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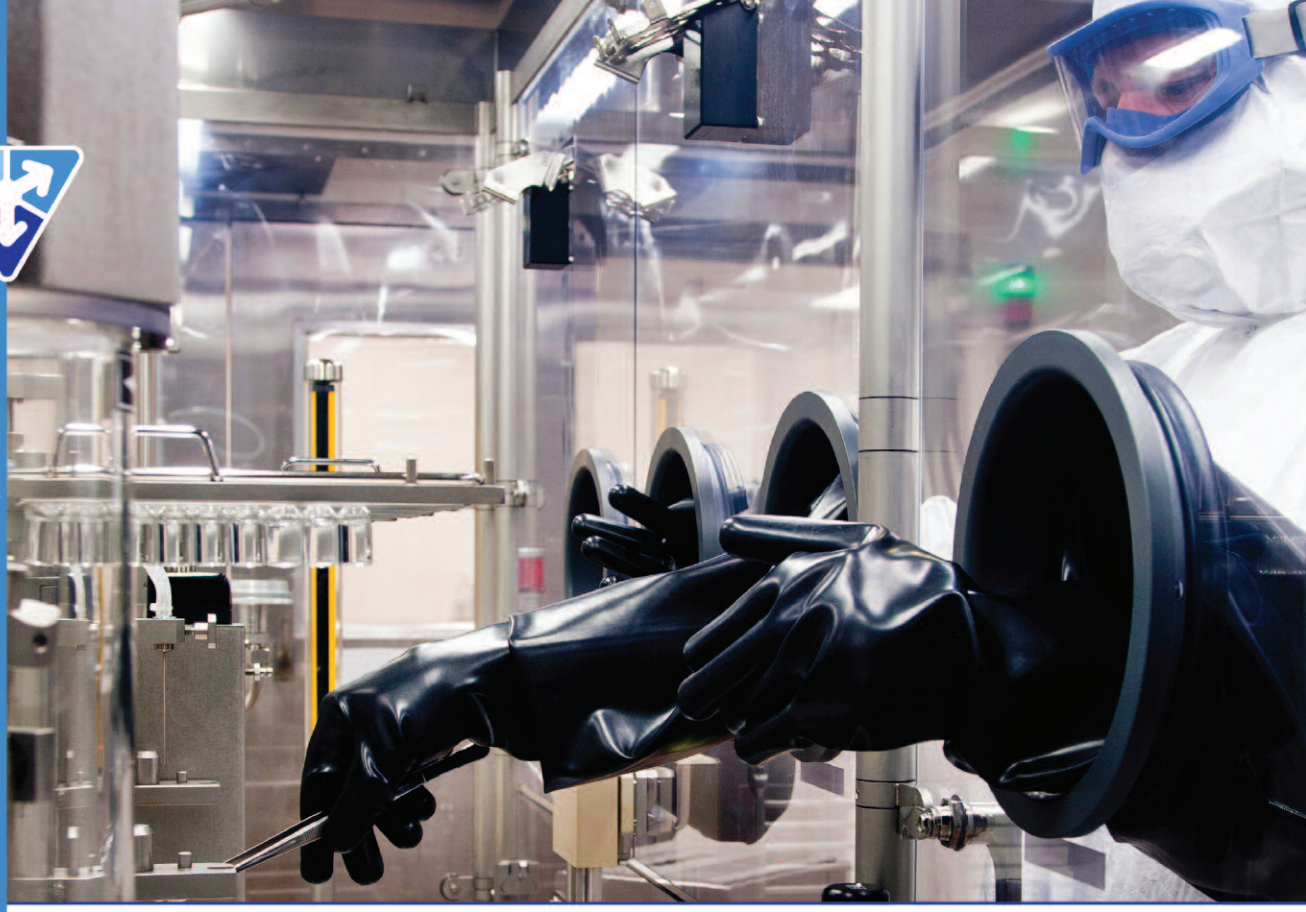

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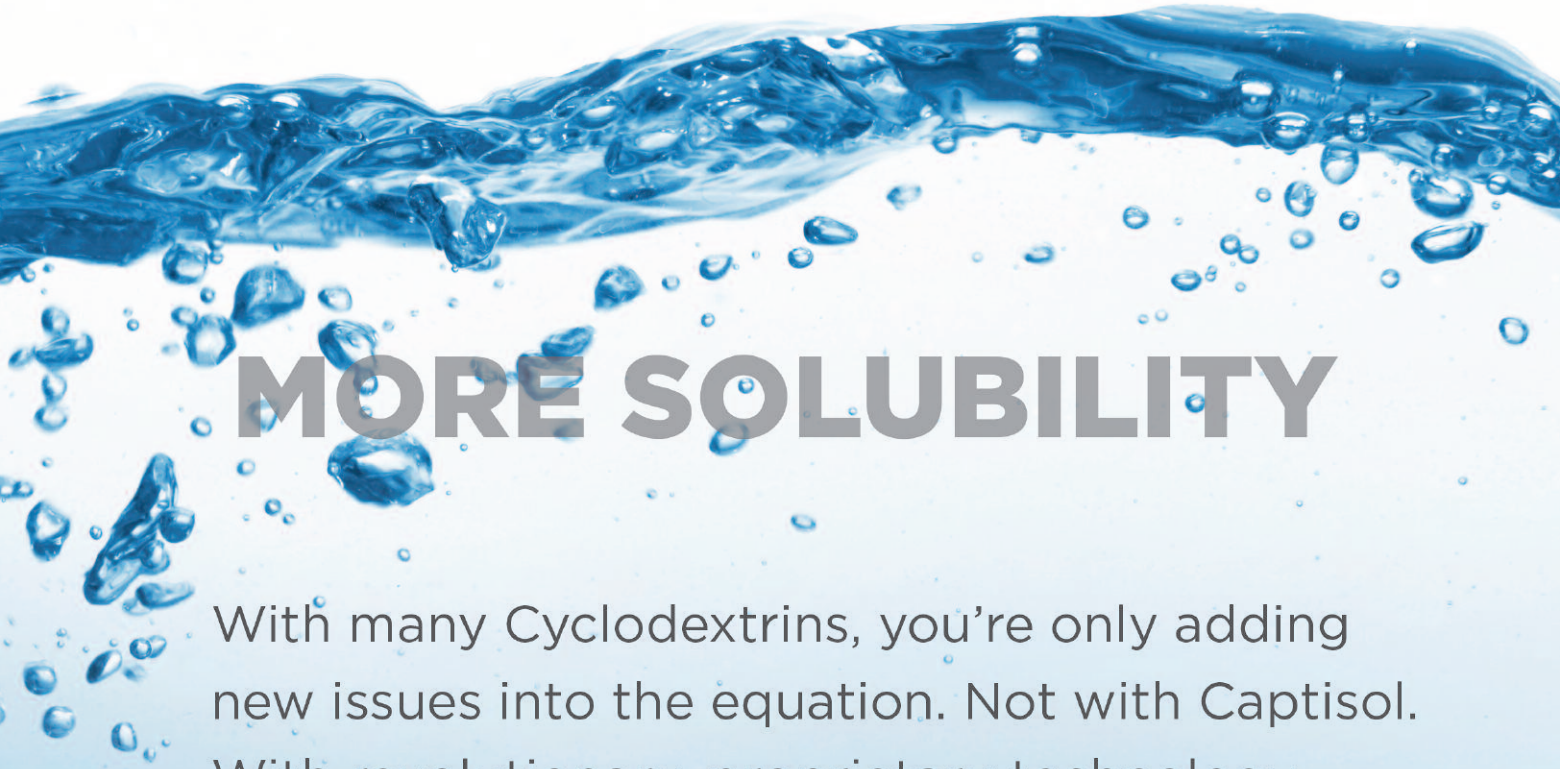

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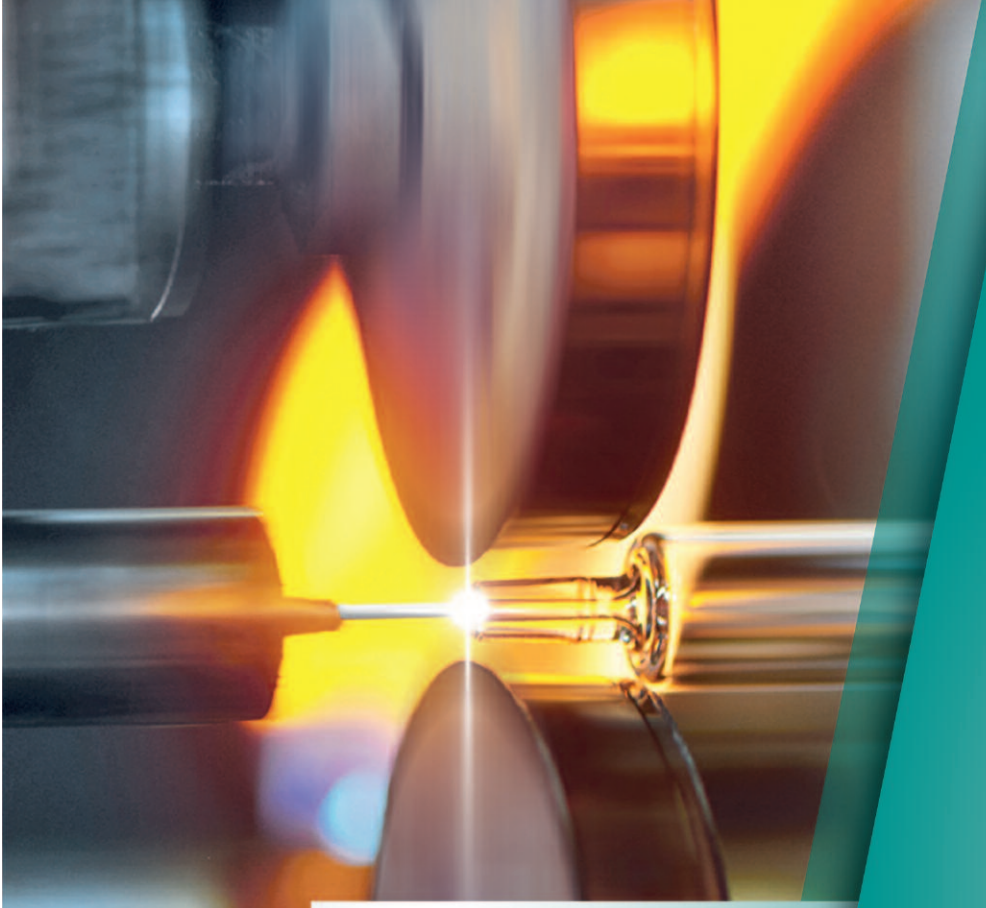

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Enteris Biopharma Doses First Woman in Phase 2a Clinical Trial

Enteris BioPharma, Inc., a biotechnology company developing innovative drug products built around its proprietary delivery technologies, recently announced the first woman has been dosed in its Phase 2a clinical trial to evaluate Ovarest, an oral formulation of leuprolide, for the treatment of endometriosis. Ovarest was developed utilizing Enteris' proprietary Peptelligence platform, a novel formulation technology that enables oral delivery of molecules that are typically injected, including peptides and BCS class II, III and IV small molecules.

Ovarest represents Enteris' most clinically advanced internal product candidate and underscores Enteris' rapidly advancing clinical development pipeline targeting underserved patient populations in women's health. The Phase 2a trial is designed as a randomized, open-label, parallel-group, active-control Phase 2a pharmacokinetics (PK)/pharmadynamics (PD) study in 32 healthy female volunteers. The study will determine the safety and evaluate the PK/PD metrics of two different oral doses of Ovarest in comparison to the leuprolide formulation approved for the treatment of endometriosis, Lupron Depot 3.75 mg, a monthly intramuscular injection.

"Initiation of the Ovarest Phase 2a clinical trial is a significant milestone for Enteris and underscores our commitment to building an internal product pipeline of innovative oral therapeutics that address underserved medical needs in women's health," said Joel Tune, Chief Executive Officer and Executive Chairman of Enteris BioPharma. "Endometriosis affects nearly six million women in the United States, and there have been few advancements in the space to provide these women with more patient-friendly treatment options. Ovarest has the potential to become a high-value and broadly adopted therapeutic for the treatment of endometriosis, and together with Tobrate, demonstrates the capabilities of our Peptelligence platform to transform currently available injectable drugs into patient-friendly oral formulations."

Since its founding in 2013, Enteris BioPharma has advanced multiple internal and external programs leveraging its Peptelligence platform. The technology has been developed and proven effective over the last decade to enable the safe delivery of peptide-based therapeutics and other molecules with low oral bioavailability. In addition to its internal development pipeline, Enteris' oral peptide delivery technology is the subject of several active external development programs, the most advanced of which include Tarsa Therapeutics' TBRIA, an oral calcitonin for patients with postmenopausal osteoporosis and Cara Therapeutics'' CR845, a potent peripheral kappa opioid receptor agonist. In January 2017, Enteris entered into separate agreements with Sanofi, Ferring Pharmaceuticals, and KeyBioscience AG (a fully owned subsidiary of Nordic Bioscience) to develop oral tablet formulations of peptide therapeutics owned by each company.

Enteris BioPharma, Inc. is a privately held, New Jersey-based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. The Company's proprietary oral delivery technology Peptelligence has been the subject of numerous feasibility studies and active development programs, several of which are in late stage clinical development.

Jupiter Orphan Therapeutics Receives Orphan Drug Designation

Jupiter Orphan Therapeutics, Inc. recently announced it has received notification from the US Food and Drug Administration (FDA) that its Orphan Drug Designation request for trans-Resveratrol has been granted.

"Orphan Drug Designation serves as an important milestone for JOT as it positions our JOTROL product as a potential treatment for FA. We are hopeful that JOTROL can ultimately provide a meaningful treatment for FA patients around the world based on the earlier Phase II trial, utilizing resveratrol, conducted by our partner Murdoch Children's Research Institute, Melbourne, Australia ("MCRI"). That trial was an open label trial and generated very encouraging results, where 4 out of 5 very important endpoints were met. We, JOT together with MCRI, expect to repeat these results through a larger placebo controlled study utilizing JOTROL to avoid the Gastro Intestinal (GI) tolerability issues. This will hopefully lead to market approval in several territories, including USA" said Chief Executive Officer, Christer Rosén of JOT.

JOT has developed a unique patented formulation of trans-resveratrol called JOTROL. JOTROL is expected to deliver the well documented high amount of resveratrol in blood plasma that is required to achieve therapeutic effects. These high doses have earlier been plagued with severe GI-side effects that has stopped utilization of resveratrol in the pharmaceutical field. JOT is expecting, based on very successful pre-clinical data, that resveratrol administration in the JOTROL formulation will deliver the necessary levels of resveratrol in plasma without generating any severe GI side-effects.

Friedreich's Ataxia (FA) is a rare inherited disease that causes damage to the nervous system as well as diminished mobility. FA usually begins in childhood and leads to impaired muscle coordination (ataxia) which worsens over time. It is caused by a defect (mutation) in a gene Frataxin (FXN). Friedreich's ataxia is recessive, meaning it only occurs in someone who inherits two defective copies of the gene, one from each parent. Although rare, FA in the most common form of hereditary ataxia, affecting about 1 in 50,000 people in the United States. There are no approved treatments available today. Visit the FARA (Friedreich's Ataxia Research Alliance) website, www.curefa.org, for further details on this rare disease.

Jupiter Orphan Therapeutics, Inc. (JOT) is a clinical stage specialty pharmaceutical company developing therapies for rare diseases. JOT, a Delaware Corporation with its principal office located in Jupiter, FL, USA, was founded in the summer of 2015. In its short period of operations, JOT has assembled a very strong management and scientific team, developed JOTROL as a platform product to treat multiple rare diseases as well as collaborating with established partners in other disease areas. For more information, visit www.jupiterorphan.com.

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Mateon Therapeutics Announces Results from Second Interim Analysis of CA4P Phase 2/3 FOCUS Study

Mateon Therapeutics, Inc. recently announced results from its second scheduled interim analysis of the ongoing Phase 2/3 FOCUS study evaluating CA4P in combination with bevacizumab (Avastin) and physician's choice chemotherapy in patients with platinum-resistant ovarian cancer (prOC).

FOCUS is designed to evaluate whether the addition of CA4P improves progression-free survival (PFS), the primary endpoint of the study, as well as objective response rate (ORR) and other measures. All patients enrolled in the FOCUS study are receiving either CA4P or placebo plus the current standard-of-care for platinum-resistant ovarian cancer, bevacizumab (Avastin) and chemotherapy. The current interim analysis is based on initial results from the first 40 patients (19 with CA4P, 21 with placebo) in the study who have been treated for at least 2 months or discontinued from the trial. A total of 91 patients have been enrolled in the Phase 2 portion of FOCUS. The next (third) interim analysis will be conducted when approximately ¾ of the enrolled patients (originally targeted at 80) have been treated for at least 2 months or discontinued from the study.

"We are encouraged that early data on the primary endpoint of the study continue to favor CA4P and that our investigational drug remains well tolerated," said William D. Schwieterman, MD, President and Chief Executive Officer. "There is a large unmet medical need in the ovarian cancer market as patients with prOC have low survival rates and few treatment options. We look forward to additional and more mature data from the third interim analysis expected just over 1 month from now – in this upcoming analysis, we will have more data on the current patients, who will have had additional time under treatment, as well as initial efficacy and safety information on approximately 25 additional patients."

PFS, the primary endpoint of the study, continues to favor the CA4P group, with a 1.68-month increase in median PFS for the patients receiving CA4P compared to control (6.64 months vs. 4.96 months; HR=0.68; p=0.456). Progression events are available from 16 of 40 (40%) patients: six patients (31.6%) in the CA4P arm and 10 (47.6%) patients in the control arm progressed or died while in the study.

Partial responses were observed in 4 of 16 (25.0%) patients treated with CA4P and 6 of 19 (31.6%) patients treated with the control regimen. Stable disease was observed in 9 of 16 (56.3%) patients treated with CA4P compared to 11 of 19 (57.9%) patients treated in the control arm.

CA4P continues to show a favorable safety profile. Most patients receiving CA4P experienced transient increases in blood pressure (BP) compared to the control arm (57.9% vs. 9.5%, respectively). BP increases generally peaked 2 hours following treatment and normalized without clinical sequelae 2 to 3 hours later. Rates of grade 3 hypertension were similar between the treatment and control arms (21.1% vs. 23.8%). There was one case of grade 4 hypertensive crisis in the CA4P arm. Adverse events that occurred in >25% of patients and more frequently in the treatment arm included nausea, fatigue, cough, and hypertension, most of which were mild to moderate in severity. Rates of neutropenia, anemia, and thrombocytopenia were low and similar between treatment arms.

Mateon Therapeutics, Inc. is a biopharmaceutical company seeking to realize the full potential of vascular targeted therapy (VTT) in oncology. VTT includes vascular disrupting agents (VDAs), such as the investigational drugs that Mateon is developing, and anti-angiogenic agents (AAs), a number of which are FDA-approved and widely used in cancer treatment. These two approaches have distinct yet complementary mechanisms of action.

Mateon believes it can significantly improve cancer therapy by employing these two complementary approaches simultaneously. When utilized this way, VDAs obstruct existing blood vessels in the tumor leading to significant central tumor cell death while AAs prevent the formation of new tumor blood vessels.

WuXi's Pharmaceutical Development Services Division Merges With STA

STA Pharmaceutical Co., Ltd. – a WuXi AppTec group company and the leading open-access capability and technology platform for small molecule pharmaceutical development and manufacturing – recently announced it has merged with WuXi AppTec's Pharmaceutical Development Services (PDS) division.

The PDS division offers preformulation development, formulation development, as well as Clinical Trial Material (CTM) manufacturing, packaging, and labeling of oral solid dosage forms, including tablets, capsules, sachets, and oral solutions/suspensions. PDS also established various enabling technology platforms for low-soluble drugs, including spray-dried dispersions, hot-melt extrusion, micro- or nanosuspensions, and liquid-filled hard gelatin capsules. Two commercial-scale drug product manufacturing facilities currently under construction are expected to become operational later this year and early next year, respectively.

STA Pharmaceutical, after this merger, will provide fully integrated small molecule Active Pharmaceutical Ingredient (API) and drug product solutions to global clients, resulting in a seamless Chemistry, Manufacturing and Control (CMC) working process. The merger enables STA to advance New Chemical Entities from preclinical stage to New Drug Application (NDA) and to market faster and more efficiently for pharma and biotech customers.

This development enhanced STA's end-to-end capabilities as a full-service Contract Development and Manufacturing Organization (CDMO), and it anticipates rapid growth in clinical trial supply, especially amongst early stage targets, where there are practical benefits in working with one CDMO.

Dr. Minzhang Chen, CEO of STA Pharmaceutical, commented "STA has been growing rapidly over the past few years. It was a natural progression for the company to add drug product to our API platform in which we are globally renowned."

"The merging of the PDS division into STA is an important step for WuXi," added Dr. Ge Li, Chairman and CEO of WuXi AppTec. "Providing API and drug product services under one STA entity further strengthens WuXi's comprehensive CDMO offering. Ultimately, our platforms advance vital new medicines through the development cycle faster, allowing our global partners to discover and develop better medicines for patients."

STA Pharmaceutical Co., Ltd. (STA), a WuXi AppTec company, is a leading small molecule pharmaceutical development and manufacturing capability and technology platform company serving the life science industry, with operations in China and the United States. STA offers our worldwide partners efficient, flexible and high-quality solutions for small molecule Active Pharmaceutical Ingredients (APIs) and finished dosage forms.

WuXi AppTec is a leading global pharmaceutical, biopharmaceutical, and medical device open-access capability and technology platform company with global operations. As an innovation-driven and customer-focused company, WuXi AppTec provides a broad and integrated portfolio of services to help our worldwide customers and partners shorten the discovery and development time and lower the cost of drug and medical device R&D through cost-effective and efficient solutions.

PolyPid Completes Enrollment in Phase Ib/II Study of D-PLEX

PolyPid Ltd. recently announced the completion of enrollment in its Phase Ib/II study of D-PLEX (Doxycycline/Polymer-Lipid Encapsulation Matrix), the company's lead product candidate, for the prevention of post-cardiac surgery sternal infection. D-PLEX is a secured antibiotic drug reservoir that provides a safe and effective local anti-bacterial prevention and treatment measure during surgical procedures.

Sternal infection following cardiac surgery is an unmet medical need and one of the most significant complications following open cardiac surgery, which, according to known literature, has a mortality rate of up to 40%.

The Phase Ib/II study of D-PLEX is a prospective, multi-center, two-part trial evaluating the safety and efficacy of D-PLEX in the prevention of sternal infection post-cardiac surgery. The study is being conducted in Israel on a total of 80 patients. PolyPid expects first line data on all patients in this trial to be available by the end of 2017. The company intends to seek regulatory approvals in the US and Europe in 2018 to conduct a Phase III trial of D-PLEX in prevention of post-cardiac surgery sternal infection.

To date, PolyPid has treated more than 100 patients with its PLEX based anti-infective products. Preliminary data from studies in orthopedic indications showed no infections in the treated organ. Moreover, D-PLEX was safe with no adverse events related to the product.

"The completion of enrollment in our Phase Ib/II study for our lead product candidate, D-PLEX, represents a key accomplishment for our company," said Amir Weisberg, PolyPid's Chief Executive Officer.

"Based on the data generated to date, including its potential effectiveness against resistant bacteria, we believe D-PLEX has the potential to be a safe and effective treatment for the prevention of post-cardiac surgery sternal infection, as well as in other surgical indications. We look forward to the availability of data from all patients in this study by the end of the year, as well as initiating a Phase III clinical trial of D-PLEX in 2018," added Dr. Noam Emanuel PolyPid's Chief Technology Officer.

PolyPid previously completed a successful pre-Investigational New Drug Application meeting with the US FDA in which the FDA agreed that D-PLEX can move directly into a Phase III trial in the US, based on satisfactory results from the ongoing Phase Ib/II study. In addition, the FDA agreed that D-PLEX would be reviewed under the 505(b)(2) approval pathway. D-PLEX was also recently designated as a Qualified Infectious Disease Product (QIDP) by the FDA, enabling the company to take advantage of certain incentives, including FDA priority review, eligibility for fast-track status and an additional 5 years of market exclusivity when marketing approval is granted for D-PLEX in preventing post-cardiac surgery sternal infection.

Monsanto & ToolGen Announce Global Licensing Agreement

Monsanto Company and ToolGen, Inc. recently announced the companies have reached a global licensing agreement for the use of ToolGen's CRISPR technology platform to develop agricultural products.

ToolGen is an early pioneer in gene-editing research. The license provides Monsanto with access to ToolGen's comprehensive suite of CRISPR intellectual property for use in plants. This agreement further expands Monsanto's broad portfolio of gene-editing tools that can be used to develop improved and sustainable crops.

"We are excited to bring ToolGen's CRISPR platform on board at Monsanto, and are continuing to bolster and diversify our capabilities in this field of research," said Tom Adams, PhD, Vice President of Biotechnology for Monsanto. "As a company, we remain committed to the development of safe, sustainable, and high-quality crops, and look forward to leveraging the CRISPR platform as we endeavor to meet the needs of farmers while answering consumer demand for food options."

In order to grow more using less, farmers need a variety of seed choices to solve their local needs – like managing changing weather, fighting plant disease, and pests, and using crop inputs and natural resources wisely. The companies noted that gene-editing technologies, like CRISPR, offer agriculture researchers significant advantages over existing plant breeding and biotechnology methods due to their versatility and efficiency, and will allow Monsanto to provide farmers with solutions to problems that have been previously unaddressed.

"We are pleased to announce our agreement with Monsanto, a global agriculture leader, and look forward to working together to build new and exciting opportunities in agriculture," said Jongmoon Kim, Chief Executive Officer of ToolGen. "This agreement further validates our platform and demonstrates the value that gene editing will hold for the future of both agriculture and biotechnology."

Monsanto is committed to bringing a broad range of solutions to help nourish our growing world. We produce seeds for fruits, vegetables, and key crops - such as corn, soybeans, and cotton - that help farmers have better harvests while using water and other important resources more efficiently. We work to find sustainable solutions for soil health, help farmers use data to improve farming practices and conserve natural resources, and provide crop protection products to minimize damage from pests and disease. Through programs and partnerships, we collaborate with farmers, researchers, nonprofit organizations, universities and others to help tackle some of the world's biggest challenges. For more information, visit monsanto.com.

