Drug Development® & Delivery

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Global Formulation Report

IN THIS ISSUE

INTERVIEW WITH **PRESAGE BIOSCIENCES'** PRESIDENT

NATHAN CAFFO

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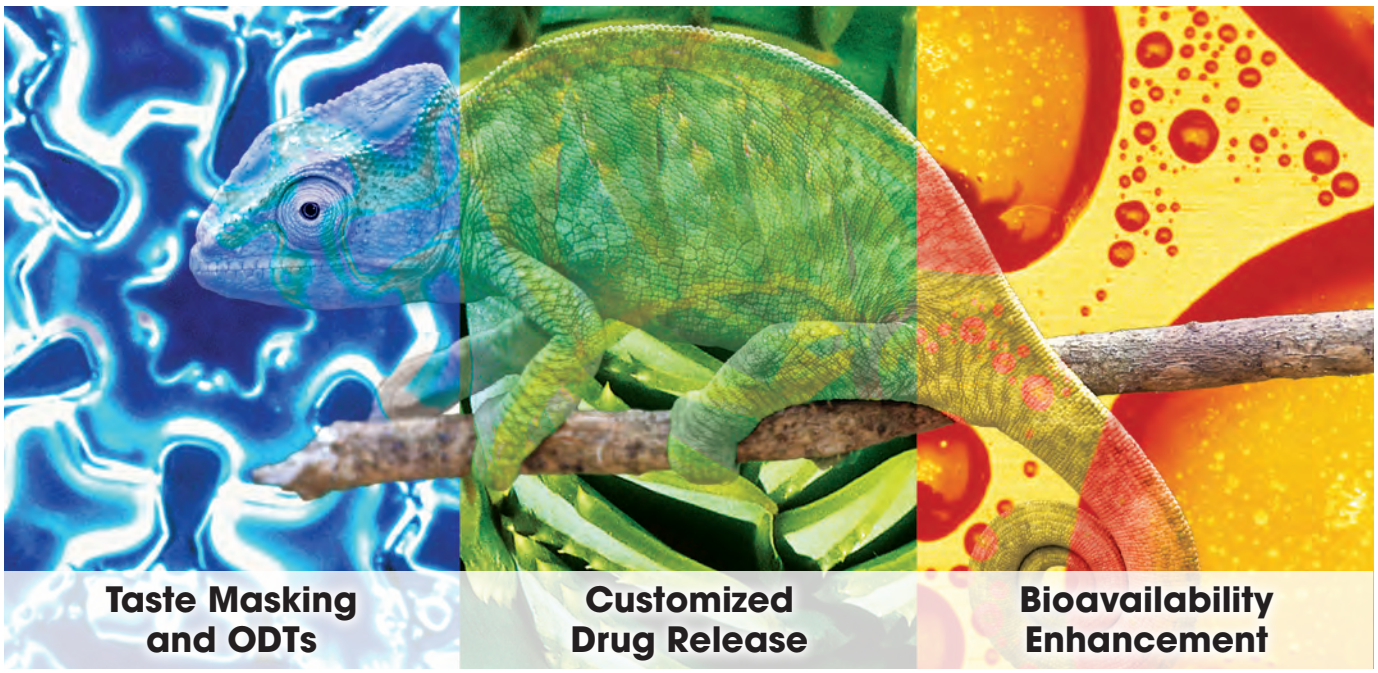

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Corporate/Editorial Office
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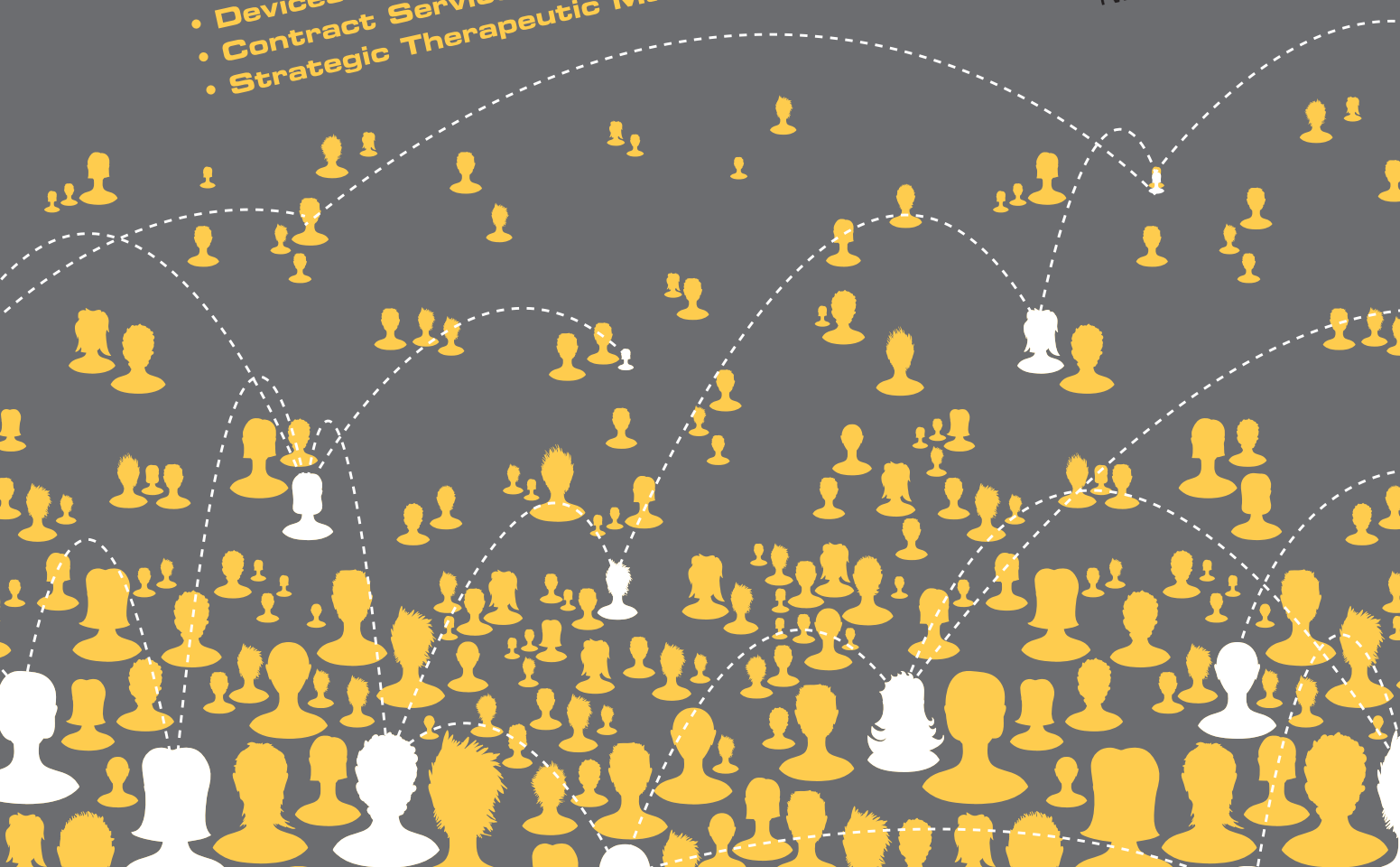


Market News and Trends

Recipharm Completes Acquisition; Broadens Development Capabilities

Recipharm recently announced that it has completed the acquisition of OnTarget Chemistry in Uppsala, Sweden. OnTarget Chemistry is a fast growing CRO company with a turnover in 2014 of close to SEK 29 million that is specialized in medicinal chemistry offering synthesis and analytical services, which include rare and demanding specialties.

With the acquisition of OnTarget Chemistry, Recipharm will significantly broaden its pharmaceutical development capabilities. The inclusion of preclinical chemistry services will give Recipharm the possibility to engage much earlier in high-potential customer projects. Furthermore, OnTarget Chemistry's synthesis capabilities will be of great value for the GMP development of APIs in Recipharm's Italian subsidiary, Edmond Pharma. Sales in 2015 show more than 60% of total revenue outside Sweden with substantial sales in Germany, Japan, and the UK. The business is profitable, and the acquisition is expected to be accretive to EPS from 2016

"With the acquisition of OnTarget Chemistry, we will be able serve both existing and new customers with high-quality development services," said Carl-Johan Spak, EVP of Development & Technology. "OnTarget Chemistry has a very skilled staff with a high number of PhDs working in a modern laboratory of very high standard. The acquisition is of strategic importance for Recipharm as it will, together with the existing development organization, fuel manufacturing sales in the long-term."

"The fit with Recipharm's development organization is very good for us. We believe we can add preclinical competence and capabilities to Recipharm, and we also look forward to contributing with a broad range of both local and international customers. This will be a great opportunity for us to continue to grow our business within Recipharm," added Fredrik Lehmann, CEO of OnTarget Chemistry.

The purchase price was SEK 15.1 million, of which 50% is paid in cash, and the remaining 50% is paid through an issue in kind of 45.838 series B shares in Recipharm. The share issue was resolved upon 15 June 2015 by the board of directors of Recipharm, based on an authorization given by the AGM 7 May 2015. Approximately 36% of the B shares in Recipharm the seller receives are subject to a lock-up of 2 years. The remaining B shares will be distributed by the seller to certain individuals that contributed their shares in OnTarget Chemistry to the seller before the transaction was consummated.

LDC to Collaborate With Johnson & Johnson to Identify & Accelerate Innovative Drug Candidates

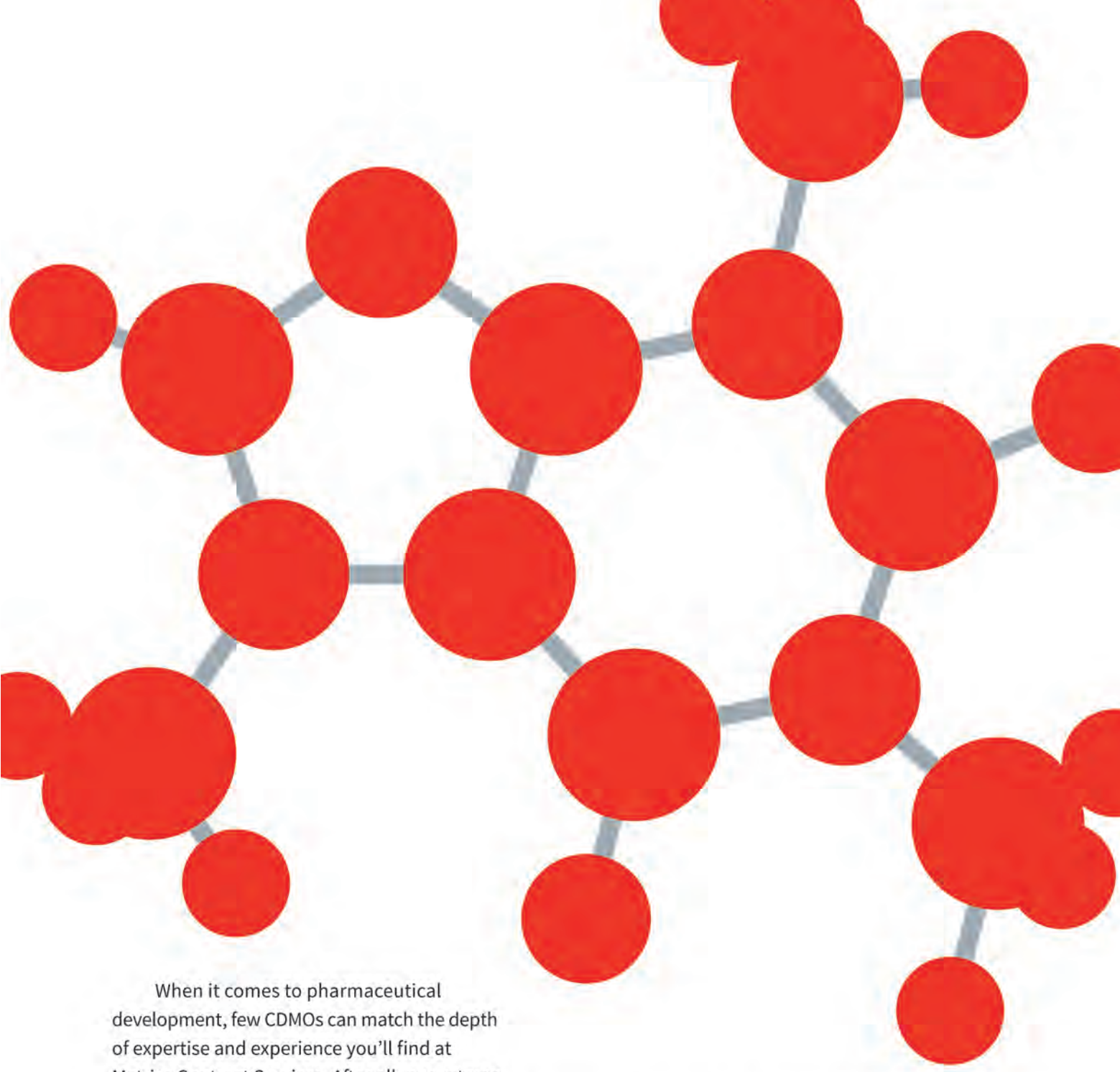
The Lead Discovery Center GmbH (LDC) and Johnson & Johnson Innovation Ltd., will collaborate to identify and accelerate innovative drug candidates for the treatment and prevention of diseases with high unmet medical needs.

