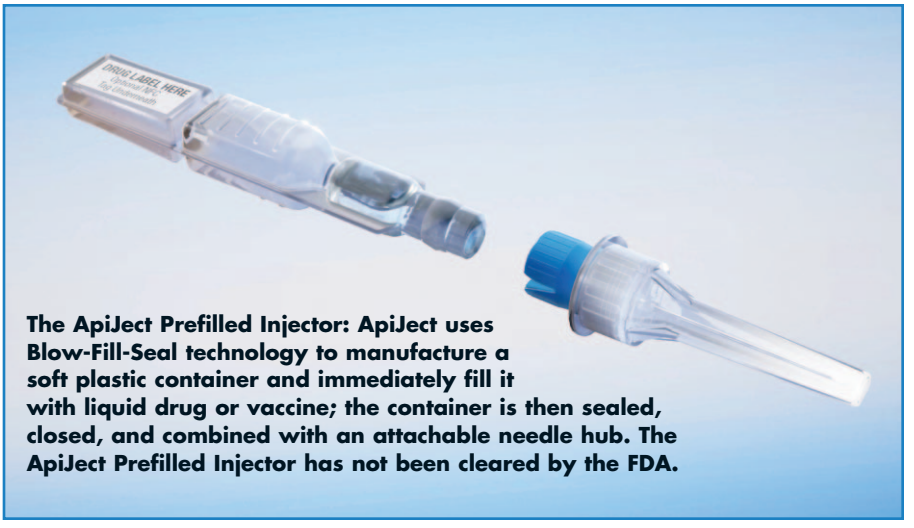
The ApiJect Prefilled Injector, which, as this article went to press, has not been approved by the FDA, is a single-unit dose, soft plastic device. It is pressure-activated rather than incorporating traditional barrel-and-plunger features. "We're developing a broad platform enabling rapid scale-up for many types of injectable applications," says Ms. Carlson. "Our targeted user naturally depends on the specific drug that is packaged in the device."

By designing a prefilled syringe that employs Blow-Fill-Seal (BFS) technology, Mr. Koska says ApiJect expects to offer advantages of safety, speed, and reliable aseptic filling at prices that are highly economical and competitive with disposable syringes and multi-dose glass vials.

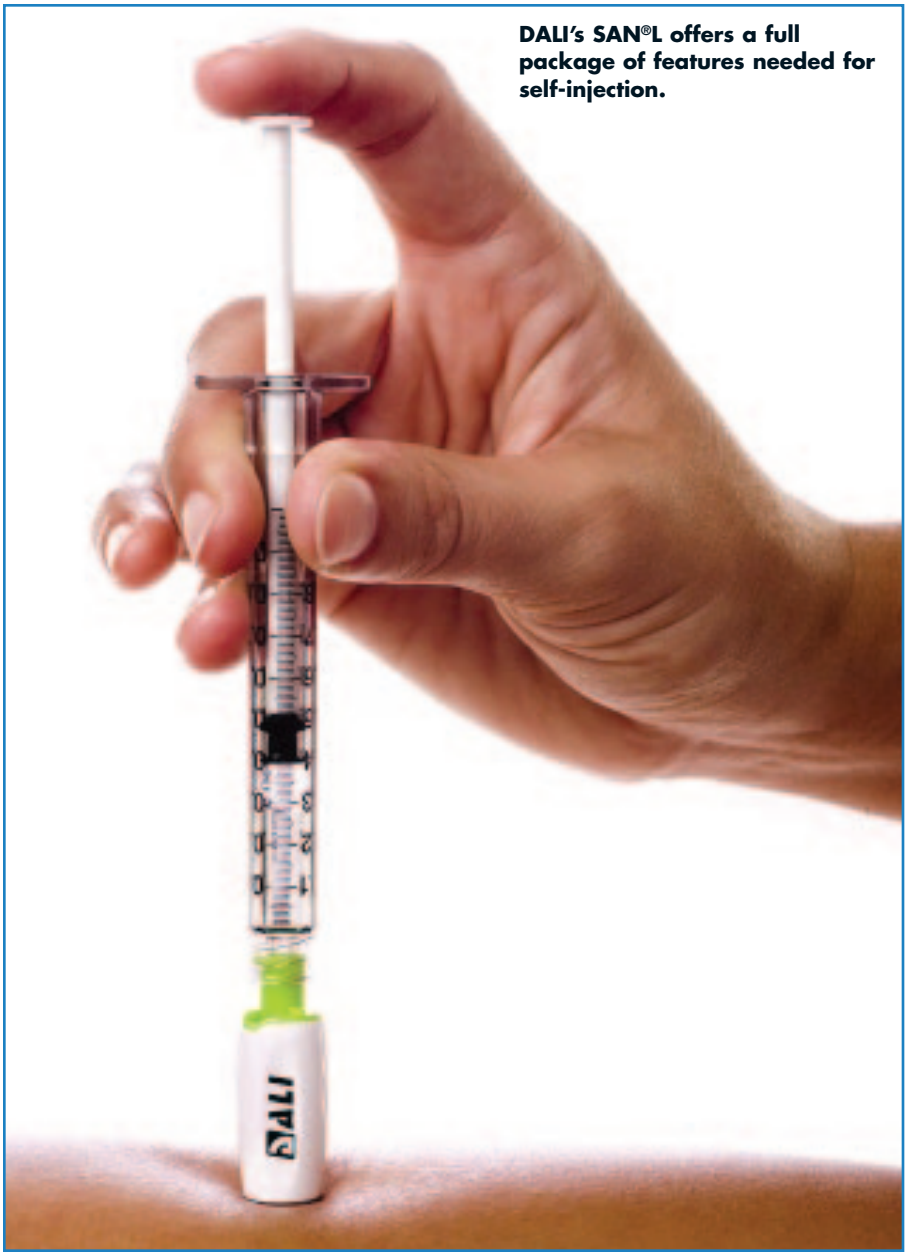
"BFS frees drug packaging from dependency on the supply chain used for glass vials, rubber stoppers, metal crimps, and other traditional syringe and vial components," says Ms. Carlson. "Our injector only requires plastic resin and an intramuscular needle. We plan to be our own needle supplier. BFS is well-established technology, widely recognized as inherently safe and effective."

"Ever since the COVID-19 crisis began, pharmaceutical companies have been struggling with global "just-in-time" supply chains for glass vials and syringes," explains Mr. Koska. "These supply chains are highly vulnerable to disruptions that range from raw materials shortages to fill-finish capacity limits and even government export bans."

Ms. Carlson adds: "The ApiJect platform uses BFS to offer pharmaceutical companies an alternative to tra-



The ApiJect Prefilled Injector: ApiJect uses Blow-Fill-Seal technology to manufacture a soft plastic container and immediately fill it with liquid drug or vaccine; the container is then sealed, closed, and combined with an attachable needle hub. The ApiJect Prefilled Injector has not been cleared by the FDA.



DALI's SAN®L offers a full package of features needed for self-injection.

ditional supply chains. Our platform enables massive production scale-up on short notice; reliable aseptic filling; and much-reduced raw materials requirements. In addition, ApiJect Prefilled Injectors combine the advantages of prefilled formats with the economy of multi-dose vials and disposable syringes."

DALI Medical Devices: Self-Injection Features in One Device

One of the most important takeaways from the COVID-19 pandemic has been the search for ways to reduce the burden and pressure on hospitals. To make this happen, self-injection treatments should be available for the home environment, says Ziv Cahani, Vice President Business Development and Marketing for DALI Medical Devices.

He says demand for DALI's SAN® product family of self-injection devices was booming this past year. The SANs offer features that directly address the patients' needs:

- Automatic needle insertion to the correct depth (SC/IM), so the patient doesn't need to worry if the needle wasn't inserted into the right depth or require assistance from a nurse or other health care professional.
- Automatic passive needle sharps protection against needlestick injuries.
- Hidden needle before and after injection for patients who suffer from needle phobia.
- Manual control of injection speed to help the patient control the pain level.

"With this one-of-a-kind combination of features, SAN-L not only meets the needs of a range of patient needs, but guarantees that the entire injection treatment is more comfortable and that the medications are delivered safely and securely," he says.

Mr. Cahani adds that more drugs (mainly biologics and biosimilars) are being developed for subcutaneous injection. Many of these have different physical and chemical parameters (e.g., viscosity), so there is a need to customize the SAN product design accordingly (e.g., adapt to different-sized needles). The SAN self-injection device's needles range is between 18 and 29 gauge.

As an example of how SAN can be adopted and adapted, one pharma company's commercial team sought a unique device to include one of its drug's self-injection kit. The drug was in a prefilled syringe. "The team

approached DALI because it was looking for a highly differentiated product, one that required special features to meet the specific design and injection requirements of the needle," says Mr. Cahani. "And, of course, too, they wanted to offer a solution that patients would like."

He adds that SAN-L is the culmination of all necessary self-injection features in one product design.

Datwyler: Cartridge Plungers Feature Rubber Coatings for Improved Drug Compatibility

The development of an injectable drug-device combination is a complex process that requires substantial investment of resources and money to achieve desired and successful outcomes. A variety of self-injection device platforms are available that offer benefits like shorter time-to-clinic, lower up-front investments, and lower project risks.

For example, on-body injector devices, also known as large-volume injectors or wearable devices, are on the rise. These devices can be a good choice for the delivery of larger volumes of highly viscous biological drugs given the even and controlled pressure profile they can offer, explains Carina van Eester, Global Product Leader, Prefilled Syringes and Cartridges at Datwyler. Various device companies develop platform devices that can handle volumes up to 20mL, most of which make use of prefilled cartridges. Cartridges utilize established materials, components, and filling processes. Datwyler's portfolio includes larger-sized plungers for cartridge barrels up to an internal diameter of 23.85mm.

In many cases, the drugs that go into these self-injection devices are biological drugs that require a coated rubber closure. Datwyler offers OmniFlex™ coated serum stoppers and NeoFlex™ plungers that have the same composition and are made out of the FM457 compound with a fluoropolymer coating on top. The components are fully coated so the drug runs no risk of touching uncoated rubber, says Ms. Eester. "The benefit of using the same rubber formulation and coating at both ends of the drug product is reduced complexity during extractable and leachable studies," she says. "Datwyler's coated solutions provide drug compatibility, functionality, and machineability. The fluoropolymer spray coating provides a barrier to extractables and leachables while ensuring smooth delivery in the field."

The NeoFlex plungers and OmniFlex stoppers are 100-percent camera inspected and meet demand for quality and performance for highly sensitive, large-molecule drugs. To complete the closure, Datwyler offers a range of aluminum seals that are produced, controlled, and tested under stringent conditions.

Duoject Medical Systems: Responding to Changing Healthcare Needs

In recent months, Duoject Medical Systems has been working on self-contained injection devices – devices that don't require additional packaging. The Maverick emergency auto-injector is a good example of this. It does not require any additional protective casing to contain the device as the patient carries it on them constantly, explains William Fortina, Business Development Director, Duoject Medical Systems.

"This is a crucial advantage for someone facing a life-threating event such as an anaphylactic shock; it allows for completing the injection faster." He adds that developing devices without extra packaging or casing can also be an eco-friendly argument.

Duoject has also focused efforts on user-step reduction, which in the context of self-administration and at-home care, makes the device more patient friendly. "This in turn increases the likelihood of patient adherence and reduces chances of user errors," says Mr. Fortina.

Some of Duoject's pharma clients are increasingly interested in platform devices that allow pharmaceutical labs to reuse a device platform for multiple applications with minimal customization required. "If a novel technology is necessary, Duoject applies its robust design process," he continues. "When designing new drug reconstitution and injection devices, we put an emphasis on early iterative prototyping and human factors testing to find out friction points and flaws early on, and eliminate them from the design before moving on to the actual device development phase."