ToolGen, Inc. is a biotechnology company focused on the development and application of genome-editing technologies. It creates and holds intellectual property rights for essential tools and technologies for editing the genetic information in microbial, plant, animal, and human cells. ToolGen's mission is to translate the potential of our innovative platform technology into transformative products for biomedicine and agriculture. For more information, visit www.toolgen.com.

Bellerophon Announces FDA Agreement on Phase 2b Study Design

Bellerophon Therapeutics, Inc. recently announced agreement with the US FDA on the Phase 2 study design for INOpulse in pulmonary hypertension associated with Interstitial Lung Disease (ILD).

The company met with the FDA in June 2017 to present positive results from its recently completed Phase 2a study in idiopathic pulmonary fibrosis (IPF), and to review clinical plans for its Phase 2b trial, entitled iNO-PF, in IPF as well as other pulmonary fibrosing diseases within ILD. Subsequently, the agency has accepted the company's proposed Phase 2b study design as well as an Investigational New Drug (IND) application to assess the effect of INOpulse on patients at both low- and high-risk for pulmonary hypertension associated with pulmonary fibrosis.

The FDA recognized the dual mode of action of vasodilation and ventilation/perfusion matching of pulsed iNO therapy, which the company believes can provide a clinically important benefit to a wide range of patients, including those that may not exhibit signs of pulmonary hypertension at rest.

"We are very pleased to have concordance with the FDA on our iNO-PF Phase 2b trial for INOpulse in ILD and to have a finalized plan to move forward with this important trial," said Fabian Tenenbaum, Chief Executive Officer of Bellerophon Therapeutics. "The proprietary targeted delivery and the dual mode of action of INOpulse may allow it to be used in pulmonary fibrosing diseases where systemic vasodilators have proven to be ineffective. The lack of approved therapies for pulmonary hypertension associated with interstitial lung diseases represents a unique opportunity to develop a new therapy in this serious and significant unmet medical need."

The iNO-PF Phase 2b study design is based on the results of the prior Phase 2a study for INOpulse in the treatment of Pulmonary Hypertension associated with Idiopathic Pulmonary Fibrosis (PH-IPF), presented at the American Thoracic Society (ATS) International Conference on May 21, 2017. This Phase 2a study met its primary endpoint, showing an average of 15.3% increase in blood vessel volume ($p<0.001$). There was a significant association between ventilation and vasodilation, demonstrating the ability of INOpulse to provide targeted selective delivery to well ventilated sections of the lung. The study also showed consistent benefit in hemodynamics and exercise capacity, with a clinically meaningful reduction of 14% in systolic pulmonary arterial pressure (sPAP) and an average improvement of 75 meters in 6-Minute Walk Distance.

The iNO-PF trial is planned for 2018 and is designed to recruit 40 subjects diagnosed with pulmonary fibrosis, half of which are at intermediate to high risk of pulmonary hypertension as determined by echocardiography. Importantly, the FDA has agreed to a Phase 2b design that eliminates the need for right heart catheterization, an invasive procedure that can present significant challenges for potential study participants.

To support the progress of its program for INOpulse in the treatment of ILDs, Bellerophon has formed a Scientific Advisory Committee chaired by Dr. Steven D. Nathan (Inova Fairfax Hospital) as well as Dr. Ganesh Raghu (University of Washington), Dr. Kevin Flaherty (University of Michigan), Dr. Marilyn K. Glassberg Ceste (University of Miami), Dr. Jeffrey Swigris (National Jewish Health – Denver) and Dr. Lisa Lancaster (Vanderbilt University Medical Center).

Heart Failure Market to Surpass $16 Billion by 2026

The heart failure space across the seven key markets of the US, France, Germany, Italy, Spain, the UK, and Japan is set to grow from $3.7 billion in 2016 to around $16.1 billion by 2026, representing an impressive compound annual growth rate of 15.7%, according to research and consulting firm GlobalData.

The company's latest report, PharmaPoint: Heart Failure - Global Drug Forecast and Market Analysis to 2026, states that the strongest driver of this rise in market value will be the growing uptake of Novartis' Entresto over the forecast period, despite initial modest sales. Other drivers will include the launch of several chronic heart failure therapies, including Amgen and Cytokinetics' omecamtiv mecarbil, and an increase in the global prevalence of chronic heart failure and incidence of acute heart failure.

Elizabeth Hamson, PhD, Healthcare Analyst for GlobalData, explains "Over the past 2 decades, chronic heart failure therapies have demonstrated success in slowing the progression of the disease and in reducing both mortality and morbidity in large-scale clinical trials. However, these successes have been limited to heart failure with reduced ejection fraction (HF-REF), showing only moderate benefits in heart failure with preserved ejection fraction (HF-PEF). Despite the lack of strong clinical evidence, guideline-recommended HF-REF therapies are widely used to treat HF-PEF. Based on this, drug developers have historically only targeted HF-REF in their drug strategies. With HF-PEF on the rise, however, this patient cohort represents a lucrative opportunity for pharmaceutical companies such as Novartis, which recently launched its first-in-class angiotensin receptor-neprilysin inhibitor Entresto in the US for HF-REF, and is currently conducting late-stage trials of the drug in HF-PEF patients."

GlobalData anticipates Entresto's label expansions to HF-PEF to be approved in 2020, which will boost the drug's uptake dramatically. Due to the lack of evidence-based therapies for HF-PEF, if Entresto proves to be efficacious in this patient, it will help Novartis further penetrate the heart failure market, undoubtedly benefitting the company immensely.

Hamson concludes "Although it is thought that Entresto will fulfill a major unmet need over the forecast period, it is important to acknowledge that others will remain. For example, effective treatment of patients with multiple comorbidities, particularly those with renal impairment, will remain elusive. GlobalData does not expect this unmet need to be fulfilled during the forecast period, although the recent FDA approval of several potassium-binding agents to treat hyperkalemia may relieve the burden of this unmet need to a slight extent."

GlobalData's mission is to help our clients decode the future to be more successful and innovative across a range of industries, including the healthcare, consumer, retail, financial, technology and professional services sectors. Please get in contact if you have any questions about this or other GlobalData products. Analysts are available to comment.

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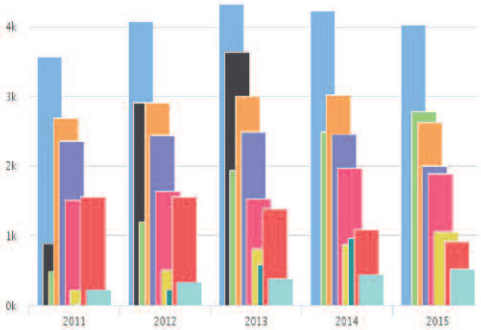

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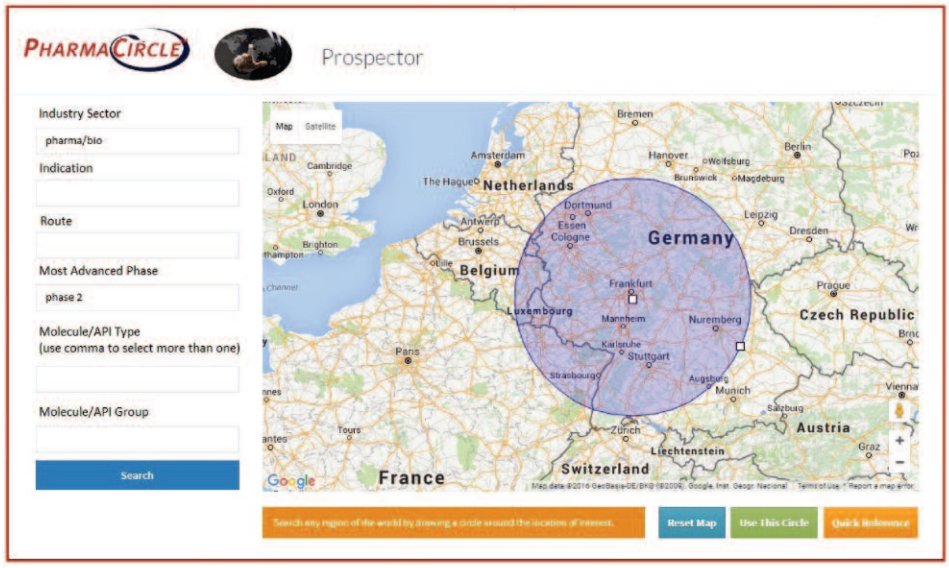

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PHARMACEUTICAL PACKAGING

How Advances in Pharmaceutical Packaging Are Better Meeting Patients' Needs

By: Detlev Haack, PhD, and Martin Koeberle, PhD

INTRODUCTION

The pharmaceutical industry is increasingly recognizing the needs of individuals who experience difficulties taking conventional tablets, and is responding with products that are easier to swallow and more convenient to take. Alternative oral dosage forms, such as orally disintegrating granules (ODGs), instant drinks, lozenges, and chewable and effervescent tablets, are becoming increasingly popular with consumers. But there is little point in formulating more user-friendly dosage forms if the packaging they come in is difficult to open or does not easily integrate into consumers' daily lives.

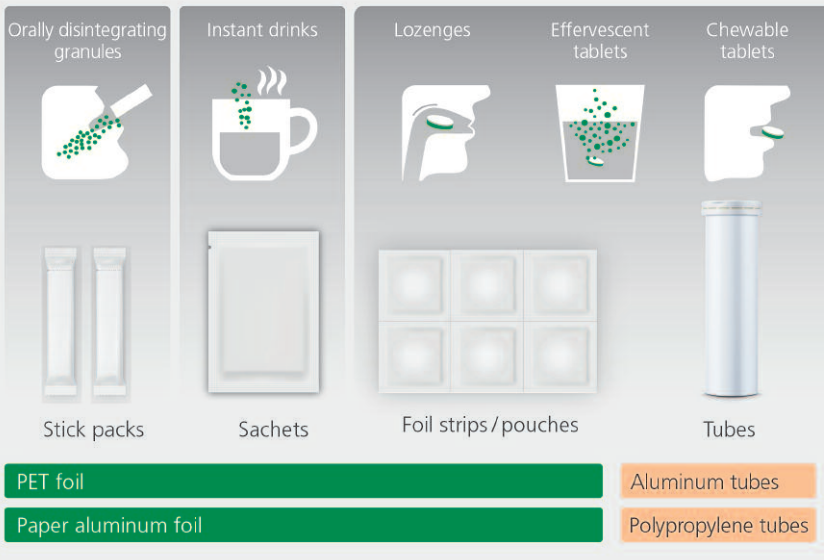
Recent advances in packaging design, materials, and technologies mean that today, there is a wide variety of user-friendly primary and secondary packaging options to choose from. Most importantly, the packaging must fulfill its primary purpose – to protect the medicine it contains. However, beyond this is a wealth of other considerations. The design elements that make packaging more convenient to open and accessible, for elderly people for example, need to be carefully balanced with child-resistant mechanisms, anti-tamper devices, and other safety features. Additionally, packaging plays an important role in shaping the product-customer relationship, and can be a way of building brand identity and boosting product value. So, what are the key packaging considerations for pharmaceutical companies when bringing a user-friendly dosage form to market?

PRODUCT PROTECTION

One of the most important functions of packaging is to shield products from the damaging effects of the external environment. Many formulations become unstable when exposed to air, moisture, or light, and therefore protection from these factors is necessary to ensure medicines remain effective and safe.

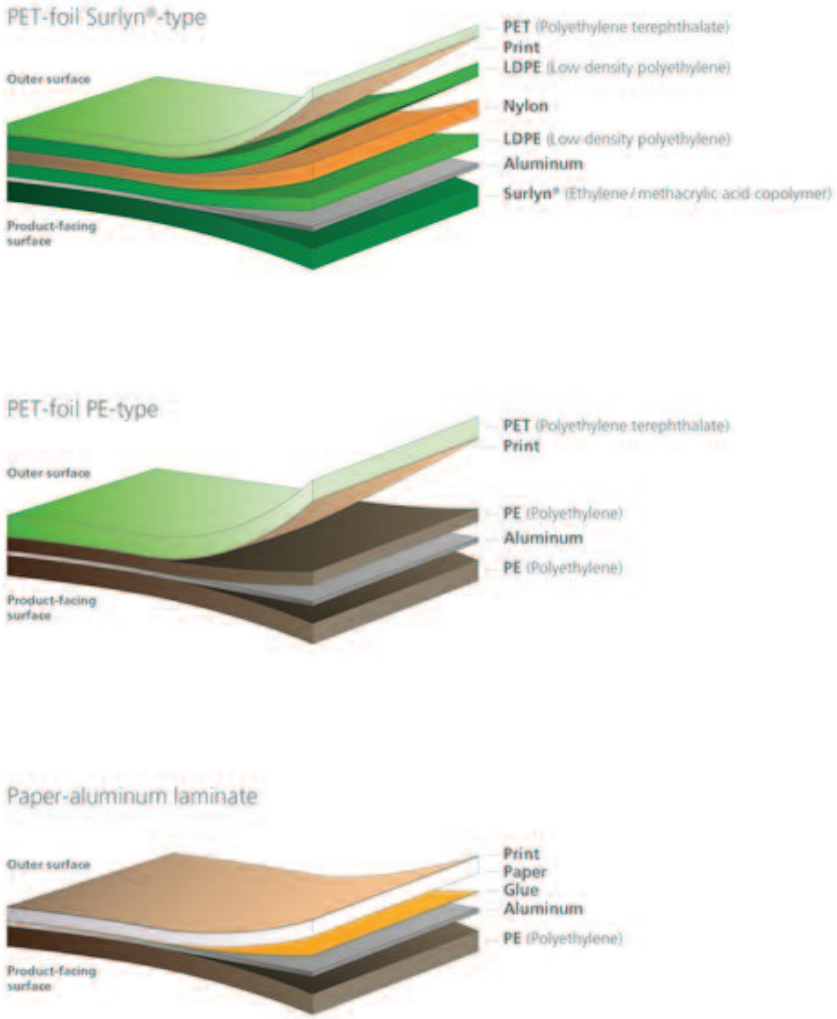
For user-friendly dosage forms, such as instant drinks, ODGs, lozenges, and effervescent and chewable tablets, four primary packaging options are commonly used (Figure 1).

FIGURE 1



User-Friendly Dosage Forms & Appropriate Packaging Options

FIGURE 2



Structure of Typical Laminated PET Aluminum Foils & Laminated Aluminum Paper Foil

For instant drink formulations, sachets are the ideal primary packaging option as they come in a range of sizes and can be made from laminated polyethylene terephthalate (PET) aluminum foil or laminated aluminum paper foil, which offer good protection against moisture and light (Figure 2). The aluminum layer present in both laminated aluminum paper foil and laminated PET aluminum foil offers a similar level of protection from sunlight and moisture.

Stick packs are ideally suited for ODGs, and just like sachets, can also be made from laminated PET aluminum foil or laminated aluminum paper foil. However, their elongated shape makes them better suited for pouring the contents into the mouth and swallowing directly. Both sachets and stick packs can be manufactured with or without tear notches for easy opening. For lozenges and effervescent and chewable tablets, foil strips/pouches or tubes are the ideal packaging solution. Foil strips/pouches can be made from laminated aluminum paper foil, whereby two, four, or six individually sealed tablets are packaged together. Alternatively, tubes can be manufactured from polypropylene (PP) or aluminum. Aluminum tubes offer the best possible protection against light and moisture. Nevertheless, PP offers good and sufficient protection against these two factors for most products and is also a more cost-effective option.

For effervescent tablets that react vigorously with water, protection from moisture is particularly important. Tubes offer a number of design features to protect their contents from humidity. As well as being manufactured from materials that prevent moisture from permeating through and reaching the contents, tube stoppers usually include drying agents, such as silica gel or molecular sieves, to absorb the humidity that can penetrate through the tube or be introduced into tubes after repeated opening and removal of tablets.

DESIGNING PACKAGING FOR OLDER PATIENTS

A significant proportion of people taking medication are elderly; however, for this patient group, product packaging can be a significant barrier to accessing medicine and complying with treatment regimens.[1,2] This is particularly true for the packaging of traditional tablets and capsules, with many older patients experiencing difficulties pushing tablets through blister packs. Another commonly reported problem is difficulty opening the tamper-evident closures and screw caps on medicine bottles.[3]

Design features can be incorporated into the packaging to make opening easier. Sachets and stick packs, for example, can be manufactured with tear notches to simplify opening. With tubes, conventional stoppers can be difficult to open, especially for people with weak hands or wrists, such as elderly persons or arthritis and osteoporosis patients. However, the latest generation of easy-to-open tube stop-

FIGURE 3

Automated Attachment of Leporellos to Tablet Tubes

pers can be removed with a short rip of the safety ring, and are easily lifted off using an ergonomic finger mold grip.

Another important usability factor to consider when choosing packaging concerns the readability of the patient information leaflet (PIL). It is a regulatory requirement that information must be clearly readable so that patients and consumers can use their medicines safely and appropriately.[4]

While a PIL can easily be added to products that require secondary packaging (such as stick packs, sachets, and strip-foils), this outer packaging can be omitted for tubes. Because the space on a tube is often too small to incorporate all the required information, a folded paper sheet (known as a leporello) can be attached directly to the tube (Figure 3).

INCREASED DEMAND FOR CONVENIENCE & CUSTOMIZATION

Modern patients and consumers increasingly expect convenience in their lives and products to be tailored to their individual preferences and needs. Pharmaceutical companies have responded to this demand and have developed medicines that can be taken on the go, such as ODGs and chewable tablets, or those that can be dissolved in water before being taken to accommodate the needs of patients having difficulties swallowing tablets or capsules.

But it's not just the medicines themselves that have evolved to meet changing consumer and patient preferences. Packaging has also adapted to become, for example, more portable and re-closeable in order to be used on the move, as the modern consumer is more mobile than ever.

The use of cardboard lids and cut-out slots to create re-closeable flaps can make secondary packaging more convenient for those who are always on the go. Flip-top cartons (Figure 4), for example, are small and re-closeable, and are ideal for packaging sachets or stick packs as they can be taken on the move and prevent the individual sachets from spilling out of the box. Moreover, packaging can be designed to be more streamlined and have fewer sharp corners in order to fit more easily into pockets or bags.

And for those who need to take only a single dose on the go, sachets and stick packs containing individual doses of medicine eliminate the need to carry around whole blister packs or medicine bottles, which are bulky and may be exposed to unsuitable conditions (such as being left in the car on a sunny day).

SAFETY CONSIDERATIONS

Ease of opening and convenience must be balanced with appropriate design to ensure packaging is resistant to opening by children. The latest user-friendly packaging options can have child-resistant features built in.

Stoppers designed to be removed by first pushing a lever at the side of the cap, before being moved upward, are more resistant to opening by children. These mechanisms are designed in a way that also ensures maximum accessibility for older people.

Sachets and stick packs can also be made child-resistant through the use of laminated PET aluminum foil. The PET-based foil is more difficult to tear than laminated aluminum paper foil, and can be opened only by cutting the packaging with scissors. It is also possible to add a specific type of tear-notch or a laser-perforation that weakens a defined area of the PET-layer (without harming the barrier properties).

The potential for product tampering is another important factor that must be con-

FIGURE 4

Small & Re-Closable Flip-Top Carton

"But it's not just the medicines themselves that have evolved to meet changing consumer and patient preferences. Packaging has also adapted to become, for example, more portable and re-closeable in order to be used on the move, as the modern consumer is more mobile than ever."

sidered when designing packaging for medicines. Many modern options can include tamper-evident safety features that allow users to identify when the packaging has been opened.

Tubes, for instance, can be designed with tamper-evident seals to identify whether the stopper has been removed. These measures not only serve to protect the safety of consumers, they can also boost consumer trust in a particular brand or product. Safety features can also be included on secondary packaging; flip-top cartons, for example, can be designed with perforations that clearly show when the box has been opened.

The latest regulations around medicine serialization, designed to safeguard patients from counterfeiting and falsification, are also adding to the packaging requirements for the pharmaceutical industry. Legislation under the US Drug Supply Chain Security Act, as well as the European Union's Falsified Medicines Directive, require an alpha-numeric code to be printed in both human-readable and two-dimensional barcode form on the packaging of prescription medicines.[5,6]

This individual identifier, containing information, such as product code, batch number, and expiry date, must be unique for each package and will be used to track and verify the authenticity of medicines at every stage – from the manufacturing plant to the patient collecting the medicine at the pharmacy.

This requirement presents an additional consideration for pharmaceutical companies, as the technology used to produce packaging and materials must be able to support the printing of small barcodes on products, and the production line must have space for this printing step to be introduced. For many manufacturers, this will require a significant investment in equipment, software, and associated workforce expertise that will enable them to comply with these new regulations.

BUILDING A STRONG CUSTOMER CONNECTION

As well as providing a practical solution to containing and protecting medicines, packaging has become a useful way of boosting brand identity, adding value to a product, and building a strong consumer connection.

Similar to fast-moving consumer goods (FMCG), for over-the-counter (OTC) medicines, it is important to ensure that a product's packaging is easily visible and recognizable, and that it differentiates the product from the competition. Shelf-ready cardboard packaging with design features such as "feet," keep the product upright while on display. They help ensure that products such as long tablets tubes packaged in folding boxes with a small base stand out on the shelf and do not fall over, while also meeting retailers' handling and shelf-presentation requirements.

Packaging is also used for information transmission. Well-designed packaging should imply trustworthiness and thus encourage potential customers to purchase the product. For high-end nutraceuticals and health supplements, the use of laminated PET aluminum foil – which has a more glossy finish than laminated aluminum paper foil – can help to establish a more premium brand.

Likewise, cartons printed on metallized or holographic board or with an embossed finish can be used to support the image of a more high-value product. Thicker card-based packaging materials such as carton board are also providing new ways of creating distinctive packag-

ing that can be molded into eye-catching shapes, whilst being more sustainable than plastic packaging.

As well as its importance for marketing purposes, distinctive packaging can also help boost patient compliance, particularly for elderly people and those who experience vision difficulties, by making the medicine more easily distinguishable from other products in the medicine cabinet.

SUMMARY

The pharmaceutical industry increasingly recognizes the needs of people who experience difficulties swallowing conventional tablets and capsules, and is responding with products that are more convenient to take. An industry-wide focus on the design of packaging that can protect these user-friendly dosage forms, as well as improve patient compliance and fit into modern consumers' lifestyles, has resulted in a wide range of primary and secondary packaging solutions. These options are helping pharmaceutical companies incorporate the necessary safety and product protection features required to ensure products are safe and effective, while better meeting the individual needs of customers. Similar to FMCG, pharma has been recognizing the importance of packaging in the marketing mix, which is particularly relevant in the OTC sector, where the consumer makes the buying decision. To improve brand recognition and differentiate products from the competition, packaging must be intelligently designed and clearly convey the product promise.◆

REFERENCES

1. Notenboom K, Leufkens HGM, Vromans H, Bouvy ML. Learning from patients: identifying design features of medicines that cause medication use problems. Int J Pharmaceut. 2017;517:128-134.
2. Thwaites JH. Practical aspects of drug treatment in elderly patients with mobility problems. Drugs & Aging. 1999;14:105-114.
3. Sormunen E, Nevala N, Sipilä S. Critical factors in opening pharmaceutical packages: a usability study among healthcare workers, women with rheumatoid arthritis and elderly women. Packaging Technol & Sci. 2014;27:559-576.
4. European Commission Enterprise and Industry Directorate-General; Guideline on the readability of the labelling and package leaflet of medicinal products for human use, Revision 1, 12 January 2009.
5. U.S. Food & Drug Administration; https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/ucm376829.htm.
6. European Medicines Agency; http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp

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BIOGRAPHIES

Dr. Detlev Haack is the Director Research & Development at HERMES PHARMA. He earned his PhD at the University of Hamburg on the subject of chemical and physical stability of Piroxicam in solid dispersion with PEG and PVP. In 1997, he received approbation as a pharmacist. From 2003-2007, Dr. Haack was Manager Sales & Business Development at Hermes Arzneimittel GmbH. He held the position of Associate Director R&D there from 2007-2012 before becoming Director R&D in 2013. His career includes a previous position as Head of Production at Altana Pharma Oranienburg GmbH.

Dr. Martin Koeberle the Head of Analytical Development & Stability Testing at HERMES PHARMA, where he is responsible for the analytical aspects of development projects, including the evaluation and implementation of new analytical techniques and approaches. Dr Koeberle earned his PhD in Pharmaceutical Sciences at the University of Strathclyde in Glasgow on the subject of ocular drug delivery and pharmacokinetics. His career includes previous positions in analytical development at AstraZeneca in the UK, Aenova in Switzerland, and an affiliate of Ratiopharm in Germany.

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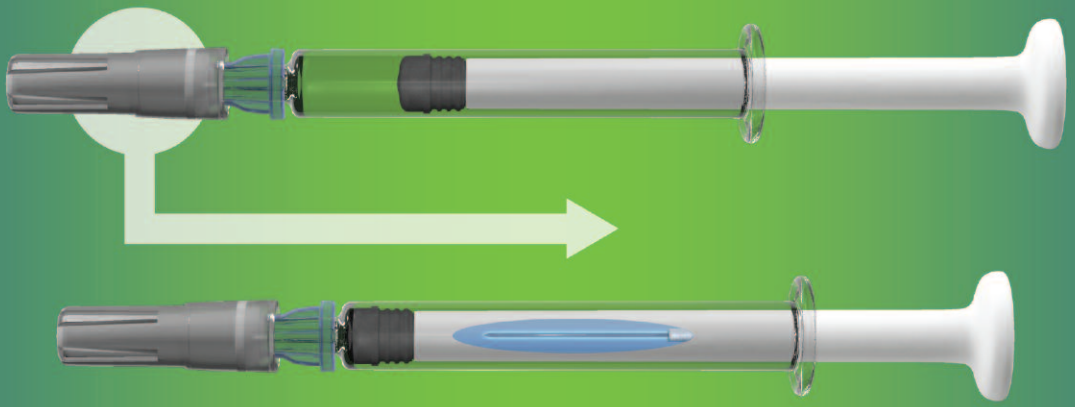

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DRUG DEVELOPMENT

To De-Risk Patient Acceptance of Biologic Drugs, Focus Early on Delivery

By: Jeannie Joughin, PhD

INTRODUCTION

The cost of developing a new prescription drug that gains market approval has reached the stratosphere, skyrocketing 145% since 2003 – adjusted for inflation – to $2.6 billion. And the average time it takes from synthesis to approval is also a big number: 10-12 years, according to a Tufts Center for the Study of Drug Development study.[1] That's about $260 million a year to move a biologic drug candidate through the pipeline, or roughly $712,000 a day.