Over a 2-year period, LDC and the team from the Johnson & Johnson's London Innovation Centre will work together to identify on an ongoing basis translational research opportunities sourced from LDC's top-tier academic network, including institutes from the Max Planck Society, the Helmholtz Association, and various universities. Johnson & Johnson Innovation will review and evaluate the opportunities with the objective of establishing drug discovery collaborations with LDC in selected projects that are aligned with the company's therapeutic focus areas.

"Through our academic network, we have access to a broad range of exciting molecular targets, pathobiological mechanisms, and new therapeutic approaches, which are the basis for project proposals with a high innovation potential for drug discovery," said Dr Bert Klebl, CEO of the LDC. "Together with Johnson & Johnson Innovation, we will now be able to offer a solution for more of our academic partners to translate their innovative findings into benefit for patients. We very much look forward to leveraging our interests, expertise, and capabilities together with Johnson & Johnson Innovation to incubate additional collaborative projects at the LDC."

For each project selected by Johnson & Johnson Innovation, the partners will negotiate a collaboration agreement for its joint development at the LDC up to the next mutually agreed milestone. The details regarding financial provisions and research activities will be agreed on a project-by-project basis to ensure a fair balance of investments and potential returns between the partners. Any revenue received from commercialization will be shared with the academic inventors and collaborating institutions.

The Lead Discovery Center (LDC) was established in 2008 by the technology transfer organization Max Planck Innovation, as a novel approach to capitalize on the potential of excellent basic research for the discovery of new therapies for diseases with high medical need. The LDC takes on promising early stage projects from academia and transforms them into innovative pharmaceutical leads that reach initial proof-of-concept in animals. In close collaboration with high-profile partners from academia and industry, the LDC is building a strong and growing portfolio of small molecule leads with exceptional medical and commercial potential. The LDC sustains a preferred partnership with the Max Planck Society and has formed alliances with AstraZeneca, Bayer, Merck Serono, Daiichi Sankyo, Qurient, Johnson & Johnson Innovation, as well as leading academic drug discovery centers around the globe.



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PDC*line Pharma Receives Advanced-Therapy Medicinal Product Classification for New Class of Therapeutic Cancer Vaccines

PDC*line Pharma recently announced that PDC*vac, its new class of therapeutic cancer vaccines based on a line of Plasmacytoid Dendritic Cells (PDC*line), was granted Advanced-Therapy Medicinal Product (ATMP) classification by the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA), in consultation with the European Commission. The EMA/CAT considers that PDC*vac fulfills the definition of an ATMP, within the Somatic-Cell Therapy Medicinal Product category.

"The granting of ATMP classification for PDC*vac is a key milestone in the development of our new class of therapeutic cancer vaccines. This classification enables us to receive centralized scientific advice and guidance from the EMA/CAT and to file for the Marketing Authorization at the European level. In addition, PDC*line Pharma is now eligible to benefit from incentives for Small and Medium size Enterprises (SME) developing an ATMP," said Laurent LEVY, Co-Founder & CEO of PDC*line Pharma.

The ATMP classification aims at regulating cell and gene therapy and tissue-engineered medicinal products by providing the pharmaceutical industry with quality compliance guidelines and best practices, including for non-clinical developments, manufacturing, and quality testing. The regulation also offers incentives to companies involved in developing ATMPs in the European Union, including fee reductions for scientific advice, scientific recommendations on ATMP classification, and evaluation and certification of quality and non-clinical data.

PDC*vac technology is the only therapeutic cancer vaccines based on a line of Dendritic Cells (DC) and the only one based on DCs of Plasmacytoid type. PDC*line is fully qualified, safe, easy to expand, and manipulate. It is loaded with synthetic peptides derived from a combination of tumor antigens relevant for the targeted cancer type. The off-the-shelf vaccine can be stored frozen for years. Once injected into a patient, it induces a potent and targeted cytotoxic T cell response against the tumor cells. The same product can be used to treat all patients with a cancer type expressing the selected antigens and expressing HLA-A2 (about 50% of the European and 36% of the US population).

Founded in April 2014 in Grenoble (France) as a spin-off of the French Blood Bank (EFS), PDC*line Pharma is a clinical-stage biotech company that develops a new class of therapeutic cancer vaccines based on a line of Plasmacytoid Dendritic cells (PDC*line). Its breakthrough technology, PDC*vac, is more potent than conventional Dendritic Cell-based vaccines, scalable, versatile to any cancer type, and synergistic with checkpoint inhibitors, such as anti-PD-1. The market potential for PDC*vac is estimated in the range of €3BN to €4.5BN.

Taiho & Servier Enter Into Exclusive License Agreement

Taiho Pharmaceutical Co., and Servier recently announced they have entered into an exclusive license agreement for the development and commercialization of TAS-102 (non-proprietary names: trifluridine and tipiracil hydrochloride) in Europe and other countries. Taiho Pharmaceutical Co., Ltd. retains the right to develop and commercialize TAS-102 in the US, Canada, Mexico, and Japan/Asia and to manufacture and supply the product. TAS-102 is an oral combination anticancer drug initially developed by Taiho Pharmaceutical Co., Ltd. for use in the treatment of refractory metastatic colorectal cancer (mCRC).

Under this agreement, Taiho Pharmaceutical Co., Ltd. will receive a total of US$130 million in an upfront payment and for MAA approval in the EU. In addition, Taiho will receive further regulatory and sales event milestone payments and royalties based on net sales. Taiho and Servier will also collaborate on the further global development of TAS-102 sharing effort and cost on an equal basis.

TAS-102 is currently under review by Health Authorities in Europe and the United States and in 2014 was approved for marketing in Japan. In the United States, Taiho Oncology Inc., a subsidiary of Taiho Pharmaceutical Co., Ltd., will market TAS-102.

"This partnership with Taiho will hopefully allow us to rapidly bring a new therapeutic option to patients suffering from refractory metastatic colorectal cancer in Europe and other countries," said Olivier Laureau, President of Servier. "We respect and value Taiho's well-known expertise in the development of oral cancer drugs and hence this collaboration will contribute to develop Servier's capabilities in oncology. Such a landmark agreement confirms Servier's strong ambition in oncology and our willingness to bring to cancer patients new therapeutic solutions through Servier's extensive portfolio of innovative treatments currently in clinical development. This is in line with our commitment to therapeutic progress for the benefit of patients."

Taiho Pharmaceutical Co., Ltd. and Servier anticipate that TAS-102, as a new treatment option, will make an even greater contribution to cancer patients in Europe and other countries through their partnership.

TAS-102 is an oral combination anticancer drug of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase. TAS-102 is commercially available in Japan and is under regulatory review in the US and the European Union for the treatment of refractory metastatic colorectal cancer.

ONL Therapeutics Provides Update on Novel Photoreceptor Protection Platform

ONL Therapeutics, Inc. recently provided an update on the company's ongoing drug development program to block the programmed cell death (apoptosis) of photoreceptors. Death of photoreceptors, which occurs in a range of retinal diseases, is the root cause of vision loss and leading cause of blindness. The company's recent research and development efforts have led to a number of key milestones, including the promotion of a new lead development candidate and the expansion of its planned clinical program to include both dry and wet forms of age-related macular degeneration (AMD) based on promising preclinical in vivo data.

As a result of ongoing research, ONL has recently identified and patented a novel, first-in-class small molecule peptide, ONL1204, with an attractive profile for inhibiting the Fas pathway, a primary mediator of photoreceptor apoptosis. Researchers have successfully demonstrated the link between Fas pathway activation and a number of retinal diseases and conditions, including retinal detachment and both wet and dry AMD. ONL1204 is an analog of Met12, ONL's first-generation Fas inhibitor, and has demonstrated significantly enhanced potency both in vitro and in vivo as compared to Met12, while also displaying improved pharmaceutical properties. Based on these significant attributes, ONL has promoted ONL1204 to its lead development candidate and intends to advance the compound into clinical trials in retinal detachment in the first half of 2016.

While initial development efforts are focused on retinal detachment, ONL has also recently generated preliminary data in two distinct dry AMD in vivo models demonstrating that its novel Fas inhibition platform protects both photoreceptors and the underlying retinal pigment epithelium (RPE). This is consistent with a growing consensus in the scientific literature about the role of the Fas pathway in dry AMD. Research is increasingly demonstrating that in dry AMD, Fas not only plays a role in photoreceptor death, but also in the death of the RPE that causes Geographic Atrophy (GA).

Based on the company's new data in AMD, ONL is expanding its preclinical and clinical development planning to validate its findings and support initiation of clinical studies in both dry and wet AMD. This work will be conducted concurrently with ONL's clinical development in retinal detachment. Combined, the estimated market for these initial indications that ONL plans to target is greater than $12 billion globally.

"We are excited about the important recent advances we have made in connection with our novel photoreceptor protection technology program. ONL1204 is a potent molecule that displays an excellent profile as a therapeutically relevant Fas inhibitor with applications to address key unmet needs of retinal disease patients," said John Freshley, ONL's President and Chief Executive Officer. "Our new data in models of dry AMD is particularly exciting as this disease has such extreme unmet needs and protection of RPE would represent a true therapeutic breakthrough."

ONL Therapeutics (ONL) is a biopharmaceutical company committed to protecting and improving the vision of patients with retinal disease. By advancing a novel breakthrough technology designed to protect photoreceptors against apoptosis, ONL is pioneering an entirely new approach to preserving sight. The death of photoreceptors, which is the root cause of vision loss and leading cause of blindness worldwide, is implicated in a wide range of retinal diseases. ONL is advancing a novel, first-in-class, small molecule peptide for the protection of photoreceptors. While initial development efforts are focused on retinal detachment, a condition for which the company has been granted orphan drug designation, preclinical in vivo data along with a growing body of literature support potential application in age related macular degeneration (AMD) and other chronic retinal diseases.

Immune Pharmaceuticals Expands Immuno-Dermatology Development Portfolio

Immune Pharmaceuticals Inc. recently announced it has entered into a binding Memorandum of Understanding with Yissum, the Technology Transfer Company of the Hebrew University of Jerusalem regarding the worldwide exclusive licensing and development of a topical, biodegradable, nano-capsule formulation of cyclosporine A. Cyclosporine A, when administered systemically (Sandimmune, Neoral), is an effective treatment for psoriasis, atopic dermatitis, pemphigus vulgaris, and other severe inflammatory dermatoses.

"Following our lead product candidate bertilimumab in bullous pemphigoid, we are excited to expand our immuno-dermatology portfolio with an innovative topical formulation of cyclosporine A. Additionally, we are further strengthening both our nanotechnology platform and our partnership with Yissum, which already includes NanomAbs," said Dr. Daniel Teper, the CEO of Immune Pharmaceuticals.

The topical nano-capsule technology and the application to cyclosporine A have been developed by the team of Professor Simon Benita, former Director of the Institute for Drug Research and Dean of the School of Pharmacy at the Hebrew University of Jerusalem. Professor Benita pioneered an ocular nano-formulation of cyclosporine A, approved for marketing in Europe for the treatment of severe keratitis associated with dry eye disease.

"We succeeded in incorporating cyclosporine A into biodegradable nano-capsules and have developed stable topical formulations able to achieve therapeutic cyclosporine A levels in the targeted skin layers. Cyclosporine A nano-capsule therapeutic effect was confirmed in two different animal models, which we believe may support a potential topical alternative to oral cyclosporine A, and to other topical immuno-suppressive drugs," said Professor Benita.

Immune Pharmaceuticals Inc. applies a personalized approach to treating and developing novel, highly targeted antibody therapeutics to improve the lives of patients with inflammatory diseases and cancer. The company's lead product candidate, bertilimumab, is in clinical development for moderate-to-severe ulcerative colitis and Crohn's disease as well as bullous pemphigoid, an orphan auto-immune dermatological condition. Immune licensed worldwide rights for systemic indications of bertilimumab from iCo Therapeutics in June 2011, while iCo retained rights to all ophthalmic indications. iCo originally licensed the exclusive world-wide rights to bertilimumab in 2006 from MedImmune, the Global Research and Development arm of AstraZeneca.

Melinta Therapeutics Announces Financing to Fund Completion of Final Phase III Study

Melinta Therapeutics recently announced the successful completion of a $67-million Series 4 equity financing. Malin Corporation plc led the round and was joined by other existing investors, including Vatera Healthcare Partners.

"Melinta has developed a novel multi-product portfolio, including the advancement of delafloxacin through its first Phase III ABSSSI trial, presenting the type of compelling investment that our firm seeks to be a part of," said Sean Murphy, Malin Corporation plc Board Director and appointee to the Melinta Board. "With a proven management team that has outstanding experience commercializing anti-infective therapies for underserved patient populations, Melinta is poised for success."

Proceeds from the financing will be used to complete the final Phase III study of delafloxacin, an investigational fluoroquinolone, currently undergoing a confirmatory Phase III study for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). Funds will also support the potential submission of a New Drug Application (NDA) for delafloxacin for the lead indication, pursuing new indications for delafloxacin including hospital-treated community-acquired bacterial pneumonia (hCABP), and advancing a lead candidate for the company's ESKAPE pathogen program.

"We appreciate the support of our new and existing investors as we continue to build a deep, differentiated pipeline while rapidly moving delafloxacin through the clinic," said Mary Szela, Chief Executive Officer of Melinta Therapeutics. "The proceeds from this financing are expected to fund our operations through a number of key milestones, including our first NDA submission with delafloxacin, which we believe holds significant potential to be a therapeutic option for treatment of patients with ABSSSI, including patients with MRSA infections. With its availability in IV and oral formulations, delafloxacin should provide the flexibility that enables patients to continue on the same therapy after discharge from the hospital."