Finally, Duoject continues developing reconstitution systems for lyophilized drugs. He says that different systems allow clients to combine different primary containers: vial-to-

vial reconstitution (Helium device), syringe-to-vial (Xenon and EZ-Link adaptors), and vial-to-cartridge (PenPrep EVO). These reconstitution systems are helpful as pharma companies develop more complex molecules and biologics, which are sometimes only stable in lyo form.

Enable Injections: Flexible & Convenient Care

The healthcare system, post-COVID, will demand flexible drug delivery options. Enable Injections has spent time with key opinion leaders to better understand the shifting patient and provider needs throughout the COVID-19 pandemic. The need to reduce patient exposure to viruses and free up healthcare resources has driven unprecedented innovation in drug delivery. As a result, patients, providers, and healthcare systems are embracing more flexible care.

The enFuse® is suited for flexible care, says Matt Huddleston, Chief Technology Officer and Executive Vice President of Business Development at Enable. "And our flexible delivery model, EnywhereCare™ with enFuse, allows a range of delivery options for patients and providers, from in-clinic to at-home self-administration of therapeutics."

As patients transition to the home in a flexible care model, maintaining the same quality of care will require delivery technology to provide solutions to connect with their physicians, other patients, training, reminders, and confirmation of delivery success. One of the many ways in which Enable is working to maintain this quality of care is through the development of the Smart enFuse, which supports next-generation patient/healthcare provider connections and enables flexibility in the site of care, explains Jennifer Estep, Senior Director, Marketing & Strategy at Enable.

In the past year, Enable has focused on the validation and clinical success of the enFuse delivery solution. Two clinical trials were recently completed, and another trial is in progress. "These clinical trials demonstrate our ability to subcutaneously (SC) deliver large volumes – 25mL and more – without the use of chemical additives or enhancers," says Mr. Huddleston. "For patients currently receiving care with a large-volume subcutaneous delivery device at home on their own, 100% of these patients reported they prefer the enFuse over the current alternative SC method of delivery. Our goal is to enable convenience for the patient, with the goal of making a positive difference in patient compliance."

Flex: Human Factors Engineering Simplifies the Complex

In this highly competitive industry, the most successful companies have established rapid product development cycles that incorporate robust usability studies. By putting people at the center of medical device design strategy, human factors engineering (HFE) can drive products that simplify the user experience.

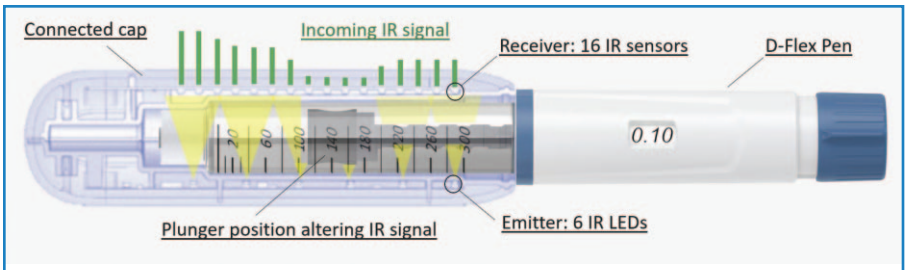
"With a deep understanding of user needs and expectations, HFE experts can be involved at each step of the development process, from early user needs definition through summative usability validation, to ensure that the disparate needs of distinct user groups are met," says Jennifer Samproni, Chief Technology Officer of Health Solutions at Flex. "The resulting product may be more complex while advantageously being perceived as more user-friendly."

At Flex, human factors and engineering teams have integrated multiple sensors into novel autoinjectors that are specifically designed to administer biologics, she explains. "This technology can vastly improve user compliance by simplifying the number of factors the user must track."

Accurate temperature sensing is also of utmost importance because many biologics require cold chain storage. The automated injector can verify the temperature of the drug and either prevent the injection from starting, warm up the drug via active heating or adjust the injection force. Rotary encoder and force sensors can be used together to arm the motor driving unit with more accurate data to support different injection profiles and deliver a consistent patient experience. "In each of these examples, smarter, more complex systems actually simplify the workflow and user experience," she says.

Haselmeier GmbH: Smart Drug Delivery in Clinical Trials

Big tech is delivering leading technologies supporting the paradigm shift in healthcare, not only with the collection of patients' data but also how they make use of that data. As a result, wearables and connected de-



D-Flex™ Cap© Haselmeier GmbH.

vices are increasingly finding their way into clinical trials. For example, Johnson & Johnson's Heartline study is using data from the Apple Watch to support earlier detection of arterial fibrillation in patients (www.heartline.com). This study, initiated in 2020, seeks to enroll 150,000 patients.

The future of clinical trials is becoming more reliant on connected medical devices: Collecting data at the point of care, reducing the need for costly patient visits and cumbersome manual data acquisition.

Therefore, Haselmeier developed the D-Flex™ Ecosystem, a connected drug delivery solution that can be integrated into mobile solutions, collecting injection data at the point of care. The system is based on a proven technology, which was successfully used in a clinical trial with 75 patients completed in July 2018, says Frank Leipold, Business Development Digital Solutions, Haselmeier. The learnings from that trial translated into the new D-Flex Ecosystem (https://doi.org/10.2337/dc18-1631).

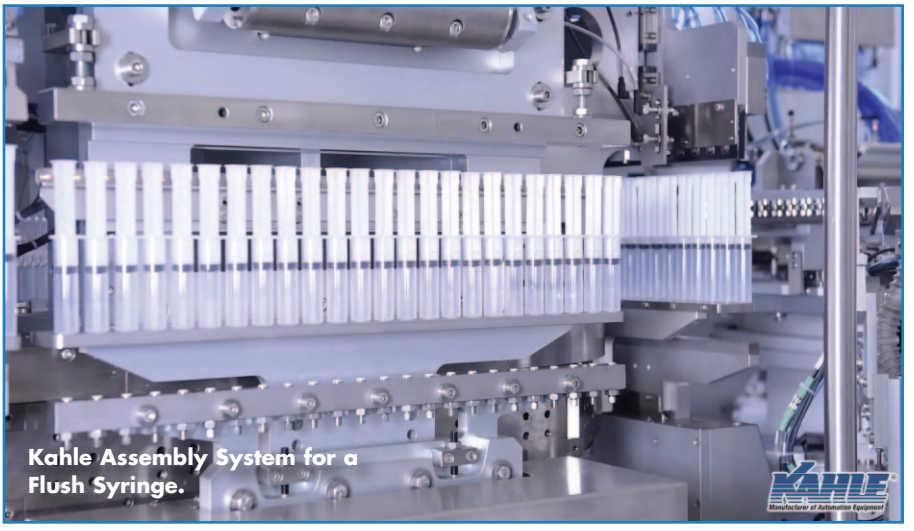
The D-Flex Ecosystem consists of the disposable D-Flex™ injection pen and the connected cap, which replaces the standard cap of the pen. The connected cap tracks injection dose, temperature, and time up to 1,000 injection events. It securely transfers data in real-time to the Haselmeier patient app and cloud or any other pre-existing data management system via Bluetooth Low Energy. As an option, customers can choose to have the data stored and forwarded to the data management system at a later date. This eliminates the need for a patient mobile phone.

The D-Flex injection pen is at the heart of this connected solution, says Terry O'Hagan, Managing Director, Haselmeier Inc. "D-Flex is a complete platform allowing for simplified adaption of specific injection dose volumes by changing only one component. This saves time and cost during clinical testing, especially with dose ranging studies, because it allows using the same pen for all clinical testing and product launch, eliminating the need for additional equivalence/user studies."

The connected cap identifies the actual dose delivered by the pen by comparing the position of the plunger before and after each injection. Six LEDs emit an infrared (IR) signal that is altered by the plunger position. Sixteen IR sensors then detect the incoming signal. The delta between the two states identifies the relative movement of the plunger, delivering the actual expelled dose during an injection. This way, the cap calculates and displays the remaining volume in the cartridge.

Kahle Automation: Custom Equipment for Various Injection Devices

According to Julie Logothetis, President of Kahle Automation, regardless of design and safety advances, the needle and syringe play an integral role in drug delivery from low dead space designs that maximize the dosing of the COVID-19 vaccine to auto-retractable syringes and unique new injection device designs that provide for economic self-contained devices that allow vaccine injections that can be easily distributed worldwide and meet single-use injec-



Kahle Assembly System for a Flush Syringe.

tion requirements.

Kahle Automation has been designing and building custom high-speed automation equipment for multiple injection device projects, providing solutions that assemble devices from 10ppm to 700ppm with completely validated manufacturing and packaging systems to meet the demands of the industry. Current projects include micro-injection devices for ocular injections, low-dead-space safety needles and syringes, auto-retractable syringes that self-destruct once the injection is delivered, and glass syringes that allow for the drug and the delivery system to be combined into one device.

Kymanox: Accelerating Device Development & Delivery

While Kymanox is not a device manufacturer, the company provides drug and device manufacturers with end-to-end solutions to accelerate device development and delivery. "Right First Time" is how Kymanox approaches product and process development and engineering, says Michael Denzer, Vice President of Technical Solutions, Kymanox. "Our integrated solutions, which include project management, quality assurance, regulatory affairs, clinical and medical affairs, and digital transformation, support and drive our clients' device development projects to deliver products to patients with optimized safety, quality, efficacy, and accessibility."

Kymanox has worked on a variety of handheld and wearable injection devices including single-use and multi-use cartridge-based devices. The therapeutic applications include critical care and emergency use as well as chronic disease management. The targeted users range from adolescents to seniors and include patients who have to prepare the treatment themselves.

"For sensitive biologics, patients must reconstitute the drug and, at times, adjust the injectable volume for their body weight," says Mr. Denzer. "These activities add confusion and anxiety to the patient. At Kymanox, we strive to simplify this process as much as possible."

SCHOTT: Syringes Aimed at Improved Compliance

Patient compliance relies on quick, pain-free injection experiences. Optimized for integration with autoinjectors, SCHOTT's syriQ® BioPure prefilled glass syringe underpins the self-injection experience through its influence on injection force and duration. With dimensional tolerances that go beyond ISO specifications, syriQ BioPure supports consistent injection times of less than 10 seconds. "Designed for sensitive biologics, with ultra-low tungsten residual levels, low particulate, and low homogeneous silicone levels, syriQ BioPure PFS supports the ideal patient experience," says Michelle Deutsch, Senior Global Product Manager, Glass Syringes, SCHOTT.

SCHOTT's primary packaging works with various industry device solutions, such as the family of YpsoMate® 1mL and 2.25mL autoinjectors from Ypsomed. The YpsoMate autoinjector is an automated disposable injection device for 1mL-long prefilled syringes. The device is triggered by push-on-skin activation. Ypsomed responds to the challenge of adherence and therapy management by providing the SmartPilot™ for YpsoMate, a reusable add-on that transforms YpsoMate into a fully connected smart product system.

In addition to syriQ BioPure glass PFS, SCHOTT TOPPAC® syringes are suitable containers to be used inside injection devices. SCHOTT TOPPAC offers customers the possibility to individualize Cyclic Olefin Copolymer (COC) containers for self-injection delivery to match their specific needs. "The flexibility and precision of injection molding the COC material with their low particulate, as well as the low silicone levels, provide an especially promising containment option in the biologics space," says Tom van Ginneken, Senior Global Product Manager Polymer Solutions at SCHOTT.

Sonceboz: Ease of Use & Implementation are Critical

Sonceboz is focused on devices that provide a balance between ease of use and ease of implementation. "While the first is a requirement by regulatory bodies, the latter should not be put out of focus," says Thomas Mayer, Business Unit Manager, Sonceboz. "A number of device programs fail because they are too complex to integrate into existing and proven pharma processes."