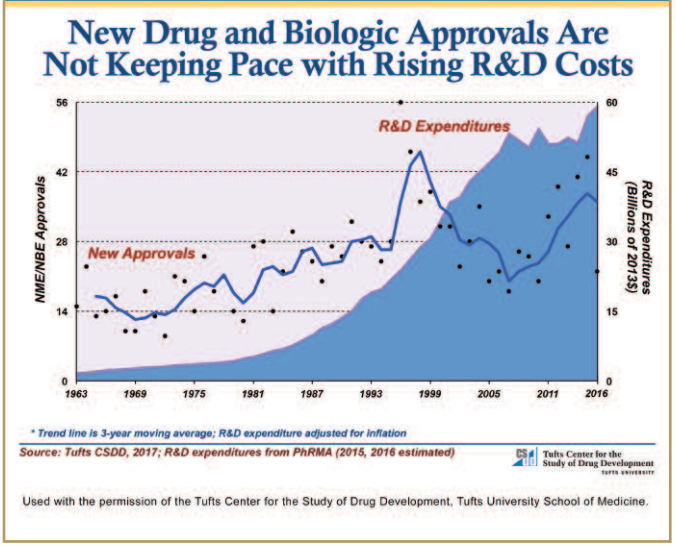
Most people, including government officials, know that developing new drugs is not only expensive but also quite risky. Only 7.1% percent of the 1,442 compounds included in the Tufts study eventually gained regulatory approval (Table 1). Despite being well aware of the extraordinary cost of biologic drug development and also of the benefits of these new treatments for patients, members of Congress continue to exert strong pricing pressure on pharmaceutical and biotech companies. Lowering drug prices became a rallying cry during the US 2016 Presidential election, and the noise hasn't abated.

So, what does a pharmaceutical company do when everyone wants more effective new therapies but no one - including third-party payers – wants to pay the price for their development?

De-risk the drug development process, in every possible way.

In the lengthy process of developing a biologic drug candidate, as with any drug, the end goal is always regulatory approval. The following discusses ways in which the path to approval is different for combination products than it is for other therapeutics and why all methods of de-risking biologics development need to occur early in the drug development process. As well, we will look at shortcuts to development time and the advantages of being first to market, not only with new drugs but also by extending a drug's lifecycle by combining it with a device.

TABLE 1



CURRENT DE-RISKING STRATEGIES

The pharmaceutical industry is certainly trying to de-risk drug development. Methods to make the translational stage more predictive and efficient are being employed, as are careful choices of disease projects. Extensive preclinical testing, identifying disease-state biomarkers using various analytical methods, and an integrated approach to the detection and evaluation of safety issues with comprehensive risk-analysis are standard de-risking strategies.

But biologics create even greater challenges. They are big drugs. They consist of mega-molecules that are frequently composed of a heterogeneous mixture of more than 1,300 weighty amino acids. Biologics are often hundreds of times the size of conventional small molecule drugs. Their size and complexity creates additional synthesis challenges for pharmaceutical companies seeking to develop the next blockbuster biologic.

NEW STRATEGY FOR BIOLOGIC DRUGS

These large-volume, often viscous drugs create the need for a new de-risking strategy, one that must be addressed in the early stages of the drug development process. That strategy is employing a new, patient-focused drug delivery system.

Because these large-volume drugs are not only hard to make, but also hard for patients to take, and the preferred parenteral route can be both painful and inconvenient, the pharmaceutical industry needs to address this question: how can the patient experience be improved significantly so patients are more likely to comply with prescribed therapy?

Large-volume wearable injectors provide the answer, and the pharmaceutical industry is rapidly adopting the new technology. According to a recent P&S Market Research report, the wearable injectors market is projected to reach $13 billion by 2024, growing at a CAGR of 23% until 2024.

AN ADDITIONAL DE-RISKING STRATEGY

Large-volume wearable injectors have been around for just a couple of years, and to date, only one combination product has been approved by the FDA. The most advanced of these on-body delivery devices (OBDDs) provide a compliance-boosting patient experience, yet are highly cost effective for the pharmaceutical industry, payers, and the healthcare system.

OBDD benefits and features for patients and pharmaceutical companies include the following:

- Subcutaneous self-injection of even the largest doses (10 mL to 50 mL) replacing IV infusion and significantly lowering healthcare system costs
- Enable unassisted patient self-injection of large dose biologics that is safe, easy, comfortable, and convenient
- Resolve drug development obstacles of viscosity, solubility, and protein aggregation, especially with the small-gauge needles patients prefer
- Platform for product differentiation in competitive markets
- Technology that responds to each patient by adjusting flow rate, reducing or eliminating anxiety and injection pain
- Simpler, faster product formulation for development teams
- Faster time to market
- Use of standard vials or syringes, eliminating the need for new container closure stability studies
- Multi-vial systems with practically no waste for filling the injector from standard vials or syringes
- Automatic warming of the drug as device fills – in seconds – removing the typical 30-minute waiting time for refrigerated vials to reach room temperature
- Automatic mixing and reconstitution of lyophilized drugs, removing any patient variability from the mixing process
- Use of the smallest possible needle size possible while still delivering even the most viscous biologics with little or no discomfort
- Low profile wearables, about the

FIGURE 1

Hand-Held Lyo System

"Large-volume wearable injectors provide the answer, and the pharmaceutical industry is rapidly adopting the new technology. According to a recent P&S Market Research report, the wearable injectors market is projected to reach $13 billion by 2024, growing at a CAGR of 23% until 2024."

size of an Oreo cookie: treatment can be administered at home, at work, or on the go with complete freedom and mobility

- Data capture to aid in monitoring patient adherence to prescribed therapy

COMBINATION PRODUCTS ADD EVEN MORE COMPLEXITY & URGENCY

Regulatory agencies are considering the new biologics delivery devices in combination with the drugs they deliver. All developers of biologic drugs, from process chemists to manufacturers, should be thinking about delivery even as the molecules are being developed and ahead of scale-up.

In fact, nearly 60% of pharmaceutical combination product experts say that the time to add the delivery device constituent is in early stages of drug development. Introducing delivery into the drug or biologic program later causes issues and compromises, according to a recent EdgeOne Medical survey.[2]

NAVIGATING THE REGULATORY PATH

Any experienced CRO and CMO will tell you that from day 1 of initiating a drug development project, their team is considering the most effective and efficient route to navigating regulatory paths in various countries.

In the US, as the FDA explains on the agency's website, technological advances continue to merge product types and blur the historical lines of separation between the FDA's medical product centers, which are made up of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).[3]

Because combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they raise challenging regulatory, policy, and review management challenges. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications.

The shortest most efficient route to regulatory approval of combination devices requires that prototype delivery devices be in the lab so that device development and the evolving chemistry occur simultaneously.

DE-RISKING BY ACHIEVING FIRST-MOVER ADVANTAGE

A McKinsey & Company report examining 492 drug launches in 131 classes over a 27-year period finds a first-to-market advantage for first movers from larger pharmaceutical companies.[4] They achieve a 6% market-share advantage. That advantage extends 10 years after launch, while later entrants' advantage is in negative numbers.

Further, companies with prior experience in a therapeutic area have almost twice the first-to-market advantage as companies with no experience with that disease state. The first mover effect is

strongest of all – a 13% market share advantage – when the first mover expands indications faster than later entrants in the first 5 years after launch.

Once again, OBDDs can play a significant de-risking role with their ability to reduce formulation time – by as much as a year or more, providing opportunity for the earliest possible market entry.

How? By circumventing injectable volume and viscosity limitations and by increasing the concentration of the active ingredient in the formulation. Scientists developing biotherapeutics spend enormous time and effort on formulation – sometimes years. This amount of time and effort can be significantly reduced by incorporating the newest biologics delivery technology.

The latest, most advanced large-volume wearable injector technology brings to market a novel product development aid that reduces formulation time and effort by enabling a simpler method of product preparation. Formulation teams can take advantage of the innovative delivery technology to speed development, producing stable, bioavailable, clinically relevant formulations more quickly.

At the same time, formulation teams can also facilitate patient self-injection of biologics by adopting drug delivery technology that aids in the following:

- Delivering more volume of product
- Delivering much higher viscosities caused by higher concentration of proteins
- Resolving biologics' greater propensity to precipitate out of solution

The time and effort savings are accomplished with automated processes performed by the most advanced LVWIs, such as the Enable Injector, which accelerates or eliminates tedious, time-consuming formulation functions for more rapid – and less costly – product development.

In addition, the requirement for formulation teams to concentrate the product in the smallest possible dose for delivery by an auto-injector (typically <1 mL) may no longer be relevant. The latest generation of large-volume wearable injectors can provide a comfortable injection experience even when delivering higher volume and viscous product.

Patient acceptance of the new OBDDs should be high because the devices support mobility, are easy to use, and minimize any injection discomfort.

Prior to the introduction of large-volume wearable injectors, subcutaneous injections of biologics, the preferred route of administration, were limited in the amount and viscosity of drug product that could be delivered and tolerated by the patient in a single injection. In most cases, that volume was limited to 1 to 2 mL. Highly viscous formulations of monoclonal antibodies, for example, could not be readily injected, particularly when smaller-gauge needles are used to reduce the patient's pain or discomfort.[5,6]

In contrast, these new LVWI systems overcome the large-volume injection challenges by allowing the patient to administer increased volumes into the subcutaneous space more slowly.

As well, their use of standard vials or syringes to fill the injector in a simple, intuitive way, eliminates the need for new container closure stability studies, shortening development time and speeding entry of the product to market.

FIGURE 2

Hand-Held System (Single Vial)

DE-RISKING WITH PATENT EXTENSIONS THAT CAN ALSO WIN PATIENT LOYALTY

Already, 11 established biologic products – representing 48% of total biologic sales – are slated to lose patent protection by 2022. However, patent extension and market share protection may be possible by creating a combination product that can deliver a much higher volume of product in a single dose.

At the same time, the combination product, specifically designed to vastly improve the patient experience, can quickly create patient preference and additional marketplace advantages.

First movers who create these combination products can also differentiate not only their new and innovative commercial products, but also those products whose patents expire in the next 3 to 5 years or beyond.

WELL BALANCED PHARMACEUTICAL PORTFOLIOS NOW INCLUDE COMBINATION DEVICES

In its 2016 Pharmaceutical Industry Report, Deloitte exhorts pharmaceutical companies to embrace innovation. The consulting firm postulates that as integration of pharmaceuticals and technology continue to gain traction and accelerates, drugs will remain important but will represent a diminishing share of what comes together to deliver an overall outcome.

Disruptive innovation that can positively impact outcomes, create patient preference, and lower drug development health system costs has arrived – wearable large-volume subcutaneous injection technology. Pharmaceutical companies that embrace the OBDD technology, and their patients, have everything to gain.

SUMMARY

Pressure to reduce costs while meeting more complex regulatory mandates, as recently reported in the *New England Journal of Medicine*, creates the difficult challenge of developing a commercial process for a drug candidate more efficiently and within a much shorter timeframe. Some of the complexity and risk inherent in developing biologic combination products could be mitigated by incorporating a newly developed, disruptive, wearable large-volume OBDD early in the drug development process, helping not only to de-risk biologic drug uptake in patients but also bring many marketable benefits for the administration of biologics. ◆

REFERENCES

1. Tufts. http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014.pdf.
2. Edge survey.
3. https://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm.
4. Myoung, Cha & Yu, Flora: McKinsey&Company:Pharma's first-to-market advantage. Pharmaceuticals & Medical Products, September 2014.
5. Collins M. Here's What's Important About Alder Biopharmaceuticals' Latest Release". Market Exclusive, July 26, 2016.
6. Burgess BE. Optimizing drug delivery for modern biologics. BioPharm Int. 2012;25(5). http://www.biopharminternational.com/optimizing-drug-delivery-modern-biologics.
7. Drazen JM, Harrington DP, McMurray JV, et al. The large pharmaceutical company perspective. NEJM. 2017;376:52-60.

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BIOGRAPHY

Dr. Jeannie Joughin is the Vice President, Corporate Development for Enable Injections, responsible for business development, strategic alliances, alliance management, marketing, and clinical activities. She works cross-functionally to select and prioritize Enable's global portfolio. She has also held various scientific positions, including Senior Research Scientist, Post-Doctorate and Senior Post-Doctorate positions in Australia at The Alfred Hospital, The Walter & Eliza Hall Institute, as well as internationally in Austria (University Clinic, Innsbruck) and Switzerland (Ludwig Institute for Cancer Research, Lausanne). She began her career as a Clinical Research Manager with Bristol-Myers Squibb. She moved into New Product Commercialization as the interface between the medical and marketing departments. From there, Dr. Joughin worked in Brand Management. After successfully completing several marketing roles in various organizations and companies, Dr. Joughin joined CSL Biotherapies in 2005 as Director, Pharmaceuticals Marketing and In-licensing. She assumed responsibility for a portfolio of pharmaceutical products from several licensing partners in various therapeutic areas. As Vice President, Business Development at CSL Behring, she was responsible for managing business licensing arrangements and relationships.

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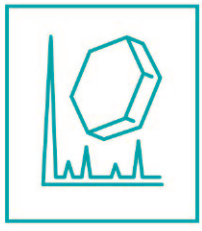
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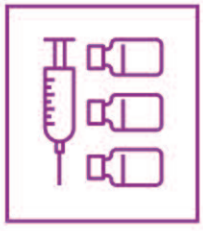
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The third annual Drug Delivery & Formulation Report,

a collaborative effort between team members at Drug Development & Delivery and PharmaCircle, provides a look back at 2016 in terms of approvals and developments in the area of drug delivery and formulation.

The report continues to cover the following significant key points of interest, with the belief that understanding the past, even the recent past, can provide insights to what is possible:

1. Drug Delivery & Formulation Technologies
2. Drug Delivery & Formulation Approvals
3. Drug Delivery Related Transactions
4. Drug Delivery Formulation Pipeline
5. Notable Drug Device Approvals
6. Combination Product Approvals

Technologies, irrespective of industry sector, see periods where there are bursts of innovation and creativity, interspersed with longer periods of technology adoption and optimization. The Pharma industry may be one of these periods where considerable attention is being placed on technology application to new and existing products.

It seems that 2016 looked back more than it looked forward in terms of drug delivery and formulation enhanced and enabled product approvals. While there were a similar number of new products approved in 2016 using drug delivery and formulation technologies as 2015, these products for the most part did little to push forward the state-of-the-art. 2016 was also a little unique in that there were no blockbuster drug delivery and formulation deals or transactions to suggest there was any shift in the industry's general strategic direction.

An overview of the current global pipeline for drug delivery and formulation enabled and enhanced products provides a sense of what is out there and what we might expect. Drug-Device enhancements over the past few years have generally been incremental and largely predictable in terms of features and performance. Prefilled syringes and autoinjectors accounted for the largest number of 2016 approvals (16/43), followed somewhat surprisingly by nasal drug-delivery products.

Combination pharmaceutical products represent an important source of commercial and therapeutic opportunity by expanding eligible patient populations, improving efficacy and safety, and extending market exclusivity. This engine of development seems to be winding down as evidenced by New Combination approvals in Europe and the U.S. for the past few years. A total of 162 new Combination Products were approved in the period between 2007 and 2016, an average of about 16 per year.

As always, we would love to get your comments on the report and suggestions for improvements in the future.

Ralph Vitaro, Publisher & President
Drug Development & Delivery
rvitaro@drug-dev.com

Tugrul Kararli, President & Founder
PharmaCircle LLC
tkararli@pharmacircle.com

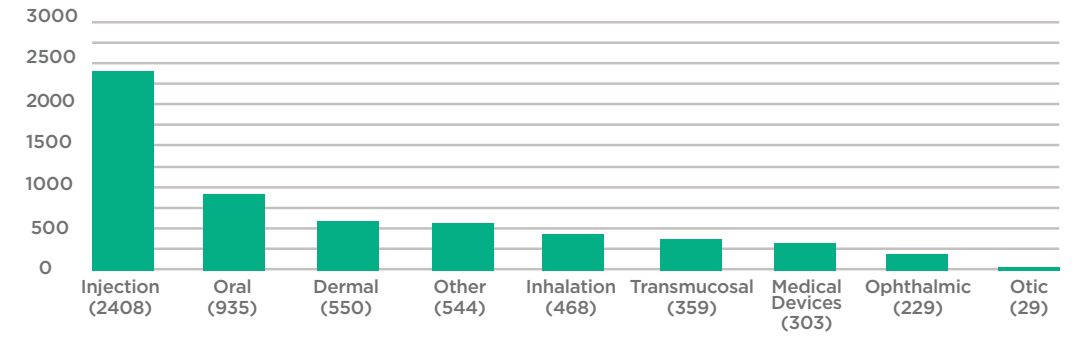
1. Drug Delivery and Formulation Technologies of 2016

Technologies, irrespective of industry sector, see periods where there are bursts of innovation and creativity, interspersed with longer periods of technology adoption and optimization. It seems that the Pharma industry is in one of these periods where considerable attention is being placed on technology application to new and existing products.

There currently is no shortage of technologies available to the drug delivery and formulation professional. A 2017 audit identified more than 4,500 active technologies related to the delivery and formulation of pharmaceuticals.

Technology Count by Technology Category

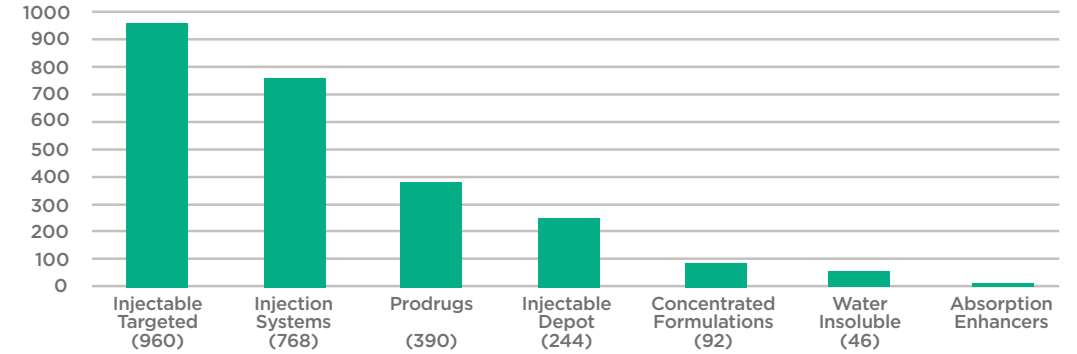
Chart 1. Drug Delivery Technology Count - Category (Source: PharmaCircle LLC)



Quick Takeaways - Chart 1:

1. The large number of Injection directed technologies is somewhat surprising.
2. The technology numbers are at odds with recent NDA approvals, perhaps suggesting an impending shift in approval numbers.

Chart 2. Drug Delivery Technology Count - Injection Category (Source: PharmaCircle LLC)

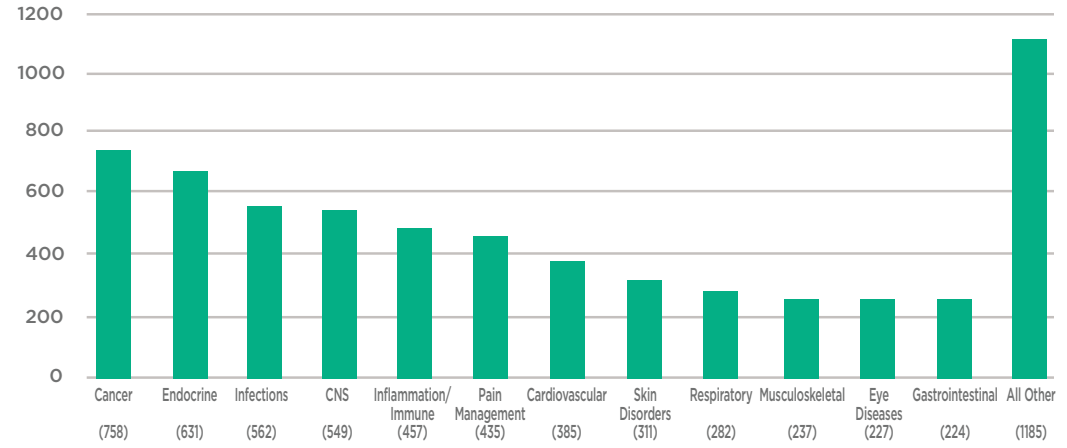


Quick Takeaways - Chart 2:

1. The largest number of Injection technologies are directed to selective delivery.
2. Infusion pumps lead the Injection Systems category, followed by Injection Pens, Autoinjectors and Reconstitution Systems.

Technology Count by Therapeutic Application

Chart 3. Drug Delivery Technology Count - Therapeutic Application (Source: PharmaCircle LLC)



Quick Takeaways - Chart 3:

1. Injectable focused indications, Cancer, Endocrine (Insulin) and Infections represent the top three indications targeted by drug delivery and formulation technologies..
2. The numbers are not additive, as some technologies do not have defined indications, and others can be used for multiple applications.

In the next section, we highlight ten technologies that caught the eye of PharmaCircle analysts in 2016, that have the potential to deliver important therapeutic benefits in the years to come. ■

Notable Drug Delivery & Formulation Technologies of 2016

Technology: Pearl Porous Particle HFA Formulations
Technology Branches: Inhalation Formulations MDI, Incompatible/Combination
Company: Pearl Therapeutics (AstraZeneca)
Dosage Form: Metered Dose Inhalation
Description: Porous low-density phospholipid particles (DSPC + CaCl2) providing for stable suspensions in HFA propellants and high performance MDI aerosols. The technology eliminates the need for special additives, such as co-solvents, or other suspension modifying agents. It effectively prevents the sedimentation of drug crystals inside MDI canisters, minimizes interaction of actives either with the canister components or each other, and keeps actives stable over long periods of time.

Notable: The technology is capable of delivering the consistent dosing of one or more actives in combination, even when delivered at ultra-low doses.

Technology: Cell-in-a-Box
Technology Branche: Cell Encapsulation
Company: PharmaCyte Biotech
Dosage Form: Capsules in Syringe
Description: Cell-in-a-Box products use Austrianova's proprietary natural cotton derived polymer Gel8 material. Cells are mixed together with polymer A (Gel8), which is physically morphed into beads. The beads are further combined with polymer to form a stable, robust shell around the capsule. The exterior capsule material is semi-permeable/porous, allowing small molecules, such as nutrients and waste products, to easily and freely pass into and out of the capsules. This ensures the viability of the encapsulated while restricting the entry or exit of larger molecules and/or cells.

Notable: The capsules are claimed not to cause tissue inflammation or degrade, even after being present in the body for two years.

Technology: Illustris Technology Platform
Technology Branches: Topical Enhancers, Ocular Topical Formulations, Buccal/Sublingual Formulations, Vaginal, General
Company: Illustris Pharmaceuticals
Dosage Form: Undisclosed
Description: The Illustris technology facilitates the delivery of actives through tissue structures by deploying decoys, many of which relax anchors that bind tissue cells together providing a portal for actives to permeate the targeted tissue site. The decoys are typically based on, or composed of, peptides or polysaccharides, derived from endogenous molecules, notably those that provide structural and biochemical support for cells.

Notable: The Illustris system is claimed to optimize the delivery of macromolecules (up to 160 KD) that cannot normally be delivered topically and non-invasively to the skin, eye and mucosal (oral or vaginal) surfaces.

Note: Technology Branches are as defined and assigned by PharmaCircle.

Technology: Clearside SCS Microinjection
Technology Branches: Ocular Delivery Devices/Dispensers, Specialty Syringes, Poration Microneedles
Company: Clearside Biomedical
Dosage Form: Drug-Device
Description: A hollow microneedle technology that delivers drugs via controlled infusion directly to the suprachoroidal (SCS) space, previously only possible through surgical procedures. Drug activity can be targeted to the posterior eye. Particle size makes a difference as the 20-nm particles spread in the SCS and within the sclera, while the 1,000-nm particles remain primarily in the SCS.

Notable: This microinjection platform provides a non-surgical approach to drug delivery to the posterior segment of the eye and retina. In contrast to standard intravitreal injections, the Clearside microinjection platform potentially represents a more targeted therapy for the treatment of retinal diseases.

Technology: PolyXen
Technology Branch: Prodrugs non-PEG Polymers
Company: Xenetic Biosciences
Dosage Form: Undisclosed
Description: Polymer polysialic acid (PSA), a pro-drug technology for injectable sustained release of proteins, is a natural, human, polymer. PSA provides a protective microenvironment or 'glycocalyx' that increases the active life of protein drugs in the circulation, and prevents them being recognized by the immune system.

Notable: The site of attachment and the length of PSA chains can enhance the properties of the therapeutic by changing the apparent hydrodynamic radius of the molecule. It can also be used with small molecule drugs.

Technology: Biochronomer Technology
Technology Branches: Biodegradable Non-PLGA Microcaps/Implants, Biodegradable Gel/Suspension, Ocular Implants/Rods/Microcapsules
Company: Heron Therapeutics
Dosage Form: Gels, Microspheres, Coatings, and Strands
Description: A bioerodible, injectable, and implantable drug delivery system for SC, IM, and intraocular applications that can take the form of a gel, microsphere, or extruded granules. Development has remained limited to injectable formulations of small molecules. Potentially applicable to ophthalmic and nucleic acid applications.

Notable: A patented fourth-generation poly (ortho ester) polymer for the preparation of bioerodible drug delivery systems. The polymer contains a copolymerized acid that controls the erosion rate.

Editor's Insight: Clearside Biomedical is developing potential therapies for eye diseases using a proprietary treatment approach where pharmacological candidates have access to the back of the eye through suprachoroidal injection. This new treatment paradigm offers potentially meaningful therapeutic benefit to patients suffering from sight threatening diseases like uveitis, retinal vein occlusion (RVO), diabetic macular edema (DME) and wet age related macular degeneration (wet AMD).

Note: Technology Branches are as defined and assigned by PharmaCircle.