Melinta Therapeutics, Inc. is dedicated to saving lives threatened by the global public health crisis of bacterial infections through the development of novel antibiotics that provide new and better therapeutic solutions. For more information, visit www.melinta.com.

Malin is an Irish incorporated public limited company. Its purpose is to create shareholder value through the selective long-term application of capital and operational expertise to private, pre-IPO, pre-trade sale operating businesses in dynamic and fast growing segments of the life sciences industry. For more information, visit www.malinplc.com.

Emulate Announces Strategic Collaboration for its Organs-on-Chips Platform

Emulate, Inc. recently announced that it recently formed a research collaboration with Janssen Biotech, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson (Janssen), to deploy Emulate's Organs-on-Chips platform across certain Janssen programs to better predict the potential human response of drug candidates and improve the drug development process.

The collaboration, which was facilitated by the Johnson & Johnson Innovation Center in Boston, utilizes Emulate's Organs-on-Chips to advance the clinical goals for three Janssen R&D programs at the stages of drug candidate design and selection. Emulate's technology will also support Janssen's effort to enhance drug discovery and development with its 3Rs program: reduction, refinement and replacement of animal testing.

The public disclosure of this collaboration coincides with the achievement by Emulate and Janssen scientists of the first functional demonstration of Emulate's Thrombosis-on-Chip platform. Using the new Thrombosis-on-Chip that models human response in an engineered living microenvironment, the Emulate and Janssen research teams are evaluating the potential for drug candidates to cause thrombosis, a potential side effect of certain drug classes such as immuno-therapeutics and oncology drugs. The Thrombosis-on-Chip is an example of the application of the range of different Organs-on-Chips within Emulate's platform for providing more predictive data on potential human response to drugs that will enable the design and selection of drug candidates that have a higher potential of success in human clinical trials.

In the collaboration's R&D program, the Thrombosis-on-Chip emulated the conditions and various physiologic parameters involved in clot formation in the human body and provided a mechanistic understanding of the factors implicated in thrombosis. The researchers demonstrated robust functionality of the Thrombosis-on-Chip.

Under the terms of the collaboration agreement with Janssen, Emulate will provide its Organs-on-Chips technology to advance the clinical goals for three research programs: the use of the Lung-on-Chip and Thrombosis-on-Chip to evaluate pulmonary thrombosis; use of the Liver-on-Chip to better predict liver toxicity, a major cause of drug failures in the clinic; and a third undisclosed research program. Emulate will obtain rights to any discoveries related to the Organs-on-Chips platform that result from the research collaboration. Janssen has the option to extend the collaboration beyond the initial three programs, to include additional organs, disease models or drug programs. Other terms of the agreement are not disclosed.

Unchained Labs Announces Major Acquisition; Second of the Year

Unchained Labs recently announced the acquisition of AVIA Biosystems, the developer of the Isothermal Chemical Denaturation (ICD) system for measuring biologic stability. This is the second acquisition for Unchained Labs this year.

The ICD system makes something that wasn't possible before the routine measurement of protein stability under denaturing conditions totally doable. It completely automates the complex sample prep and data analysis needed to make these measurements, giving formulation scientists a true walk-away solution. The ICD system is also a perfect complement for Unchained Labs' first product, the UNit, which simultaneously measures the top two biologic stability indicators, protein unfolding, and aggregation temperatures.

"We are totally committed to improving biologics characterization tools, and the ICD is a great new tool that can actually help predict future drug stability," said Tim Harkness, Founder and CEO of Unchained Labs. "The ICD and the UNit are a perfect pairing and really help establish us as the experts in protein stability. We have done a lot and done it quickly at Unchained Labs, but we are unwavering in our pledge to acquire any product or business that can make a real difference for biologics researchers."

"I'm really looking forward to joining forces with the Unchained Labs team," said Dr. Rick Brown, Co-founder and President of AVIA Biosystems. "Together, our products will give drug discovery researchers the power to characterize and understand their biologics better than they ever could before."

Unchained also announced the addition of $6 million to its Series A Financing, bringing the total Series A round to $31 million. The original syndicate partners, Novo Ventures, Canaan Partners, and TPG Biotech all participated in the financing.

Unchained Labs is committed to building the first cool biologics tools company. One that matters. One without old school rules. One with products that'll make a real difference in the research scientists do every day. The company plans to buy businesses and product lines and then add its magic touch for developing breakthrough products and selling them aggressively. For more information, visit www.unchainedlabs.com.

Egalet Announces Top-Line Study Results

Egalet Corporation recently announced top-line results from a randomized, four-way crossover alcohol-interaction study in healthy male and female moderate drinkers with Egalet-002, an abuse-deterrent, extended-release, oral oxycodone-based product in development for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate. Top-line results from this clinical study demonstrated that Egalet-002 did not dose dump or rapidly release the drug in a shorter period of time after being administered with different concentrations of alcohol.

With almost 30% of individuals living with chronic pain using alcohol to alleviate pain, it is important that extended-release opioids do not dose dump when used in the presence of alchohol. The primary objective of the study was to evaluate the effect of alcohol administration in varying concentrations on the pharmacokinetic (PK) parameters of an 80-mg dose of Egalet-002 under naltrexone blockade. This study was conducted to characterize the effects of alcohol on Egalet-002, an important safety issue that must be evaluated for an extended-release, long-acting opioid product in development.

The study examined Cmax, Tmax, and AUC in the Egalet-002 plus 4%, 20%, and 40% alcohol arms compared to the Egalet-002 plus water arm. There was no evidence of alcohol dose dumping based on the mean ratios of Cmax and AUC derived from the Egalet-002 plus water arm compared to the Egalet-002 plus alcohol arms. There was also no difference in the median Tmax values between any of the treatment arms.

Egalet's Guardian Technology was developed to deliver commonly abused prescription medications in an abuse-deterrent form. The unique plastic injection molding manufacturing process results in abuse-deterrent features designed to resist the most common methods, as well as more rigorous methods, of abuse for morphine and oxycodone - injection and snorting, respectively. The Guardian Technology can be applied broadly across different classes of pharmaceutical products. Egalet's two lead abuse-deterrent product candidates, Egalet-001 and Egalet-002, are oral formulations of morphine and oxycodone, respectively, developed with the Guardian Technology to make particle size reduction difficult and resist dissolution. They are in late-stage clinical development for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate.

Egalet, a fully integrated specialty pharmaceutical company, is focused on developing, manufacturing, and commercializing innovative pain treatments. The company has two approved products: OXAYDO (oxycodone HCl, USP) tablets for oral use only CII and SPRIX (ketorolac tromethamine) Nasal Spray. In addition, using Egalet's proprietary Guardian Technology, the company is developing a pipeline of clinical-stage, opioid-based product candidates that are specifically designed to deter abuse by physical and chemical manipulation.

GLOBAL FORMULATION REPORT

If coders are the anonymous engineers and architects of the software that drives computers, handhelds, and the worldwide web, then formulators and drug delivery professionals are the anonymous engineers and architects who drive the pharmaceuticals that are changing medical treatment paradigms. It's the formulators and drug delivery professionals who ensure that increasingly complex molecules are delivered to the right organ, in the right dose, and at the right time to optimize efficacy and safety.

The new therapeutic molecules coming out of the chemistry and biotech labs are neither well-behaved from a physiochemical perspective nor easily tamed. Too often, they are highly insoluble or are too quickly excreted to be of any practical therapeutic benefit without the help of formulation and drug delivery. And at the same time, the right drug is only as useful as the patient's willingness to take it according to the prescribed schedule. Making drugs easy and simple to use helps ensure the patient and the healthcare system receives the optimal benefit from these new breakthrough pharmaceuticals. It's the job of formulation and drug delivery professionals to ensure products provide optimal efficacy, safety, and convenience.

The importance of formulation, the common denominator in all pharmaceuticals, is too easily ignored by industry pundits and the public in the same way they ignore the coders of the software running our tools and toys. This Global Formulation Report takes a closer look at the business and science of formulation and drug delivery as revealed by the past year. The subjects covered range from new formulation-enhanced drug approvals, to combination products, to the technologies and deals underpinning these products, and much more. A panel of industry experts also offers their thoughts on what is yet to come.

The Report is a collaborative effort between the well-respected team at Drug Development & Delivery, and the information, analysis, and writing team of the delivery and formulation experts at PharmaCircle (Kurt Sedo, Tom DePaul, and Josef Bossart). The format is intended to provide an overview of what happened in 2014 and how these events are likely to shape the coming years. We hope you enjoy this issue. Please drop us a line if you have suggestions for how we can improve future issues.

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

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

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10 Ten Notable Drug Delivery & Formulation Technologies of 2014

The Drug Delivery and Formulation professionals' toolbox continued to expand this past year with new technologies being imagined, technologies being validated through clinical trials, and established technologies finding new uses and applications.

The biggest technology accomplishment in 2014 most certainly was the validation of Mannkind's Technosphere formulation and Dreamboat device with the FDA's approval of Afrezza. Smaller and more patient-friendly than Nektar's Exubera, it remains to be seen if strong technical and design performance will translate into physician and patient acceptance as well as payor reimbursement. With Afrezza now approved, the question is whether the Technosphere and Dreamboat platforms can be successfully applied to the systemic delivery of macromolecules. Dreamboat wasn't the only inhalation device to gain traction in 2014. GlaxoSmithKline's Ellipta device continued to gain momentum with the approval of two additional products. Ellipta provides a number of important advantages over the tried and true Diskus dry powder inhaler that should translate into improved patient outcomes.

PEGylation was well represented with two major product approvals in 2014. Biogen's Plegridy, a PEGylated version of their interferon beta-1a was a very obvious line extension. More interesting was the approval of Nektar's Movantik, a PEGylated small molecule. Using a markedly smaller polyethylene glycol polymer, and ether linkage, Movantik is defining a new set of applications for the use of PEG. Nektar also pushed the frontiers of PEGylation with its prodrug PEG irinotecan tetramer (NKTR-102). Using releasable linkages, the intention is to have the macromolecule preferentially taken up by tumors where the active, irinotecan in the case of NKTR-102, will be released. Recent disappointing Phase III results may, however, give Nektar cause to pause and reconsider this strategy. Enzon tried a similar approach using high molecular weight PEG conjugated anticancer agents more than a decade ago with discouraging results.

Drug delivery and formulation advances in 2014 highlighted the merging of protein technologies with, and into, drug delivery. There has been little argument as to whether PEGylation, the attachment of polyethylene glycol to proteins, is a drug delivery technology. But what about the various protein fusion technologies? These technologies depend on genetic engineering to create a single polypeptide that retains the properties of the therapeutic protein but with the customized benefit of a linked protein. Unlike first- and second-generation PEGylation, the resulting product does not require subsequent chemical conjugation and is a relatively well-characterized molecule. Smells like drug delivery, but with a whole new set of tools. Among the many products approved in 2014 using protein fusion technologies, two employed Biogen's Synfusion technology that was part of Biogen's acquisition of Syntonix. GlaxoSmithKline's fusion protein, Tanzeum, an albumin fusion for the treatment of diabetes that arrived with the acquisition of Human Genome Sciences protein, was also approved last year.

The whole issue of macromolecule delivery continues to be an area of focus for formulation- and device-oriented companies. While the dream of orally active macromolecules remains a significant challenge, many companies recognize that injections are effective and safe, but not patient friendly. To that end, several companies have made progress with devices that simplify and disguise the process of injection. The prospects for microneedle injections were boosted by Lilly signing on to Zosano's clinical-stage parathyroid hormone product, ZP-PTH. Success in Phase III could be just the validation needed to spur more development in this area. Crossject and Enable Injections advanced their platform injection devices based on traditional injection technologies, needle and needle free, by disguising and simplifying the devices with non-traditional form factors to make them appear less needle-like and less threatening. Both companies have rejected the traditional syringe and pen look for their devices.

Large-volume subcutaneous administrations were further validated by the approval of Roche's MabThera-PH20 using Halozyme's Enhanze technology, human recombinant hyaluronidase. With several Big Pharma partners, approved products and a remarkably full pipeline, Enhanze technology seems to have a bright future. Sometimes the best idea is to work with what works and make it better.

Many more drug delivery and formulation technologies made strong moves in 2014. Ten technologies have been selected that provide a snapshot of the developments in 2014 and perhaps point to where drug delivery and formulation are headed.

Technology: Accurins

Type: Nanoparticles, Emulsion/Polymerization, Receptor/Carrier

Company: BIND Therapeutics

Applicability: A wide range of drug classes, including peptides, proteins, small molecules, and siRNA. The system is also applicable to the delivery of diagnostic and prophylactic agents.

Products/Partners

Phase II: BIND-014/BIND

Preclinical: AZD2811/AstraZeneca, BIND-510/BIND, Bind/Pfizer Accurins Program/Pfizer, KSP Inhibitor Program/Merck,PLK1 Inhibitor Program/Merck, Roche Non-Oncology Nanomedicines/Roche

Notable: A novel technology portfolio that extends the applicability of nanoparticles to long circulating polymers that can be further tagged with targeting ligands.

Technology Overview: Long circulating, PEGylated, biodegradable polymer (PLGA-PEG, PLA-PEG, etc)-based targeting nanoparticles that deliver high drug concentrations to target cells and tissues resulting in increased efficacy and reduced toxicity. The platform permits the engineering of libraries of drug-encapsulated targeted nanoparticles that differ systematically in their biophysico-chemical properties and the selection of nanoparticles that provide optimal properties.The targeting groups on the surface of the particles (attached to the biodegradable polymers) can be small molecule, peptide, protein, nucleotide or antibodies.