As an example, he points to primary drug containers. "Primary packaging is key in protecting the integrity

The Sonceboz large-volume injector with vial, 20mL.

and safety of a drug product and barriers for change are high. For this reason, we focus on compatibility with standard vials in our lead device, the LVI-P20." While the lead device is built for compatibility with any vial container, a later lifecycle management device, such as the LVI-P20, is focused on maximum ease of use with reduced use-steps.

Mayer explains that the Sonceboz devices deliver large volumes, up to 20mL and more, in a compact package and are flexible as well. "We work with existing and proven containers, we cater to complex use cases involving multiple containers, and offer an innovative business model that allows our partners to innovate based on our core architecture composed of the GentleTouch™ fluid path and pump, as well as WhisperDrive brushless motors."

West Pharmaceutical Services, Inc.: Digitally Enabled Product Strategy

"West believes the solution lies in simplifying the journey for the patient, physician, and pharmaceutical company," says Lawton E. Laurence, Senior Director, Applied Research & Technology for West.

To that end, the SmartDose® 10 Injector has seen increasing customer demand driven by its ease of use, flexible performance, and the company's experience with commercializing wearable injectors, he continues. "In comparison to burdening oncology clinics with developing bespoke programs to safely administer drug therapies at home, a drug approved for use with our SmartDose 10 injector means those requirements are addressed through the system's patient-centric design and validated through rigorous human factors studies."

Mr. Laurence says one concern West has heard from oncologists is around patient adherence. "For cancer patients, a missed or delayed dose can have life-changing ramifications that don't necessarily exist with other diseases. Based on this therapeutic specific insight, we are developing a solution that would add remote dose capture and an injection metric data stream without sacrificing the user experience that has been so well received. The result is our concept development effort for the connected SmartDose 10 injector, which will leverage our IoT technology platform and the West digital ecosystem."

With the advent of this system, the patient care team will receive critical information regarding the patient's adherence and experience. When the injection is successful, confirmation will be registered in real time along with any qualitative experiential data the patient records in an automated post-injection report. In the event a dose is overdue, an escalating series of interventions will be triggered. Starting with a text message reminder and potentially progressing up to a home

The SmartDose® Platform from West offers a wearable, subcutaneous injector with an integrated drug delivery system that incorporates human factors and usability testing to deliver a truly patient-centric approach to self-administration.

Ypsomed's ready-to-use YpsoDose patch injector delivers up to 10mL in a simple two-step process: patch and inject.

visit, the intervention protocol will be customized based on the therapy's risk profile. "We believe a digitally enabled combination product strategy produces the best possible experience for patients, helps accelerate therapy availability where it's needed, and lowers the overall cost to the healthcare system," he says.

Ypsomed: Smart, Reusable Prefilled Pens

Smarter injection devices are part of the current innovation life cycle and will be an integral part of digital therapy management ecosystems. The complexity of the smart componentry depends on the type of therapy. For example, Ypsomed sees demand for smart, reusable, prefilled pens for short-acting insulin to treating Type 1 diabetes in combination with continuous glucose monitoring and dedicated apps. This provides patients with a real-time bolus calculator and HCPs with an overview of blood-sugar levels over time, explains Ian Thompson, Vice President Business Development, Ypsomed Delivery Systems.

"For prefilled autoinjectors, there is always the question of what level of smartness works best for a particular therapy," says Mr. Thompson. "A connected, reusable add-on provides advanced patient guidance and detailed injection logging, but adds user steps, which may be best suited to certain therapies where patient behavior is critical and closely monitored. As many patients receive support from therapy apps for their conditions, we also see a demand for prefilled devices with built-in electronics that will provide basic device guidance and injection logging."

YpsoDose is a cartridge-based patch injector that is prefilled, preassembled, and electromechanical in this device category. For infrequent large injections of antibody therapies currently administered intravenously, Mr. Thompson expects YpsoDose to provide a safe and easy-to-use format for the hospital/clinical environment and for specialist therapies in the home setting. "In the hospital setting, YpsoDose will free up valuable infusion infrastructure, reduce the risk of dosing errors, and save time for healthcare professionals treating patients with life-saving oncology drugs," he says. YpsoDose is currently being industrialized for use in clinical trials.

"Patient compliance is improved by simplifying the user handling steps to "patch and inject," and providing audible and visual feedback, which has been confirmed in comparative human factors testing," says Mr. Thompson.

Congruence Medical Solutions: Pioneering Flexible Dosing Solutions

Congruence Medical Solutions is developing a number of drug delivery device platforms aimed at applications involving microliter dosing, maximizing injection flexibility, and minimizing drug waste. Emerging needs of injectable drugs currently in development require more flexibility than most injection device platforms can currently provide, explains Phil Green, PhD, Head of Commercial and Business Development at Congruence. Several variables inform development and selection of a device platforms, including injection volume, formulation viscosity, regulatory compliance, needle safety, cost, human factors, and more.

Manual injection embodiment of the Congruence Flexible Dosing Syringe (FDS) incorporating standard 2.25mL standard PFS.

"These afford flexibility for a pharmaceutical partner across the entire portfolio of drugs irrespective of stage of clinical development," says Dr. Green. "Development of the Congruence Flexible Dosing Syringe (FDS) platform aims to provide this flexibility to pharmaceutical companies."

Some potent immunotherapeutic agents in oncology require a range of dose volumes based on patient weight or other factors. Also, drugs with pediatric indications may require significantly different dose volume than for adults. The maximum dose for most pen injectors, which allows variable dosing, is 1mL or less. The FDS has been developed to accommodate a wide range or injection volumes (50 microliters through 2.25mL). "Flexibility in injection volume also may be an important capability for dose ranging studies during clinical trials; minimizing re-formulation costs for a clinical stage drug," Dr. Green says.

While water-like viscosity is preferable from an injection system standpoint, increasingly formulations are getting more viscous. The FDS platform accommodates increasing viscous formulations, and has demonstrated ability to inject formulations as high as 1500cP with standard prefilled syringes.

"It is beneficial for a device platform to afford greater flexibility necessary during clinical drug development, but also bridge to a commercial embodiment with minor modifications. The flexibility afforded by the Congruence FDS can help bridge the clinical embodiment of the injection device with corresponding commercial embodiment. For example, a manual FDS injection device could be used in clinical trials, but an FDS autoinjector could be the commercial embodiment," he says. The Congruence FDS can be made available in both a manual injection and an autoinjector format. ◆

References

1. Injectable Drug Delivery Devices Global Market Report 2021: COVID-19 Growth and Change to 2030, ResearchandMarkets.com, March 21, 2021, https://www.businesswire.com/news/home/20210521005182/en/Global-Injectable-Drug-Delivery-Devices-Market-Report-2021-Market-is-Expected-to-Reach-25.79-Billion-in-2025---COVID-19-Impacts-Growth-and-Changes-to-2030---ResearchAndMarkets.com.
2. Drug Delivery Devices Global Market Report 2021: COVID-19 Implications and Growth to 2030, ResearchAndMarkets, Aug. 6, 2021, https://www.businesswire.com/news/home/20210806005310/en/Drug-Delivery-Devices-Global-Markets-Report-2021-Oral-Injectable-Topical-Ocular-Pulmonary-Nasal-Transmusocal-Implantables---ResearchAndMarkets.com.

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Drug Development
EXECUTIVE

Eric M. Ostertag, MD, PhD
Chief Executive Officer
Poseida Therapeutics

POSEIDA THERAPEUTICS

Poseida Therapeutics: Creating the Next Wave of Cell & Gene Therapies With the Capacity to Cure

Poseida Therapeutics is a clinical-stage biopharmaceutical company bringing together scientists, entrepreneurs, and inventors united behind one goal – using advanced genetic engineering to change how diseases are treated. With its core proprietary technology platforms spanning gene insertion, gene editing, and delivery tools, Poseida aims to make the promise of single-treatment cures, greater accessibility, and off-the-shelf therapies a reality for patients in need.

Drug Development & Delivery recently interviewed Eric M. Ostertag, MD, PhD, Chief Executive Officer of Poseida Therapeutics, to discuss the company's innovative approach to develop safer, more effective, accessible and affordable cell and gene therapies for patients.

Q: Your CAR-T product candidates are developed using your proprietary piggyBac® DNA Delivery System. How does this work and what are its benefits?

A: Our uniquely designed, non-viral piggyBac DNA Delivery System is a transposon technology that efficiently delivers extensive genetic cargo into cells.

The piggyBac platform offers many advantages over the retroviral systems. First, piggyBac can accommodate a much larger therapeutic transgene than the viral systems, allowing us to insert greater cargo, including useful tools, such as a safety switch that could be activated to eliminate cells in a person at any point after

administration, if desired. It is also more efficient at gene insertion, offers a safer insertion profile, and is less costly to manufacture. However, the most significant advantage of using piggyBac for the creation of chimeric antigen receptor T (CAR-T) cell therapies is that it preferentially inserts into a highly desirable T cell subtype called the stem cell memory T cell, or Tscm, while the retroviral technologies are almost completely excluded from infecting and transducing the Tscm cell type. Not surprisingly, the type and quality of the cells that comprise a cell therapy will determine how well the cell therapy functions in a person. As it turns out, the Tscm phenotype is directly correlated with the best responses in the clinic and, in some patients, remarkable duration of response. It also results in significant safety advantages, thereby enabling fully outpatient dosing and increasing patient access.

In fact, we recently highlighted initial results in the current trial for our CAR-T in prostate cancer where we've seen early signs of meaningful clinical response - one in a patient with a >50% decline in prostate-specific antigen (PSA) just two weeks after treatment; and now a second patient with >96% decline in PSA and a 70% reduction as shown in PET imaging of target lesions at four weeks after CAR-T treatment. Though early, this undoubtedly is an encouraging response.

Q: In addition to your autologous CAR-T candidates, the company is also working to develop allogeneic CAR-T product candidates. Why is this an exciting next step?

A: At Poseida, we have combined the power of the non-viral piggyBac DNA Delivery System with the safe and efficient Cas-CLOVER™ Site-Specific Gene Editing System to create fully allogeneic versions of our high-percentage Tscm CAR-T product candidates. The cells in these investigational products are derived from younger, healthier donors than the autologous counterparts and have even higher percentages of the desirable Tscm cells. Therefore, the allogeneic versions demonstrate even higher efficacy than the best autologous versions of our product candidates in our most predictive animal models.

In addition, Dr. Devon Shedlock, Senior Vice President, Research & Development at Poseida, has invented a technology that we call the booster molecule, which uniquely allows Poseida to maintain the Tscm cells in our fully allogeneic products, while expanding the cells to create hundreds of doses from a single manufacturing run from a single healthy donor. This invention will lower the cost of CAR-T to the same range as that of a monoclonal antibody or a bi-specific T cell engager (BiTE). We expect the first version of our fully allogeneic CAR-T, P-BCMA-ALLO1, to enter the clinic in the third quarter of this year. We have also developed a "pan solid tumor" version of a fully allogeneic CAR-T, P-MUC1C-ALLO1, that is expected to enter the clinic by the end of this year. We are optimistic that high Tscm, fully allogeneic CAR-T will enable accessible and safe treatments with low manufacturing costs for various cancer types, including both blood and solid tumors.

Q: We are seeing increased interest in gene therapies. What is unique about your gene therapy development and delivery compared to others in this space?

A: Poseida's powerful and versatile set of industry-leading genetic engineering tools lays the foundation for developing a safer, more durable, and more efficient suite of treatments, with the goal of single treatment cures for patients with high unmet medical needs.

The great majority of genetic diseases manifest in the pediatric population. These patients are often typically the most severely affected. Unfortunately, almost all gene therapy strategies, such as adeno associated virus (AAV) and nanoparticles delivering therapeutic mRNA, are non-integrating, and are therefore transient. Non-integrating technologies are especially ineffective in the pediatric patient population because these patients have a rapidly dividing liver that will quickly eliminate expression from mRNA or non-integrating transgenes. Some AAV companies have increased the viral doses in order to compensate for this low-level and transient expression, but high viral doses can have lethal side effects.