Technology: Microglassification
Technology Branches: Stabilization Technologies, Concentrated Suspension/Viscous Solution
Company: Lindy Biosciences
Dosage Form: Powders for Inhalation, Solid Suspensions for Injection or Controlled Release
Description: Microglassification is an alternative to lyophilization for preserving biologics. The process uses compatible solvents to remove water from the protein without exposing it to high temperatures or harsh interfaces. Final products are pure, solid, spherical, amorphous protein microbeads (~1 g/mL) that rapidly dissolve back into solution. Microglassification only exposes proteins to a low-energy liquid-liquid interface, and the drying process is completed within seconds to minutes, minimizing stress on the protein. In this state, biologics are often stable enough for long-term storage, transport, or incorporation in to drug delivery.

Notable: Microglassification formulated biologics are often stable enough for long-term storage, transport, or incorporation into drug delivery formulations. Suspensions of Microglassified proteins have a much lower viscosity at a given concentration. Preliminary formulations have been delivered through a 27-G needle at >500 mg/ml.

Technology: PRINT Ocular Implants
Technology Branch: Ocular Implants/Rods/Microcapsules
Company: Envisia Therapeutics (Liquidia Technologies)
Dosage Form: Ophthalmic Implant
Description: An ocular implant based on biodegradable polymers and the unique PRINT particle engineering technology to provide extended treatment effects ranging from weeks to months following a single dose. Implants can be administered to the posterior (intracameral, intravitreal) and anterior (subconjunctival) segments of the eye. PRINT is broadly compatible with a wide range of biodegradable polymers and drugs including small molecules, nucleic acids, enzymes, and monoclonal antibodies.

Notable: PRINT implants feature a very narrow particle size distribution in any desired shape (spherical, square, arrow, boomerang, hexagonal, doughnut etc.) with controlled surface characteristics. PRINT particles can be designed to, a) actively or passively target specific cells and tissues, b) modulate circulation times, c) have pH, temperature, or enzyme dependent release, and d) accommodate a high drug loading.

Editor's Insight: Microglassification™ is a process that gently removes a majority of the water from solutions of proteins, or other biologics, resulting in solid, spherical, amorphous microbeads. In this dry state, biologics are often stable enough for long-term storage, transport, or incorporation into drug delivery formulations.

Note: Technology Branches are as defined and assigned by PharmaCircle.

Technology: Precision Particle Fabrication Technology
Technology Branches: NP spray drying/electrospray, Taste Masking, Oral Liquid MR, Biodegradable PLGA Microcaps/Implants, Otic Delivery Formulations/Devices
Company: Orbis Biosciences
Dosage Form: Injection Suspension, Oral Powder for Suspension
Description: Precision Particle Fabrication provides a single step process for particle manufacturing that permits precision control over particle size, encapsulation, and porosity. Processing involves forming particles by accelerating a stream of a liquid and vibrating the stream to form particles. Particles can be micro- and nano-sized with extraordinarily narrow size distributions. Polymeric shells can be filled with suspensions, oils, or even water-based materials. The technology can be used for sustained release injectables, taste masking and otic applications.

Notable: A single step continuous flow, high-volume nozzle based technology for micro-encapsulation and particle manufacturing.

Technology: InCube/Rani Swallowable Device
Technology Branches: Ingestible Delivery Devices, Oral Peptide/Protein/Macromolecule, Colonic Release, Poration Microneedles
Company: InCube Labs, Rani Therapeutics
Dosage Form: Drug-Device - Capsule
Description: A biodegradable ingestible robotic pill that delivers drugs into the intestinal wall or other GI lumen. The device consists of an indigestible polymer and tiny hollow needles made of sugar that are designed to safely deliver, via intestinal injection, drugs to the small intestine. The capsule contains chemical compartments composed of citric acid and sodium bicarbonate in two chambers separated by a valve, and an inflatable balloon-like structure with hollow microneedles preloaded with the therapeutic peptide. Once past the duodenum and pH reaches 6.5, the outer shell (capsule) dissolves exposing the valve and triggering the chemical reaction. The microneedles push into the intestinal wall (intra-enteral injection), detach from the capsule, and slowly dissolve. Once the needles are delivered, what remains is a deflated polymer balloon with the consistency of a tomato skin that the patient can safely pass.

Notable: The technology is potentially useful for the oral delivery of drugs that are poorly absorbed, tolerated, and/or degraded within the GI tract, including peptides, proteins, antibodies, RNAi therapies, and select vaccines.

Editor's Insight: Orbis Biosciences has a diverse product portfolio to leverage where Precision Particle Fabrication™ technology differentiates products. It is focused on creating novel oral and injectable therapeutics to improve compliance and patient satisfaction. Orbis' products address clinical needs and are at various stages of development. Many of the products are based on strategic partnerships with pharmaceutical companies and foundations.

Note: Technology Branches are as defined and assigned by PharmaCircle.

2. Drug Delivery & Formulation Approvals: 2016 in Review

It seems that 2016 looked back more than it looked forward in terms of drug delivery and formulation enhanced and enabled product approvals. While there were a similar number of new products approved in 2016 using drug delivery and formulation technologies as 2015, these products for the most part did little to push forward the state-of-the-art, with the exception of two gene and cell therapy products.

In some respects, perhaps 2016 represented a major shift for drug delivery and formulation in general, and therapeutics in particular, with the European approval of Strimvelis and Zalmoxis. Unlike UniQure's Glybera million dollar gene therapy approved in 2012 for the treatment of Lipoprotein Lipase Deficiency and reportedly only used with only one patient, Strimvelis and Zalmoxis are likely to see much wider usage.

Outside of Strimvelis and Zalmoxis, the list of Notable 2016 Drug Delivery and Formulation Approvals mostly followed the well-beaten paths of drug delivery and formulation enhancement of well-characterized small molecule pharmaceuticals. This included extended-release and quick-dissolve oral tablet formulations (Adzenys XR, Belviq XR, Dexilant Solutab, Troxyca ER, and Xtampza ER), long-acting injectables (Probuphine and Sustol), and one vaginal insert (Intrarosa). What was missing, at least in contrast to previous years, were any new PEGylated or fusion proteins, as well as any novel inhalation products. For the third year running, there were no new transdermal approvals in the US. One wonders if there is a deficit of creativity in the field of drug delivery and formulation, or if the once deep well of approved small molecules has been pumped dry.

An Overview of Drug Delivery and Formulation Approvals in 2016

One way to get a sense of what happened in 2016 is to review the products approved by the US FDA as a function of Dosage Form (Table 1) and Route of Administration (Table 2). (Note: US FDA data is used because it offers a consistent system of approval categorizations that makes it easier to analyze and understand trends)

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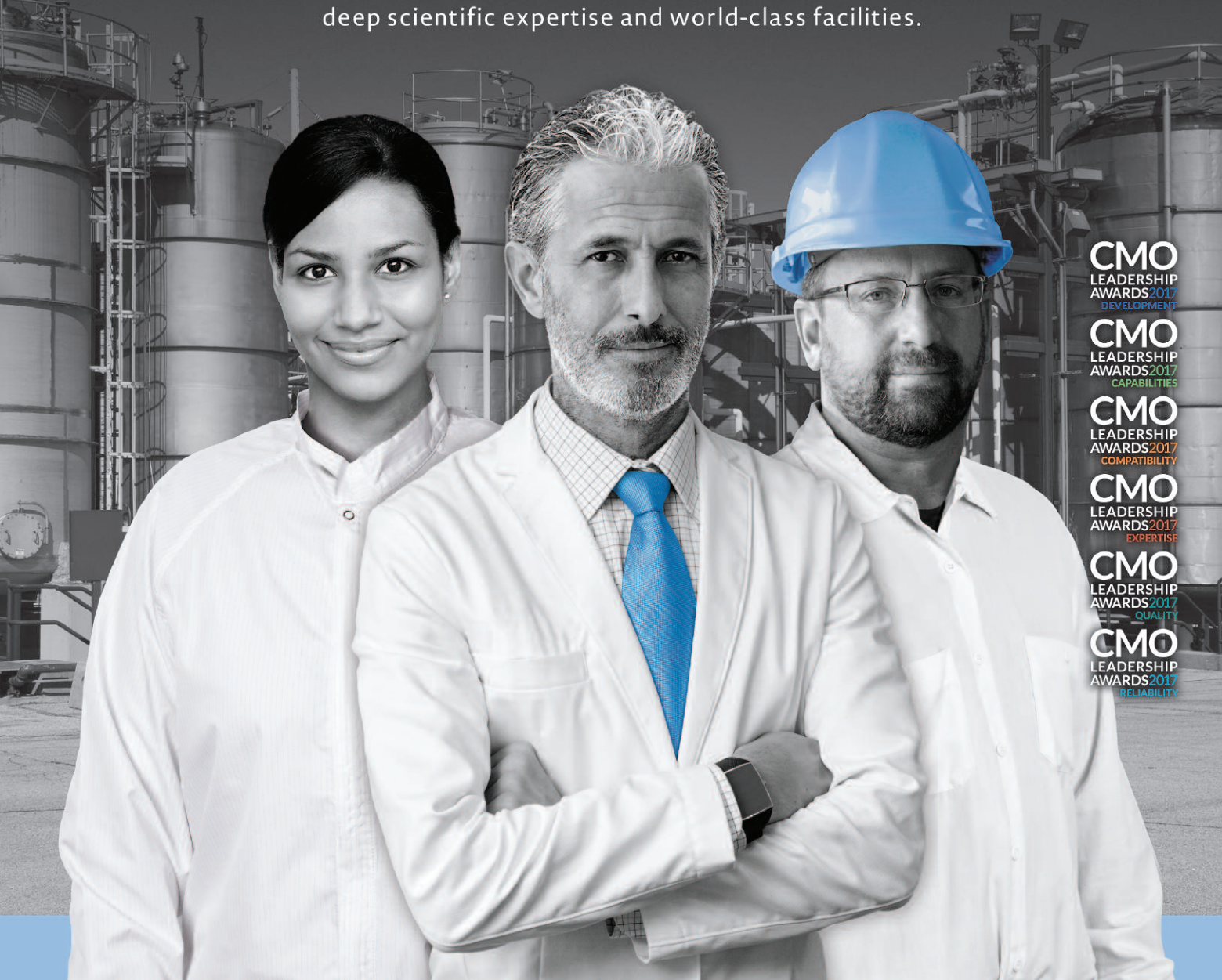

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Table 1. 2011-2016 FDA Approvals by Dosage Form

(Source: PharmaCircle LLC)
* -indicates dose modified products

Dosage Form	2011	2012	2013	2014	2015	2016
Aerosole, Metered/Foam*	-	3	1	4	2	1
Capsule	3	8	11	16	12	2
Capsule, Modified Release*	5	5	10	6	3	5
Cream/Emulsion*	2	1	3	1	1	1
Film*	-	1	-	1	1	-
Film Extended Release*	1	3	2	2	-	-
For Solution	-	2	1	-	2	2
For Suspension	1	1	2	2	2	1
For Suspension Modified Release*	-	2	1	2	-	-
Gel*	2	4	4	6	1	2
Granule*	-	-	-	-	3	-
Implant*	-	-	-	1	-	1
Injectable	29	21	14	17	18	19
Injection, Extended Release*	-	-	-	-	-	1
Insert*	-	-	-	-	-	1
Intrauterine Device*	-	-	1	-	1	1

Dosage Form	2011	2012	2013	2014	2015	2016
Liquid	-	-	1	-	-	-
Lotion/Ointment*	2	1	1	-	1	1
Paste/Patch*	-	1	-	-	-	1
Powder, All*	3	7	5	13	13	7
Solution, All*	16	13	17	26	25	34
Spray*	-	1	2	-	1	1
Spray, Metered*	2	1	1	3	5	2
Suspension, All*	4	3	3	2	5	5
Tablet	33	26	23	20	32	20
Tablet, Delayed Release*	-	2	3	1	1	2
Tablet, Effervescent*	-	1	-	-	-	1
Tablet, Extended Release*	9	5	6	7	4	9
Tablet, Orally Disintegrating*	2	1	-	-	-	-
Tablet, Orally Disintegrating, Modified Release*	-	-	-	-	-	3
Vial	-	1	1	-	-	-

Quick Takeaways - Table 1:

1. There has been a clear trend to more dose-modified product approvals. Some 42% of products in 2011 involved some sort of dose modification. That figure has risen to 48% in 2012, 56% in 2014, and 66% in 2016. It seems more and more products require some amount of drug delivery and/or formulation modification to optimize performance.
2. Much of the drop in unmodified dosage form approvals is accounted for by a drop in simple tablet approvals, which accounted for 29% of all NDA approvals in 2011, but only 16% in 2016.

Table 2. 2011-2016 FDA Approvals by Administration Route

(Source: PharmaCircle LLC)

Route	2011	2012	2013	2014	2015	2016
Buccal, Sublingual	2	2	2	2	3	2
Implantation	-	-	-	-	-	1
Inhalation	2	3	3	7	8	3
Injection	24	13	7	13	14	20
Intramuscular, Subcutaneous	2	6	6	8	6	4
Intrauterine	-	-	1	-	1	1
Intravenous (All)	13	11	14	19	18	19
Nasal	1	3	2	3	3	2
Ophthalmic	2	5	4	2	3	6
Oral	61	56	63	56	65	55
Otic	-	-	-	1	1	1
Subcutaneous	2	4	3	6	8	6
Topical	3	6	7	7	5	4
Transdermal	3	5	3	4	-	-
Vaginal	-	-	-	1	-	1
Other	1	3	2	3	2	0

Quick Takeaways - Table 2:

1. Despite the significant commercial success of Injectable products (IV, IM, SC) there is no obvious shift away from the approval of other administration routes.
2. Although there appears to be a drop in plain tablet approvals, there seems to be no drop in the approval numbers for oral dosage forms over the past 6 years.
3. Transdermal approvals, after a strong showing from 2011 through 2015, have seemingly lost their appeal. This may be an issue of the more complex molecules now being developed not being appropriate candidates for transdermal delivery.

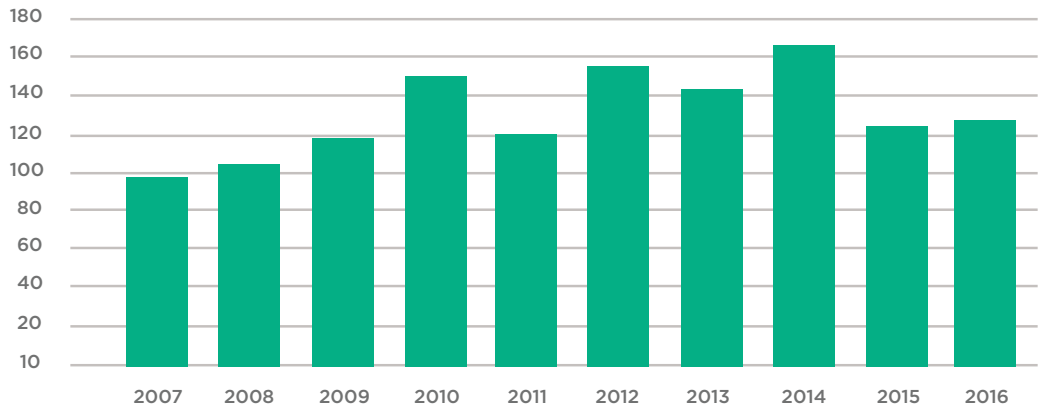
Drug Delivery & Formulation Approvals — A 10-Year Perspective, Europe & the US

It's worth reviewing the bigger picture in terms of geography and years. Chart 1 provides a summary of new drug delivery and formulation modified product approvals for the years 2007 through 2016 in the US and Europe. These approvals represent only the first approval for a drug delivery and formulation modified product. For example, a product approved in Europe in 2008, and then the US in 2009, would only be counted once, 2008 in Europe. In addition, these approvals do not include approvals for new indications of products that were previously approved, unless it represents a new dosage form and is categorized by PharmaCircle as a new product.

Takeaways from 2007-2016 US & EU Drug Delivery & Formulation Product Approvals:

There seems to be a general increase in combined EU & US drug delivery and formulation first approvals over the past 10 years ignoring usual year-to-year fluctuations. Comparing

Chart 1. 2007-2016 US & EU Drug Delivery & Formulation Product Approvals (Source: PharmaCircle LLC)



the combined European and US approvals for drug delivery and formulation products by Administration Route (Table 3) with the comparable FDA approvals (Table 2) reveals some geographic differences. Most notable is the relatively large number of European approvals for ophthalmic, inhalation, and topically administered products. These differences may be accounted for by smaller European companies gaining approvals in local markets. In general, it's most useful to look at trends rather than absolute numbers. With respect to trends, it seems that inhalation and ophthalmic products have very much been on the rise over the past few years.

Table 3. 2007-2016 US & EU Drug Delivery & Formulation Products, Approvals by Route (Source: PharmaCircle LLC)

Route	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Buccal, Sublingual	0	3	6	3	2	2	2	2	8	1
Inhalation	10	4	7	8	10	16	17	23	22	15
Injectable Total	24	28	32	20	24	20	24	28	24	28
Intrauterine	-	-	-	-	-	4	1	2	-	2
Nasal	3	4	4	3	5	12	9	13	3	5
Ophthalmic	7	15	10	55	32	45	45	59	27	31
Oral	29	27	30	30	23	30	27	20	18	20
Otic	-	-	-	4	3	2	-	4	2	2
Topical	14	13	20	18	18	21	15	11	18	13
Transdermal	8	6	3	2	5	3	3	3	5	10
Rectal	-	-	2	3	-	-	-	-	-	-
Vaginal	1	1	2	3	-	-	2	1	1	3
Other	4	4	3	5	4	1	2	3	1	1

Quick Takeaways - Table 3

1. After subtracting US approvals, there are a surprisingly large number of ophthalmic approvals in Europe, often from smaller companies with their own proprietary formulations using multisource actives.

2. There are also a relatively large number of European approvals for Inhalation products, possibly due to less onerous approval requirements.

Table 4. 2007-2016 US & EU Drug Delivery & Formulation Products, Approvals by Molecule Type

Molecule Type	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Small Molecule	83	104	94	144	130	139	137	160	123	126
Antibody	1	3	8	5	0	1	6	3	3	9
Carbohydrate	3	0	2	2	1	2	0	0	2	0
Cell Therapy & Gene	-	-	-	1	1	2	1	1	1	2
Oligonucleotide	-	-	-	-	-	-	1	-	-	-
Peptide	2	4	5	2	19	15	2	8	3	4
Protein	14	10	14	6	9	14	7	13	10	7
Small Molecule % of Total	81%	86%	76%	90%	81%	80%	89%	86%	87%	85%

In terms of the molecule types involved in drug delivery and formulation products, there seems to be little change over the past 10 years. As a percent of all new approvals, small molecule products have consistently accounted for about 85% of all approvals.

Final Thoughts

Overall, the number of drug delivery and formulation enhanced and enabled product approvals has gradually risen over the past decade in the US and European markets. What really hasn't changed is the types of technologies underlying these products and the benefits they offer. Significant opportunities lie in developing technologies that can improve the specificity and convenience of macromolecules. Some of these newer technologies are presented in the Notable Technologies section of this report. ■

Notable Drug Delivery & Formulation Approvals of 2016

Adzenys XR

Active: amphetamine
Molecular Weight[1]: 135
Indication: ADHD
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Neos Therapeutics
First Approval: 2016-01-27 (US)
DD Category: Conventional Melt Tablets, Oral Ion Exchange MR, Taste Masking
Technology Provider: Neos Therapeutics
Dosage Form: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: 4.3 Years
Notable: Adzenys XR is another in the line of differentiated dosing options for amphetamine-based ADHD medications targeting the pediatric population. Adzenys XR hits a formulation trifecta of sorts, taste masking, extended release and ODT technologies all wrapped up in a patient friendly dosage form.

Belviq XR

Active: lorcaserin
Molecular Weight[1]: 196
Indication: Obesity
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Arena Pharmaceuticals
First Approval: 2017-01-04 (US)
DD Category: Oral Matrix MR
Technology Provider: Undisclosed
Dosage Form: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: 2.5 Years
Notable: A logical follow on to immediate release Belviq that was approved by the FDA in 2012. Belviq XR extends the dosing interval from twice- to once-daily. Development and approval time was a rather short 2.5 years as estimated from the date of the IND filing.

Probuphine

Active: buprenorphine
Molecular Weight[1]: 468
Indication: Opioid Dependence
Delivery Route: Implant
Dosing Interval: 6 Months
Company: Braeburn Pharmaceuticals
First Approval: 2016-05-26 (US)
DD Category: Injectable Non-biodegradable Polymeric Implants
Technology Provider: Titan Pharmaceuticals (ProNeura Implant)
Dosage Form: Injection - Implant
Review Status: Priority Review (FDA)
Development/Approval Time[2]: ~13 Years
Notable: Probuphine is comprised of a set of four rod shaped implants that are inserted into the upper arm. Offering 6 months of continuous buprenorphine release, Probuphine eliminates the need for patient compliance and in many ways reduces the potential for abuse and misuse. Market acceptance a year after launch is slow with one analyst estimating 2020 sales to reach about $70 million.

Dexilant Solutab

Active: dexlansoprazole
Molecular Weight[1]: 369
Indication: Esophagitis, Gastroesophageal Reflux
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Takeda Pharmaceutical
First Approval: 2016-01-26 (US)
DD Category: Oral Enteric/Delayed Release, Conventional Melt Tablets
Technology Provider: Takeda Pharmaceutical
Dosage Form: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: Unknown
Notable: Another product in Takeda's extensive portfolio of lansoprazole derived pharmaceuticals. Dexilant Solutab is the active isomer of lansoprazole formulated using delayed release and oral disintegrating technology. Interestingly, this (R)-(+) enantiomer has the same binding affinity as the (S) enantiomer but a five-fold greater AUC.

1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
2. Development times are calculated from the earlier submission of a first IND, or first clinical trial, through to first approval in the USA and represent both clinical development and regulatory review times.

Intrarosa

Active: prasterone
Molecular Weight[1]: 288
Indication: Vaginal Atrophy
Delivery Route: Vaginal
Dosing Interval: 24 Hours
Company: EndoCeutics
First Approval: 2016-11-16
DD Category: Vaginal Insert/Devices
Technology Provider: Not Disclosed
Dosage Form: Vaginal Insert
Review Status: Standard Review (FDA)
Development/Approval Time[2]: Unknown
Notable: More companies are looking to underserved markets for therapeutic and commercial success. Vaginal formulations, like rectal formulation, are rarely developed except for locoregional indications. Prasterone (dehydroepiandrosterone) is more notable for its pharmacology, it is a weak androgen that still has somewhat selective effects on estrogen receptors.

Strimvelis

Active: Transfected Autologous CD34+ Cells
Molecular Weight[1]: Not Applicable
Indication: Adenosine Deaminase Deficiency
Delivery Route: Injection, Intravenous
Dosing Interval: One Time Only
Companies: Fondazione Telethon, GlaxoSmithKline
First Approval: 2016-05-26 (EU)
DD Category: Retrovirus Vectors
Technology Provider: MolMed
Dosage Form: Injection Suspension
Review Status: Unknown
Development/Approval Time[2]: 12+ Years
Notable: Trials that started more than 25 years ago have resulted in the European approval of Strimvelis, CD34+ cells transfected with the ADA gene. This approach promises long term, possibly lifelong, treatment of ADA deficiency and suggests additional opportunities for more common genetic diseases associated with protein deficiencies that are currently treated with replacement protein therapy. It's possible to imagine the development of a gene therapy for ADA that is administered directly, without the need and expense of ex-vivo transfection.

Troxyca ER

Actives: oxycodone, naltrexone
Molecular Weights[1]: 315, 341
Indication: Chronic Pain
Delivery Route: Oral
Dosing Interval: 12 Hours
Company: Pfizer
First Approval: 2016-08-19 (US)
DD Category: Oral Barrier Film & Microparticles, Abuse Resistant, Oral
Technology Provider: Alpharma (Pfizer)
Dosage Form: Oral Capsule
Review Status: Standard Review (U.S.)
Development/Approval Time[2]: 10 Years+
Notable: This is the Alpharma/King/Pfizer product that has been in development for more than a decade. It is a partner to Pfizer's Embeda (morphine/naltrexone) combination approved in 2009 that has been on and off the market since then. While the combination of oxycodone and naltrexone is well known, this formulation incorporates extended release technology for the oxycodone component.

Xtampza ER

Active: oxycodone
Molecular Weight[1]: 315
Indication: Chronic Pain
Delivery Route: Oral
Dosing Interval: 12 Hours
Company: Collegium
First Approval: 2016-04-26 (US)
DD Category: Oral Barrier Film & Microparticles, Abuse Resistant, Oral
Technology Provider: Collegium
Dosage Form: Oral Capsule
Review Status: Standard Review (FDA)
Development/Approval Time[2]: 9 Years
Notable: Xtampza ER represents the second extended release oxycodone oral tablet approved by the FDA with abuse deterrent/resistant labeling. Xtampza is expected to compete with Purdue's OxyContin, with little to distinguish it beyond it being a capsule in contrast to OxyContin's tablet. Xtampza ER is expected to capture sales in excess of $20 million in 2017 that will is forecast to grow to about $400 million by 2022.

1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
2. Development times are calculated from the earlier submission of a first IND, or first clinical trial, through to first approval in the USA and represent both clinical development and regulatory review times.

Sustol

Active: granisetron
Molecular Weight[1]: 312
Indication: Nausea, Emesis
Delivery Route: Injection, Subcutaneous
Dosing Interval: >7 Days
Company: Heron Therapeutics
First Approval: 2016-08-09 (U.S.)
DD Category: Biodeg. Non-PLGA Microcaps/ Implants
Technology Provider: Heron Therapeutics
Dosage Form: Injection Liquid
Review Status: Standard Review (US)
Development/Approval Time[2]: 11.5 Years
Notable: Unlike other antiemetics that have a duration of action of up to 48 hours, Sustol is claimed to offer a full 5 days of protection. Acceptance is expected to be positive with analysts forecasting peak sales in excess of $500 million.