Technology: Cosmo Multi-Matrix

Type: Colonic Release, Oral Matrix MR, Taste-Masking

Company: Cosmo Pharmaceuticals

Applicability: Drugs with solubility properties ranging from freely soluble to practically insoluble. Drugs noted in patent applications include budesonide, metformin, gabapentin, levodopa, carbidopa, ibuprofen, diclofenac sodium, and chlorhexidine. The MMX technology may also be used for diagnostics targeting the gastrointestinal tract.

Products/Partners

Marketed: Lialda/Shire, UCERIS/Salix (Valeant), Zacol NMX/Dr. Falk Pharma

Phase III: CB-17-01/Cosmo Pharmaceuticals: Rifamycin SV MMX/Dr. Falk Pharma

Preclinical: CB-01-12/Cosmo Pharmaceuticals, CB-01-16/Cosmo Pharmaceuticals, Bioker Diabetes Program/Bioker

Notable: The importance and commercial value of drug delivery and formulation technologies specific for gastrointestinal conditions was further validated in 2014 and early 2015 by the increasing sales of products targeted to these conditions and the bidding war for Salix, a specialty pharma company with a gastrointestinal focus.

Technology Overview: Multi-Matrix System (MMX) comprises controlled-release and taste-masked tablet compositions containing one or more drugs inglobated in a three-component matrix structure, i.e., a structure formed by successive amphiphilic, lipophilic (or inert) matrices, and finally inglobated or dispersed in a hydrophilic matrix. Compositions are coated with pH-resistant acrylic copolymers that delay the release until the tablet reaches the indicated intestinal location where the programmed dissolution begins.

Technology: Ellipta

Type: DPI (Dry Powder Inhalers)

Company: GlaxoSmithKline

Applicability: Small molecule single agent and drug combinations.

Products/Partners

Marketed: Anoro Ellipta/Theravance, Arnuity Ellipta/GlaxoSmithKline, Breo Ellipta/Theravance, Incruse Ellipta/GlaxoSmithKline

Phase III: GSK2384425/GlaxoSmithKline

Notable: With four products now approved, two in 2014, the Ellipta dry powder inhaler has become the device workhorse of the GlaxoSmithKline inhalation portfolio. An update to the well-validated Diskus inhaler, Ellipta offers a number of important benefits for patients and formulation developers.

Technology Overview: A dual-strip, multidose, disposable dry powder inhaler device. Each strip can contain a different active or be configured for delivery of a single medication. The device includes a dose counter and is designed to prevent the patient from taking a double dose in one inhalation.

Technology: Enhanze

Type: Injection Site Absorption Enhancers

Company: Halozyme, Inc.

Applicability: All biologics and small molecule medications up to 200 nm.

Products/Partners

Marketed: Hylenex/Halozyme, HyQvia/Baxter, MabThera/Biogen, Herceptin SC/Roche

Phase II: PEGPH20 Oncology/Halozyme, Analog Insulin-PH20/Halozyme, HTI-501/Halozyme

Phase I: Enhanze Artificial Pancreas Program/Yale, Actemra-PH20 SC/Roche

Preclinical: rHuA1AT-PH20/Intrexon, RN316 (PCSK9)-PH20/Pfizer, Rivipansel–PH20/Pfizer, Daratumumab SC Program/Janssen

Notable: The list of products and partnerships are testament to the versatility of the Enhanze technology. Not included are a number of co-therapy programs being undertaken by Halozyme involving approved insulins and chemotherapeutics. The ability to deliver large-volume macromolecules subcutaneously without the need for prolonged infusion provides benefits for patients and caregivers. Halozyme has a number of active collaborations: Janssen - 5 targets, Pfizer - 6 targets, and Roche - 8 targets.

Technology Overview: Recombinant human hyaluronidase enzyme is used as a drug delivery enhancement system. The enzyme digests hyaluronic acid, which facilitates the penetration and dispersion of other drugs by temporarily opening flow channels under the skin/or into tumors that accumulate hyaluronic acid. Molecules as large as 200 nm may pass freely through the perforated extracellular matrix. The technology is being applied to local anesthesia, especially ophthalmology, solid tumor malignancies, and to improve the absorption of injectable products. The technology makes large-volume subcutaneous injections practical.

Technology: Enable Injector

Type: Patch Pumps/Micropumps/Microinfusors, Reconstitution Systems, Large-Volume Injectors, Concentrated Suspension/Viscous Solution

Company: Enable Injections

Applicability: All biologics and small molecule medications.

Products/Partners: Undisclosed (Preclinical)/CSL Behring

Notable: A novel small body-worn single-use device that permits subcutaneous dosing using a standard container closure system while providing tactile feedback. The Enable Injector is intended to allow for extended injection times and deliver volumes up to 20 ml.

Technology Overview: A circular shaped, mechanical-driven patch pump injection device designed to deliver 2-10 cc or 10-20 cc in volume (two sizes of device). The device accepts standard vials and cartridges and is able to automatically reconstitute lyophilized products. It also automatically warms the drug during the transfer from the vial in to the injector. The injector is ready for use immediately, eliminating the 30-min wait time for refrigerated medications. The device is activated with a push of a button and when injection is complete, the needle retracts. The device can deliver 1-100 cp solutions at 1 ml/min through a 29 G needle. Flow rates and delivery volumes can be modified to meet requirements of products.

Technology: Nektar Polymer Drug Conjugates

Type: Prodrugs, PEG Polymer

Company: Nektar Therapeutics

Applicability: Nektar's very low molecular weight polyethylene glycol (PEG) conjugation technology is most suitable for small molecules. The higher molecular weight releasable PEG technology is applicable to both low and high molecular weight actives.

Products/Partners

Marketed: Movantik/AstraZeneca

Phase II: NKTR-102 (etirinotecan)/Nektar, NKTR-181/Nektar

Phase I: NKTR-171/Nektar

Preclinical: NKTR-174/Nektar, NKTR-192/Nektar, NKTR-195/Nektar, NKTR-196/Nektar, NKTR-214/Nektar

Notable: Movantik (naloxegol), approved in 2014, embodies Nektar's new approach to the use of polyethylene glycol polymers conjugated to small molecules for the purpose of restricting distribution. NKTR-102, using hydrolyzable PEG linkers, recently hit a bump in the road with Phase III results in advanced breast cancer showing an improvement, albeit not statistically significant, in median overall survival.

Technology Overview: These latest iterations of the use of polyethylene glycol (PEG) involves:

1. The attachment of very low molecular weight PEG polymers to small molecules to restrict distribution of the conjugate to the periphery and prevent CNS uptake.

2. The use of hydrolyzable linkers with higher molecular weight PEG polymers permitting the inactive PEG conjugated chemotherapeutics to be preferentially taken up by tumors followed by release of the active agent.

Technology: ZP Patch

Type: Poration Microneedles

Company: Zosano Pharma Corp.

Applicability: The ZP Patch technology can deliver peptides, small water-soluble molecules, biopharmaceuticals, and vaccines with good non-refrigerated stability. The technology has been applied to a variety of molecules, including PTH, hGH, PTHm EPO, GSCF, GLP-1, antibodies, BNP, fentanyl, granisetron, naratriptan, sumatriptan, zolmitriptan, and various vaccines.

Products/Partners

Phase II: Daily ZP-PTH/Lilly, ZP-Glucagon/Zosano

Preclinical: ZP-Triptan/Zosano GLP-1/Novo Nordisk

Notable: The most advanced generation of microneedle delivery technology, Zosano's ZP-PTH is partnered with Eli Lilly and is will be entering Phase III testing. This will largely determine the fate of microneedle technologies given that several companies developing similar technologies have failed. With the development of easy-to-use needle and needle-free devices, including inhalation, the market for macromolecule delivery is becoming very congested which should benefit patients.

Technology Overview: A user-friendly transdermal delivery system that incorporates Zosano's thin titanium Macroflux microneedle array technology into a patch the size of a coin with a reusable, spring-loaded applicator to create holes in the stratum corneum and deliver drugs systemically. The microprojections are dry coated with the active. The patches contain an adhesive backing and are typically worn for up to 30 mins. The Macroflux microarrays can be used in conjunction with iontophoresis.

Technology: Synfusion

Type: Prodrugs, Antibody-ADC

Company: Biogen

Applicability: Proteins, by coupling a therapeutic protein, such as factor VIII and factor IX, to the Fc domain of an immunoglobulin.

Products/Partners

Marketed: Alprolix/Swedish Orphan Biovitrum, Eloctate/Swedish, Orphan Biovitrum

Notable: Two Synfusion products, Alprolix and Eloctate, were approved in 2014 for the treatment of Hemophilia-related conditions. The use of fusion proteins is becoming more and more common and achieves drug delivery outcomes using the genetic engineers toolbox.

Technology Overview: Novel Fc-fusion constructs that link a single copy of a therapeutic protein to the Fc region on an antibody so as to optimize the pharmacokinetic and pharmacodynamic properties of the biopharmaceutical. The constructs are optimized to bind to FcRn in the endothelial cells that line the blood vessels, effectively "recycling" the drug to increase its circulating half-life.

Technology: Technosphere/Dreamboat

Type:

Technosphere: Inhalation Formulations, DPI, Oral Peptide/Protein/ Macromolecule, Nasal Formulations

Dreamboat: DPI-Dry Powder Inhalers

Company: Mannkind Corp.

Applicability: Technosphere is a dry powder formulation for inhalation that can deliver potent peptides, small water-soluble molecules, biopharmaceuticals, and vaccines with good non-refrigerated stability. Technosphere has been applied to a variety of molecules, including PTH, hGH, PTHm EPO, GSCF, GLP-1, antibodies, BNP, fentanyl, granisetron, naratriptan, sumatriptan, zolmitriptan, and various vaccines.

Dreamboat is an easy-to-use, whistle-like, low-cost, multidose DPI device platform that is adaptable to a broad range of products, including proteins and peptides.

Products/Partners

Marketed: Afrezza/Sanofi

Preclinical: Mannkind Bone Agent Program/Mannkind, MKC180/ Mannkind

Notable: Technosphere (Formulation) and Deamboat (Device) are the technologies behind Mannkind's Afrezza. The performance and portability of this dry powder inhalation treatment addresses physician and patient needs with a good chance of establishing the value of inhalation as an alternative to injections for macromolecules.

Technology Overview: Technosphere - A platform technology based on a novel and inert excipient that forms microparticles appropriately sized, between 0.5 and about 5 µm, for inhalation into the deep lung without the traditional requirement for subsequent processing, ie, milling, sizing etc. The microparticles have a very rapid dissolution profile and can mimic the PK of intra-arterial administration. The Technosphere platform is broadly applicable to other delivery routes, including nasal, oral, as well as SC or IV injection.

Dreamboat - Dreamboat is a smaller, more discrete, easier to use, dry powder inhalation device that requires lower airflow and less powder to deliver clinically meaningful plasma concentration. It shows little change in performance over a wide range of airflow rates.

Technology: Zeneo

Type: Needle-Free Injector

Company: Crossject

Applicability: The technology platform has been clinically proven for intradermal, subcutaneous, and intramuscular injection of small molecules, therapeutic proteins, and vaccines, both for human and animal health applications.

Products/Partners

Phase I: Fluarix Needle-Free/GlaxoSmithKline, Methotrexate Supergeneric/Crossject, Epinephrine Supergeneric/Crossject

Preclinical: Sumatriptan, Supergeneric/Crossject

Notable: An injection device using needle free technology and that doesn't look, or operate, like more traditional needle and needle-free injection systems. The device offers customizable delivery depths from subcutaneous to intramuscular. The winner of several design awards.

Technology Overview: A single-use, prefilled, fixed-dose needle-free injector utilizing a novel gas-generating technology adapted from the automobile safety field (similar to airbags), as the power source. Device is proven to be suitable for intradermal, subcutaneous, and intramuscular injections.The injector is customizable for different volumes (0.1-0.6 ml) and viscosities.

10 Ten Notable Drug Delivery & Formulation-Related Transactions of 2014

The PharmaCircle database lists a total of 1,277 transactions in 2014 involving PharmaBio assets. This total included 325 transactions that directly involved technologies, products, or companies related to drug delivery and formulation. Table 1 provides a breakdown of drug delivery and formulation transactions for the years 2012, 2013, and 2014 as classified by PharmaCircle. There is often overlap in categories; Product Deals might well include technology assets, and Company Acquisitions are likely to include the acquisition of products. These types of transactions are not "double-counted."

Table 1. Drug Delivery & Formulation Transactions (2012-2014)

	2014	2013	2012
Amendment Deals	33	44	10
Company Acquisitions	18	30	14
Technology Deals	58	113	128
Joint Venture	2	4	0
Option Agreement	4	6	5
Pharma Services Deals	19	29	22
Product Acquisitions	22	18	17
Product Deals	146	158	43
Termination Deals	23	12	16
Total	**325**	**419**	**355**

As is apparent from the table above there is sufficient variability in year-to-year to make firm conclusions regarding trends. What does jump out is the substantial drop in the number of Technology Deals from the years 2012 and 2013 to 2014. Is this an anomaly or does it reflect an actual shift in the need for companies to access proprietary technology and know-how? Do companies already possess the necessary technology and expertise to be able to "do it in house?" Is the cost of sourcing external technology too high in terms of financial resources and partnership management? It's hard to tell, but there was no uptick in technology transactions in the first quarter of 2015. A total of 64 drug delivery and formulation transactions were reported in the first quarter of 2015, with 17 classified as Technology Deals.