At Poseida, we have been developing a substitute for viral delivery that is still able to stably integrate a therapeutic transgene, enabling a potential single treatment cure. There are two crucial components to this viral substitute.

The first component is a safe and efficient system for insertion of therapeutic transgenes into the genome, and the solution is to use the piggyBac DNA Delivery System. The second component, the ability to deliver therapeutic transgenes into a specific cell or tissue without triggering the immune system, is provided by Poseida's proprietary biodegradable DNA and RNA nanoparticle technology. These two technologies combine to uniquely enable potential single treatment cures for children affected with otherwise untreatable metabolic and other genetic diseases.

Q: What initial indications for gene therapy are you targeting, and why were they chosen?

A: We have several gene therapies in development addressing life-threatening metabolic diseases, including Ornithine Transcarbamylase (OTC) deficiency, a rare metabolic disorder in which the liver cannot efficiently remove ammonia from the body, which then causes potentially fatal toxicity. OTC deficiency is caused by mutations in the OTC gene responsible for the final metabolic step in the urea cycle. We are also studying the use of our nanoparticle-based gene therapy system as a potential single treatment cure for hemophilia A.

When determining the disease indications we wanted to target, we focused on the unmet medical need and in particular are targeting the pediatric patients that cannot be treated successfully with standard gene therapies. In the case of OTC deficiency, there are few approved treatments, and they are expensive and not completely effective. Liver transplant can be curative, but it is not always available to children who need one and is fraught with high cost and high morbidity and mortality. However, the fact that liver transplants can be curative tells us that sufficient expression of the therapeutic transgene in the liver should result in a complete cure. We know that we have a huge competitive advantage in the pediatric population because typically transient gene therapies will not work. In the case of hemophilia A, there is a large number of pediatric patients who would benefit from our potential single treatment cure approach. Here again, standard non-integrating gene therapy approaches will not work. Furthermore, the therapeutic transgene for this disease, Factor VIII, is too large for AAV-based delivery.

Q: The company is working on gene therapy delivery mechanisms with the goal of replacing AAV with nanoparticle technology. Could you share more about your nanoparticle technology and its benefits versus AAV?

A: Poseida's nanoparticles are made from biodegradable materials. Like a virus, they are able to carry DNA or RNA into a specific cell. Unlike a virus, they do not trigger the full wrath of the immune system and are therefore a much safer alternative. As additional advantages, patients do not have pre-existing immunity, and they don't develop immunity so they can be re-dosed if necessary. In addition, nanoparticles have a much larger cargo capacity than AAV so can be used to treat a larger range of diseases, and they are easier and less costly to manufacture.

At Poseida, we have designed fully biodegradable nanoparticles that can encapsulate nucleic acids, such as those required by the piggyBac DNA Delivery System or the Cas-CLOVER Site-Specific Gene Editing System. We have already demonstrated that we are able to encapsulate the piggyBac system and achieve long-term stable transgene expression in animal models with a single injection of these safe and effective viral substitutes. While the road to safe and effective gene therapy vectors has been a long one, we are now on the verge of achieving single treatment cures for numerous genetic diseases.

Q: Where do you see your gene therapy program going and what are the next steps?

A: Our goal is to develop gene therapies that will cure a disease rather than just treat it. It may sound ambitious, but our technology platforms have the potential to correct the underlying genetic problem that causes these diseases and permanently correct or replace the gene, thereby providing a potential lifelong cure.

The next important steps will be continuing our preclinical work with researchers and clinicians who are the world experts in particular diseases and then extending our work into the clinic. It will also be important to address any skepticism around gene therapy. With the FDA approval of mRNA vaccines for COVID-19 and the 2020 Nobel Prize awarded for CRISPR gene editing technology, more people outside of the life science industry are learning about how these types of therapies work and the promise they hold. ◆

DIGITAL CUSTOM PLATFORM

PCI Pharma's Digital Transformation: Reaching New Levels of Customer Experience

By: Wayne Hull and Rebecca Coutts, PhD

INTRODUCTION

Approximately 2 years ago, we began to incorporate digital transformation as core to our business strategy at PCI. This decision was based on increasing evidence that investment in digital solutions provides real and measurable returns. And now, digital transformation is a key differentiator for us as we work to build even more collaboration and efficiency across our global organization.

NOVEL DIGITAL PLATFORM PROVIDES REAL-TIME VISIBILITY

As part of our 3-year digital strategy, this past year, we launched pci | bridge – an innovative, first-of-its-kind digital customer platform designed to transform the customer experience. pci | bridge is all about transparency. It gives our customers immediate, real-time visibility and tracking of their clinical and commercial supply chain, which allows for greater collaboration with PCI's teams, along with instant data and insights to inform decision-making.

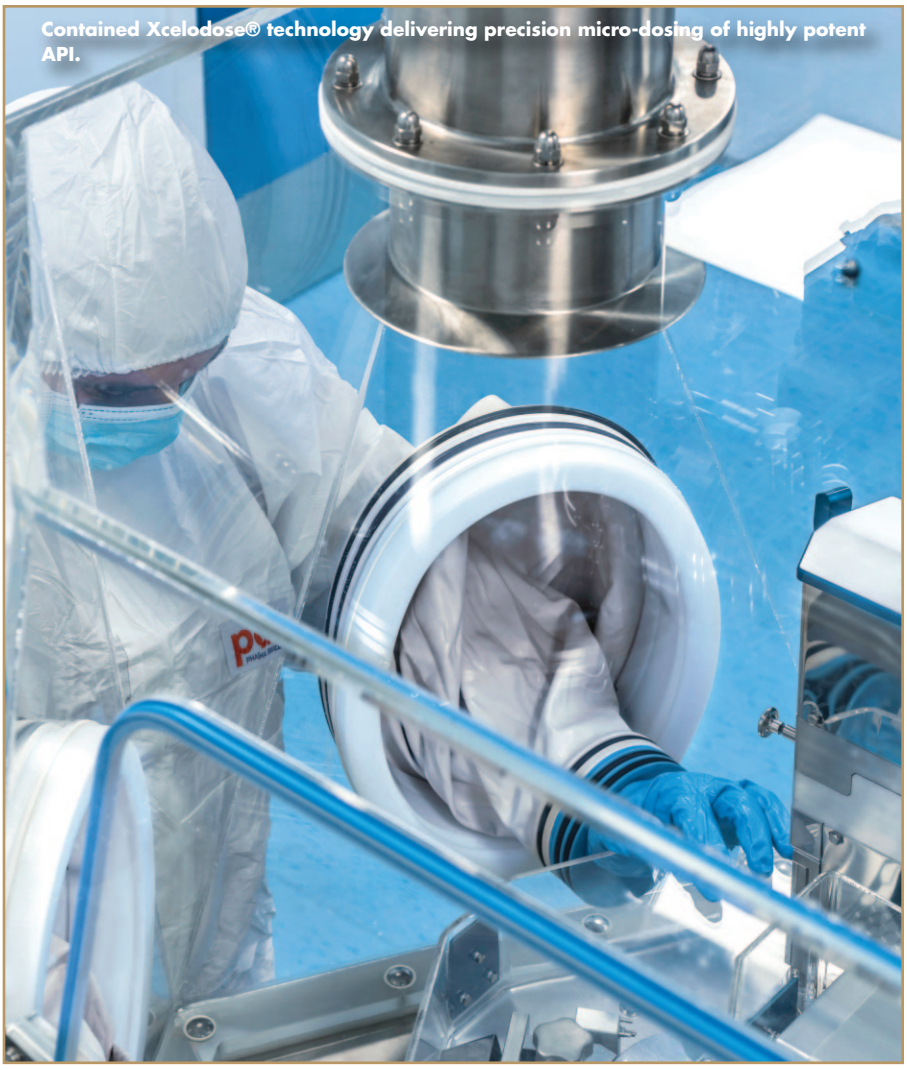
PCI Pharma Services Tredegar, a center of excellence for the development and manufacturing of high potent molecules.

The platform technology closely and securely integrates PCI's systems for customers so that the supply chain can be managed from both sides while eliminating time-intensive manual processes. It works by connecting many different technologies at multiple sites and presents data through an easy-to-access, simple industry-leading interface. With clinical trial management, for example, the platform helps customers better manage that process from beginning to end, from shipments to temperature control, with seamless functionality. While pci | bridge is currently focused in our commercial and clinical trials business, we plan on introducing it on the manufacturing side in the future.

COMMITMENT TO TRANSPARENCY: MANUFACTURING SERVICES & RECENT EXPANSIONS

Looking at our technology on the manufacturing side, PCI's commitment to transparency becomes clear. Transparency is essential for quality control and accuracy, particularly with our specialized high-potent processing equipment. The operation must be repeatable as per the defined specification to ensure that medicines are accurately produced with no cross-contamination. With unparalleled capabilities and experience in the contained manufacture of highly potent compounds, our Tredegar site in the UK excels as PCI's center of excellence for drug development and manufacture.

Significant investment in cutting-edge technologies and world-class award-winning facility design has enabled a truly market-leading service for the development and manufacture of highly potent clinical- and commercial-scale products. Services provided out of Tredegar for our global clients include formulation and analytical development, clinical trial supply, and commercial manufacturing of solid oral dose, powders, liquids and semi-solids, supported by in-house packaging and labelling services and on-site testing and release services.



Contained Xcelodose® technology delivering precision micro-dosing of highly potent API.

In early 2019, we completed a significant investment to double our tableting capacity at the existing contained manufacturing facility (CMF) at Tredegar due to the increased need for high-potent manufacturing we had seen throughout the past few years. In 2020, we also expanded our analytical services by 30%, building a three-story bespoke facility, increasing capacity to deliver capabilities including method development, method validation, stability, and analytical release testing to support ongoing growth in high-potent manufacturing requirements.

As the market continues to grow, we've seen an increasing number of clients look to us to provide manufacturing services across the spectrum of dosage forms. To keep pace, we are building a second CMF due for completion in early 2022. When the original CMF (CMF 1) was opened in 2013, just 25% of new chemical entities coming into market were classified as high potent; now it's more than 40% with no signs of slowing. CMF 2 will replicate the original facility, in effect doubling processing operations in terms of dispensing and fluid bed granulation of high-potency products at both the clinical


Contained isolator technology for the dispensing of highly potent actives.

and larger commercial scale. It is also worth noting that soon after the opening of the original contained facility, additional investment was made adding contained roller compaction technology to support clients in need of development and manufacturing services for highly potent products sensitive to heat and moisture. This ensured that we were able to offer the full spectrum of wet and dry granulation techniques for such specialized potent products.

While many companies involved in the processing of highly potent molecules may use traditional methods and personal protective equipment (PPE), our safety is primarily achieved through engineering design. Operations are conducted using fully contained engineering technologies to protect workers and the environment, which also gives operators more dexterity and control when operating the equipment. The processing technology is managed via a digital interface, considered leading edge.

The Tredegar expansion will double our large-scale manufacturing capacity to ensure that new and existing customers have their development and supply needs met both now and in the future. These investments in Tredegar are part of our ongoing business strategy to remain flexible in an ever-changing marketplace to better service our clients who require a supply chain partner able to deliver an end-to-end service, from drug development to commercialization.