Zalmoxis

Active: HSV-TK Expressing Allogeneic T-Cells
Molecular Weight[1]: Not Applicable
Indication: Stem Cell Transplantation Immune Reconstitution
Delivery Route: Infusion, Intravenous
Dosing Interval: 21 to 49 Days
Company: MolMed
First Approval: 2016-08-18 (EU)
DD Category: Cell Encapsulation
Technology Provider: MolMed
Dosage Form: Injection suspension, Frozen
Review Status: Unknown
Development/Approval Time[2]: 12+ Years
Notable: This adjunctive therapy to Stem Cell transplantation represents one of the future directions for drug delivery, the incorporation of a cellular 'factory' in transplanted cells that produce desired therapeutics or therapeutic effects. These drug delivery 'factories' offer the potential for extended durations of action and possible regulation through administered agents. In the case of Zalmoxis, ganciclovir can be used to downregulate or kill the T-cells carrying the HSV-TK 'suicide gene'.

1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
2. Development times are calculated from the earlier submission of a first IND, or first clinical trial, through to first approval in the USA and represent both clinical development and regulatory review times.

2015 Drug Delivery & Formulation Approvals: One Year Later

Product: Adynovate (Baxalta/Shire)
Update: With the acquisition of Baxalta by Shire mid-2016 Adynovate sales performance figures are no longer available but have been rolled into the general Legacy Hemophilia Brands category for the purpose of reporting. This category though is expected to grow from $1.7 billion in 2016 to $2.9 billion by 2020.

Product: Belbuca (BioDelivery Sciences)
Update: Originally licensed to Endo, the rights to Belbuca were returned to BDSI in late 2016, with BDSI taking over commercialization responsibilities. Sales for 2017 are forecast to reach $20-25 million and grow to over $70 million by 2020.

Product: Dyanavel XR (Tris Pharma)
Update: Little information is available concerning the performance of this product beyond a press release announcing its commercial launch by Tris in April of 2016.

Product: Spritam (Aprecia Pharmaceuticals)
Update: Approved in July of 2015, there is little information available concerning Spritam's commercial performance. It is currently being marketed by Prasco Laboratories who describe themselves as focused on "generics and targeted brand opportunities."

Product: Quinsair (Raptor Pharmaceuticals)
Update: Raptor is no more, acquired by Horizon Pharma in the fourth quarter of 2016. Sales of Quinsair have been disappointing, totaling only $1 million in 2016 with analyst sales estimates ranging from $20 to $60 million by 2020.

Product: Onivyde (Baxalta/Shire, Merrimack)
Update: Following approval in late 2015, Merrimack divested Onivyde and a Doxil generic to Ipsen for $575 million in April 2017. US sales for Onivyde reached $53 million in 2016.

Product: Invega Trinza (Janssen Pharmaceuticals)
Update: Approved by the FDA as a 3-month depot medication for the treatment of schizophrenia, Invega Trinza was subsequently approved for the same use in Europe in 2016. The Invega depot franchise, comprising Sustenna and Invega, grew to $2.2 billion worldwide in 2016 from $1.8 billion the previous year.

Product: Otiprio (Otonomy)
Update: Otiprio, a longer acting formulation of ciprofloxacin for pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement, gained limited uptake in 2016 with reported sales of less than $1 million. Analyst estimates have Otiprio sales growing to about $50 million by 2020.

Product: Aristada (Alkermes)
Update: Alkermes' Aristada seems to be on a positive trajectory with sales of almost $50 million in 2016 that are forecast to reach $500 million by 2020. A 2016 submission to the FDA requested extending the dosing interval from 6 weeks to 2 months.

Product: Zohydro ER (Pernix)
Update: This extended-release formulation of hydrocodone approved in early 2015 and launched midyear, captured sales of $16 million and $25 million in 2015 and 2016, respectively. The company announced a manufacturing issue with one of the dosage strengths in May 2017 that would restrict supply of the 20-mg strength through to 2018.

3. Drug Delivery Related Transactions: 2016 in Review

2016 was a little unique in that there were no blockbuster drug delivery and formulation deals or transactions to suggest there was any shift in the industry's general strategic direction.

Overall, Drug Delivery related transactions continue to be depressed relative to the high-water mark of 2007 when one deducts amendment and termination deals from the total (New Deals). 2016 was in many ways comparable to 2014 and 2015 in terms of New Deals, with a total of 341 transactions, 12% below the 10-year average. Overall Pharma transactions, including Drug Delivery related transactions, have averaged 1,519 per year with 2016 being about 6% over the 10-year average.

Table 1. Deals and Transactions - Ten Year Summary (Source: PharmaCircle LLC)

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Company Acquisitions	28	19	13	9	21	14	30	24	22	19
DD Technology Deals	164	113	126	115	128	122	120	89	89	92
Discovery Technology Deals	6	4	4	7	6	7	6	6	5	9
Joint Venture Deal	4	1	5	4	4	0	4	2	2	1
Option Agreement	3	6	5	12	9	8	10	5	6	6
Pharma Services Deals	23	28	22	28	26	26	36	29	23	31
Product Acquisitions	17	19	26	16	19	17	19	25	18	12
Product Deals	241	230	221	179	172	147	164	163	166	168
Technology Acquisitions	6	8	12	8	6	1	4	2	4	3
Amendment Deals	15	13	19	22	12	12	46	40	43	30
Termination Deals	18	9	10	19	19	16	12	27	17	19
Grand Total	525	450	463	419	422	370	451	412	395	390
'New Deals'	492	428	434	378	391	342	393	345	355	341
All Pharma 'New Deals'	1526	1440	1422	1470	1517	1464	1600	1479	1670	1603

The drop in transactions falls primarily in the areas of Drug Delivery Technology Deals and Product Deals involving Drug Delivery technologies. While Drug Delivery Technology Deals in 2016 were consistent with the figures for the previous two years, they were down about 20% from the 10-year average. In the case of Product Deals, 2016 totals were down about 9% versus the 10-year average.

The only area of deal making in 2016 that saw an uptick was Pharma Service Deals, which totaled 31, about 14% over the 10-year average. This figure doubtlessly underestimates the number of these Pharma Service Deals, although it may capture the overall trend, as it only tracks announced deals.

If these figures represent the macro view of Drug Delivery and Formulation transactions in 2016, there is more to be learned by examining the types of transactions and their particulars. The more interesting segments, Drug Delivery Technology, Drug Delivery Product, and Drug/Device Transactions as well as Drug Delivery Asset Acquisitions, are examined in more detail further on.

Drug Delivery and Formulation Transactions

Technology Transactions

There were a total of 92 Drug Delivery Technology deals in 2016 as captured by PharmaCircle. None of these deals seemed to define a new paradigm, or suggested a new area of interest for drug delivery related products. Among the transactions there were four themes worth noting – Technologies (Abuse Deterrent), Drug-Device, Products, and Company Acquisitions.

Abuse Deterrent Formulation Transactions

Despite a downward trend in opioid prescribing in the U.S., there continued to be interest in developing new abuse deterrent formulations for the U.S. market. Deals involving abuse deterrent technology ranged from technology licenses to product commercialization agreements.

Transaction	Deal Type	Technology Owner	Licensee / Partner	Stage of Development	Technology	Product(s)	Territory	Deal Value
KemPharm Licenses Acura Abuse-Deterrent Technology	Technology License	Acura Pharmaceuticals	KemPharm	Phase 1	Aversion	KPR201/IR KP606/1R	Not Disclosed	$3.5M
Grunenthal Selects Patheon for Abuse Deterrent Formulations Technology	Technology Development	Grunenthal	Patheon (CMO)	Undisclosed	INTAC	Undisclosed	World	Not Disclosed
Daiichi Sankyo Licenses Inspirion Abuse - Deterrent Formulations Technology	Product License	Inspirion Delivery Sciences	Daiichi Sankyo	Approved	SentryBond	MorphaBond ER	USA	Not Disclosed
SkyePharma Licenses Lucideon's Abuse-Deterrent Technology	Technology License	Lucideon	SkyePharma (Vectura)	Preclinical	iCRT-deter	Undisclosed	USA	£4M

Other Technology Transactions

Beyond abuse deterrent transactions, there were no consistent themes in terms of drug delivery and formulation technology related transactions. For the first time in several years, Halozyme didn't announce an Enhanze licensing deal. The Monosol agreement with Lupin in the area of pediatric formulations using their PharmaFilm technology represents a low risk initiative to treat a largely ignored market segment. On the other hand, Daiichi Sankyo's agreement with Nitto Denko to develop products based on their Passport Patch technology seems to be speculative. The Passport Patch technology has been in development for almost two decades with no approved or, at present, clinical stage products to show for the investment.

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Other Technology Transactions

Transaction	Deal Type	Technology Owner	Licensee	Stage of Development	Technology	Product(s)	Territory	Deal Value
Lupin to Develop Pediatric-Focused Products	Technology License	MonoSol RX	Lupin	Research	PharmFilm	Pediatric Programs	Not Disclosed	Not Disclosed
Accelarating Commercialization of PassPort System	Technology / Product Collaboration	Nitto Denko	Daiichi Sankyo	Research	PassPort Patch	Not Disclosed	Not Disclosed	Not Disclosed

Drug-Device Transactions

Drug-Device transactions continued in 2016, mostly in the area of Injectables. A notable exception was Vectura and Propeller entering into a joint development agreement for digitally connected inhalers that remind patients to take their medications and record actual usage for physician follow up.

Drug-Device Transactions

Transaction	Deal Type	Technology Owner	Licensee	Stage of Development	Technology	Product(s)	Territory	Deal Value
Inovio Acquires Needle-Free Injection Technology	Company Acquisition	Inovio Pharmaceuticals	Bioject Medical Technologies	Phase 1 & 2	Biojector 2000 Zetajet Iject	Multiple	Worldwide	$5.5M
Aptar Licenses Novel Auto-Injector	Joint Development	Aptar Pharma	Becton Dickinson	Not Disclosed	Pro-JectBD Neopak BD Hypak SCF Glass	Not Disclosed	Not Disclosed	Not Disclosed
SmartDose Technology Used with Pushtronex System	Product Approval Announcement	West Pharmaceutical Services	Amgen	Marketed	SmartDose Electronic Patch Injector	Repatha SmartDose	Not Disclosed	Not Disclosed
Ypsomed Collaboration for Insulin Pump Therapy	Product Approval Announcement	Ypsomed	Novo Nordisk	Marketed	YpsoPump	NovoRapid PumpCart	Not Disclosed	Not Disclosed
Insulet Agreement with Eli Lilly for OmniPod	Development Agreement	Insulet Corp.	Eli Lilly	Phase 1	Omnipod for Humalog U200	Humalog U200 Omnipod	Not Disclosed	Not Disclosed
Vectura and Propeller Health to Develop Digitally-Connected Inhalers	Joint Development	Vectura Group Plc	Propeller Health	Not Disclosed	GyroHaler Propeller	Not Disclosed	Not Disclosed	Not Disclosed

Company Acquisitions

The past year saw the acquisition of two companies that had been very visible players in the Drug Delivery sector. SkyePharma, founded on the basis of Jago technology, was a major player in the 1990s and the early 2000s with a diversified platform of Oral, Inhalation, and Injectable technologies that were parlayed into a large number of approved products worldwide. With time, ongoing financial challenges, and a seeming inability to reinvent itself, Skyepharma was acquired last year by Vectura for £441 million. Alexza, dedicated to developing inhaled psychotropics based on its Staccato inhalation technology, managed to get a number of products to the clinic but only one, Adasuve, to approval. Even after approval, Adasuve continued to be a drain on the Alexza resources, ultimately leading to its acquisition by one of its Adasuve licensees, Grupo Ferrer for $35 million. ■

Company Acquisitions

Transaction	Deal Type	Acquirer	Acquired	Stage of Development	Technology	Product(s)	Founded	Deal Value
Vectura Acquires Skyepharma	Company Acquisition	Vectura Group	SkyePharma	Marketed Products	Multiple (Oral, Inhalation, Injectable)	Multiple	1983 (Jago)	£441M
Ferrer Acquires Alexza	Company Acquisition	Groupo Ferrer Internacional	Alexza Pharmaceuticals	Marketed Products	Staccato (Inhalation)	Adasuve	2000	$35M

2015 Drug Delivery Related Transactions: One Year Later

Licensor / Licensee: Janssen / Depomed
Product(s): Nucynta (tapentadol) Franchise
Update: This billion dollar licensing deal has led to 2016 sales of $281 million. Analysts project Nucynta franchise sales to reach $360 million by 2020. Good but not great, the brand is being negatively impacted by the concern about the opioid prescription contribution to the opioid epidemic in the U.S.

Seller / Acquirer: Sigma-Tau / Baxalta (Shire)
Product(s): Oncaspar, calaspargase pegol
Update: A $900 million dollar deal that perhaps contributed to the Shire acquisition of Baxalta in 2016. Oncaspar is now approved in 37 countries with sales in the range of $100 million. Calaspargase pegol is currently listed as in Phase 3 for ALL.

Licensor / Licensee: Emisphere / Novo Nordisk
Technology(s): Eligen (Oral Bioavailability Enhancer)
Update: Novo Nordisk has an Eligen formulated GLP-1 receptor agonist, semaglutide, in Phase 3 testing for the Treatment of Type 2 diabetes.

Company: BioDelivery Sciences International
Product: Onsolis (fentanyl buccal)
Update: After reacquiring the U.S. rights to Onsolis from Meda in 2015, BioDelivery Sciences International proceeded to license the rights to Collegium in 2016 in a $25 million, a largely back loaded, deal. The product is awaiting FDA approval for a Prior Approval Supplement before being relaunched in 2018.

Licensor / Licensee: Halozyme / AbbVie
Technology: Enhanze (Injection Site Absorption Enhancer)
Update: The agreement permitted AbbVie to apply Enhanze to as many as nine targets. The first target, Humira, entered Phase 1 testing in 2016 and was discontinued later in the year. No other targets have been publicly disclosed.

Licensor / Licensee: Acura / Egalet
Product: Oxaydo (IR oxycodone)
Update: Licensed and launched in 2015, Egalet grew Oxaydo sales to $5 million in 2016. Analysts have it growing to $40 million by 2020. While not a large product in terms of sales, it allows Egalet to establish a commercial presence while their proprietary pipeline progresses to approval in the U.S.

Licensor / Licensee: Luitpold / Egalet
Product: Sprix (Nasal ketorolac)
Update: Egalet also licensed in this nasal analgesic in 2015 and reported sales of $11.9 million in 2016. This may be close to the high water mark for Sprix as analysts expect sales to drop to $4 million by 2020. In an attempt to bolster sales Egalet partnered with Septodont in 2016 to extend promotion to dentists.

Licensor / Licensee: AstraZeneca / Daiichi Sankyo
Product: Movantik (U.S.)
Update: AstraZeneca partnered with Daiichi Sankyo in 2015 to co-promote Nektar's Movantik. Sales in 2016 seem to be lagging expectations totaling $90 million in the U.S., in its second full year post launch.

4. The Drug Delivery & Formulation Pipeline

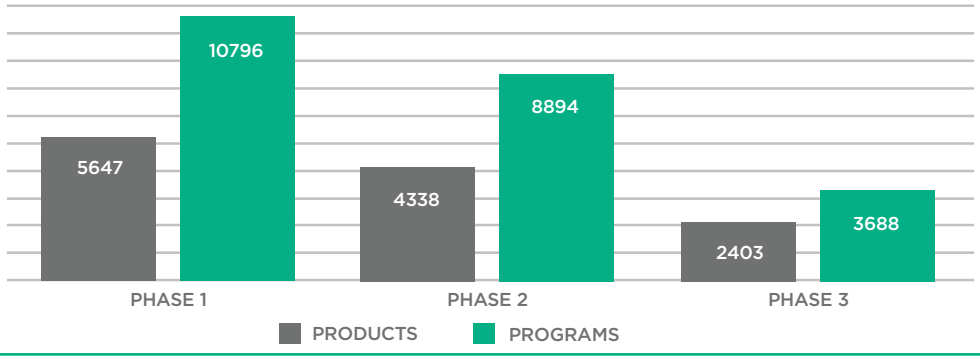
An overview of the current global pipeline for drug delivery and formulation enabled and enhanced products provides a sense of what is out there and what we might expect. This short review uses the terms Products and Programs. A Product is, well, a product, an entity that is unique in terms of its dosage form, active, and manufacturer.

A Product may have different dosage strengths and different distributors. Two companies selling the same product, will be considered different Products. For this analysis, generics have been excluded. That may still mean that two separate companies might be selling separate Products that are not generics but have similar characteristics. An example would be the many different abuse deterrent formulations of oxycodone approved and in development.

Programs refer to the various development programs, or indications, for a Product. These Programs are counted by development phase. A clinical stage product being developed for breast, colorectal, and lung cancers would be considered as one Product and three Programs. In many ways, Programs better represent pipelines as a Product may fail for one indication but be successful in another.

Assessing whether a Product or Program includes a drug delivery or formulation technology is tricky, and is determined by PharmaCircle analysts according to standard methodology. Early stage Products in many cases offer little information about their formulation status. This helps explain why the proportion of drug delivery and formulation products and programs increases as products progress from Phase 1 to Phase 3. Drug delivery and formulation impacted Products and Programs, identified as DDS in the tables, include those products and programs for which some substantial technology has been applied. This can vary from the use of controlled release technology, a delivery device, to a solubilizing agent or milling processes. In general, simple oral and injectable formulations are not considered to be DDS products.

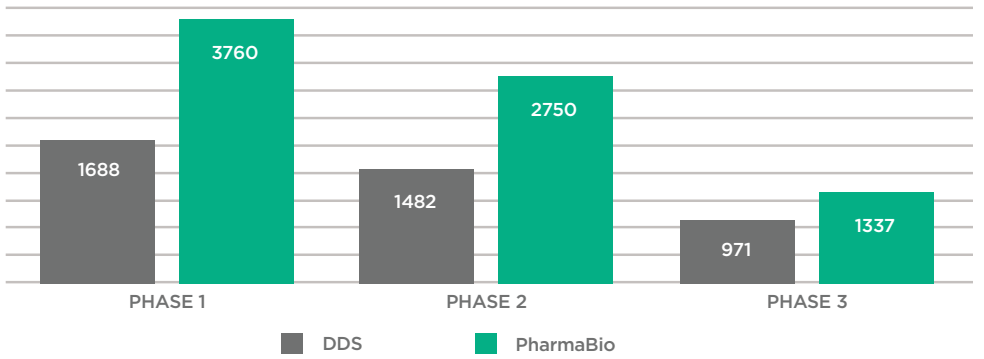
Chart 1. Pharmaceutical Pipeline, Products and Programs by Phase (PharmaCircle, 2017-07)



Quick Takeaways - Chart 1:

1. There are on average about two Programs for each Product.
2. Early stage Products and Programs are underrepresented as there is limited disclosure of early stage Products and Programs.

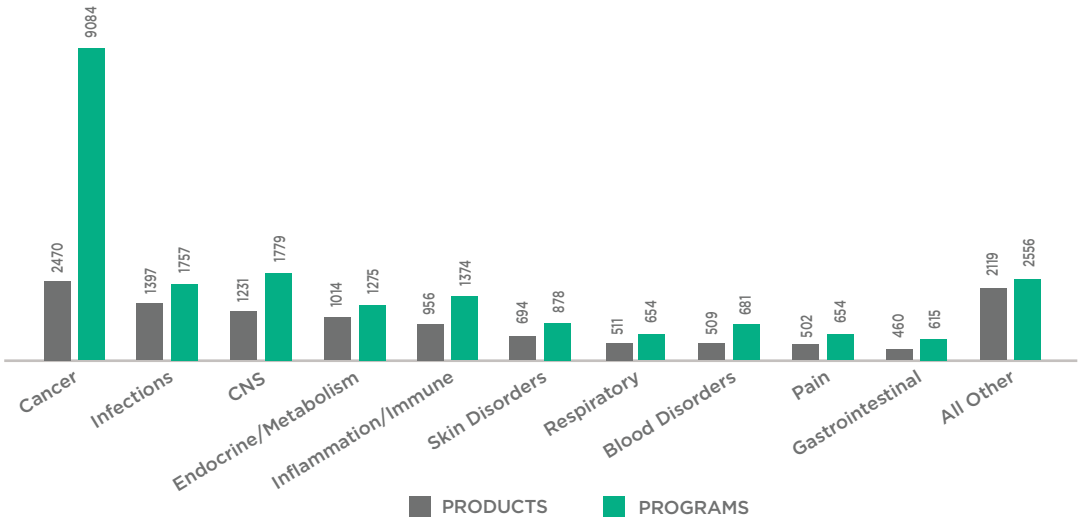
Chart 2. Pharmaceutical Pipeline, Products by Phase (PharmaCircle, 2017-07)



Quick Takeaways - Chart 2:

1. The figures in Chart 2 relate to Products only.
2. The number of drug delivery and formulation Products increase in the more advanced phases possibly because of additional information revealing their underlying technologies.

Chart 3. Therapeutic Categories, Total Products and Programs Phase 1, 2 & 3 (PharmaCircle, 2017-07)



Quick Takeaways - Chart 3:

1. Cancer based therapeutics are clearly the number one therapeutic area of pipeline development and sport an almost 4 to 1 ratio of Programs to Products.
2. All Other includes, in decreasing order of Product and Program numbers; Musculoskeletal, Ophthalmic, Genitourinary, Women's and Men's Health, as well as multiple other therapeutic categories with 50 or less identified Products in clinical development.

5. Notable Drug-Device Approvals: 2016 in Review

Drug-Device products are a loosely related combination of pharmaceutical active and integral delivery device. These integral delivery devices can vary widely, from coronary stents to metered dose inhalers to autoinjectors.

What is, and isn't, an integral device can be debated. For the purpose of this analysis, in terms of injection related systems, prefilled syringes are included, as are autoinjectors, but not products that require an external infusion device. Drug-Device products that require a device for pulmonary or nasal delivery are also included. Table 1 below, summarizing global approvals for the years 2007 to 2016, provides a sense of the pace of global drug-device approvals over the past 10 years.

Table 1. Drug-Device First Approvals 2007-2016 (PharmaCircle LLC)

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Injection	18	18	42	18	23	18	19	26	23	20
Surgical Insertion	4	7	7	11	6	6	6	8	2	2
Inhalation	6	0	6	5	5	6	7	13	6	5
Nasal	2	4	6	2	7	3	2	3	1	6
Ophthalmic	0	2	4	1	2	3	1	1	1	2
Topical	3	2	2	0	1	0	1	1	1	1
All Other	0	3	0	1	2	3	1	1	3	2
Total	33	26	67	41	48	40	39	58	41	43

Quick Takeaways - Table 1:

1. Injection related drug-device approvals are by far the most common and represent in large part the industry's move to enable outpatient self-administration of biologics, notably insulin.
2. The large bump in 2009 approvals is related to a variety of intradermal injection drug-device approvals for cosmetic related indications, notably in Asia.
2. Surgical Insertion refers primarily to drug coated stents.

Drug-Device enhancements over the past few years have generally been incremental and largely predictable in terms of features and performance. Prefilled syringes and autoinjectors accounted for the largest number of 2016 approvals (16/43), followed somewhat surprisingly by nasal drug-delivery products. Among the autoinjector approvals there was little apparent innovation, often limited to enhanced grips or triggers for autoinjectors. Two exceptions were Companion Medical's InPen, an insulin pen that interfaces with a smartphone, and Amgen's hands-free delivery system, Repatha Pushtronex, using West Pharmaceutical Services SmartDose technology to permit once monthly dosing. Both products provide a greater integration of smart device type technologies than has been the norm in this sector.

Nasal delivery saw a couple of interesting twists with Avanir's Onzetra Xsail using an unusual device to direct the force of the patient's exhalation to efficiently deliver sumatriptan to the nasal sinuses. Kovanaze ingeniously delivers a tetracaine/oxymetazoline combination with a simple needleless syringe to the patient's sinuses area to provide dental anesthesia. While the device technology is far from cutting edge, the concept of providing patients with an alternative to dental injections should prove popular.

For the most part though, the 2016 drug-device approvals leaned on well-worn strategies and validated technologies. The significant hardware and software advances seen in other areas of industrial and consumer technology have yet to be applied to drug-device pharmaceutical products. The needs and necessary technologies exist to deliver a new generation of drug-device products, the question is when will we see these new products reach the marketplace.

Notable Drug-Device Approvals of 2016 highlight last year's more interesting approvals, with a little bit of detail. ■

Notable Drug-Device Approvals of 2016

Product: Onzetra Xsail
Indication: Migraine
Delivery Route: Nasal
Approval: 2016 (U.S.)
Company: Avanir (Otsuka)
Technology/Device Provider: OptiNose US
Active: Sumatriptan
Formulation Type: Nasal Powder
Integral Device: OptiNose Powder Device
Notable: This rather unusual drug-device combination uses the force of breath exhalation to deliver the therapeutic efficiently and effectively to the nasal passages. By placing the delivery tube into one nostril and then exhaling through another tube the drug is efficiently delivered to the sinus cavities while preventing delivery to the pharyngeal area.

Product: Breelib/Ventavis
Indication: Pulmonary Arterial Hypertension
Delivery Route: Inhalation, Nebulization
Approval: 2016 (EU)
Company: Bayer Healthcare
Technology/Device Provider: Vectura Group
Active: Iloprost
Formulation Type: Inhalation Solution
Integral Device: FOX Smart Nebuliser
Notable: This new drug-device combination targeted to the treatment of pulmonary arterial hypertension uses the established Ventavis formulation delivered with Vectura's FOX inhalation device. The Breelib/Ventavis combination co-ordinates delivery with patient breathing to better ensure deposition in the well-ventilated portions of the lung. Inhalation times are also significantly reduced from 11 to 3 minutes.

Product: MiniMed 670G
Indication: Type 1 Diabetes
Delivery Route: Infusion, Subcutaneous
Approval: 2016 (U.S.)
Company: Medtronic
Technology/Device Providers: Medtronic, Ascensia Diabetes Care
Active: Insulin
Formulation Type: Injection Solution
Integral Device(s): MiniMed 670g, Guardian Sensor
Notable: Medtronic captured a pair of approvals in 2016 for their MiniMed 630G and 670G insulin pumps that further improve the performance and convenience to the systems. The MiniMed 670G system offer a hybrid closed loop system that self-adjusts to keep glucose levels in the target range.