Over the same period, there appears to be an uptick in the number of Product Deals and Product Acquisitions, perhaps reflecting the industry's increasing focus on applying technologies to products that validate the technology and provide very saleable assets. The first quarter of 2015 had 25 Product Deals and 4 Product Acquisitions. It has become obvious the real value of drug delivery is in the products that can be developed with the technology, not the technology itself. This is more apparent if we look at the number of products at some stage of preapproval development, Research to Phase III. PharmaCircle identified 10,461 active drug delivery or formulation-related products at some stage of premarket development, including 863 in Phase III as of the end of the first quarter of 2015.

Examining individual transactions reveals a common theme – caution; limited upfronts in the product and technology deals, with a much greater portion of the value being back-loaded in regulatory and commercial milestones. In these back-loaded deals with limited upfront payments, the development costs are most often taken on by the licensee, providing for a reasonable sharing of risk. The drug delivery company has taken the risk to develop the technology, while the licensee takes on most of the development risk going forward. Not what drug delivery companies were used to in the 1990s, but a pragmatic approach to the financial realities of the 2010s.

The big drug delivery deal of the year certainly was Mannkind's Afrezza deal with Sanofi. Even this deal, with $150 million upfront, is relatively small when one considers the preapproval investment that Pfizer had made in Nektar's Exubera.

A number of transactions have been selected for examination to provide a bit of insight into the mood of licensors and licensees. These are not the megadollar acquisitions seen in the larger BioPharma area, but the types of transactions that help finance the drug delivery and formulation sector, spur additional investment, and lead to breakthrough technologies and products.

Product Development – Long-Acting Depot

Type: Technology Licensing/Product Option
Active: buprenorphine hydrochloride
Indication: Opioid Dependence
Delivery Route: Injectable - Depot
Dosing Interval: 30 days
Licensor/Licensee: Evonik/BioDelivery Sciences

Agreement Announcement: 2014-10-28
Technology: Biodegradable PLGA Microparticles (FormEZE)
Current Status: Preclinical
Estimated Development Time[1]**:** 4 years (current stage to NDA filing)
Deal Value: Undisclosed

Deal Summary: Evonik will be applying their FormEZE technology to developing a one-monthly injectable formulation of buprenorphine. BioDelivery Sciences has an option to license "Phase I ready formulations" in exchange for milestones and royalties to Evonik.

Comment: BioDelivery Sciences has made the transition from an Emerging Stage Specialty Pharma Company developing products through development to approval to a Commercial Stage Specialty Pharma Company with a USA sales and marketing effort. Their first commercialized product, Bunavail (buprenorphine/naloxone film) targeted to the management of opioid dependence has been launched in the USA. This deal beefs up their development pipeline with a complementary product for their portfolio, albeit at a very early stage. It's unlikely that any product coming out of this agreement would be marketed before 2020.

This transaction reinforces the value of companies such as Evonik who have the necessary technology, intellectual property and expertise to develop 'higher tech' pharmaceutical formulations. Although not reported it is likely that Evonik is conducting the formulation development at their own expense, or with limited financial support from BioDelivery Sciences. While this represents a risk it allows Evonik to further explore and validate their FormEZE technology with the comfort that a willing and capable licensee is waiting to take it through clinical developments.

Technology Licensing – Subcutaneous

Type: Collaboration/Licensing Agreement (Worldwide)
Active: Five Undisclosed Targets
Indications: Undisclosed Dependence
Delivery Route: Injectable - Subcutaneous
Licensor/Licensee: Halozyme/Janssen Biotech
Agreement Announcement: 2014-12-17

Technology: Injection Site Absorption Enhancer (Enhanze)
Current Status: Preclinical
Estimated Development Time[1]**:** 5 years (current stage to NDA filing)
Deal Value: $581 million plus Royalties

Deal Summary: Janssen will be permitted to apply Halozyme's subcutaneous enhancing human hyaluronidase enzyme (rHuPH20, Enhanze) to a total of five proprietary targets. The deal terms include $15 million upfront and $566 in development, regulatory and sales related milestones, plus royalties.

Comment: Halozyme appears to be walking a very pragmatic line between developing their own pipeline while providing technology and 'materials' to partners and customers. Halozyme has significant partnerships with five Big Pharma companies to apply Halozyme's Enhanze technology to their proprietary products, of which three products are already approved and providing ongoing revenue. Their proprietary pipeline includes three products in clinical development. Halozyme also markets and sells recombinant hyaluronidase, Hylenex, as a prescription product to enhance tissue permeability of co-administered drugs. Sales of Hylenex accounted for about $13 million in 2014. Sales of bulk rHuPH20 to partners accounted for an additional $25 million.

The late 2014 deal with Janssen further validates the Enhanze technology and provides the potential for additional revenue without adding additional risk or resource demands on Halozyme. The $15 million upfront is a pragmatic balance of receiving value for a license to the asset and encouraging a deal that can have significant value going forward.

Despite receiving more than $75 million in revenue in 2014 Halozyme reported an Operating Loss of $63 million, largely based on research and development expenses of almost $80 million, of which more than two-thirds was invested in their propriety product pipeline.

1 Development times are estimated by Pharmanumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.

Product Licensing - Inhalation

Type: Product Licensing Agreement (Worldwide)
Product: Afrezza
Indication: Diabetes, Type 1 and Type 2
Delivery Route: Inhalation – Dry Powder
Licensor/Licensee: Mannkind/Sanofi

Agreement Announcement: 2014-08-11
Technology: Dry Powder (Technosphere), Device (Dreamboat)
Current Status: Marketed (USA), Phase 3 (ROW)
Forecast Development Time[1]**:** Not Applicable
Deal Value: $925 million milestones plus profit sharing.

Deal Summary: Sanofi gains worldwide commercialization rights for Afrezza, Mannkind retains certain manufacturing rights. In addition to an upfront payment of $150 million, and $775 million in milestones to Mannkind, the parties will split profits 35%/65%, Mannkind/Sanofi.

Comment: This was doubtless the biggest drug delivery related deal of 2014 with Mannkind's Afrezza finding a substantial partner in Sanofi. It appears to be a win-win for both parties. Mannkind is able to bring Afrezza to the market with the resources of a diabetes market leader that will be essential if Afrezza is to be a success. Sanofi at the same time picks up a new product option that has considerable market appeal and can elevate awareness of their whole diabetes portfolio.

With an accumulated net loss of almost $2.5 billion, largely related to Afrezza development, Mannkind depends on a strong market acceptance of Afrezza to recoup their investment and turn any type of profit. Even with the $150 million upfront payment the larger cost to Sanofi will be related to the product launch expenses and the lost opportunity it might entail if Afrezza is not a blockbuster. Early market returns indicate that Afrezza is not being taken up as quickly as some analysts had forecast causing peak sales forecasts to be lowered to $1 billion annually.

The approval of Afrezza in its current presentation is a big step forward for the delivery of inhaled macromolecules. Assuming there are no untoward safety issues, and the product is not completely rejected by the market, there is an opportunity for Mannkind to leverage their inhalation platform with other partners' actives and finances.

Product Acquisition – Buccal Spray

Type: Product Acquisition Agreement (Worldwide)
Product: ZolpiMist
Indication: Insomnia
Delivery Route: Buccal - Spray
Licensor/Licensee: NovaDel/Amherst
Agreement Announcement: 2014-09-22

Technology: Buccal Spray (NovaMist)
Current Status: Approved (USA)
Forecast Development Time[1]**:** Not Applicable
Deal Value: $2.2 million of debt assumption plus royalties

Deal Summary: NovaDel Pharma transfers all assets related to ZolpiMist to Amherst Pharmaceuticals in exchange for Amherst assuming $2.2 million in fees owed to the FDA and a 10% royalty on sales aggregated to a total of $500,000.

Comment: This is the type of deal that gets done as the lights are being turned off. NovaDel in its various incarnations has been around for more than two decades managing to get two products through to FDA approval, NitroMist (nitroglycerin) and ZolpiMist (zolpidem). Neither product though was able to find a strong partner able to capture market share from competing simple oral and sublingual dosage forms.

The deal basically hands off ZolpiMist to Amherst in exchange for assuming the costs of the product's FDA approval fees, and penalties for late payment. The product was approved in 2008 and never managed to gain significant market acceptance.

NovaDel is representative of many other smaller drug delivery technology companies who developed products that offer a new dosage form, with no therapeutic benefits and limited convenience improvements. It's a cautionary tale for other companies. While a major pharmaceutical company may be able to succeed with this as part of a lifecycle management strategy, that opportunity is not available to smaller emerging companies.

1 Development times are estimated by Pharmanumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.

Product Licensing – Needle Free, Nasal

Type: Product Licensing Agreement (Worldwide)
Product: Sumavel DosePro
Delivery Route: Injection – Needleless Device
Licensor/Licensee: Zogenix/Endo
Agreement Announcement: 2014-04-24
Technology: Needle Free Injection (DosePro)
Current Status: Marketed (EU, USA)
Deal Value: $85 million plus $20 million in commercial milestones

Type: Product Licensing Agreement (USA, Mexico)
Product: Natesto
Indication: Hypoandrogenism
Delivery Route: Nasal – Gel and Device
Licensor/Licensee: Trimel/Endo
Agreement Announcement: 2014-11-24
Technology: Nasal Gel, Nasal Device
Current Status: Marketed (USA)
Deal Value: $25 million plus unspecified milestones

Comment: These two product deals by Endo in 2014 highlight the continuing need of non-research based specialty pharma companies to feed their commercial infrastructure. These two deals provide limited upside but fit well with Endo's CNS and male health portfolios.

Endo acquired the rights to Sumavel DosePro for about three-times 2013 sales, a little lower than the five-times norm, perhaps reflecting future prospects for the product. Zogenix seems to have made a major shift in clearing out their commercial stage assets, most recently their marketed opioid Zohydro ER.

The $25 million upfront paid for Natesto probably covers Trimel's development and licensing costs with perhaps a little left over to reinvest in their pipeline. The rewards for Trimel will depend on commercial success in the USA and selling overseas marketing rights. They seem committed to building their own Canadian sales and marketing infrastructure, a strategy that was developed by Biovail with mixed success.

These two deals reflect the pragmatic behavior of licensors and licensees. The parties to these two transactions did as well as they could given the opportunities presented. Companies with sales and marketing resources will continue to in license even small products so long as they generate sufficient sales to offset a portion of the salesforce costs. At the same time smaller companies without the resources to establish or support commercial operations will wisely depend on a partner to generate the necessary sales to support their development of additional products. The challenge for these small companies is to develop a future product with sufficient potential to allow them to make leap to the commercialization stage. It seems Zogenix took this step and has decided to step back. It's a big step, and it's not easy.

Product Licensing - Transdermal

Type: Product Licensing Agreement (Worldwide)
Product: ZP-PTH
Indication: Osteoporosis
Delivery Route: Transdermal
Licensor/Licensee: Zosano/Eli Lilly
Agreement Announcement: 2014-12-02

Technology: Microneedle Patch (ZP Patch)
Current Status: Pre-Phase 3
Forecast Development Time[1]: 3 years (current stage to NDA filing)
Deal Value: $440 million plus royalties

Deal Summary: Eli Lilly invests $15 million coincident with Zosano's initial public offering. Additional payments will be made for the achievement of regulatory and sales milestones, up to $300 million and $125 million respectively, plus double digit royalties on sales.

Comment: In many ways this seems to have the feel more of an option rather than license agreement. The upfront amount is small for a pre-Phase 3 stage product and made as an investment in Zosano. Should ZP-PTH make it through to the market and enjoy market success both companies will be well rewarded. If the product fails in development there will be little loss for Lilly. An upfront investment of $15 million represents a relatively inexpensive option for a valuable product.

The benefit for Zosano was the validation of a large and successful partner like Eli Lilly that allowed them to successfully secure their initial public offering that netted them $45 million. Zosano will be responsible for all expenses through to approval but have the benefit of Lilly's expertise in the area of endocrinology and osteoporosis.

Technology Licensing - Long-Acting Injectable

Type: Technology Licensing/Exercise of Option
Active: Factor VIII
Indication: Hemophilia
Delivery Route: Injection
Licensor/Licensee: Amunix/Biogen Idec
Agreement Announcement: 2014-04-21

Technology: Prodrug, non-PEG Polymer (XTEN)
Current Status: Preclinical
Forecast Development Time[1]: 6 years (current stage to NDA filing)
Deal Value: $39 million plus Royalties

Deal Summary: Following a research collaboration signed in 2011 Biogen has exercised its option to license the XTEN technology for novel, fully-recombinant Factor VIII products. The agreement includes $1 million upfront, $38 million in development and commercial milestones, and royalties on commercial sales.

Comment: This seems to be a 'throwback' Big Pharma – Drug Delivery company deal with a limited upfront payment with rewards for Amunix mostly back loaded as milestones and royalties that are unlikely to exceed mid-single digits. The technology offers a number of benefits over PEGylation for extending in vivo half-life of macromolecules. But at this point there is limited data and no approved products to validate the safety and scalability of the technology. The technology does offer partners a degree of intellectual property protection that is no longer possible with PEG technology.