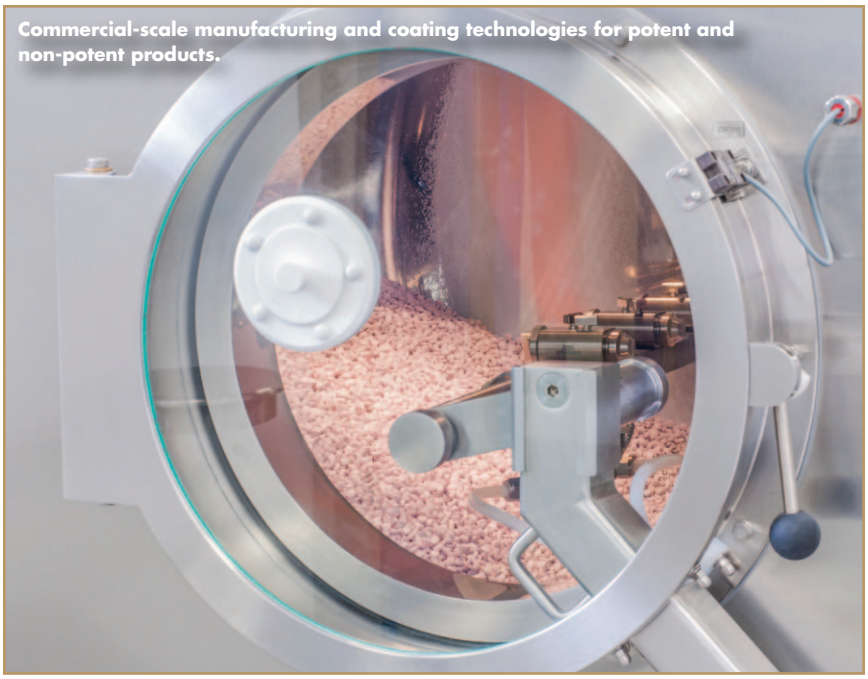
In the US, we have seen a swell of activity from biotech companies on the West Coast in early stage compounds, and we have a strong interest in working with them, so it makes good strategic sense to add early stage manufacturing capabilities in this area. We are exploring the option of adding such early stage manufacturing services at our San Diego site to complement ex-US manufacturing services. Currently at the Tredegar center of excellence, we are able to offer micro-dosing Xcelodose® technology for early phase proof-of- concept activities. Xcelodose® delivers drug directly into capsules or vials, removing the need for initial formulation development and associated stability, and leading to faster first-in-man studies and cost efficiencies. The fully programmable system ensures exceptional levels of accuracy and precision while minimizing drug substance waste.

DIGITAL PROCESSES, MONITORING & QUALITY MANAGEMENT

When we look specifically at the manufacture, distribution, and packaging of high-potency materials from a digital perspective, the equipment is highly complex and computerized. We have a validation team trained in testing of the computer systems, which further increases the level of confidence of the operations team. The computer systems help us follow the latest compliance guidelines and quality regulations. We also ensure that we have the most up to date batch report systems and process manager technology, so that when we conduct our commissioning activities, especially toward new facilities, we know that our teams have received all relevant training on compliance guidelines.

Because additional batch reporting is needed with tablet compression machines, we have also invested in fully automated online process checking technology so that at any point in the process, the team can simply check the human machine interface (HMI) screen. The benefits include real-time monitoring of variations in tablet parameters against a defined specification, and can allow for accurate and fast modifications. And from a commercial standpoint, we have the capabilities to run the machine in automatic modes, ensuring an efficient process.

Our high-potent granulation and fluid bed drying technology utilize a process manager system for recipe management, data recording, batch reporting, security synchronization, and electronic signature control. In addition, fully automated wash recipes ensure robust and repeatable performance for routine and high-containment potent products.



Commercial-scale manufacturing and coating technologies for potent and non-potent products.

Other critical aspects of our process are our Building Management systems (BMS) and Environmental Management systems (EMS). PCI Tredegar uses EMS to monitor ISO 8 cleanroom environmental conditions with all EMS systems being fully validated and calibrated to monitor critical environments at all times. The systems are 21 CFR Part 11 compliant, which requires that all system data is auditable, password protected, and fully secure. Alarms indicate when any of our environments are outside their specified limits. We use both hard wired and wireless telemetry systems to monitor all critical environments on site.

The systems are fully calibrated, and all EMS probes are certified to be within their specified accuracy. The systems are also set up to automatically send emails to departmental managers in the event of an alarm activation, and are monitored by appropriately trained staff when the site is unmanned. The EMS and BMS systems demonstrate that the ISO 8 cleanrooms operate within their correct temperature, relative humidity conditions, and pressure differentials.

The next steps in our digital evolution are to go fully electronic with our batch documentation.

THE FUTURE

For the future, we are looking forward to seeing the results of our digital transformation touch all pillars of our business from manufacturing to clinical to commercial. We are confident that our digital and technology strategy will deliver new levels of customer experience and differentiation, as we are already seeing the significant value our new digital processes are creating for our customers and business. As PCI continues on its digital transformation journey, challenging the status quo and listening to our customers as we go, we are enhancing all aspects of our operations to get life-changing treatments to patients faster. ◆

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BIOGRAPHIES

Wayne Hull is a Digital Transformation Global Leader, strategizing and operationalizing digital value at scale. His current global leadership role in PCI Pharma Services, a global pharma supply chain leader, includes Digital, I.T., and Marketing across North America, Europe, and Asia Pacific.

Dr. Rebecca Coutts graduated from the University of Bath, UK, with a Bachelors in Pharmacy before earning her PhD in Pharmaceutics from Cardiff University. She is also a registered member of the General Pharmaceutical Council. Over her 25-year career, she has shown a clear passion for development services and currently holds the role of General Manager for PCI Pharma Services Tredegar site, PCIs center of excellence for manufacturing services. Prior to this, she held roles including Director of Development for the site with specialist expertise in the development and processing of highly potent molecules and Associate Director of Contained Manufacturing. Before joining PCI, she held multiple roles, including Head of Pharmaceutical Development for Vectura and Group Leader, Manufacturing, Science, and Technology Services at Abbott Laboratories.

HOT MELT EXTRUSION

API Bioavailability: Suspending Hydrophobic Drugs in a Solid Solution

By: Ameya Deshpande, MS

INTRODUCTION

As defined in the International Conference on Harmonization (ICH) Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs), an API is any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product.[1] The API, when used in the production of a drug, becomes an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. While many APIs have therapeutic potential, that doesn't mean they automatically function as effective drugs. Some APIs are innately hydrophobic, with poor bioavailability. Others are more hydrophilic, which results in higher bioavailability leading to a lower dose requirement to exhibit the intended pharmacological effect.

Of the new chemical entities currently in development, many present challenges for drug developers. More than 50% are excessively hydrophobic and fall into the Biopharmaceutical Classification System (BCS) Classes II, having high permeability, and IV, low permeability, through the gut wall, respectively.[2] An additional ~25% fall into BCS Class III and are hydrophilic but display low permeability. It's up to formulation scientists to determine how to incorporate these APIs into a drug formulation that is easily dissolved and absorbed in the body – preferably at the lowest effective concentration possible to minimize potential side effects. This is when hot melt extrusion (HME) comes into play. This technique enables the formulation of drugs into a solid dispersion, thereby increasing efficacy and safety of the drug product. HME can also be used to create time-release formulations that precisely control the concentration of a drug delivered to a patient over time.

While HME is a uniquely valuable tool for pharmaceutical developers, it requires specialized knowledge. As discussed further, not all APIs are compatible with HME and hence may not be a candidate for the method. For those that are, careful attention to the formulation quality attributes that include excipient selection, dosage form design, analytical testing, and stability are required to maximize the efficacy and quality of the final product.

BALANCING SOLUBILITY & STABILITY

Generally, APIs that are hydrophobic or that have a high molecular weight need to be "modified" for human metabolism, above and beyond the standard additives that are used for preservation, stability, and dosage form design. Furthermore, poorly soluble, lipophilic APIs are most stable in a crystalline state, which lessens bioavailability. Formulation scientists must overcome these conflicting requirements to create drug product formulations that can be easily absorbed by the body, while compensating for the reduction in stability associated with conversion of APIs from crystalline to an amorphous state. In some cases, the result is a compromise, where manufacturers create a formulation that allows an API to remain in a partially bioavailable state to preserve its stability. However, the per unit dose of API is usually increased to compensate for this reduction in bioavailability.

Although this technique delivers the necessary amount of API with required bioavailability to the body, it can produce a number of undesirable effects as the API concentrations rise. Drug product manufacturers may encounter safety concerns in production related to higher API concentration, increased risks of patient toxicity, and higher costs per unit dose. While challenging, HME can overcome each of these drawbacks.

The world needs you to succeed.

Let us help you get there faster, and safely.

Only a few ever reach the summit – those who possess the right combination of intelligence, resilience, bravery, and respect – backed up by a team of experienced and expert partners.

As the challenge to deliver COVID-19 related vaccines and treatments continues, you can count on Aptar Pharma to help you achieve your goal.

Our PremiumCoat® film-coated solutions can help derisk your drug development and support the specific needs of your COVID-19 projects.

PremiumCoat® stoppers, our proven multidose vial containment solution, can reliably accommodate up to 20 piercings, enabling HCPs to vaccinate and treat more people, more efficiently. Our platform approach with PremiumCoat® 1mL long and 1-3mL syringe plungers facilitates your transition to Pre-Filled Syringes to anticipate long term vaccination strategies.

Aptar Pharma. Enabling the rapid deployment of your vaccines worldwide.

To reach the summit faster, and with less risk, contact **Estelle Verger**, Business Development Senior Manager, Aptar Pharma, at **estelle.verger@aptar.com**

Delivering solutions, shaping the future.

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HME APPLICATIONS

HME is a highly efficient continuous manufacturing process that uses high heat and shear forces to disperse a chemical in a mixture to form a solid dispersion. A solid dispersion created by HME is the distribution of one or more hydrophobic APIs into an inert hydrophilic carrier at solid state prepared by melting (fusion), which increases the surface area of the particles and in turn increases the dissolution rate, resulting in an increased bioavailability of a poorly soluble drug. However, because of the extreme conditions required for the HME manufacturing process, only relatively thermostable APIs are candidates for this approach. While any thermostable APIs can be formulated using HME, hydrophobic compounds that cannot be processed by other techniques are also prime candidates. This technique increases their bioavailability and dissolution rates, reducing the amount of API necessary for each dose, while other excipients can be leveraged to preserve their stability.

In addition to bioavailability, drug manufacturing with HME offers additional advantages, including the following:

- Masking the taste of bitter APIs in the final product
- Developing timed-release oral formulations or implantable devices
- Producing thin films (an increasingly popular and convenient method of oral drug delivery)

While HME addresses a key niche in pharmaceutical manufacturing, it is not a pharmaceutical invention. The technique originated in lead pipe manufacturing in the late 1800s. During the 1900s, manufacturing applications for HME took off in the rubber, plastic, and food industries in a wide variety of products. The common requirement is that all components of the mixture need to be evenly distributed at a molecular level. In the 1970s, pharmaceutical manufacturers adopted the HME technique for drug production, realizing its potential to generate chemical mixtures that overcame long-standing roadblocks in the field.[3]

TABLE 1

Excipient	Purpose
Matrix carrier	Dissolves and entraps the API
Bulking agents	Adds desired volume to the formulation
Release modifying agents	Modulate release of API
Thermal lubricants	Enhances stability of API during processing.
Polymers and plasticizers	Improves processing conditions and physicochemical stability of the product.
Antioxidants	Counteract the oxidation of the API
Stabilizing agents	Counteract degradation of API
Miscellaneous additives	Tailored to suit specific drug delivery goals

HME Functional Formulation Excipients.