Product: Repatha SmartDose
Indication: Evolocumab
Delivery Route: Infusion, Subcutaneous
Approval: 2016 (U.S.)
Company: Amgen
Technology/Device Providers: Medimop Medical Projects, West Pharmaceutical Services
Active: Evolocumab
Formulation Type: Injection Solution
Integral Device: SmartDose Electronic Patch Injector
Notable: An alternative to three separate injections using a prefilled autoinjector, the SmartDose on-body infuser is a two component, semi-disposable electronic patch injector system for the subcutaneous injection of high volume, high viscosity medications. Dosing is programmable. The system features integrated needle technology, audible and visual instructions, and compatibility with pre-filled Crystal-Zenith cartridges. The infusion period is about nine minutes.

Editor's Insight: The MiniMed 670G system with SmartGuard® HCL technology offers two new levels of personalization: The Suspend before low option avoids lows and rebound highs proactively by automatically stopping insulin 30 minutes before you reach your pre-selected low limits, then automatically restarts insulin when your levels recover, all without bothersome alerts. The Auto Mode option automatically adjusts basal insulin delivery every 5 minutes based on sugar levels to keep users in their target range, all day and night.

Product: Taltz Autoinjector
Indication: Psoriasis
Delivery Route: Injection, Subcutaneous
First Approval: 2016 (U.S.)
Company: Eli Lilly
Technology/Device Provider: Eli Lilly
Active: Ixekizumab
Formulation Type: Injection Solution
Integral Device: Taltz Autoinjector
Notable: Another year and another crop of autoinjectors with improved ergonomics. The Taltz device is disposable after single use and is designed with user friendly features, such as a non-slip grip, audible and visual injection confirmation, a flared base, which also serves as protective cap, and a locking mechanism to prevent accidental activation.

Product: NovoRapid PumpCart
Indication: Diabetes
Delivery Route: Injection, Subcutaneous
Approval: 2016 (EU)
Companies: Novo Nordisk, Roche
Technology/Device Provider: Ypsomed Holding
Active: Insulin
Formulation Type: Injection solution
Integral Device: YpsoPump
Notable: An insulin pump for continuous infusion of insulin. YpsoPump consists of a reusable module: power unit including motor, control, and energy source; and a Disposable module: integrated 3-ml insulin cartridge and infusion set. YpsoPump is fully compatible with NovoRapid PumpCart, eliminating the need for patients to manually fill the insulin reservoir.

Product: Cimzia AutoClicks
Indication: Rheumatoid Arthritis
Delivery Route: Injection, Subcutaneous
Approval: 2016 (EU)
Company: UCB Pharma
Technology/Device Providers: Bespak, Oxo
Active: Certolizumab Pegol
Formulation Type: Injection Solution
Integral Device: AutoClicks
Notable: This new device option for Cimzia is intended to provide a patient-friendly benefit to better compete with other drug-device injectables. Cimzia AutoClicks, a disposable consumer-friendly design and features a button-less injection activator autoinjector, is based on Bespak's ASI platform developed in partnership with OXO, a household products company.

Product: InPen
Indication: Diabetes
Delivery Route: Injection, Subcutaneous
Approval: 2016 (U.S.)
Company: Companion Medical
Technology/Device Provider: Companion Medical
Active: Insulin
Formulation Type: Injection Solution
Integral Device: InPen
Notable: The InPen smart insulin delivery system is a wireless-enabled reusable insulin pen with a proprietary mobile application compatible with Humalog and Novolog rapid acting insulins. In addition to the usual pen performance, InPen offers a dose calculator, a logbook, a display of last dose and remaining insulin, and the ability to share a usage summary with healthcare providers. The InPen currently has an Apple iOS HealthKit app with an Android app in development.

Editor's Insight: Following the successful and controlled launch of the mylife™ YpsoPump® during 2016 in Germany, the Netherlands, and the UK, Ypsomed Group has decided in favor of geographic expansion. In addition to the existing home markets, such as France, Italy, Switzerland, Austria, and Scandinavia, the innovative insulin pump is also to be launched in Belgium, Spain, and India during 2017. The mylife™ YpsoPump® is already available in Czechia since January 2017, where the subsidiary was established at the end of 2016, mainly for its distribution.

Product: Flexilev
Indication: Parkinson's
Delivery Route: Oral
Approval: 2016-04-01 (EU)
Company: Sensidose
Technology/Device Provider: Sensidose
Actives: Carbidopa, Levodopa
Formulation Type: Micro Tablet, Device
Integral Device: MyFID
Notable: What sets Flexilev apart is the use of the MyFID device to dispense micro tablets allowing for more precise dosing and compliance management. Each micro tablet (5 mg) represents about 1/20th of a usual starting dose (100 mg). The number of tablets dispensed can be adjusted by the patient as per physician instructions. The device also provides dosing reminders, records doses dispensed, and permits the recording of patient symptoms.

Product: Zembrace SymTouch
Indication: Migraines
Delivery Route: Injectable, Subcutaneous
Approval: 2016 (U.S.)
Company: Dr. Reddy's
Technology/Device Provider: SHL Group
Active: Sumatriptan
Formulation Type: Injection Solution
Integral Device: SymTouch (Molly)
Notable: Another fixed single-dose disposable autoinjector, Zembrace SymTouch offers users a simple two-step button free injection process. SymTouch is a customized version of SHL's Molly Disposable Autoinjector technology.

2015 Drug-Device Approvals: One Year Later

Product: Duodopa (AbbVie)
Update: First approved in 2004 in Europe, Duodopa received U.S. approval in 2015, and Japanese approval in 2016. Sales in the U.S. reached $37 million with rest of world sales accounting for another $256 million. One analyst estimate has Duodopa exceeding $600 million in sales globally by 2021.

Product: Liletta (Medicines 360/Allergan)
Update: Much of the news surrounding Liletta in 2016 concerned Medicines 360 expanding product access for this intrauterine device internationally. Allergan reported sales of $23 million in 2016, versus $15 million in 2015.

Product: Repatha Pen (Amgen)
Update: The big news in 2016 concerned Amgen's successful defense of their patents claiming monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9). Analysts forecast Amgen's sales of the Repatha franchise will reach $2 billion by 2021.

Product: Praluent Pen (Regeneron/Sanofi)
Update: Following approval in the U.S., Praluent pen has been approved in Europe (2015) and Japan (2016). The flip side of Amgen's patent win with Repatha was Sanofi/Regeneron's patent loss with Praluent, which is now estimated to reach annual sales of about $1.5 billion by 2021.

Product: Ionsys (The Medicines Company)
Update: Following approval in the U.S in early 2015, Ionsys was approved in Europe later in the year. Sales for 2016 were $16 million. The company recently announced the withdrawal of the product from the U.S. market for commercial reasons. Plans for the European and Japanese markets have not been announced.

Product: Toujeo SoloSTAR (Sanofi)
Update: Toujeo, the apparent successor to Lantus, had a very successful 2016, recording sales of $700 million. Analyst forecasts suggest sales on the order of $1.5 billion by 2021.

Product: Zalviso (AcelRx/Grunenthal)
Update: Approved in Europe in 2015, this sufentanil tablet dispensing device has not yet been approved in the U.S. Analyst forecasts range from $70 to $150 million by 2021, split between sales by Grunenthal (EU) and AcelRx (U.S.).

Product: Vantobra (Pari Pharma)
Update: There is little recent information available for this orphan drug-device combination for the treatment of infections in patients with Cystic Fibrosis. The product's only approval to date is in Europe.

Product: Narcan Nasal Spray (Opiant/Adapt)
Update: This simple to use treatment for opioid overdose has been well received by health professionals and the public. Adapt Pharma claims that more than 700,000 doses have been donated or sold in the first year of this product's availability in the U.S. At a unit price of $37 this suggests a potential market penetration of about $25 million.

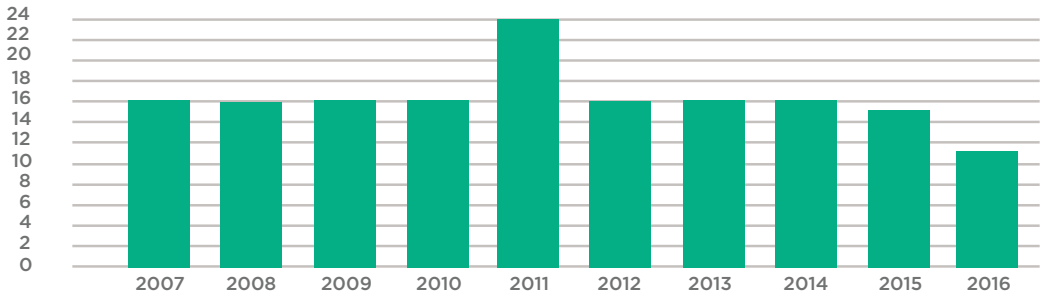
Product: Stiolto Respimat (Boehringer Ingelheim)
Update: Following a first approval in Europe, Stiolto Respimat has been approved in all major markets including the U.S. and Japan. No information is publicly available concerning the product's financial performance

6. Combination Product Approvals: 2016 in Review

Combination pharmaceutical products represent an important source of commercial and therapeutic opportunity by expanding eligible patient populations, improving efficacy and safety, and extending market exclusivity. This engine of development seems to be winding down as evidenced by New Combination approvals in Europe and the U.S. for the past few years. A total of 162 new Combination Products were approved in the period between 2007 and 2016, an average of about 16 per year.

After reaching a peak of 24 approvals in 2011 there has been a steady drop in new Combination Product approvals in the past 5 years to the 2016 total of 11 approvals (Chart 1).

Chart 1. Combination Product Approvals 2007-2016 (Source: PharmaCircle LLC)



Note: the following tables and analysis refer to New Combination Product approvals only, not the same combination in different dosages, or equivalents introduced by other companies.

Perhaps 2007 to 2011 reflected an unusual uptick in approvals; this was a period where a large number of new Combination Products for the treatment of HIV were approved, accounting for 21 approvals. Since then, HIV Combination Product approvals have totaled eleven. The 2007-2011 period saw a total of 19 cardiovascular combination product approvals. In the following 5 years that total dropped to 12. A dozen or so annual Combination Product approvals may be the new normal.

Table 1. New Combination Product Approvals by Therapeutic Indication, 2007-2016 (Source: PharmaCircle LLC)

Therapeutic Indication	
HIV	32
Cardiovascular	31
Diabetes	10
Respiratory	10
Endocrinology	8
Ophthalmic	7
Neurology	6
All Other	58

In terms of drug delivery and formulation parameters, the most common delivery route used for Combination Products was the Oral Route, followed by Injection and Inhalation. A total of 59 of the 162 Combination Products approved over the past decade were identified by PharmaCircle as utilizing some form of drug delivery or formulation technology.

Table 2. New Combination Product Approvals by Route, 2007-2016

Route	(Source: PharmaCircle LLC)
Oral	125
Injection	12
Inhalation	10
Topical / Transdermal	6
Ophthalmic	6
Nasal	2
Other	1

Combination Product Approvals in 2016

There were a total of 11 new Combination Product approvals in 2016, two targeted to HIV, two to HCV and two to cardiovascular disease. The HIV and HCV products followed well-worn therapeutic paths with new molecular entities or combinations of previously approved actives.

One interesting Combination Product approval in 2016 was St. Renatus' Kovanaze, a combination of two well-known pharmaceuticals – tetracaine and oxymetazoline. Administered intranasally the product is indicated for dental anesthesia, more specifically for regional anesthesia while performing a restorative procedure on specific teeth. It effectively eliminates the need for a traditional nerve block with a local anesthetic such as lidocaine administered by dental syringe. The product is approved for use in adults and larger children.

Notable Drug Delivery & Formulation Approvals of 2016

Kovanaze

Actives: tetracaine, oxymetazoline
Molecular Weights[1]: 264, 260
Indication: Dental Anesthesia
Delivery Route: Nasal
Dosing Interval: As Required
Company: St. Renatus
First Approval: 2016-06-29 (U.S.)
Formulation Type: Nasal Spray
Review Status: Standard Review (FDA)
Development/Approval Time[2]: >6 Years
Notable: A novel therapeutic approach, this combination product uses a nasal spray to eliminate the need for the usual injected local anesthetics for uncomplicated dental restoration procedures. Kovanaze is approved for children weighing 40 kg or more.

Epclusa

Actives: sofosbuvir, velpatasvir
Molecular Weight[1]: 529, 883
Indication: Hepatitis C Infections
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Gilead Sciences
First Approval: 2016-06-28 (U.S.)
Formulation Type: Oral Tablet
Review Status: Priority Review (FDA)
Development/Approval Time[2]: 2.8 Years
Notable: Epclusa represents the latest iteration of the oral combination antiviral product strategy pursued by Gilead for the treatment of HCV. Epclusa has once again raised the treatment bar by providing patients with a once daily pan-genotypic (Genotypes 1-6) oral tablet treatment.

Zepatier

Actives: grazoprevir, elbasvir
Molecular Weight[1]: 767, 882
Indication: Hepatitis C Infections
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Merck & Co.
First Approval: 2016-01-19 (U.S.)
Formulation Type: Oral Tablet
Review Status: Priority Review (FDA)
Development/Approval Time[2]: >5 Years
Notable: What would have been a breakthrough 5 years ago has become another competitor in a competitive marketplace. While not offering a particularly broad a coverage of HCV genotypes, Zepatier has reported very high response rates in Genotype 1 and 4 patients.

Descovy

Actives: emtricitabine, tenofovir alafenamide
Molecular Weight[1]: 247, 476
Indication: HIV, AIDS
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Gilead Sciences
First Approval: 2016-04-04 (U.S.)
Formulation Type: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: Unknown
Notable: This is a rework of the previously approved Truvada. Tenofovir disoproxyl has been substituted by tenofovir alafenamide analog in a much lower dose (10-25 mg versus 150-300 mg). The alafenamide analog is reported to also have better distribution into lymphoid tissues.

1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
2. Development times are calculated from the earlier submission of a first IND, or first clinical trial, through to first approval in the USA and represent both clinical development and regulatory review times.

Odefsey

Actives: rilpivirine, emtricitabine, tenofovir alafenamide
Molecular Weight[1]: 366, 247, 476
Indication: HIV, AIDS
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Gilead Sciences, Janssen
First Approval: 2016-03-01 (U.S.)
Formulation Type: Oral Tablet
Review Status: Priority Review (FDA)
Development/Approval Time[2]: Unknown
Notable or Not: This is a rework and update to Complera (rilpivirine, emtricitabine, tenofovir disoproxil), first approved by the FDA in 2011, with a considerably lower dose of tenofovir (25 mg for alafenamide analog versus 300 mg for disoproxil analog). Rilpivirine and emtricitabine dosages are maintained at the previously dosages.

Qtern

Actives: saxagliptin, dapagliflozin
Molecular Weight[1]: 315, 408
Indication: Diabetes, Type 2
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: AstraZeneca
First Approval: 2016-07-15 (EU)
Formulation Type: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: Unknown
Notable: This fixed-dose combination of saxagliptin and dapagliflozin provides DPP-4i and SGLT-2i activity in a single tablet presentation. At the time of its approval, Qtern was the first DPP-4i/SGLT-2 Combination Product approved in Europe.

Bevespi Aerosphere

Actives: glycopyrrolate, formoterol
Molecular Weight[1]: 398, 344
Indication: COPD
Delivery Route: Inhalation
Dosing Interval: 12 Hours
Company: Pearl Therapeutics (AstraZeneca)
First Approval: 2016-04-25
Formulation Type: Inhalation Formulation, MDI
Review Status: Standard Review (FDA)
Development/Approval Time[2]: >6 Years
Notable: This is the second glycopyrrolate/beta-2 agonist Combination Product to be approved in the U.S., and the first presented as a pressurized metered dose inhaler. Pearl's (AstraZeneca's) Co-Suspension Technology permits the consistent delivery of single and multiple pharmaceutical agents from a single pMDI.

Byvalson

Actives: nebivolol, valsartan
Molecular Weight[1]: 405, 43**5**
Indication: Hypertension
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Forest Laboratories (Allergan)
First Approval: 2016-06-03
Formulation Type: Oral Tablet
Review Status: Standard Review (FDA)
Development/Approval Time[2]: ~5 Years
Notable: This fixed-dose combination of nebevilol, a mostly selective beta-1 blocker, with valsartan, an angiotensin receptor blocker, permits nebevilol to be used in lower doses. Lower doses of nebevilol in turn results in greater beta-1 selectivity, with enhanced cardioselectivity and minimized beta-2 side effects.

Editor's Insight: Using proprietary particle science and manufacturing technology, Pearl is developing a broad portfolio of products in the MDI format for the treatment of prevalent chronic respiratory diseases, including COPD, asthma, and rhinosinusitis. MDIs are the most widely used drug delivery format for inhaled treatments for respiratory diseases. Yet, major therapies, particularly dual and triple combinations of well-known inhaled medicines, have proven to be difficult to develop in MDI format due to formulation challenges, such as inconsistent dosing, instability over time, and partial or variable delivery to the airways.

1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
2. Development times are calculated from the earlier submission of a first IND, or first clinical trial, through to first approval in the USA and represent both clinical development and regulatory review times.

2015 Combination Product Approvals: One Year Later

Product: Entresto (Novartis)
Update: Introduced as a new therapeutic approach for the management of congestive heart failure, Entresto uptake has been slower than expected, partly a result of the cautious approach taken with CHF treatment and hesitance to switched treatment plans. That should change with time as confidence grows and newly diagnosed patients are started on Entresto. Sales in 2016 of $170 million are expected to grow to more than $2 billion by 2021.

Products: Synjardy, Glyxambi (Boehringer Ingelheim, Lilly)
Update: The 2015 Synjardy approval for Type 2 diabetes was followed in late 2016 by the approval of Synjardy XR, offering once-daily dosing. Commercial performance figures for Synjardy and Glyxambi, the other combination product from the Boehringer Ingelheim-Lilly partnership approved in 2015, are not publicly reported. Sales figures for both products are grouped in with Jardiance, the single entity empagliflozin formulation approved in 2014.

Product: Tuzistra XR (Tris Pharma, Vernalis)
Update: Developed by Tris Pharma and marketed by Vernalis, this cough and cold formulation has struggled since launch with 2016 sales reported as less than $2 million and analyst expectations of $50 million in annual sales by 2019.

Product: Technivie (AbbVie)
Update: The successor to AbbVie's Viekira Pak with a simplified dosing schedule, the product has struggled to capture a significant portion of the multi-billion dollar Hepatitis C treatment market despite aggressive pricing. Combined sales of Technivie and Viekira Pak totaled $1.5 billion in 2016 with prospects for sales to increase to more than $2 billion in the coming years.

Radiesse Plus (Merz Pharma)
Approved in the U.S. in 2015 for the treatment of skin wrinkles, European approval was received in 2016. Little information is available regarding the product's commercial performance.

Product: Orkambi (Vertex Pharmaceuticals)
Update: Approved mid-2015 in the U.S. for the treatment of Cystic Fibrosis, Orkambi has been a success for Vertex, hitting sales of almost $1 billion in 2016. Analysts suggest sales will triple by 2021.

Product: Raplixa (Mallinckrodt)
Update: An alternative to traditional staples and stitches for surgical use, Raplixa was divested by The Medicines Company to Mallinckrodt early in 2016 as part of a hemostasis portfolio.

Product: Genvoya (Gilead)
Update: Another billion dollar baby for Gilead, Genvoya provided an additional once daily dosing option for the treatment of HIV/AIDS. Sales of $1.5 billion in 2016 are expected to peak at close to $5 billion in 2022 before sliding down thereafter.

Product: Dutrebis (Merck)
Update: This is a strange one. Approved in 2015 in both the U.S. and Europe as a twice-daily treatment for HIV/AIDS, Dutrebis has been discontinued in the U.S. and withdrawn in the EU. There is no information available regarding the product's approval or launch in other territories.

Drug Development
EXECUTIVE

Torsten Maschke
CEO

Datwyler Sealing Solutions

DATWYLER

BioCare, PharmaCare, MedCare: Datwyler's New Health Care Offering

Today's healthcare industry and market is ever-changing and provides suppliers and manufacturers with an abundance of opportunities as well as certain challenges. A consistent strategy focused on the present, near, and distant future has to be the core of any company development. Datwyler, a Swiss-based industrial supplier, introduced new healthcare offering at the beginning of this year. Guided by the company's values and key principles, the three categories show how a pharmaceutical supplier today can fully cater to its customers. *Drug Development & Delivery* recently interviewed Torsten Maschke, CEO of Datwyler Sealing Solutions, to speak about the opportunities and challenges the current healthcare industry poses and how they are met by Datwyler's strategy and products.

Q: Can you provide an overview of Datwyler as a company and your most important markets segments? How would you describe your position in the healthcare industry?

A: The Datwyler Group is a Swiss-based focused industrial supplier with two divisions and leading positions in global and regional market segments. In our Sealing Solutions division, we provide customized sealing solutions to manufacturers and companies in five segments: healthcare, automotive, consumer goods, civil engineering, and general industry. Building on more than 100 years of experience, our products and services combine high-quality material, innovative technologies, outstanding engineering, and process know-how. We have a global manufacturing footprint and a diverse portfolio

that caters to a variety of business sectors. We possess expertise in different fields and segments, a diversity which we see as one of our biggest assets.

Datwyler is a globally acting company, constantly developing our sites all around the world. We have facilities and manufacturing plants on three continents and sell to customers in over 100 countries. Our more than 6,000 employees make it possible for us to constantly improve and strive for the best-in-class products, no matter if it is an elastomer component for a tunneling project or an aluminum cap to package sensitive medication.

All industries that we cater to are of great importance, both on their own and as a part of Datwyler Sealing Solutions. No matter if we are talking about the automotive or the healthcare industry, innovative solutions and the manufacturing of safe and reliable products are what matters most to us and our customers.

Q: Could you explain the individual business segments of Datwyler Sealing Solutions in more detail? What products are characteristic for each one?

A: In each business segment, Datwyler Sealing Solutions focuses on solutions for sealing or closing different industrial products and product packaging. At the same time, our experts are looking for ways to improve the products of our customers and, consequently, to support the challenging targets of our customers and their customers.

Our most important segment, the healthcare unit, provides a unique range of future-proof healthcare sealing solutions and services for primary and secondary packaging, including the most advanced elastomer formulations, proprietary coatings, sterilization options, and aluminum seals for high-efficiency production lines. The healthcare segment is consistently geared toward the future and new solutions and developments for our customers. In the healthcare industry especially, developments and new products are coming fast. It is very important to us to not only know trends but to shape them. With our newly presented healthcare offering and strategy, we are achieving exactly that.

That ambition is present in all our business segments. In the automotive segment, we develop and manufacture components and solutions for braking systems and elastomer components for SCR systems used for the after-treatment of exhaust gases. Every second car worldwide features a Datwyler component. Our work provides safe and emission-reducing solutions through innovative technologies.

In the consumer goods segment, we develop and manufacture sealing solutions for goods from industries, such as the food industry, and actively pursue maximum safety in this field.

The civil engineering segment focuses on solutions in tunneling, building construction, civil infrastructure, and track superstructure. The solutions Datwyler provides in this business segment contribute greatly to human mobility, convenience, and safety.

Our segment general industry includes four market sub-segments, namely small engines and non-automotive vehicles, electrical components and electronics, building and mechanical engineering, and processing technologies.

Q: Datwyler has just presented a new healthcare offering. What motivated this development?

A: With the ambition to set a new benchmark and stay a key market player in the healthcare industry, we have just recently shaped our strategic approach and identified three key opportunities in the healthcare industry, which are directly linked to the categories of our new healthcare offering. Since we are partnering with the world's top pharmaceutical and medical companies, it is important to underline our strong sense of future trends and that we are prepared to respond to every development in the current healthcare market. Our approach combines global knowledge and local manufacturing expertise. We strive for shaping the future of the healthcare industry. Our three identified key opportunities – Patient Safety, Future Health, and Global Leadership – contribute to this target.

Subsequently, the new healthcare offering provides three categories that will ensure more transparency for our solutions and meet our customers' needs and expectations: Bio Care offers solutions for the most sensitive, large molecule injectable drugs. Components of this category also provide the lowest available particle levels in the industry. Pharma Care addresses the needs of small molecule injectable drugs that require production flexibility and outstanding quality. Med Care offers medical companies a broad range of materials and technical support.

Q: Are there any particular services or products that distinguish Datwyler in the healthcare segment?

A: In the healthcare segment of Datwyler, we develop and manufacture sealing solutions for primary and secondary drug packaging and medical devices that are supplied to leading pharmaceutical and medical companies worldwide. This includes a number of different components and coatings that can be customized to specific needs and products.

Our cleanroom manufacturing, state-of-the-art facilities, and the resulting products are a distinctive asset for us. Our production facilities are aligned to our First Line standard and are specially designed to operate in a fully integrated good manufacturing practice (GMP) cleanroom environment. The process flow, gowning protocols, personnel, and material flow result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry. Additionally, it includes automated production cells, fully automated camera inspection, and a unique validated washing process. The approach exceeds the most stringent quality standards of the European and US regulatory authorities and is certified to ISO 15378. All facilities aligned with the First Line approach incorporate rational and lean production flows in accordance with the Six Sigma methodology.

Q: Which products are produced in these specialized facilities?

A: A key product range that is exclusively manufactured in our facilities in accordance with the First Line standard is our Omni Flex series. Based on the research of our experts and the monitoring of markets trends within the parenteral packaging industry, we found that there is a growing demand for fluoropolymer-coated elastomeric closures on the market, primarily to mitigate risks related to drug stability and compatibility.

An example: For a therapeutic protein, the exact chemical make-up and three-dimensional conformation can influence the efficacy of the drug product. Interactions with leachables, including silicon oil, can present a risk to the safety of therapeutic proteins. Therefore, many manufacturers of biologics or biosimilars are already relying on fluoropolymer-coated closure solutions today. We can supply this demand with our Omni Flex-coated components and especially with the Omni Flex Coated Plunger for pre-filled syringes. Omni Flex provides total coverage of the product, including the benefit of a total barrier coating, meaning the need for siliconization of the plunger rills is eliminated. The plunger, as the largest source of subvisible (silicon) particles, is therefore eradicated. As a result, the particle levels of Omni Flex Coated Plunger are some of the lowest in the industry.

Q: What are the next steps for Datwyler? Which markets do you see the most opportunities in?