With a couple of Big Pharma product development deals in hand Amunix has the basis to validate its technology and secure more attractive future deals. PEGylation will continue to be a lower cost competitor.

Deal Termination – Roche / Chiasma

Type: Product Deal Termination
Product: Octreolin (octreotide)
Indication: Acromegaly
Delivery Route: Oral
Licensor/Licensee: Chiasma/Roche AG

Termination Announcement: 2014-08-13
Technology: Permeability Enhancer (TPE – Transient Permeability Enhancer)
Current Status: Phase 3
Original Deal Value: $595 million plus Royalties

Deal Summary: The original deal, signed in 2013, granted Roche a worldwide license to Chiasma's Octreolin in exchange for $65 million upfront, $530 million in milestones and double digit royalties. The parties announced a year later that the deal had been cancelled.

Comment: The sun rises and the sun sets on deals as well as the day. Despite the significant upfront investment by Roche a year and a half earlier, they chose to terminate the agreement. The reasons are not obvious. Chiasma claimed "the drug had favorable results in Phase 3 clinical trials" and suggested that the decision was in part related to Roche's waning interest in the endocrinology sector. Chiasma stated their intention to move forward with the product.

The deal termination highlights a couple of important considerations. Deals like all relationships are not predictable and companies need to protect themselves from the fallout of a termination. Following termination of the deal with Roche, Chiasma has gone back to existing and new investors to raise an additional $70 million, and more recently brought in a new CEO. Significant upfront payments, such as the $65 million received by Chiasma, are needed to ensure continuity in the event a deal is terminated for reasons unrelated to product performance.

What is the future of technologies for the oral delivery of macromolecules? With injection formulations and devices becoming increasingly convenient and painless is there really a need for oral delivery if there is any question on the part of the clinician regarding efficacy? The recent clinical results for Octreolin support its ability to treat acromegaly, but perhaps not as reliably as the injectable comparator. In the end it seems that the market is most interested in delivery systems that are effective, safe and convenient, probably in that order. New delivery systems need to ensure they can match on efficacy and safety, and exceed in the area of convenience if they are to succeed.

1 Development times are estimated by Pharmanumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.

Company Acquisition – Archimedes Pharma

Type: Company Acquisition
Company: Archimedes Pharma Ltd.
Business Sector: Specialty Pharma
Therapeutic Area: Central Nervous System

Acquirer: ProStrakan Group (Kyowa Hakko Kirin)
Agreement Announcement: 2014-08-06
Deal Value: $361.9 million

Deal Summary: ProStrakan purchased the share capital of Archimedes for £230 million. The deal values Archimedes at about 5.5 times 2013 sales.

Comment: Archimedes, founded in 2004, managed to assemble a commercial portfolio of a dozen marketed products through in licensing, acquisition and internal development. Focused primarily on CNS products the company in licensed complementary products. Its first pipeline product, a nasal fentanyl for the treatment of breakthrough cancer pain was approved in Europe in 2010 (PecFent) and in the USA in 2011 (Lazanda). To date it has achieved limited sales.

ProStrakan, a commercial stage specialty stage pharma company, was itself acquired by Kyowa Hakko Kirin in 2011. It continues to be active acquiring and in licensing commercial stage products for promotion by European sales and marketing teams.

Company Acquisition – Activaero

Type: Company Acquisition
Company: Activaero GmbH
Business Sector: Drug Delivery Technology
Technology Area: Inhalation - Nebulization

Acquirer: Vectura Group Plc
Agreement Announcement: 2014-03-13
Deal Value: $33.6 million

Deal Summary: Vectura, best known for their dry powder respiratory technologies, products and pipeline, with the acquisition of Activaero gained access to Activaero's unique proprietary nebulized device technology and a late stage corticosteroid for asthma.

Comment: Critical mass continues to be a requirement for technology focused drug delivery and formulation companies. In this case Vectura gains access to a complementary inhalation platform, collaboration partners, and a late stage development candidate that will complement Vectura's pipeline and technology activities. Activaero in turn receives access to the resources necessary to further develop and successfully commercialize its AKITA and FOX liquid aerosol delivery systems.

It's not clear that investors in Activaero were rewarded with the acquisition of the company. But at the same time there was a meaningful transaction that provides a benchmark value for similar companies. The AKITA technology has been in development for more than a decade and a half and clearly needed to be pushed forward.

10 Ten Notable Drug Delivery & Formulation Approvals of 2014

Drug Delivery in 2014 continued to deliver on the promise of enhanced efficacy, safety, and convenience in an ever-increasing breadth of products that spanned the range from cancer to neurological disease to ophthalmic indications. Drug Delivery has left behind the novelty and excitement it enjoyed in the 1980s and 1990s, where a few select companies seemed to be practicing alchemy, turning well-worn actives into pipeline gold. The 2010s has seen Drug Delivery demystified and become a discipline that has many experienced professionals practicing with an art and science that was not anticipated even a decade ago, bending the performance of a molecule to the needs of the patient.

Among the many drug delivery and formulation-enhanced approvals of 2014, we have selected 10 that effectively summarize the current focus of drug delivery and formulation in terms of therapeutic products. All of these products have a little something extra in terms of technology, or have managed to fill an important gap in the therapeutic armamentarium of clinicians. Products that benefit from both formulation and device enhancements can be found in the Ten Notable Drug-Device Approvals of 2014 section of this report. In some cases the differences were not so obvious, and certain products might well have been placed in either category, or both.

PEGylation, a technology conceived in the 1970s with its first approvals in the 1980s and followed by massive commercial success in the early 2000s, features prominently in the list of Top Ten Drug Delivery & Formulation Approvals of 2014. Plegridy, a PEGylated version of Biogen's Interferon beta-1a, follows closely the trail blazed by the Peginterferon alphas (PegIntron and Pegasys), offering extended dosing intervals and patient-friendly injection formats. It's interesting to speculate as to why the Plegridy approval lagged behind the Interferon alphas by more than a decade. Was it a technical challenge or a commercial decision? Interestingly, Plegridy does not seem to use technology from the two leading companies in the field of PEGylation, Enzon and Nektar.

The more remarkable PEGylated product approval in 2014 was Nektar's Movantik. As the first-approved PEGylated small molecule product, Movantik has defined a new whole class of applications for polyethylene glycol conjugates. Enzon took a run at small molecule PEGylation in the early 2000s with its PEGylated anticancer agents hoping to preferentially accumulate PEG-linked antineoplastic agents at the site of the tumor based on preferential uptake and retention of macromolecules. The strategy with Movantik is simpler and arguably more elegant; restrict the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the gastrointestinal system, Movantik acts to bind the unabsorbed opioids that can lead to constipation, a simple and elegant solution to a troubling issue in the hospital setting. The general protocol for discharge after surgery is that you need to have a bowel movement before you can leave. Intraoperative and postoperative opioids can slow down that process, but Movantik has been proven to make that happen a little sooner.

Sustained-release opioid approvals were also noteworthy. Purdue managed to scoop Zogenix by gaining approval for Hysingla, an abuse-deterrent formulation of hydrocodone with FDA abuse-deterrent labeling. Zogenix had previously introduced a non-abuse-deterrent formulation, Zohydro ER, which had received some criticism for being too easily tampered with and misused. Zogenix's follow up, an abuse-deterrent version, was approved in late January 2015 but without abuse-deterrent labeling from the FDA. Since then, Zogenix seems to have tossed in the towel announcing in March 2015 it was selling the Zohydro franchise to Pernix Therapeutics. With a large number of abuse-deterrent opioids lining up at the FDA for review and approval, it's not obvious if these agents will make a dent in opioid abuse and misuse. The whole issue of abuse and misuse of prescription opioids is largely an American phenomena with very few abuse-deterrent opioids in development or approved for the Europen and Asian markets.

The second opioid approval of note in 2014 was Mallinckrodt's Xartemis XR. A sustained-release formulation of oxycodone and acetaminophen using DepoMed's AcuForm Diffusional technology, Xartemis XR really doesn't break much new ground from the therapeutic or technology perspective, but it seems to have met a regulatory and patient need, with the FDA having granted it priority review status. The combination of acetaminophen or acetylsalicylic acid with an opioid has been a *de facto* abuse-deterrent strategy used for several decades. Including either of these non-opioid analgesics generally permits an opioid to be classified by the DEA at a lower Controlled Substance Schedule, with looser prescribing restrictions, but in this case, Xartemis XR still carries a Schedule CII classification perhaps because it incorporates oxycodone.

MabThera-PH20, Alprolix, and Eloctate offer their own unique take on what formulation and drug delivery mean in the second decade of the 21st century. The well-equipped Drug Delivery and Formulation toolbox now includes technologies normally associated with protein chemists and gene jockeys. MabThera-PH20, Alprolix, and Eloctate all provide the types of benefits associated with drug delivery, more convenient dosing, and extended circulating life, respectively, but through the use of generic engineering.

Each of these ten products offers insight into the opportunity offered by the creative use of drug delivery and formulation technologies to new and previously approved actives. The products highlighted provide additional detail on each of the products with information gleaned from the PharmaCircle database. Four of the Notable Products of 2014 are presented with additional information because, in our opinion, they point to where drug delivery and formulation is likely to head in the years to come.

Movantik

Active: naloxegol oxalate
Molecular Weight[1]: 652 Da
Indication: Opioid-induced constipation
Delivery Route: Oral – Tablet
Dosing Interval: 24 hours
Company/Partner: Nektar Therapeutics/AstraZeneca
First Approval: 2014-09-16 (USA)
Formulation Type: Oral, PEG-Conjugate

Technology Provider: Nektar Therapeutics
Device: None
Review Status: Priority (FDA)
USA Development/Approval Time[2]: 6.9 years
Sales Potential: $1 billion +
Notable: First FDA approved oral small molecule PEG conjugate.

Comment: As an oral PEG small molecule conjugate Movantik's distribution is intended to be limited to the gastrointestinal tract. By acting to block opioid binding at mu-opioid receptors Movantik is able to antagonize the constipating effects of opioids, particularly oral opioids, most importantly in the post surgical setting. Chemically Movantik is a reduced ketone naloxone derivative conjugated to a 7-unit polyethylene glycol linear chain through a 14-position alcohol. This is a rather simple but previously untried drug delivery strategy that does not depend on any particular uptake preference for the PEG-conjugated narcotic antagonist to be effective. Nektar's late stage PEG-small molecule targeted to cancer, NKTR-102 a novel topoisomerase I inhibitor, depends on preferential uptake and retention in tumors to provide for a greater therapeutic index. Recent results in the clinical setting have been disappointing.

Opioid-induced constipation is a significant issue for hospitalized patients and a major cause of discharge delay. Nektar has publicly stated that their commercial partner, AstraZeneca who has partnered with Daiichi Sankyo for the USA market, is expecting sales to top $1 billion annually.

Hysingla

Active: hydrocodone bitartrate
Molecular Weight[1]: 299 Da
Indication: Chronic Pain
Delivery Route: Oral, Tablet
Dosing Interval: 24 hours
Company: Purdue Pharma
First Approval: 2014-11-20 (USA)
Formulation Type: Oral, Abuse Deterrent, Modified Release

Technology Provider: Purdue Pharma
Device: None
Review Status: Priority (FDA)
USA Development/Approval Time[2]: 15 years
Sales Potential: Not disclosed, >$500 million
Notable: First extended release single agent formulation of hydrocodone with FDA abuse deterrent claims.

Comment: Purdue Pharma is the clear industry leader in developing abuse deterrent opioid formulations to approval and securing abuse resistant labeling from the FDA at launch. The Hysingla approval follows by four years the approval of OxyContin OTR an abuse resistant formulation of oxycodone, and severely diminishes the commercial value of Pernix's Zohydro ER once it receives similar abuse deterrent claims. Another Purdue abuse deterrent formulation approved by the FDA in 2014, Targiniq, a combination of naloxone and oxycodone addresses the abuse deterrence market with an agonist/antagonist strategy. This is similar to the strategy used with Pfizer's Embeda, a morphine and naloxone combination, which has been on and off the market since its approval in 2009.

There are no reported forecasts for Hysingla ER but it is reasonable to expect that it will capture a significant share of the extended release opioid market, presumably at a premium price. Peak annual sales in excess of $500 million annually seem reasonable considering that sales of Purdue Pharma's abuse deterrent OxyContin top $2 billion annually.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Plegridy

Active: peginterferon beta-1a
Molecular Weight[1]: ~44,000 Da
Indication: Multiple Sclerosis (Relapsing)
Delivery Route: Injectable – subcutaneous
Dosing Interval: 14 days
Company/Partner: Biogen
First Approval: 2014-07-18 (EU)
Formulation Type: Injection, PEG-Conjugate

Technology Provider: Biogen
Device: Prefilled Syringe and Pen
Review Status: Priority (FDA)
USA Development/Approval Time[2]: 6.9 years
Sales Potential: $2 billion +
Notable: First PEGylated interferon for the treatment of multiple sclerosis.

Comment: With the increasing availability of oral treatments for multiple sclerosis the multi-injection per week requirements of the interferon betas are facing a serious competitive challenge. And at the same time there are three unPEGylated interferon beta agents on the market all jockeying for market share with a very similar set of features and benefits. Plegridy moves the 'needle' on convenience, requiring dosing every two weeks rather than two or three times per week. This is a multibillion-dollar market where even a couple of points shift in market share can mean an increase of tens of millions of dollars.