FIGURE 1

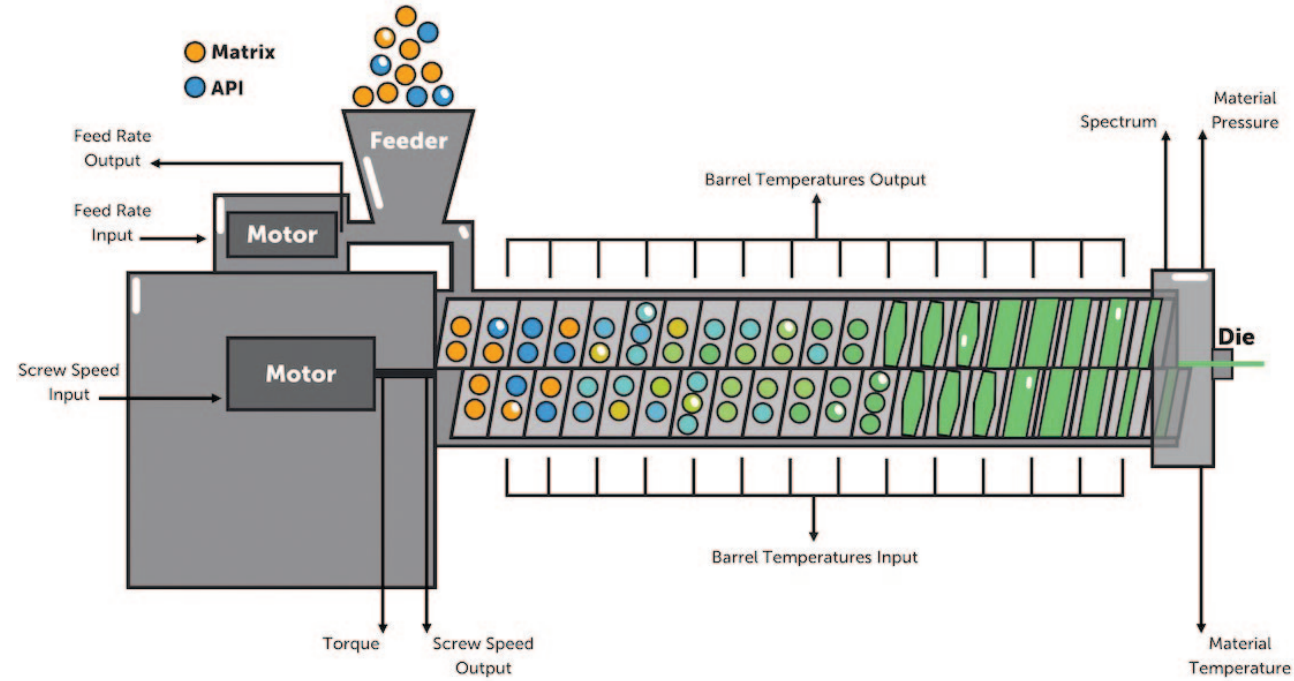

Diagram of a Hot Melt Extruder

SELECTING THE RIGHT EXCIPIENTS

Every API has unique chemical properties that facilitate its pharmacological effect. To ensure an API's efficacy, each additional drug ingredient (excipient) must be carefully selected to complement these properties and its intended function.

Selecting the correct material and carrier composition of these functional excipients is critical to the HME manufacturing process. In fact, the precise combination directly affects the ease with which an API is converted into a molecular dispersion of sufficient purity. In the manufacturing process, excipients need to be carefully selected to minimize API degradation during the high heat and shear conditions, maximizing the stability and pharmacological performance of the final product.

As with a wonderful food recipe, every HME formulation has a base component (the food product) that is modified as needed by additional ingredients (such as the seasoning the food product is enhanced with: salt, pepper, garlic, onion, sugar, oil, butter, etc). The matrix carrier forms the base of the API drug formulation. As such, the most important quality of a matrix carrier its miscibility – it's ability to dissolve an API in molten form and then, when solidified, release it into the surrounding environment at an appropriate rate. As an API can only be dissolved in a carrier's molten state, the melting temperature and/or glass transition temperature of a carrier must be low enough that it minimizes temperature-induced degradation of the API and thereby the generation of impurities. Furthermore, due to temperature changes during the HME manufacturing process, matrix carriers must be capable of maintaining their integrity throughout the cycle of melting, mixing, and solidification. Finally, once cooled after manufacturing, a carrier must be stable and functional in its final dosage form. Common materials that meet these requirements tend to be low melting point waxes (eg, microcrystalline wax) or polymers (eg, ethyl cellulose, povidone polymers).

Other classes of functional excipients must also be carefully selected to support the API's activity. These include bulking agents, release-modifying agents, polymers and plasticizers, antioxidants, and other stabilizing agents (Table 1).[4,5] Developers should consider working with a manufacturing partner, such as Avomeen, for guidance on which chemicals in each class will form a pure molecular dispersion of the API. This in turn maximizes the drug's performance and reduces its degradation during manufacturing, distribution, and storage.

THE PROCESS

To perform HME, all ingredients are fed through a feeder into an extruder consisting of a barrel and pipe (Figure 1). The temperature and shear forces within the barrel controlled in a fashion to convert all ingredients into a molten form. Subsequently, depending on manufacturing needs, one or more rotating screws push the mixture through the extruder. This process creates a uniform molecular dispersion, ultimately forcing the mixture through a die that gives it the correct size and shape. An added benefit is that the HME technique is very versatile - the product may also be flattened into a thin film or formed into a pellet or sphere.

The ingredients of any formulation have a unique chemical makeup, and elements of the HME manufacturing process must be optimized to suit these chemical properties. At the basic level, the temperature at which the process occurs must be tailored to prevent the degradation of any of the formulation materials. Additional considerations include the screw design, pitch, and rate at which the screw pushes the mixture through the extruder and the fluidity of the mixture, both of which are important for creating conditions for a complete molecular dispersion.

Throughout a drug's development and manufacturing, the quality of the product must be inherent to process (quality by design) and evaluated and controlled throughout the process and production train.[6] For these purposes, Avomeen can offer partners in-process controls, process analytical technology, analytical capabilities like Raman and Near Infrared (NIR) spectroscopy, Differential Scanning Calorimetry (DSC) systems, and ultrasound to assess the quality of the final product.

WHY CHOOSE HOT MELT EXTRUSION?

Developing a formulation using HME can be a complicated process that requires the conditions, ingredients, and their concentrations to be optimally balanced to suspend the API into the polymer matrix. So why do some developers prefer this technique? There are several important factors: HME can be adapted for continuous manufacturing, it is modular, and it is an efficient method that produces highly efficacious drugs with lower concentrations of API per dose, making them safer for patients to take. Furthermore, HME is compatible with in-process controls and process analytical technology that enable developers to fine-tune their manufacturing processes in real time. Additionally, HME manufacturing is cost efficient and safer for workers because harmful solvents are not required to dissolve APIs, which are instead well-contained in closed systems as they are being prepared. This limits accidental drug exposure to employees and limits the amount of ingredients that escape into the environment during manufacturing. HME is also a fast process, with downstream steps seldom needed to reach a finished product. For this reason, there is some flexibility when it comes to an API's stability in the face of high temperatures: while highly thermostable APIs are natural candidates for HME, APIs and excipients that are moderately thermostable, particularly those not suitable with other manufacturing techniques, may be considered. However, some APIs, such as antibiotics, proteins, and peptides, are categorically not thermostable and therefore cannot be formulated using HME.

In all, the rules dictating which APIs and excipients are suitable candidates for HME are highly nuanced. Only after the proper preformulation activities, design of experiments (DOE), and methodical characterization of a specific API's stability can developers and their partners determine if a formulation will lend itself well to this technique. Although complicated, HME is worth considering because it introduces a wide range of formulation possibilities. The technique can incorporate numerous poorly soluble APIs into virtually any kind of solid, stable dosage form, including immediate, orally disintegrating, and controlled-release tablets, softgel capsules, thin films, microencapsulated drugs, nanoparticles, floating drug delivery systems, targeted drug delivery systems, intravaginal rings, stick packs, and intraocular or subcutaneous implants. No matter the dosage form, the HME manufacturing process enhances the bioavailability of poorly soluble APIs by incorporating the API into a hydrophilic matrix and/or pre-dissolving the API in a non-crystalline, amorphous state.

In an HME formulation, it is possible for a greater proportion of the API to reach the systemic circulatory system, requiring a lower concentration to produce the desired therapeutic effect. Formulations with smaller doses usually result in fewer off-target side effects and are therefore safer for patients to take. Moreover, for APIs that must be administered in relatively large amounts, a boost in bioavailability can significantly reduce the volume or number of doses a patient must take. HME formulation can also be remarkably effective at masking unpleasant tastes of APIs. For example, by adding an excipient that entraps the bitter tasting API into its matrix, thereby reducing the interaction of the API with the taste buds. Collectively, these benefits all promote drug compliance by improving the patient's experience.

Complex dosing strategies may also

be incorporated into drugs manufactured through HME. Specific polymer carriers, such as ethyl cellulose or carnauba wax, can be used to control an API's diffusion rate so that a precise dose is released into the body continuously over days, months, or even years. Elaborate formulations can also be made using polymeric carriers of varying molecular weights combined with low molecular weight sugars, sugar alcohols, and waxes to produce drugs that carry reservoir systems capable of releasing varied amounts of one or more APIs at the same time. Overall, these controlled-release drugs ensure that a patient is receiving a uniform dose of the API while reducing the need for patients to manually control how much of a drug is in their system at a given time.

MANUFACTURING PARTNERS CAN HELP

To facilitate the process of HME formulation, developers can draw on the expertise of a manufacturing partner, such as Avomeen, that is well-versed in the HME technique from start to finish. Developers can save time and money by leveraging the experience of a suitable partner to efficiently select optimal excipients in the formulation that are best suited to a particular API, fine-tune the processing parameters, and develop analytical methods that satisfy regulatory guidelines.

At minimum, a partner's experience in pharmaceutical formulation development should extend to novel drug delivery systems, including HME. A practice of utilizing the Quality by Design (QBD) approach to develop drug products for Investigational New Drug (IND) Applications and Abbreviated New Drug Applications (ANDAs) is also beneficial, as this tactic is meant to create products of the highest quality while minimizing future unexpected problems.[3] Partners should also have knowledge of preformulation testing, including DOE, drug-excipient compatibility testing, wettability and solubility profiling, rheological studies, determination of flow properties, and physicochemical testing of early stage drug product prototypes, such as structural and stability characterization and impurity profiling. Finally, it is advantageous if a manufacturing partner can support the development and validation of analytical methods to test the quality attributes of a new formulation. These methods should be developed and comply with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Food and Drug Administration (FDA) and Current Good Manufacturing Practice (cGMP) guidelines. Important parameters include analytical guidelines for in-process control, release testing, and stability monitoring of pharmaceutical formulations. Together, a developer and a manufacturing partner with a strong understanding of the principles of HME can support successful HME-based drug development from start to finish. ◆

REFERENCES

1. International Conference on Harmonisation (ICH) Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (API), September 2016.
2. Nikolakakis I, Partheniadis I. Self-Emulsifying Granules and Pellets: Composition and Formation Mechanisms for Instant or Controlled Release. Pharmaceutics. 2017;9(4):50. Published 2017 Nov 3. doi:10.3390/pharmaceutics9040050.
3. Patil H, Tiwari RV, Repka MA. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation. AAPS PharmSciTech. 2016;17(1):20-42. doi:10.1208/s12249-015-0360-7.
4. Crowley MM, Zhang F, et al. (2007) Pharmaceutical Applications of Hot-Melt Extrusion: Part I. Drug Development and Industrial Pharmacy, 33:9, 909-926, DOI:10.1080/03639040701498759.
5. Repka MA, Battu SK, et al. (2007) Pharmaceutical Applications of Hot-Melt Extrusion: Part II, Drug Development and Industrial Pharmacy, 33:10, 1043-1057, DOI: 10.1080/03639040701525627.
6. Yu LX, Amidon G, Khan MA, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-783. doi:10.1208/s12248-014-9598-3.