A: Datwyler will continue to bring their products and manufacturing concepts to even more customers around the world – in keeping with the motto "Think global, act local." Two facilities incorporating the First Line manufacturing concept are being built and/or expanded and will start operating to full capacity in India and in the US in 2018. They will complement the entity in Alken, Belgium, which has been producing components aligned with the First Line standard since 2009. The expansion of our facility in Pune, India, emphasizes our strategy to drive our role as a key player in the global healthcare industry and shows our commitment to the national Indian market and the Asia Pacific region. India as a substantial force in the global pharma market provides a great opportunity to introduce the First Line manufacturing standard to the global and local markets. Our commitment also includes hiring and involving the local community. While the facility is currently employing 290 people, staff numbers will rise to a total of 350 employees by the time production starts.

In the US, we are currently constructing the third facility that will manufacture aligned with the First Line standard. Although we have been present in the US since 1981, our new facility in Middletown, Delaware, will be one of Datwyler's key manufacturing plants worldwide. Production is scheduled to start in 2018. This facility will allow us to cater locally produced components to our US-based customers, thus reducing lead times and time-to-market. This ongoing expansion of our presence and resources in the largest pharmaceutical market worldwide will further strengthen Datwyler's position as a reliable and competent partner to the global healthcare industry. ◆

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Special Feature

Injectable Drug Delivery: New Technologies Deliver Biologics and Differentiate Brands

By: Cindy H. Dubin, Contributor

The increasing use of biologics, a rise in the prevalence of chronic diseases, increasing occurrence of needlestick injuries, and the benefits of injections (convenience, ease of use, and reduced pain) are increasing the demand for safety syringes, prefilled syringes (PFS), and autoinjectors.[1] Thus, the global injectable drug delivery market is projected to reach $624.50 billion by 2021, up from $362.38 billion in 2016.

At the center of developing injection device designs is human engineering inputs and patient preference research. It behooves a pharmaceutical company to work closely with device developers to influence therapeutic product decisions and create devices that differentiate brands, prevent packaging and drug interactions, and ensure patient adherence.

However, many hand-held devices are only capable of administering drugs with dosing volume close to 1mL. With more than 900 biologics being developed (most of these are highly viscous and are required to be delivered in volumes greater than 1mL), there is a growing demand for self-administration devices than can overcome this unmet need. Large-volume wearable injectors, an advanced version of the existing self-injection devices, are expected to gather interest from a wide customer base.[2]

This year's *Drug Development & Delivery* injectable device report showcases the features of newly developed, and soon-to-be-commercialized technologies that address the issues of ease of use, high viscosity delivery, and brand differentiation.

SiO_2 utilizes advanced materials science and precision manufacturing to create pharmaceutical products, labware, and consumables that are durable, dimensionally consistent, and have the barrier properties approaching that of glass.

Aptar Pharma: Committed to Lowering Particulate Levels

As more complex and expensive drugs — including complex proteins — are developed, the challenge for organizations like Aptar Pharma is to deliver higher standards of cleanliness in elastomeric components. For more than 50 years, Aptar Pharma has been developing elastomer solutions and its formulations feature best-in-class extractable and leachable profiles, says Adam Shain, Director of Global Business Development Injectables, Aptar Pharma. "But we recognize we need to continue to go further and our PremiumCoat™ offer takes our commitment on lowering extractable levels and particulates to even greater levels of reassurance."

PremiumCoat are film-coated elastomeric plungers and stoppers that represents a step change by reducing particulate levels. "The Particulate Count Index (PCI) achieved today is an unrivalled, market leading PCI of 1.3, compared to the market gold standard of 2.9," says Mr. Shain.

PremiumCoat features a Fluorinated (ETFE) film that is applied during the manufacturing process. This approach delivers a completely homogenized coating, resulting in a more effective barrier than some rival coating technologies, Mr. Shain says. This makes the component easier to inspect with automated vision systems. The process also ensures that only the area that comes into contact with the drug is treated, ensuring security of closure.

PremiumCoat is available in Ready to Sterilize (RTS) and Ready to Use (RTU) variants. The RTS product is designed for organizations that have sterilization facilities in place. PremiumCoat is compatible with steam sterilization and uses Aptar Pharma's proprietary washing process.

Aptar Pharma's range of elastomeric stoppers featuring PremiumCoat™ technology.

The RTU product is sterilized by gamma irradiation, which provides flexibility and convenience. There is a reduction in the number of human operations as well as improved productivity, as the stoppers may be used immediately and can be directly placed into RABS or isolators. In addition, gamma sterilization is proven to be a more effective means of sterilizing stoppers than steam sterilization. Gamma irradiation has the advantage of sterilizing the vial stoppers while they remain in their packaging, limiting contamination risks during transfer, eradicating moisture, improving productivity, and controlling exposure, says Mr. Shain.

Manufacturing is housed in two mirrored sites, both based in France. Both sites are fully compliant with international regulations ISO 15378:2011, as well as three Drug Master Files (type III and type V). To be closer to its customers in the United States, Aptar Pharma has invested in a new manufacturing facility in Congers, NY.

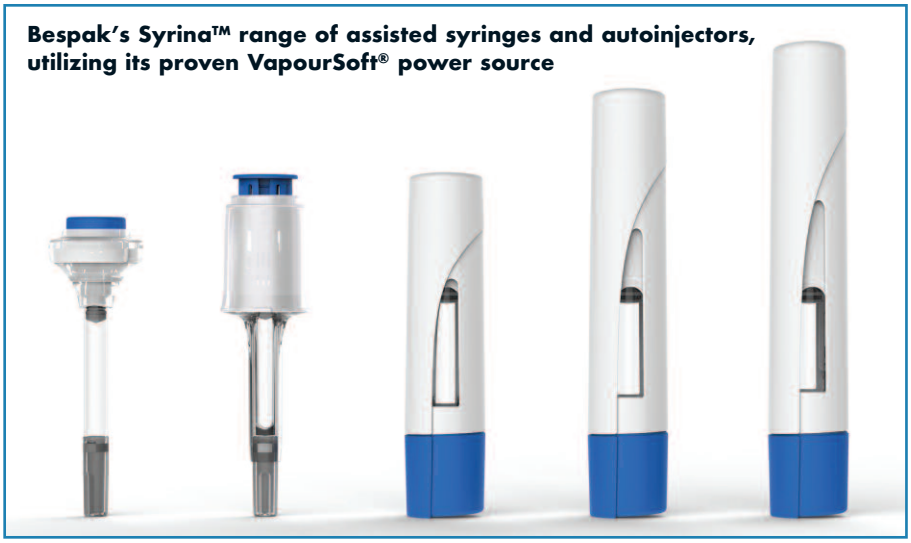
Bespak: Focused on Self-Injection Devices for a Variety of Volumes & Viscosities

The demand for injection devices with increasingly advanced and automated features that support self-administration has Bespak focusing on expanding its VapourSoft™ powered Syrina™ range of injectable devices. The range spans simple assisted syringes to fully automatic autoinjectors, and is capable of handling drug formulations of different viscosities and volumes, explains Steven Kaufman, Bespak's Global Business Development Lead.

When creating injection devices for self-administration, it's important that the design easily allows the patient to deliver the correct dose, with minimal discomfort to improve compliance. Adding safety features such as automatic needle insertion and retraction help to make the process simpler for some patient groups, and also reduce the risk of needlestick injuries.

For example, Syrina S has a small form factor, is suitable for 1mL or 2.25mL syringe, and has a user-controlled needle insertion and removal mechanism. Syrina AS is primarily set to be a 2.25mL autoinjector featuring automatic needle insertion with an initial extension. Syrina AR is a fully-automatic autoinjector and is the latest addition to the range. Launched in October 2016, Syrina AR 2.25mL offers automatic needle insertion, drug delivery, and needle retraction, with a single push-on-skin operation. These devices are specifi-

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



cally designed for use with high-value biotherapeutics ($100 or more per injection), with viscosities from aqueous solutions to those that are hundreds of centipoise (cP), and a range of injection volumes from .2mL to 2mL.

For delivery of biologics, Bespak offers two power sources for drug delivery devices. The Syrina and Lapas™ ranges of injectable devices use Bespak's proprietary compact energy source, VapourSoft, a miniaturized canister of liquefied gas, designed to deliver viscous drug formulations in a smooth manner, minimizing discomfort for patients as well as providing solutions that can manage injections with cP in the hundreds to thousands with next-generation enhancements. Bespak's proprietary spring-based autoinjector technology offers solutions for viscous injectables, with a device launched last year in Europe that can inject the highest viscosity in a 1mL PFS device configuration, says Mr. Kaufman.

"The injection devices we develop for our customers are driven by patient feedback and input from human factors experts, invited at an early stage in the design process," says Mr. Kaufman. "To create an injectable device that's easy and safe to use, we focus on creating ergonomic designs that accommodate the needs of the specific patient group."

The external appearance of Bespak's injectable devices are highly customizable, allowing collaboration with pharmaceutical customers to address preferences for style and incorporate their company branding, in addition to meeting patient needs. Mr. Kaufman says Bespak is seeing greater demand for sleek and compact solutions, as well as designs that offer differentiation from competitors. In addition, he says there is a strong desire from pharmaceutical customers for platform devices such as autoinjectors that can use either 1mL or 2.25mL PFS, and require only one component change.

Biocorp: Connected & Passive Devices Reassure Patients

During the past three years, Biocorp has developed a range of connected devices in the field of injection to help patients better manage their diseases. These include: Datapen, a reusable electromechanical pen injector, compatible with standard cartridges, that automatically records each dose injected and sends the information in real-time to a mobile app or a data platform; and Easylog, a smart sensor (or smart cap) that turns regular pen injectors into connected devices. The system is compatible with all major pen platforms and automatically collects each dose injected with a 100% level of accuracy, says Eric Dessertenne, COO of Biocorp.

Several development programs are now active on these two products in various therapeutic areas: diabetes, growth hormone, Parkinson's, and rare diseases.

Connected solutions ease self-administration by guiding the patient in every step thanks to visual and audio signals and provide them with feedbacks and monitoring solutions through the app.

Datapen can be specifically helpful for the delivery of biologics, says Mr. Dessertenne. "First, it provides a high level of accuracy (0.5 microliter), which is a key requirement for the administration of certain biologics. Additionally, many biologics are high-viscosity products and need reconstitution before the injection.

The Biocorp Easylog is a smart sensor for pen injectors.

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These training devices are custom developed to simulate OEM standard prefilled syringes and prefilled syringes with safety systems and can also include proprietary needle simulation technology options to help decrease needle anxiety and increase user confidence.

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- Needle Force & Feel Simulation*
- Reusable Safety Systems*
- Plunger Force / Viscosity Simulation*
- Plunger Lockout Feature*
- Device & Plunger Color Adjustments
- Needle Shield Options
- Pad Printing
- Finger Flange

1. Noble. (2016). *The relationship between anxiety, injections and device training.* Poster presentation PDA [User study].
2. Noble. (2014). *Multisensory training reduces errors.* Poster presentation PDA [User study].

*Noble Patents Pending

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Datapen can significantly ease reconstitution processes thanks to electro-mechanical features and user instructions directly on the screen to minimize human errors.

To bring connectivity to the injection field, Biocorp offers integrated solutions or "add-ons." "Integrated solutions are devices natively designed with embedded elecryonic features," explains Mr. Dessertenne. "Their form, shape, and process are like regular products on the market, but they incorporate electronics and can communicate treatment information in real time to a mobile app or data platform. Add-ons are smart sensors that can be attached to regular devices on the market, turning them into connected products. Typically, these require no modification to the existing devices and have no impact on the regulatory and industrial processes. It solves an important issue for pharma companies: Bring connectivity to disposable pen injectors. The add-ons can be reused over two years on several disposable devices, making it a cost-effective solution."

Aside from connected devices, Biocorp is launching a passive safety system for prefilled syringes, the NewGuard, directly integrated to the PFS with no impact on regulatory and industrial processes. The ultra-compact version fits 0.5mL and 1mL PFS, with the same device. NewGuard will replace the rigid needle shield and will be assembled in the syringe manufacturer's production line.

Mr. Dessertenne says that human factor and user studies have a major impact on the way Biocorp designs and develops its products, including NewGuard. Its shape is similar to a traditional PFS but looks less daunting and more familiar, making patients feel safe before, during, and after injections.

"At an early stage of our developments, we gather feedback from end users and integrate them in the design phase," he says. "First, we have understood the importance of reducing the number of steps for the patients and design products with seamless integration. Second, we have identified a need for additional comfort and security in the field of injection."

Credence MedSystems: A Platform That Differentiates Brands While Protecting Patients & Drug Integrity

The Credence Companion® platform offers pharmaceutical and biotech customers an accelerated path to commercialization of a delivery system that can drive market differentiation and minimize risk by providing compliance, says Mark Hassett, Vice President, Business Development, Credence MedSystems. The Companion platform offers a pre-attached needle, a use-attached solution (luer lock), and multiple dual-chamber reconstitution offerings.

"Across the lineup, the user has a consistent experience that blends the familiarity of conventional syringes with important usability advantages," says Mr. Hassett. "Multiple human factors evaluations have been performed on Companion syringes. Feedback indicates that users are consistently impressed with the ease and intuitiveness-of-use, as well as the syringe functionality, and that users strongly value the information provided by the syringe's feedback cues."

Additionally, Mr. Hassett claims that Credence's technology allows pharma to provide end users with the benefits and market differentiation while preserving freedom to maintain sourcing strategy and supplier preferences. Pharma manufactur-

ers can select their preferred primary package container and their choice of components (stoppers, needle shields, tip-caps) from their preferred suppliers. "Pharma's ability to choose the design elements they already use and have previously validated minimizes disruption to their development, regulatory, and supply chain efforts," he says. "The Credence approach also preserves pharma's current aseptic filling manufacturing processes while removing incremental costs and investment related to secondary packaging."

Companion also features a passive, integrated needle retraction system. Upon completion of the injection, the user hears and feels the end-of-dose click and then the needle is automatically retracted through the stopper and into the plunger rod/glass barrel. The syringe is thereby disabled from reuse. "The Companion technology helps protect healthcare protectors, self-injectors, and those downstream from accidental needlestick and the potential spread of infectious disease," says Mr. Hassett. "It also protects patients from being exposed to disease through syringe reuse.

However, the less obvious, yet equally critical, protection the Companion provides is to the integrity of the drug. Credence eliminates glue from the needle-attachment mechanism. "This vital improvement over the age-old conventional approach eliminates the risk of any unwanted interaction between glue and drug product and enables silicone-controlling techniques that were previously incompatible with staked syringes. By protecting the integrity of the drug, the Companion system has become an enabling technology for the industry's sensitive biologic drugs."

DALI's SAN-P for prefilled syringes with staked needles, featuring a hidden automatic needle insertion, allowing patients control of the drug injection speed for maximum comfort.

DALI Medical Devices: Auto-Needles for Biosimilar & Generic Pharma

In the past year, DALI has been focused on developing a customized versions of its SAN-Light premium passive-automatic safety needle and the SAN-L automatic needle insertion device for a specific pharma company; progressing the design of the SAN-DV Pro and SAN-DV drug transfer, reconstitution and injection systems; working with Elcam Drug Delivery Devices (E3D) on developing various disposable and reusable next-generation autoinjectors, with customization projects for a number of major pharma and biosimilar companies; and developing an injector for pharmaceuticals to the posterior segment of the eye.

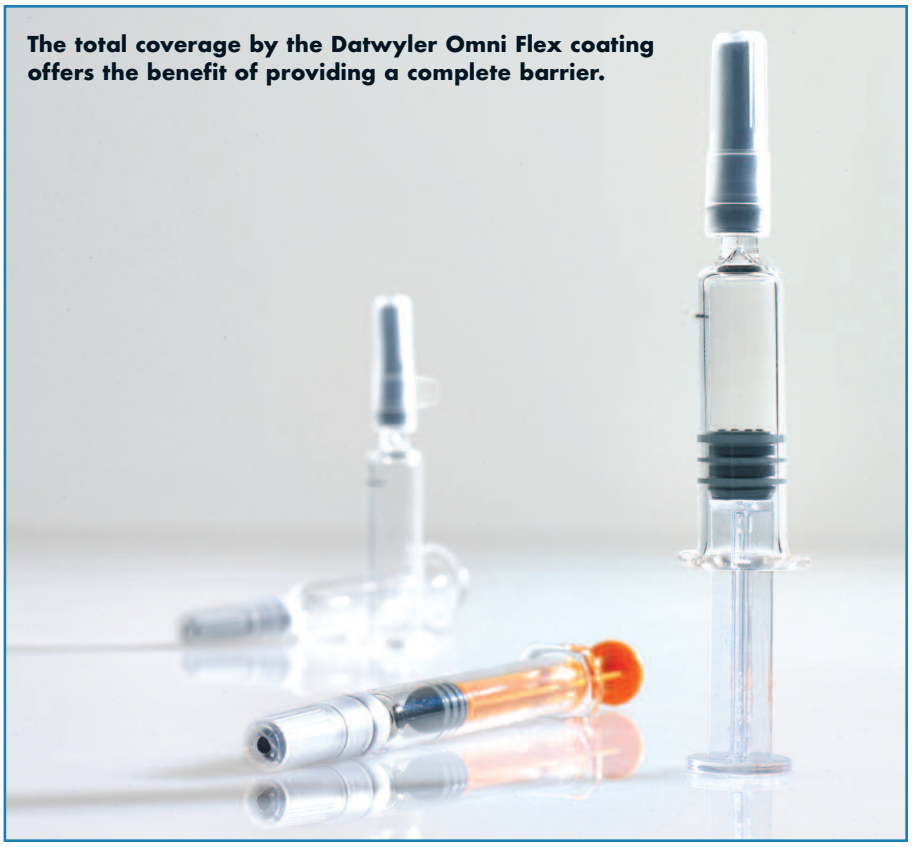
During development of the various injectors, DALI conducts human factor studies to get input from target potential users, whether they are self-injecting patients, caregivers, nurses, or physicians, says David Daily, MSc, MBA, CEO & Co-Founder of DALI Medical Devices.

"As an example, during one of our recent studies of the customized SAN-Light performed with a pharma client, we found that some nurses would prefer not only to see the tip of the needle before giving an injection, allowing easy priming and orienting the needle at the injection site, but would also like to see the needle has been completely removed after injection (so nothing is left in the body)," he says. "To achieve such an easy view of the needle after withdrawal from the skin and passive retraction of the needle guard has occurred, a few design modification options were proposed, and one modification that does not increase cost of goods was chosen."

Addressing patient-centered challenges in injectable drug delivery, all SANs (excluding the SAN-Light) feature automatic needle insertion, passive-automatic sharps protection, and a needle that is hidden at all times. And SAN products combine these features with manual control of injection speed for maximum comfort.

In addition, depending on the configuration and the pharma clients' preferences, the SANs are packed either in a blister pack or an injection-molded cap sealed with a Tyvek® lid. These designs allow either separate unit package or kit-

packaging together with the drug, depending on the client requirements. The package designs allow also EtO (ethylene oxide) or gamma-irradiation sterilization processes, when required.



The total coverage by the Datwyler Omni Flex coating offers the benefit of providing a complete barrier.

Datwyler: Understanding & Improving Syringe Performance

The therapeutic biologics industry has been growing significantly over the last few years. In 2015, more than 3 billion prefilled syringes were sold worldwide. While anticoagulants and vaccines traditionally dominated the PFS market, the number of biologics stored and administered in prefilled syringes today is constantly increasing. This also triggers a growing complexity of formulations and the surge in novel device designs.

"Due to the sensitivity of biologics during storage and their complexity during administration, primary packaging components used for biologics are facing demanding requirements than those used for any other kind of injectable drug," says Rahul Thakar, PhD, Technical Key Account Manager, Datwyler Sealing Solutions. "Prefilled syringes (including the glass barrel and the elastomeric closure) need to act as a chemically inert and secure delivery system. The rise of autoinjectors and the integration of additional safety features add to this complexity. That's why manufacturing of primary packaging materials is considered to be an extension of the drug manufacturing process."

The impact of elastomeric plunger design on syringe delivery forces is a complex problem that depends on the material properties of the elastomer, the lubrication system, the plunger rod design, the aging conditions, and the drug formulation properties. Furthermore, challenges like needlestick injuries, silicone sensitivity, and the need for consistent delivery forces have to be considered. Finite Element Analysis (FEA) is a powerful tool for building a fundamental understanding of how the components of a prefilled syringe increase the overall performance of the system.

As a partner for biotechnology, pharmaceutical, and medical device companies, Datwyler provides customized solutions, from early developmental stages through scale-up to full production. For example, with biologic drugs, a major concern is the generation of proteinaceous particles (prions) in prefilled syringes. Under certain circumstances, therapeutic proteins can interact with syringe components, and in particular with the silicone oil that is typically used as a lubricant on both the barrel and the plunger. To mitigate such risks, Datwyler uses lubricious barrier Omni Flex coatings, which do not require siliconization. Omni Flex Coated Plungers utilize a proprietary, flexible fluoropolymer spray coating technology designed to be an inert barrier and impart a low coefficient of friction. This barrier function directly relates to an even cleaner extractable profile.

"The lubricous nature of the coating supercedes the need for siliconization that directly translates into highly consistent delivery forces – a must for self-administration," says Dr. Thakar.

As a development partner of elastomeric components, Datwyler recently developed a customized solution for a wearable injector. A custom plunger and septum with fluoropolmer coating was needed that requires the lowest level of particulate with highly functional requirements and chemical compatibility with biological drugs, says Dr. Thakar.

"Combining wearables with drug administration could result in new therapeutic measures and devices, for example for the treatment of diabetes," he says. "A wearable insulin pump can directly and independently administer the exact amount of insulin the patient needs."

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EG-GILERO: Partnering with Pharma to Design Devices

EG-GILERO doesn't market its own products, but partners with pharmaceutical and device companies to design, develop, and manufacture devices. Most devices are disposable, both multi- and single-use, but occasionally they work with reusable systems like IV pumps, syringe pumps, and novel variants, explains Jim Fentress, Director of Engineering, EG-GILERO. Therapeutic applications vary, typically addressing parenteral routes, as well as ophthalmic and implantable systems.

Human engineering inputs and patient preference research affect EG-GILERO's designs, depending on their intended use. "For example, dental syringes need to inject into tissues with substantially higher back pressures than intradermal or intramuscular syringes," says Mr. Fentress. "This drives designs, which lower the required application force while still achieving injection pressures. Simultaneously, the higher injection forces drive ergonomic considerations that will make the syringe easier to activate and maintain position during injection."

Self-administration devices are always driven by specific needs of target populations, Mr. Fentress says. "When designing these devices, a fundamental understanding of the population and concomitant health problems is critical. The most effective solutions start out by exposing device concepts and variants to the target population early in the process. This kind of development effort avoids making mistakes that are expensive to correct later."

As important as the design is the packaging. Packaging is product specific and driven by primary considerations. Does the packaging have to be a sterile barrier? Does the package prevent some form of device activation (i.e. preventing a permanent needle guard from triggering)? Does the package provide long-term device protection (i.e. an autoinjector that might be carried in a backpack)?

Typically, disposable devices gravitate towards the most cost-effective solutions. An exception exists for devices intended for non-clinician use. For these devices, the packaging often becomes an integral part of the instructions for use, directing untrained individuals towards safe and effective application. Most disposable injection devices developed by EG-GILERO incorporate needle shielding or lock-out to prevent injury.

Enable Injections: High-Volume Drug Delivery Supplants IV Infusion

Enable Injections has been developing large-volume (up to 50mL) wearable injectors for subcutaneous delivery of high-viscosity formulations. In addition, Enable Injections is developing easy-to-use systems that facilitate the rapid transfer of biologics and drugs from their original primary container closure to its wearable injectors.

"Our transfer systems were designed to warm the refrigerated biologic/drug products to room temperature through simple convection (no heating elements), thus reducing the typical 30- to 45-minute patient wait time," says Mike Hooven, President and CEO of Enable Injections.

Although the wearable large-volume injection systems are not yet approved or commercialized, Enable Injections' devices have undergone numerous human factors tests and evaluation protocols as well as user market research. The wearable large-volume injectors are purely mechanical and designed for ease of use with the ability to initiate injections in three simple steps, explains Mr. Hooven. The injection device has a smooth, low-profile exterior with rounded components that prevent the device from catching on clothing. The device adheres readily to the skin. Patients then press the injection button to initiate subcutaneous injection. When the injection is complete, the button and needle automatically retract with an audible "click" and the device is then easily and safely removed. The device also allows patients to actively pause their injection by holding down the button.

"Of note, Enable Injections' system is designed to supplant the need for IV infusion of biologics in many cases, and reduce monetary costs and time burden of

The new Enable handheld syringe transfer system minimizes waste and volume.

establishing an IV infusion of a biologic by healthcare professionals," says Mr. Hooven. "Our ability to use any standard pharma industry container closure with a delivery system that is preferred by patients and caregivers saves costs and reduces drug development time by months. Also, by pairing standard container closure systems with our injection system, the clinician is afforded the flexibility to establish effective dose regimens tailored to the individual patient when needed."

Mr. Hooven adds that Enable Injections has designed its packaging around the concept of simplicity of use, which reduces the volume of hardware and requisite instructional material compared with more complex electro-mechanical drug delivery systems. "Ultimately, the products' packaging focuses on minimizing waste and volume while accommodating a single-use, disposable device that ensures a safe and sterile environment for biologic/drug delivery."

Enable injections has partnered with Flex to develop the Enable Smart Device, a next generation communication device that uses Bluetooth Low Energy technology by means of broadcast mode. The Enable Smart Device can be pre-integrated into a company's Digital Health Platform, giving Enable's pharma partners immediate access to patient data across multiple devices and gaining direct engagement with patients to drive adherence. "The Enable Smart Device adheres to our overall strategy of designing simple systems for maximum effectiveness with minimal interaction," Mr. Hooven says.

Gerresheimer: Reducing Interactions Between Drug & Container

Primary packaging for parenteral formulations has strict requirements with regard to the likelihood of component/dosage form interactions, especially for biotech-based and other sensitive drug products. New product developments at Gerresheimer reflect this trend.

Gerresheimer offers a range of prefillable COP syringes produced by its long-standing Japanese partner, Taisei Medical Co. Ltd. The company is now extending its portfolio of the new Gx RTF® ClearJect syringe, available in a 1mL-long version, using standard rigid needle shield and fluoropolymer-coated plunger stoppers.