It's not clear why it took so long for Biogen to file for approval. The therapeutic benefits and commercial value of a PEGylated interferon had been well demonstrated with Schering-Plough's PegIntron and Roche's Pegasys. Both products also demonstrated the comparative benefits of differering PEGylation strategies. The development time of almost 7 years suggests the product was only introduced into the clinic in 2008, some eight years after the first PEGylated interferon alpha had been approved.

Plegridy could also have been included in the list of Ten Notable Drug-Device approvals of 2014. At this point the industry has come to recognize that prefilled syringes, and especially pens, are a requirement for the successful uptake of any injectable in the outpatient setting.

Xartemis XR

Active: oxycodone hydrochloride, acetaminophen
Molecular Weight[1]: 299 Da
Indication: Acute Severe Pain
Delivery Route: Oral, Tablet
Dosing Interval: 12 hours
Company: Mallinckrodt Pharmaceuticals
First Approval: 2014-03-11 (USA)
Formulation Type: Oral, Modified Release (AcuForm)

Technology Provider: DepoMed
Device: None
Review Status: Priority (FDA)
USA Development/Approval Time[2]: 3.8 years
Sales Potential: Not disclosed, <$100 million
Notable: First extended release oxycodone/ acetaminophen combination.

Comment: Good ideas don't always stay hidden. That seems to be the case with Mallinckrodt's Xartemis XR offering twice-daily dosing convenience. While immediate release oxycodone-acetaminophen, and hydrocodone-acetaminophen products have been an approved mainstay of pain management for decades, Xartemis XR represents the first approved sustained release formulation. A product idea worthy of FDA Priority Review designation.

Product development seems to have been well managed taking a very short 3.8 years between IND submission and FDA approval. This was no simple bioequivalence type program. There were a total of fourteen studies involving 705 patients, including two Phase 3 efficacy studies and a relative abuse potential study in normal volunteers. Xartemis XR received no abuse deterrent claims in their labeling.

Sales forecasts are unavailable for Xartemis XR. Given the significant competition it faces and the lack of any explicit abuse deterrent claims in the product label, hitting $100 million in annual sales seems to be a stretch objective.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Alprolix

Active: eftrenonacog alfa
Molecular Weight[1]: ~98,000 Da
Indication: Hemophilia B
Delivery Route: Injection – intravenous
Dosing Interval: 7-10 days (prophylaxis)
Company/Partner: Biogen
First Approval: 2014-03-21 (Canada)
Formulation Type: Injectable, Fc Fusion (Synfusion)
Technology Provider: Biogen
Device: Syringe/Vial
Notable: Protein-immunoglobulin fusions represent a next generation prodrug approach that blur the line between protein engineering and traditional formulation.

MabThera-PH20

Active: rituximab
Molecular Weight[1]: ~144,000 Da
Indication: Cancers (Multiple)
Delivery Route: Injection – subcutaneous
Dosing Interval: 24 hours
Company/Partner: Biogen/Roche
First Approval: 2014-03-21 (EU)
Formulation Type: Injectable, Absorption Enhancer (Enhanze)
Technology Provider: Halozyme Therapeutics
Device: None
Notable: A novel formulation approach incorporating a proprietary enzyme to digest hyaluronic acid and permit a product normally administered by slow infusion to be delivered intravenously.

Bunavail

Actives: buprenorphine hydrochloride / naloxone hydrochloride
Molecular Weight[1]: 468 / 327 Da
Indication: Opioid Dependence
Delivery Route: Oral, Buccal
Dosing Interval: 24 hours
Company/Partner: BioDelivery Sciences Intl.
First Approval: 2014-06-06 (USA)
Formulation Type: Transmucosal (BEMA)
Technology Provider: BioDelivery Sciences Intl.
Device: None
Notable: A next generation formulation approach providing greater convenience and requiring half the dose of the two actives to achieve similar plasma levels as Suboxone.

Iluvien

Active: fluocinolone acetonide
Molecular Weight[1]: 452 Da
Indication: Diabetic Macular Edema
Delivery Route: Injection - Ocular implant
Dosing Interval: Up to 36 months
Company/Partner: Alimera Sciences
First Approval: 2012-05-07 (EU)
Formulation Type: Implant, Non-erodible Intravitreal (Durasert)
Technology Provider: pSivida
Device: Preloaded 25-gauge needle
Notable: Only approved in the USA in 2014 this 36 month implant provides enhanced convenience and outcomes for ophthalmic conditions that require constant intraocular glucocorticoid levels.

Copaxone (Concentrated)

Active: glatiramer
Molecular Weight[1]: [624]n Da
Indication: Multiple Sclerosis, Relapsing, Remitting
Delivery Route: Injection – subcutaneous
Dosing Interval: ~48 hours
Originator/Partner: Teva
First Approval: 2014-01-28 (USA)
Formulation Type: Injectable, Mannitol Solution
Technology Provider: Not Applicable
Device: Prefilled Syringe
Notable: A simple lifecycle management high-dose formulation that enhances convenience and promises to extend the commercial prospects of the Copaxone franchise.

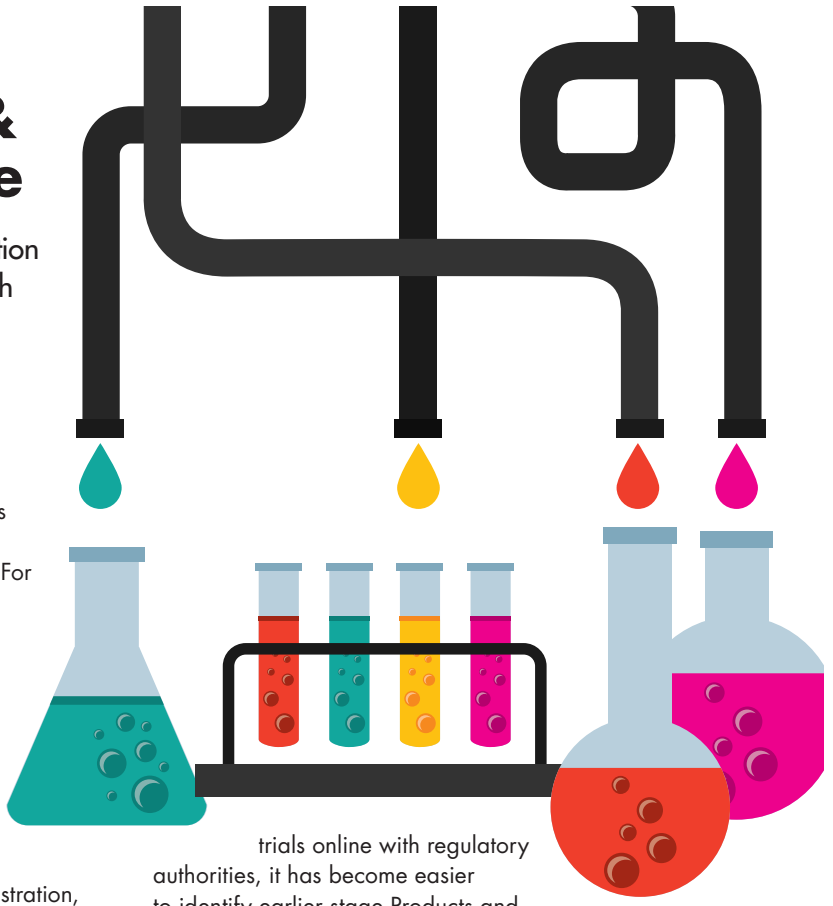
Eloctate

Active: Efmoroctocog alfa
Molecular Weight[1]: ~26,000 Da
Indication: Hemophilia A
Delivery Route: Injection – intravenous
Dosing Interval: 4 days
Company/Partner: Swedish Orphan Biovitrum/Biogen
First Approval: 2014-06-06 (USA)
Formulation Type: Injectable, Fc Fusion (Synfusion)
Technology Provider: Biogen
Device: Kit (solvent in prefillled syringe)
Notable: An Fc fusion protein for the treatment of hemophilia permitting an extended dosing interval of every four days for prophylaxis.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.

The Drug Delivery & Formulation Pipeline

So what does the Drug Delivery & Formulation Pipeline look like? How does it compare with the non-drug delivery enhanced/enabled pharmaceutical product pipeline? It's easier to understand if we define and explain the terminology we will be using:



Product - a Product is a pharmaceutical entity that is defined by its brand name and dosage form, but is independent of stage of development or geography. For example Celebrex Capsules is a product.

Program - a Program is a Product approved or being studied for a defined indication, independent of geography. For example, the Product Celebrex Capsules is approved or being studied for a total of 11 different indications, all Programs, that range from inflammation to cancer to women's health.

Drug Delivery & Formulation - Products and Programs that depend on some element of formulation technology to provide for tailored administration, distribution, metabolism, and/or excretion of a pharmaceutical active.

DDEP - Drug Delivery Enabled/Enhanced Product or Program, refers to any agent that requires the use of an integral device and/or drug delivery or formulation technology.

PharmaBio - Products and Programs that do not incorporate tailored formulation technologies. The opposite of a DDEP.

The figures presented are qualified with respect to whether they refer to Products or Programs. Numerically, it can make a very big difference. Why not just stick to Products and ignore Programs? In many cases, Programs can provide a better sense of what's actually in the pipeline. For example, a product that may have been approved, and is now marketed for depression, might be in Phase III for dementia. It's the same dosage form, perhaps a sustained-release tablet. The Phase III activity may incorporate the same Product, but it represents a different Program. If it were being developed as a different dosage form, perhaps a sustained-release capsule, it would be a different Product. We'll clarify as appropriate in the accompanying text. Comparing Products to Programs is like comparing apples to oranges; they are both fruits in the larger sense, but they are quite different if you look more closely.

It's worth noting that it is only possible to count Products and Programs that are publicly disclosed. Most emerging and smaller biopharmaceutical companies are quite happy to disclose their pipelines. In many cases, they are obligated to disclose this information because it is material to their operations. This is not the case with the larger biopharmaceutical companies who prefer to limit early Program disclosure and have no obligations to do so at an early stage of Product development. With the more recent requirement for all companies to list clinical trials online with regulatory authorities, it has become easier to identify earlier stage Products and Programs, particularly those that are post-Phase I.

This pipeline analysis for the most part does not make reference to marketed Products and Programs. This is because there are a large number of generic products that unreasonably dilute and skew the relative figures. For every approved innovator product, there may be a half dozen approved generics. Pipeline generic products are also not included because they are, for the most part, only disclosed when filed for approval or approved.

It's also important to understand what constitutes a Drug Delivery and Formulation Enhanced/Enabled Product (DDEP) for the purpose of this pipeline analysis. In practice, all pharmaceutical products are formulated to some extent, if only with lactose. This review considers any oral product that does not incorporate a specific drug delivery or formulation technology, ie, extended release, nanoparticles, specialized coatings, to be a PharmaBio product or Program. In a similar fashion, any injectable that does not require specialized excipients or processing, and is not a modified active, ie, PEGylated, is considered to be a PharmaBio Product or Program.

A final note, the data provided in this section refers to the pipelines as they existed as of the end of the first quarter of 2015.

Products and Programs by Phase

It's interesting to compare the Drug Delivery & Formulation (DDEP) and PharmaBio Product and Program pipelines. What might seem to be a rather simple analysis is actually complicated by a number of issues that cloud the results and their interpretation.

Figure 1 summarizes the pipeline for DDEP versus PharmaBio Products. Figure 2 presents the same for Programs. The first

thing one notes is the larger number of products at all stages of development that do not depend on drug delivery or formulation technology, the PharmaBio Products. This is most notable at the Research Stage (3,129 versus 772), a difference that becomes much smaller by the time we look at Phase III Products (609 versus 456). This might suggest there is a trend toward less Drug Delivery & Formulation technology being incorporated in the developing pipeline portfolios of companies. This is probably not the case. In general, there is little formulation-related information available for early stage products. A company might well announce they have an oral product in development for Alzheimer's disease. While it might require nanoparticle or enteric coating technology, that information is unlikely to be shared publicly until a later stage of development, perhaps only Phase II. In the absence of hard information to support incorporation of a drug delivery or formulation technology, a Product or Program will by default be assigned to PharmaBio. At the same time, an earlier stage Product/Program designed for the treatment of asthma by inhalation will be designated as a DDEP even if the general inhalation technology is not defined. This helps explain why the number of PharmaBio and Drug Delivery & Formulation Products converge as we move from Research to Phase III Products. More advanced products provide more detailed information about dose and dosage form.

Another apparent oddity is the relatively equal number of Phase I and Phase II Products and Programs. This may again be an issue of disclosure with larger companies choosing not to report their Phase I products.

Despite these limitations, there are still conclusions that can be made regarding the current state of DDEPs.

1. Drug Delivery & Formulation Products and Programs realistically represent a little less than half of all Products and Programs in Phase III development.

2. Each Product is, on average, associated with about 1.5 to 2 Programs. This is not a surprise as additional Programs represent a limited incremental expense for a more advanced Product. All follow-on products with a different dosage form, for example, extended release, are considered a separate Product not a Program.

It would be nice to look at these figures and estimate the success rate of products transitioning from one phase to another, but given the lack of consistent early stage product information, this type of analysis is unreliable. More reliable is the relative Phase II and Phase III data. The Phase II and Phase III information sources include government clinical trials registries, which are, for the most part, complete and consistent.

What does make more sense is comparing information within a well-defined population rather than comparing disparate, potentially incomplete, datasets.

Top Ten Therapeutic Classes

It's interesting to compare DDEPs, Figures 3 and 4, as a function of their therapeutic focus. Because Phase I and Phase II information is often limited and incomplete, emphasis is on the Top Ten Therapeutic Classes for Phase III Products and Programs.