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BIOGRAPHY

Ameya Deshpande is a Formulation Scientist at Avomeen, where he leverages his extensive experience in pharmaceutical formulation development and knowledge of novel drug delivery systems, including hot melt extrusion. He earned his MS in Industrial and Physical Pharmacy from the University of Toledo. He and Avomeen's team of formulators routinely go above and beyond to deliver to clients.

ADVANCED STOPPER SOLUTION

PremiumCoat®: Proven Compatibility With Current Vial Standards

By: Sebastien Cordier, Bruno Morchain, and Estelle Verger

INTRODUCTION

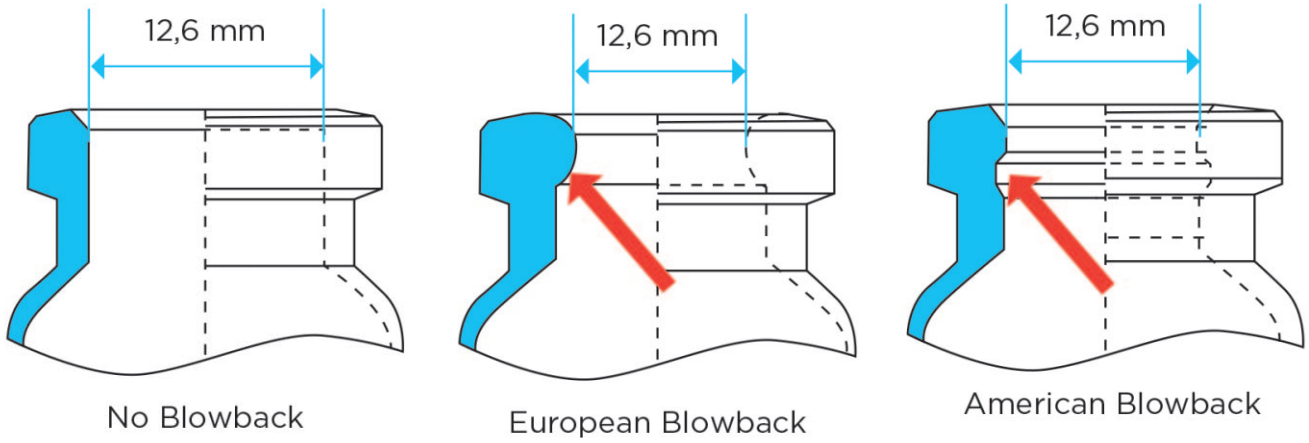
Whether in the development of new drug products and generics or when repurposing existing drugs, the importance of packaging should never be underestimated. An understanding of the materials involved and an awareness of their compatibility is essential to achieve a secure, hospitable environment that protects a drug until it needs to be used.

The primary container, which is in direct contact with the drug product, plays a critical role in preserving the drug's integrity from the initial point of production through to packaging, distribution, short- or long-term storage, and the moment at which it is administered. Any failure associated with the primary container has the potential to result in serious adverse effects for the patient or the healthcare practitioner, which, aside from the human impact, can have significant financial implications for the drug manufacturer.

One of the key functions of the primary container is to maintain closure integrity during the whole life cycle of a drug product. In the case of glass vials - the most common type of primary container for injectable drugs - a key requirement in achieving this closure integrity is the need for seamless compatibility between the glass vial and the rubber stopper.

Even though the dimensions of vials are standardized (ISO8362-1 for manufactured from glass cane and ISO8362-4 for molded glass vials), compatibility issues can still arise, resulting in excessive insertion forces, stoppers accidentally popping off prior to crimping, or container closure integrity being com-

FIGURE 1



Representation of the three main types of vial neck designs: European, and American blowback and non-blowback. The red arrows point out the blowback.

promised. This can lead to significant operational difficulties and even present a risk to patient safety. Selecting the right stopper/vial combination, therefore, is an important choice that can impact both the development of the drug's packaging as well as the filling and finishing operations.

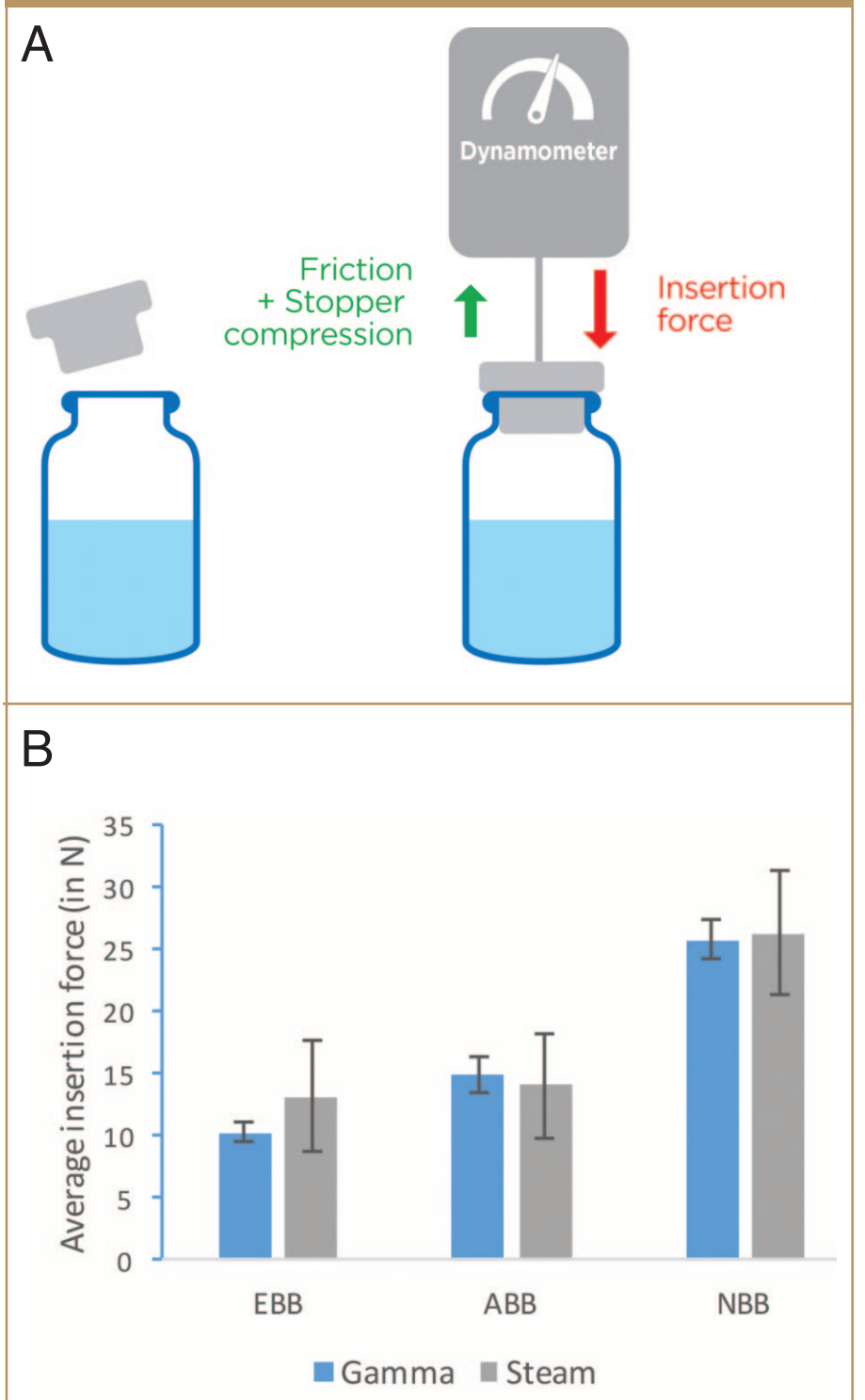
Aptar Pharma's expertise in this area has been developed over 50 years of collaboration with pharma and biotech partners, during which time it has addressed challenges with vaccines, biotech drugs, and small molecules. PremiumCoat®, one of Aptar Pharma's proprietary innovations, combines state-of-the art elastomer formulation with market-proven film-coating technology to create a highly advanced stopper solution. PremiumCoat's unique design has been extensively tested in conjunction with a leading glass supplier to demonstrate compatibility with standard ISO vial designs. For our pharma partners, PremiumCoat can be relied upon to deliver swift packaging validation and regulatory approval.

PREMIUMCOAT: MINIMIZING INSERTION FORCE

The ability to carefully control insertion force is a key factor in promoting operational efficiency and consistency. This is directly dependent on a number of variables, including the dimension of the stopper and vial, the design of the stopper's skirt as well as the hardness of the elastomer. If these parameters are not optimized, the stopper may become difficult to insert, which may hinder the filling line efficacy, or too loosely inserted, which may lead to the stopper accidentally popping off before the crimping stage.

Aptar Pharma's expert team assessed the insertion force of PremiumCoat stoppers on three ISO8362 standard vial neck designs (European blowback, American blowback, and non-blowback, Figure 1) after gamma ray or steam sterilization and after 24 months of aging, which corresponds to the product's shelf-life. The insertion force was measured with a dynamometer while inserting the stopper at a rate of 100 mm/min. The results of the average insertion force (across the aging

FIGURES 2A&B



A: Representation of the experimental set-up and forces involved in stopper insertion. B: Required insertion force of 20 mm PremiumCoat stopper on European blowback (EBB), American Blowback (ABB), and non-blowback (NBB) vial designs. The data were collected after 24-month aging.

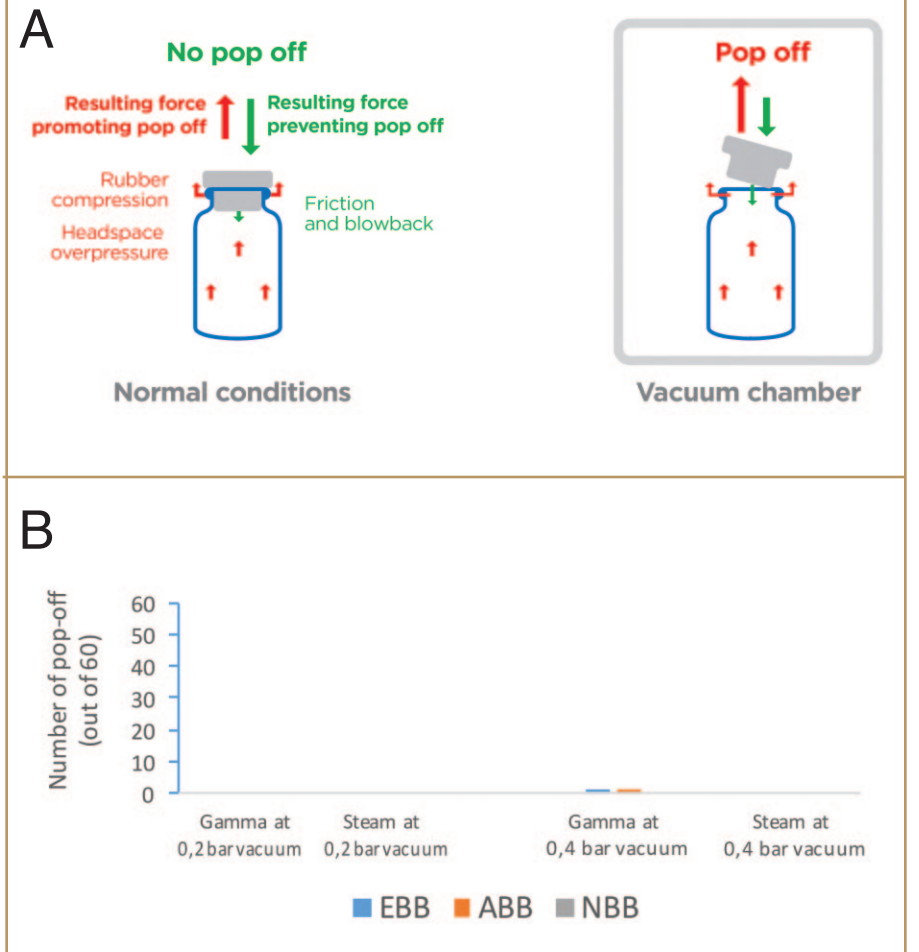
period) are summarized in Figure 2.