"Biotechnologically developed drugs pose challenges for the container, as they can be very sensitive," says Bernd Zeiss, Manager Technical Support Medical System, Gerresheimer. "There may be interactions with syringe components such as tungsten, silicone oil or the barrel material itself. Using a barrel material such as COP may have advantages with a drug compared to a glass syringe."

Gerresheimer offers a syringe with an integrated safety system to avoid needlestick injuries.

Addressing the unmet needs in prefillable syringes is the key to successful pharma products. The metal-free syringe with a high quality luer lock adapter (TELC) is a good example of how Gerresheimer finds solutions for its pharma clients. "Solving the tungsten issue is an important step to minimize syringe container-induced interactions with a sensitive drug," says Mr. Zeiss. "Substituting the tungsten pin used in the manufacturing of glass syringes with an abrasive-free and non-cytotoxic ceramic extends the range of biopharmaceuticals that can be administered by means of a prefilled syringe."

Reducing silicone oil is another customer need addressed by Gerresheimer. The Gerresheimer Gx RTF baked-on siliconization reduces the silicone levels significantly and make the syringe suited for sensitive biopharmaceuticals as well as for the stringent ophthamologic USP requirements with regard to subvisible particle loads, Mr. Zeiss says.

Gerresheimer will complete its product portfolio of prefillable syringes made of glass and plastics with an integrated, passive syringe safety solution, acquired through an exclusive license from West Pharmaceutical Services, Inc.

The D-Flex platform can be flexibly configured to suit the desired dose values from the first clinical study to series production (Haselmeier).

Haselmeier: New Product Platform is Suited for Clinical Trials

The D-Flex Pen is a disposable pen for use with 3mL cartridges. The D-Flex can be configured for several fixed doses, bridging the gap between fixed and variable-dose pens. These dose values can be freely selected when designing the pen. This is especially of interest for dose-escalation studies. The system does not allow any intermediate settings between the set doses, reducing the risk of a wrong dose and enhancing safety for the patient, says Konrad Betzler, Chief Pharma Officer at Haselmeier, GmbH.

"The D-Flex pen means that only one device needs to be used throughout the clinical trial, making trials much easier for the pharmaceutical company," says Mr. Betzler. "Regulatory bodies may impose a device design that enables dial-labelled doses, which would disqualify the use of current prefilled pens that have intermediate dose increments."

Using D-Flex for clinical trials, and later as serial device, means that the customer has the freedom to decide the preferred set-up for market introduction. Mr. Betzler says: "This makes the D-Flex the ideal, flexible platform for adapting to set doses in accordance with the therapy."

Additionally, the platform has been developed and validated so that only minimal molecule-specific and customer-specific adjustments are necessary; they can be integrated into the clinical supply chain process seamlessly up to serial production following market authorization.

Haselmeier has also integrated final device assembly into its operations and can now provide finished combination product supply. "This capability adds significant value to our customers by further simplifying and integrating the supply chain process," says Terence O'Hagan, General Manager of Haselmeier, Inc.

Nemera: New & Improved Platforms Feature Add-On Safety Devices

Nemera has developed Safelia®, two-step autoinjector platforms for subcutaneous and intramuscular injections of fluid and viscous formulations. Thanks to its patented cam-driven mechanism, injection force and speed can be adjusted by design to fit formulation and patient needs. Safelia allows delivery of viscous formulations through thinner needles (up to hundreds of centipoises). Disconnect needle insertion and syringe emptying allow drug delivery at the right depth, limit the risks of glass breakage, and ensure safety, says Adrien Tisserand, Nemera's Global Category Manager for Parenteral.

He says: "The Safelia autoinjector received two recognitions in 2017: The Patient Centricity & Customization Innovation Award at Pharmapack Europe; and the Editor's Choice category at INTERPHEX."

Nemera has also established and confirmed compatibility between the Safe'n'Sound® platform, an add-on passive sharps injury protection device for prefilled syringes and Terumo PLAJEX™ COP prefillable syringes. "Safe'n'Sound aids in the protection from accidental needlestick injuries and facilitates the injection process through ergonomic features, such as an optional extended finger flange to improve handling, gripping, and comfort for the user," says Mr. Tisserand.

Nemera's Safelia autoinjector is suited for subcutaneous and intramuscular injections of viscous formulations.

Noble offers a range of patient onboarding support for biopharmaceutical companies and OEMs, including training products for autoinjectors, prefilled syringes, and on-body devices.

Noble: Injection Training Improves Patient Onboarding

Noble has developed many patient-centric onboarding solutions to address the challenges stakeholders face with the growing injection drug delivery market. To address needlestick injuries and other device errors, improving patient onboarding and adherence has been Noble's focus. This can be achieved with a variety of injection training products and solutions for standard and large-volume autoinjectors, prefilled syringes, safety systems, and on-body systems across multiple therapeutic sectors, explains Craig Baker, Executive Vice President of Noble.

"Noble follows an end-user design approach with a focus on keeping patient needs and considerations at the forefront of our development process," says Mr. Baker. "Through collaboration with our pharmaceutical clients and OEM partners, we leverage human factor inputs throughout the development process to ensure that training and onboarding solutions maximize value and satisfy user needs. The results of putting the end user first indicate proper training and onboarding with patient-centric injection training solutions can reduce errors, increase patient confidence, decrease anxiety, and promote adherence in patients using combination therapies."

Noble takes a similar end-user approach with packaging. Mr. Baker says Noble works with pharmaceutical clients to develop packaging solutions designed to provide patients with ergonomically-friendly components and mechanisms to help reduce dexterity challenges.

Noble has also developed multiple training platforms designed to connect wirelessly to smartphone applications, computers, smart packaging, and ancillary training technologies. These connected training platforms have the capability of monitoring, tracking, and guiding patients during the onboarding process. Mr. Baker says: "Smart platforms with error-correcting technologies incorporating audio and/or video training guide patients through simulated injection process using a wirelessly connected device trainer."

Portal Instruments: A Design That Works for Patients & Processes

Portal is developing a needle-free drug delivery platform technology to transform the administration of medications and improve the patient experience for chronic diseases. Portal is targeting the subcutaneous delivery of biologics, the administration of which is typically cumbersome given the nature of their high volume, viscosity, and concentration profiles. Portal's technology enables the administration of biologic drugs with less discomfort and delivers a 1mL injection via a jet the size of a strand of hair in less than half a second, describes Patrick Anquetil, CEO and Co-founder of Portal Instruments. The Portal platform is also cloud-connected, providing reminders and real-time tracking of injections to improve adherence and communication be-

Portal's needle-free drug delivery system is a next-generation alternative to autoinjectors and prefilled syringes for self-administration at home.

tween the patient and care teams.

Portal's development process is based on a design, build, test, and iterate model throughout which Portal depends heavily on inputs of patients and expertise of healthcare providers. "We've run rigorous human factor studies, including contextual inquiries, formative, and other heuristic evaluations," says Mr. Anquetil. "In-depth interviews with patient groups revealed challenges and needs, and provided valuable insight about how the device could affect their quality of life. These findings were built as inputs into the engineering design and risk assessment process."

Feedback indicated the importance of good device handling and grip, especially among patients with limited joint mobility and dexterity. Visual cues were highlighted as necessary to facilitate the administration process. Interactions with patients indicated that they cared most about all the medication being delivered into their body.

"Portal's technology is a patient-centric, user-friendly, next-generation alternative to autoinjectors and prefilled syringes for self-administration at home," says Mr. Anquetil. "There is no risk of needlestick injuries as there is no needle. The technology is agnostic to drug concentration and viscosity, making it well-suited to the delivery of biologics." Lab experiments indicate that the technology can handle viscosities up to 200cP.

Mr. Anquetil explains that not only did the system have to be user friendly, it had to align with pharma processes. So, Portal developed a primary container that leverages the nest and tub standard and is compatible with standard pharma fill/finish lines. The patient just needs to place into the device before administering a medication.

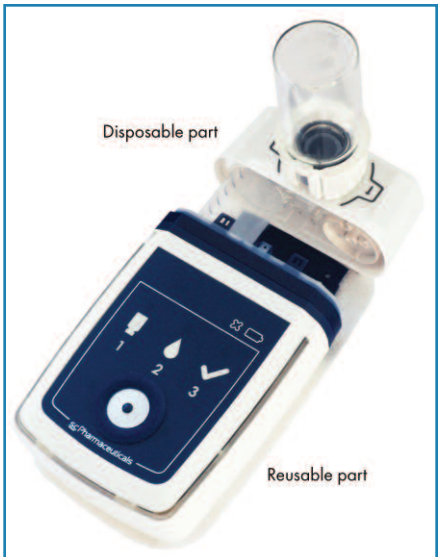
A significant part of Portal's value proposition is tracking medication adherence to treatment regimens. Mr. Anquetil says there is an opportunity to collect patient-reported outcomes data between physician visits that can inform treatment decisions. The first generation of devices will incorporate Bluetooth connectivity and 3G functionality to facilitate the seamless transfer of information."

Sensile Medical AG: Subcutaneous Delivery Reduces Risk & Cost

Sensile Medical has been concentrating on two platform devices, both of which are worn on or off body with an integrated needle or a luer lock connection to an external infusion set. The SensePatch Small Volume delivers up to 3mL from a standard cartridge whereas SensePatch Large Volume can pump up to 20mL from an external container to an internal reservoir. Neither device is restricted to any specific indication and both are tailored to the specific needs of the correspondent therapy.

Dr. Paul Senn, Vice President Business Development of Sensile Medical AG, explains that a proprietary two-part rotary piston pump (SenseCore) is flexible in volume and material, and allows pumping and dosing of small and large molecules in viscous solution. The SensePatch devices also incorporate a proprietary needle injection and retraction mechanism whereby the needle is automatically injected/retracted immediately before/after the volume is delivered, reducing the risk of needlestick injury.

Heart failure is a clinical syndrome resulting from the inability of the heart to pump enough blood. If untreated, it may lead to peripheral edema, fatigue and difficulty breathing, and hospitalization. The majority of these hospitalized patients are just there to receive an intravenous diuretic. It is estimated that about half the patients could receive the treatment at home.



The Sensile Medical SensePatch Large Volume device uses SenseCore technology in a wearable device that delivers drug product under the skin using an autoinjectable and retrievable needle.

One of the most frequently used diuretics, Furosemide, is currently used in tablet form or in solution for intravenous administration. "Subcutaneously delivered Furosemide would offer a new option to treat patients with heart failure, reducing risks and costs," says Dr. Senn.

Sensile Medical and scPharmaceuticals developed the SensePatch Large Volume device for subcutaneous administration of Furosemide. The drug-device combination uses the SenseCore technology in a wearable device that delivers the pharmaceutical drug product under the skin using a very small autoinjectable and retrievable needle. The device consists of a reusable part (containing the motor, a rechargeable battery, the hardware and software components, etc.), and a disposable part (containing the fluidic path from the reservoir, the pump to the needle).

"This innovative product is expected to provide rapid and more effective diuretic therapy that can be used at home under

physician guidance when the patient experiences symptoms of decompensation," says Dr. Senn. "It is expected that this will avert the need for emergency or in-hospital care, and for those patients who still require hospitalization, their hospital stay will be shortened and their outcomes improved."

SHL's Molly is a single-use, two-step autoinjector designed for ultimate safety and comfort.

SHL: Patients Indicated Preference for Two-Step Autoinjectors

SHL offers a wide portfolio of devices that support the needs of its pharmaceutical and biotech partners. Within the past year, SHL has worked on a number of single-use autoinjectors using prefilled syringes or cartridges for therapeutic indications ranging from pain and obesity to autoimmune diseases. However, with the rise of biologics and the trend to prescribe less frequent injections, SHL has also focused on developing solutions that support formulations that come in larger volumes and higher viscosities.

Bertha™, for example, is a two-step autoinjector that supports highly viscous liquids in both 1mL and 2.25mL volumes. The company has also developed the Rotaject® Technology to support drugs with even higher viscosities of up to several hundred centipoise. Using a patented technology to provide constant force, Rotaject ensures safety and comfort throughout the entire injection process when delivering high-volume/viscosity biologic formulations. The technology can also be used with a 1mL or 2.25mL disposable autoinjector.

While SHL's injection systems have been developed to be compatible with either prefilled syringes or cartridges, its cartridge-based autoinjectors are built with Needle Isolation Technology (NITTM), which allows a needle to be pre-attached to the device. "With the needle permanently hidden throughout the entire handling process, the chances of needlestick injuries can be significantly reduced," says Magnus Fastmarken, Global Director Marketing, SHL.

In addition to reducing needlestick injuries, the patient is at center of device design at SHL. "One of the key findings from our human factor research shows that simple two-step devices are the most preferred by the majority of patient groups," says Mr. Fastmarken. "By eliminating the activation button, we are able to improve usability while minimizing the need for training." Human factor elements also support packaging configurations, handling and opening of the carton, and retrieving the device, to determine how to best support the patient population.

To collect and further analyze real usage data, SHL has invested in a new design center that will include an in-house interview studio for recording and documenting the patient experience and feedback in human factors and usability studies.

In fact, SHL's pipeline includes several patented sensors that can be used to collect and share data. One of them is the Molly C Recording Unit, a concept design that demonstrates how connectivity can be utilized in an existing autoinjector to collect real user data, including time, date, and potentially location. "While the unit can be paired with a smartphone to support patient adherence, the concept is part of a larger cloud-based system that allows us to offer additional value for other stakeholders such as pharma companies, clinical researchers, and payers," says Mr. Fastmarken. "For example, some of the areas that we are currently exploring include improving patient experience, learning, and treatment. We are also looking at wireless connectivity as a means to enable device traceability, life-cycle management, and more."

Mr. Fastmarken explains how Molly was recently used with a drug for an inflammatory condition where simplicity of use was crucial to patient handling. Featuring a compact design and buttonless two-step operation, Molly met the partner's request for a device providing optimum safety, usability, and confidence. "As a preconfigured program, Molly also offers lower costs and faster development times," he says.

SiO_2 Medical Products, Inc.: COP Mitigates Sensitivity Risks

SiO_2 manufactures various containers for laboratory and parenteral pharmaceutical use. They are made from cyclic olefin polymer (COP) and typically utilize chemically modified contact surface areas. For parenteral vials, syringes, and cartridges this entails a plasma-enhanced chemical vapor deposition of a series of thin layers of silicates designed to mitigate oxygen and other chemical ingress or egress. Targeted applications are pharmaceutical

projects that would benefit from the cleanliness, break resistance, and dimensional consistency of plastic, but because of certain (typically oxygen) sensitivities, cannot use standard plastics. Because of the inherent robustness of COP containers, patients who are sensitive to glass breakage (e.g. hemophiliacs) can safely self-administer their medications without risk.

Eugene Polini, Principal Scientist, Technical Service, SiO_2, explains how one client successfully used the product to contain an injectable radiopharmaceutical. "This drug product had an extreme sensitivity to metals from the glass packaging. Their switch to the use of COP mitigated any risk from this issue because of its very low inorganic contaminant level. This allowed for the successful storage and delivery of the drug product with reasonable shelf life."

Sonceboz: Simplified Use Avoids Manual Filling & Eases Comfort

Sonceboz is focused on developing a wearable device platform that delivers large volumes from known primary containers. The company designs both a drive and device platform solution that can be quickly adapted to specific intended use-cases: single-container devices for large-volume injection; dual-container injectors for sequential drug delivery; and a wearable injection device featuring automatic reconstitution of lyophilized biologics.

"We are designing the core of our technology platform (user interface, user-steps, internal mechatronics, and pumping system) for challenging therapeutic applications such as Rheumatoid Arthritis," says Thomas Mayer, Sales and Application Manager, Sonceboz. "However, we are also targeting the biologics and biosimilars

Flexible drug delivery platform from Sonceboz.

applications offering vast possibilities to our pharma partners."

Sonceboz designed its device platform based on user input from patients suffering from Rheumatoid Arthritis. "We selected RA as our intended use-case because we believe this condition displays a challenging application due to symptoms such as impaired movement or dexterity, as well as a very homogeneous patient group," says Mr. Mayer. In October, Sonceboz will have the results from formative human factors studies.

From the first design iteration, the focus is on ease-of-use, offering simple preparation steps and avoiding the manual filling of the device. "In our design, the user simply inserts a drug-cassette that contains the primary container as filled by the pharmaceutical company," explains Mr. Mayer. "This ensures ease-of-use for the patient and enables the use of known primary drug containers."

To avoid needlestick injuries, the platform comes with a Dynamic Needle Insertion System that only engages the injection needle once proper skin contact is established, and immediately retracts the needle into the device after initial skin piercing, leaving behind only a soft-cannula for increased patient comfort.

Mr. Mayer adds that Sonceboz has integrated Bluetooth Low Energy communication technology into its wearable device platform, intended to provide one-way data transmission from the injection device to a third-party device such as a smartphone.

West: Designing Devices that Fit into a Patient's Lifestyle

Given the industry trend toward self-injection delivery systems for the treatment of chronic conditions such as diabetes and Rheumatoid Arthritis, West has focused on creating products that are designed with the patient in mind. "In particular, we're seeing a lot of interest in integrated delivery systems that meet the unique challenges of containing and administering biologics," says Eric Resnick, Vice President & Chief Technology Officer, West Pharmaceutical Services, Inc.

One of the most promising options for administering these treatments is wearable drug delivery technology that combines the drug and its primary containment system in a patient-friendly system that delivers the prescribed dose electronically.

West Pharmaceutical Services' SmartDose® platform, for example, was designed with extensive human factors testing and anlysis to integrate into a patient's lifestyle. The platform is a single-use, electronic wearable injector that adheres to the patient's body, usually on the abdomen. Discreet, intuitive, and designed to minimize discomfort, SmartDose technology incorporates a polymer-based drug container (made from Daikyo Crystal Zenith® cyclic olefin polymer) with a drug delivery device that can be pre-pro-

West's SmartDose® platform offers a wearable, subcutaneous injector with an integrated drug delivery system.

grammed to deliver high volumes of viscous or sensitive drug products over time, making it easier for patients to self-administer medication outside of the clinical setting, explains Mr. Resnick.

West collaborated with Amgen, which needed to deliver a high monthly single-dose (420mg) of its drug Repatha® (evolocumab) via injection. "Ultimately, Amgen selected our SmartDose platform because it could support that dosing level, and improve the patient experience, allowing them to perform moderate physical activity (such as walking, reaching or bending) as the drug is delivered subcutaneously," Mr. Resnick says.

West has also partnered with HealthPrize Technologies to integrate their Software-as-a-Service medication adherence and patient engagement platform with West's injectable drug delivery systems, effectively providing an end-to-end connected health solution to pharma companies and the patients they serve. The app tracks when patients take their medication, educates and engages patients to help increase adherence and medical literacy, and rewards them for compliance. Next-generation devices under development currently will include expanded connected functionality.

In addition to easing the self-administration process, the heightened focus on quality by regulatory agencies, especially in particles, extractables and leachables, and container closure integrity, is a focus for West. This, combined with the growing use of biologics and the trend toward self-administration, means manufacturers need to select packaging components that have high levels of reliability, consistency and compatibility with sophisticated drug products, says Mr. Resnick. "That's why we use quality components for our SmartDose platform such as a Daikyo Crystal Zenith drug container with elastomer components using FluroTec® barrier film. Once we have quality accounted for, it's our human factor analysis that helps keep our delivery systems easy and appealing for patients to use." Mr. Resnick adds that the secondary packaging design has to take into consideration the user interface so that the device and drug container are easily acceptable while also providing the necessary product protection and sterility assurance.

Ypsomed: Self-Injection Devices Designed with Patients & Apps in Mind

Following the overall success of its customizable disposable UnoPen and 1mL and 2mL YpsoMate platform products, some customers are looking for higher constant injection forces for increased drug viscosities and to decrease the injection time for 1-2ml injections. For these applications, Ypsomed has developed YpsoMate 2.25 Pro which is being adopted by a number of pharma clients.

Ypsomed is also focusing on the large-volume 2-10mL YpsoDose patch injector, which is attached to the skin during injection. The targeted therapeutic indications are biologic drugs that require the injection of higher volumes with potentially reduced injection frequency compared to a treatment with autoinjectors. As a wearable device, YpsoDose is a prefilled and preassembled, electromechanical, cartridge-based, connected device, based on a versatile platform that may be customized into product specific variants, explains Ian Thompson, Vice President Business Development, Ypsomed.

In the area of connectivity, Ypsomed is focusing on the smart, connected add-ons such as SmartPilot for YpsoMate. SmartPilot transforms the standard YpsoMate autoinjector into a fully connected device, detecting and communicating different use states of the autoinjector to a smartphone, providing real-time, step-by-step instructions in written, animated, and audible formats, improving patient adherence and therapy outcome. In a commercial setting, SmartPilot connects the patient with different stakeholders (doctors, pharma industry, payers) that may take advantage of the collected data. SmartPilot may also be used during a clinical study; Ypsomed will demonstrate

(From left to right) YpsoDose, a next-generation, large-volume injector; SmartPilot for YpsoMate, a resuable add-on transforming the YpsoMate autoinjector into a fully connected device; and YpsoMate 2.25 Pro, the constant-force, large-volume autoinjector.

a clinical use-case during the 2017 PDA conference in Vienna.

New wearable injectors are more complex than autoinjectors and need to be handled simply, safely, and effectively by patients. YpsoDose is being developed to keep the number of handling steps to an absolute minimum. YpsoDose is attached to the skin and activated by pressing a button. Needle insertion, injection, and needle safety are performed automatically. All usability aspects such as patch characteristics, size and weight, and visual/audible feedbacks are being tested with patients in parallel to the technical development process.

"Connected devices, such as YpsoDose and SmartPilot require new approaches to Human Factors testing," says Mr. Thompson. "The attention of the patient is no longer focused solely on the device, but also on the use of smart apps, so it is important to test the device in combination with the connected smartphone."

As an example, Ypsomed is applying eye-tracking methods in the development of SmartPilot to track the attention of the user during device operation to help improve both the device and app interfaces. ◆

References

1. Injectable Drug Delivery Market by Type (Device, Formulation), Therapeutic (Cancer), Usage Pattern (Immunization), Administration (Skin, Musculoskeletal), Distribution Channel (Hospital), Patient Care Setting (Hospital, Home Care) - Forecast to 2021, marketsandmarkets.com, Feb. 2017,http://www.marketsandmarkets.com/Market-Reports/injectable-drug-delivery-market-150.html.
2. Large Volume Wearable Injectors Market (3rd Edition), 2017-2027, Reportlinker, Feb. 23, 2017, http://www.prnewswire.com/news-releases/large-volume-wearable-injectors-market-3rd-edition-2017-2027-300413116.html.

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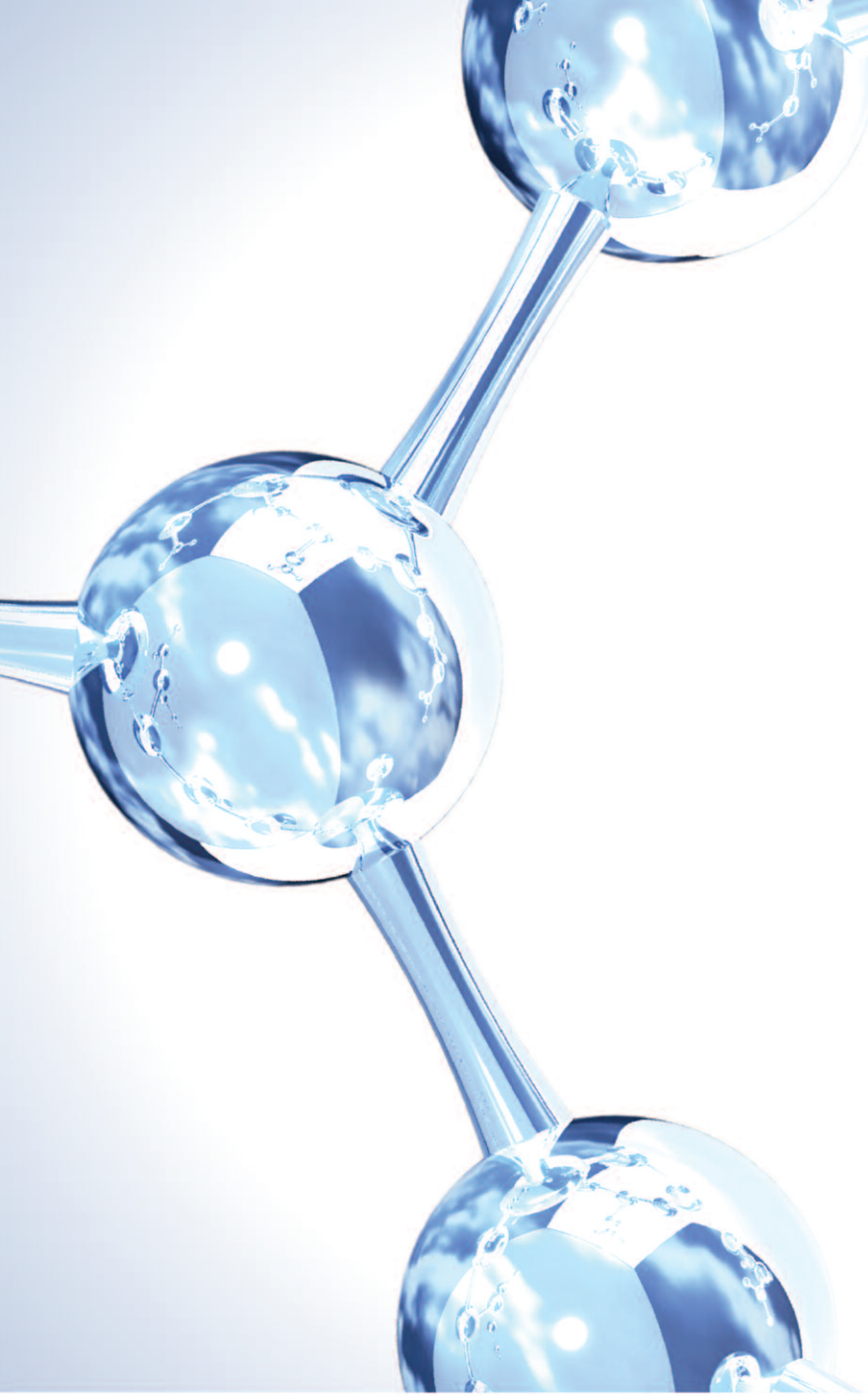

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