The test results show that, for each design, the sterilization method does not significantly affect the insertion force (Figure 2), with European blowback and American blowback showing similar insertion forces. While the insertion force required for the non-blowback vial is higher, it remains largely within the operational capabilities of standard filling line machinery. These results confirm that the design of Aptar Pharma's PremiumCoat stopper allows for easy insertion into standard vials and that the sterilization method does not impact the insertion force required. PremiumCoat stoppers can, therefore, contribute to optimizing operational efficiency and can be sterilized with either steam or gamma methods, without impacting machinability.

PREMIUMCOAT: LIMITING THE RISK OF POP-OFF OCCURRENCES

Once the stopper is inserted into the vial's neck, a number of forces are at work to determine whether it will maintain its position. On the one hand, the insertion of the stopper causes a pressure to build up in the headspace, thus generating a force that pushes the stopper out of the vial's neck. On the other hand, the friction between the glass and the rubber works to hold the stopper in place. Depending on the glass neck and stopper's design, compression of the rubber against the glass may secure the stopper on the neck or push it out. If the forces that maintain the stopper in the neck are too weak (for example, when friction is reduced by the excessive adjunction of silicon), the stopper is dislodged from the vial's neck – an event called "pop-off" – that inevitably leads to the loss of the drug dose on the filling line.

FIGURES 3A&B



A: Representation of the forces involved in pop-off mechanism and of the experimental set-up. B: Number of PremiumCoat 20 mm stopper pop-off events observed when placed on European blowback (EBB), American blowback (ABB), and non-blowback (NBB) vial designs. The experiment was performed in a vacuum chamber at 0,2 and 0,4 bar of vacuum with a sample size of n=60.

The only way to avoid pop-off issues is to test the compatibility of the vial with the stopper. Packaging companies, seeking to further limit the risk of pop-off, have also developed specific "blowback" designs for vials and stoppers. The blowback forms a protuberance and/or notch in the neck of the vial (Figure 1) against which the stopper pushes, generating a mechanical force working against pop-off. While specific stopper designs have been developed to work exclusively with blowback vials, non-specific designs can offer similar levels of performance and work equally well with both standard and blowback vials.

Aptar Pharma's technical teams evaluated how the shape of the PremiumCoat film-coated stopper contributes to reducing the risk of pop-off when used with three standard vial designs. The assessment compared the impact of gamma ray and steam sterilization, with data collected after 24 months of aging. Because no pop-off could be observed in normal conditions (atmospheric pressure), the experimental setting simulated a worst-case scenario by gradually inducing a pressure difference that would favor pop-off events. The results are shown in Figure 3.

The results shown in Figure 3 indicate that at 0.2 bar of vacuum outside the vial, which already represents an abnormal scenario because the pressure difference is pushing the cap out of the vial's neck, no pop-off event was observed regardless of the sterilization method. When the vacuum is further increased, the steam-sterilized stoppers did not suffer from pop-off. For the gamma-sterilized stoppers, only one pop-off was observed for the blowback vial designs and none for the non-blowback design.

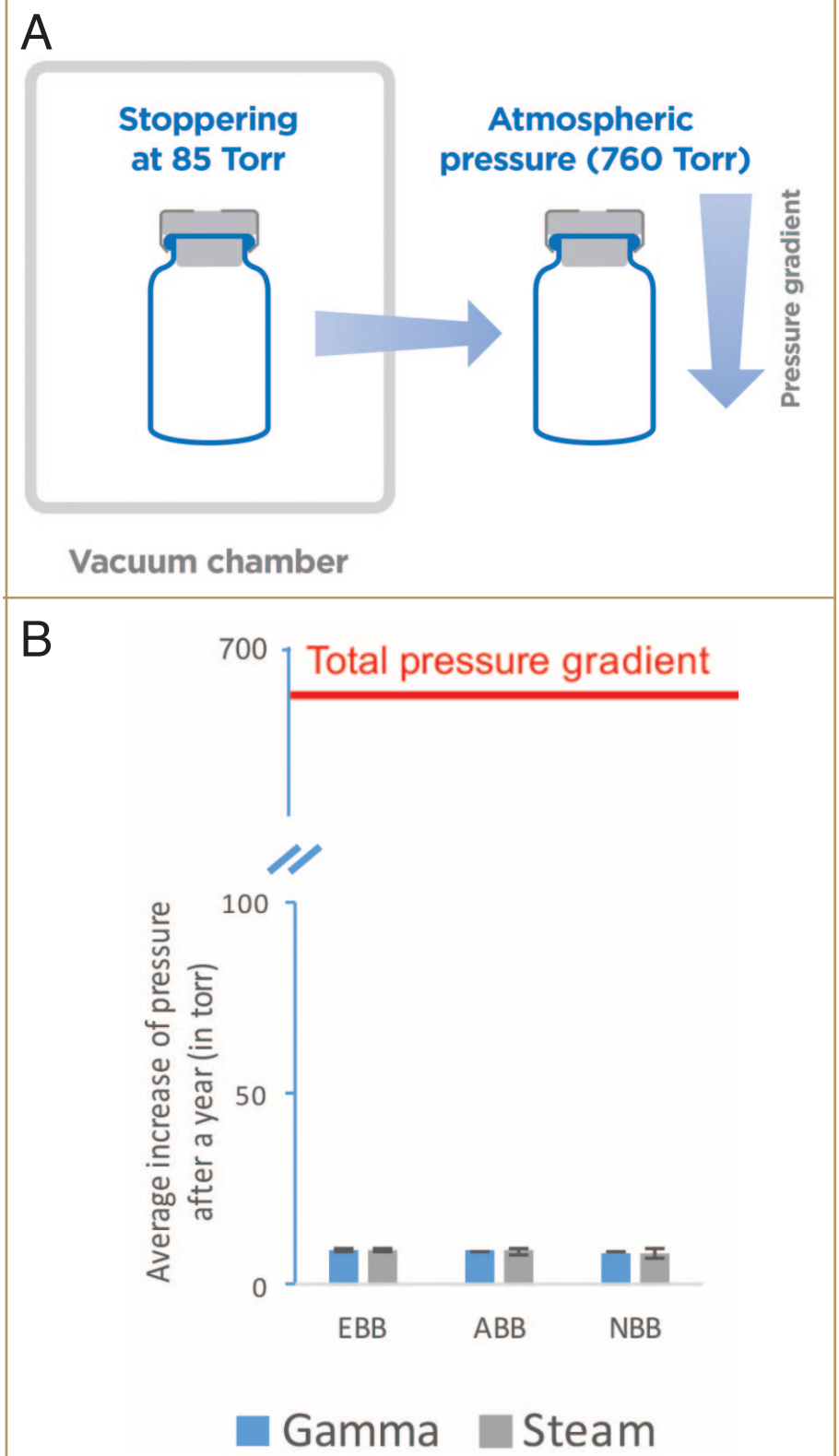
These results demonstrate that, even in sub-optimal conditions in which a depression is working toward increasing the risk of pop-off, Aptar Pharma's PremiumCoat stoppers remained tightly secured on the neck of the vials. As such, regardless of the sterilization method used or the vial's design, PremiumCoat stoppers would maintain the integrity of the drug product on filling lines.

PREMIUMCOAT: MAINTAINING CONTAINER CLOSURE INTEGRITY OVER TIME

Once inserted into the neck of the vial and secured in place with aluminium crimping, the stopper plays a key role in ensuring the container remains tightly closed and preventing any exchanges with the outside environment. This container closure integrity is essential for the conservation of the drug and preventing contamination thus, ensuring patient safety.

Aptar Pharma experts evaluated the ability of PremiumCoat stoppers to maintain container closure integrity. The three different vial designs were stoppered under partial vacuum, and the inner pressure of the vial was measured for up to 1 year to monitor the increase. Though this

FIGURES 4A&B



A: Representation of the experimental set-up. The data were collected using near infrared spectroscopy to measure the pressure and moisture within the headspace of the vial. B: Evaluating the container closure integrity with PremiumCoat 20 mm stoppers inserted in European blowback, American blowback, and non-blowback vials. The data are represented as the average increase of pressure within the vial after one year for stoppers placed on each vial's design. The stoppers are sterilized by steam or gamma ray methods. The Y-axis scale represents the total pressure difference (675 Torr) between the outside (760 Torr) and inside (85 Torr) of the vial.

strategy represents an extreme case compared with a situation in which the vial's inner pressure is closer to atmospheric pressure, it provides the means to identify any potential defects in container closure integrity. Similar experiments were repeated to evaluate the impact of the sterilization method on container closure integrity.

The results shown in Figure 4 indicate that, even when the stopper has reached the end of its shelf life (2 years of aging) and regardless of the neck design or the sterilization method, the vial pressure increased by less than 10 Torr over 1 year. This differential corresponds to less than 1.5% of the total pressure difference (675 Torr) between the outside (760 Torr) and inside (85 Torr) of the vial, and could be attributed to the natural permeability of Bromobutyl elastomer. Experience tells us that significant leaks result in a fast increase of the inner pressure of the flask (several hundred Torr) within hours or days.

In demonstrating its efficiency at maintaining container closure integrity over the product life cycle and independently of the sterilization method chosen, it can be concluded that Aptar Pharma's PremiumCoat is a proven, versatile solution for enhancing the protection of a drug during storage.

PREMIUMCOAT: DEMONSTRATING COMPATIBILITY WITH STANDARD VIALS

Across these extensive testing strategies, Aptar Pharma's PremiumCoat proved to be compatible with the three main vial standards and the two main sterilization methods. In all situations, PremiumCoat was found to be an efficient and reliable solution for pharma partners by:

- Promoting operational efficiency regardless of vial design or sterilization method
- Protecting the drug on the filling lines by preventing the stopper from popping-off the vial's neck
- Preserving drug product integrity during its storage by maintaining container closure integrity ◆

REFERENCES

Data source: Aptar Pharma internal report, 2020, [#TR20-0204], Villepinte, France

BIOGRAPHIES

Sébastien Cordier is the Technical Product Manager for PremiumCoat projects at Aptar Pharma's Injectables division. A graduate of MINES ParisTech and EDHEC Business School in France, he first spent over 15 years in the automotive industry, where he developed a strong expertise in plastics and elastomers, before joining Aptar Pharma in 2020. In his current role as Technical Product Manager at Aptar Pharma, he is responsible for the PremiumCoat platform of vial stoppers and syringe plungers, and is dedicated to supporting customer development projects involving coated elastomeric solutions.

Bruno Morchain is Manager of the Technical Center in Villepinte, France, for Aptar Pharma's Injectables division. A graduate in Mechanical Engineering from the University of Technology of Compiègne, he has over 18 years of experience in the pharmaceutical industry. He joined Aptar Pharma in 2012 as a Technical Support Engineer, where he was in charge of supporting customers on elastomeric primary packaging selection, validation, filing, and use during the product life cycle. In 2018, he became Technical Center Manager, where he leads a technical team involved in developing new products, evaluating their performance and conducting studies to support customers and their projects.

Estelle Verger is the Business Development Senior Manager for PremiumCoat-coated solutions for Aptar Pharma's Injectables division, and is responsible for the growth of the PremiumCoat platform in the global injectable market. A graduate from ESSEC Business School and Fachhochschule Dortmund, with a Masters degree in International Business Management, she joined Aptar Pharma in 2011 as a Sales Manager, Injectables. She then moved to Aptar Pharma's Consumer Healthcare division as a Product Manager, where she was responsible for Airless Dispensing Solutions for pharmaceutical applications for a number of years, before returning to the Aptar Pharma Injectables division in 2020.

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