Cancer ranks number one for Products and Programs in Phase III development, with many more Programs than Products. This is not surprising and reflects the industry's interest in exploring the full range of opportunities for their anti-cancer products. Many of these Phase III Programs may well be associated with products that have been approved for one cancer-related condition, for example breast cancer, with additional clinical-stage Programs in ovarian and lung cancer.

The willingness to try an agent for a variety of related conditions may also explain the relatively large jump in the number of Phase III Infections Programs versus Phase III Infections Products. An anti-infective agent may be useful for a variety of different indications, which would represent different Programs.

A similar distribution of Phase III Therapeutic Classes is seen with PharmaBio Products. Cancer sits at number one, followed by infections and inflammation/immune, Figure 5.

Top Ten Drug Delivery Category

There is generally more information provided for the general delivery category of a product in development, even in the earlier stages of development, whether it is a DDEP or PharmaBio product. That information might be as simple as defining it as an oral or inhalation agent. This allows us to look a little further upstream in the pipeline to understand what trends there might be in terms of delivery categories.

Figure 6 summarizes Phase II and Phase II DDEP Products by drug delivery category. It is obvious and perhaps surprising to see the large number of Products in development that are based on the injection route. Looking back at the therapeutic class data (Figures 3 and 4), it begins to make sense given the large number of Products in Phase II and Phase III development requiring an injection delivery route, notably anti-cancer and anti-infective agents. Looking at the distribution of DDEP Programs in Phase II and Phase III (Figure 7), one sees a similar emphasis on injection-based Programs with skin and oral swapping positions for second place. Most Products and Programs defined as employing the skin delivery route are DDEPs rather than PharmaBios.

Following the injection, oral, and skin delivery categories are transmucosal (nasal, buccal, sublingual, rectal, and vaginal), ophthalmic, and inhalation, all at about the same level for Products and Programs in Phase II and Phase III. Looking at the corresponding Phase I information (not shown), the distribution is the same, with perhaps an uptick in the relative number of injection products, which shouldn't be a surprise considering the number of biologics now entering the clinic.

Injectable Delivery

The increasing emphasis on injection for the delivery of DDEP warrants taking a look at the intended routes of injectable administration. A cursory look at Figure 8 reveals that the greatest attention, even in Phase III, is on the infusion and subcutaneous routes of injectable administration. These are followed by intramuscular and intravenous, neither of which are well suited to patient self-administration. The growing focus on the use of biologicals for maintenance outpatient treatments suggests those injection routes that can be made patient friendly are most likely to grow in importance.

The increased attention to more patient friendly injection systems has meant more and more injectable Products are launching with prefilled syringe or pen dosage forms. Identifying these Products in the pipeline is a challenge as this information is not public. But with more than 7,100 ongoing Phase III clinical

trials involving injectables, it's likely that many involve some sort of autoinjector, prefilled syringe, pen, or needle-free injection device.

Delivering Antibodies

Antibodies constitute an increasingly important segment of the pharmaceutical market. The PharmaCircle database identified a total of 169 antibody Products in Phase III development, corresponding to 356 Programs. This includes DDEP and PharmaBio Products and Programs. Of the 169 Products, 34 were identified as incorporating an integral device; 28 used prefilled syringes, and 6 used autoinjectors.

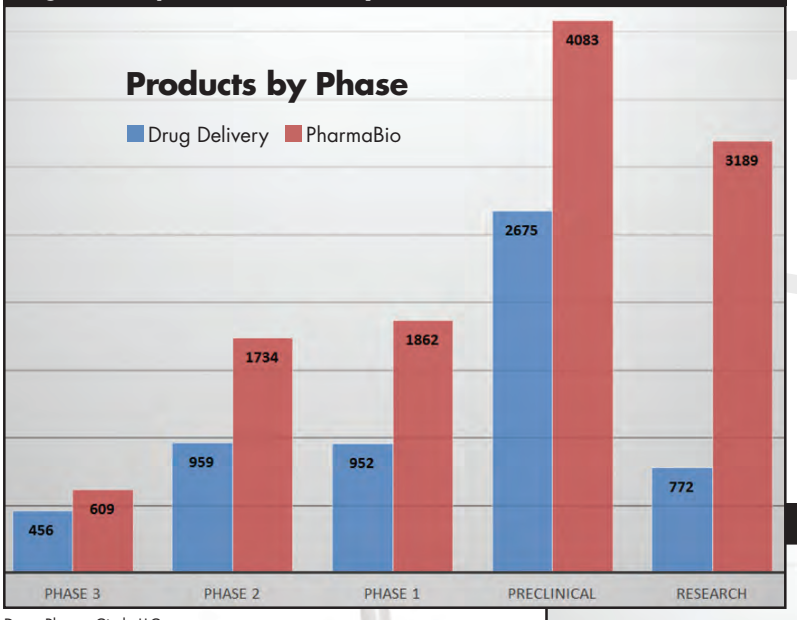
Monoclonal antibodies are now in development for almost all therapeutic categories, with inflammation/immune and cancer being the most important for Phase II and III Products and Programs, Figure 9.

More interesting for Drug Delivery and Formulation professionals is understanding the delivery routes and formulation types being used for the antibodies in the development pipeline. In terms of delivery route (Figure 10), infusion IV is the preferred route for both Phase II and Phase III Programs, followed by injectable subcutaneous and injectable IV. The other delivery routes are negligible in comparison with this big three.

In terms of antibody dosage forms (Figure 11), injection solution, lyophilized powder for injection, and injection powder for solution represent more than 98% of the total.

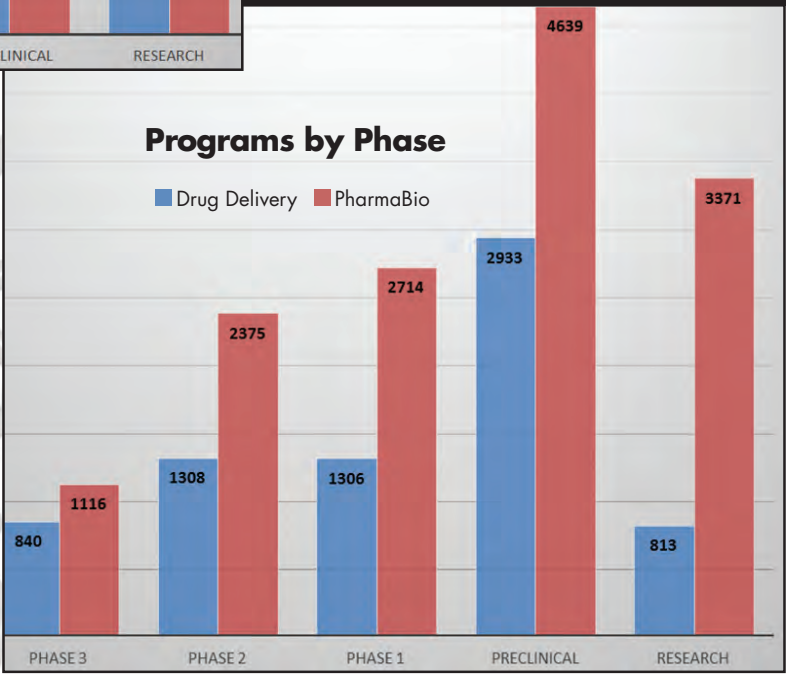
Surprisingly, even in early 2015, it seems there is relatively limited sophistication in terms of the Drug Delivery and Formulation technologies being applied to antibodies. This seems an area of significant opportunity given the industry's increasing investment in the use of antibodies in the outpatient setting, where success will depend on patient ease of use.

Figure 1. Pipeline, Products by Phase



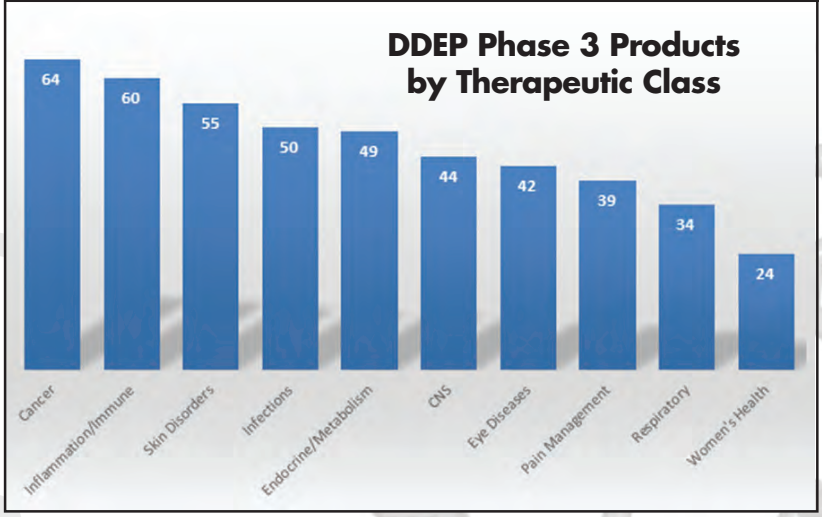
Data: PharmaCircle LLC

Figure 2. Pipeline, Programs by Phase



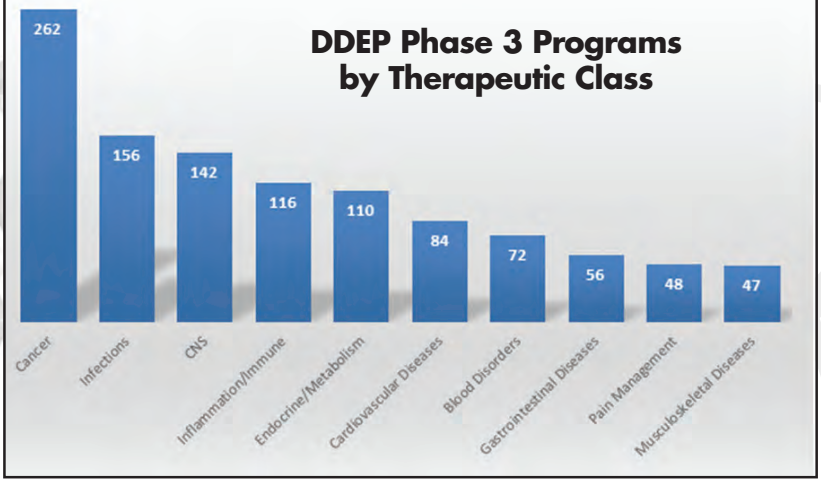
Data: PharmaCircle LLC

Figure 3. DDEP Phase 3 Products by Therapeutic Class



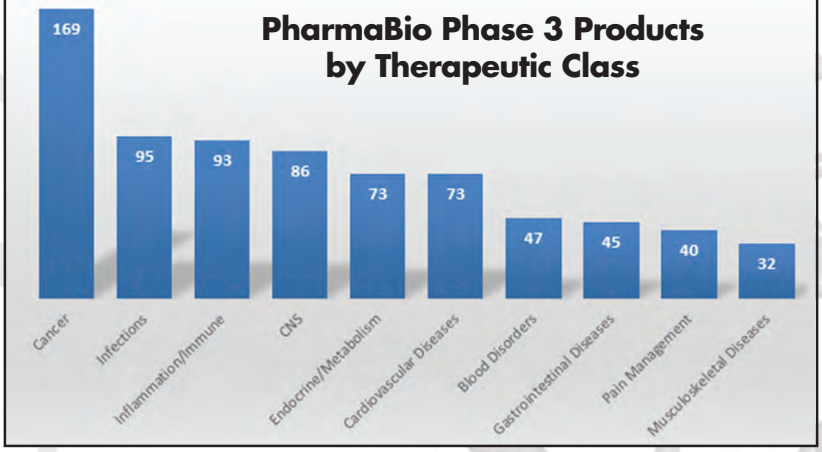
Data: PharmaCircle LLC

Figure 4. DDEP Phase 3 Programs by Therapeutic Class



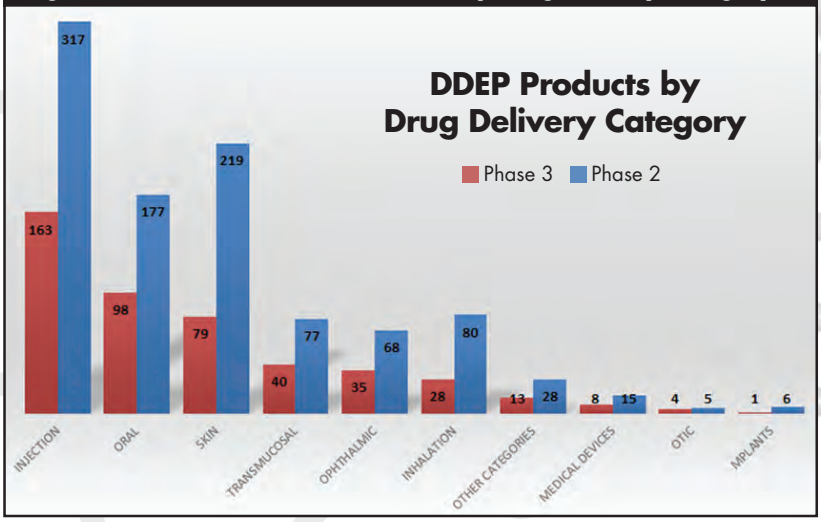
Data: PharmaCircle LLC

Figure 5. PharmaBio Phase 3 Products by Therapeutic Class



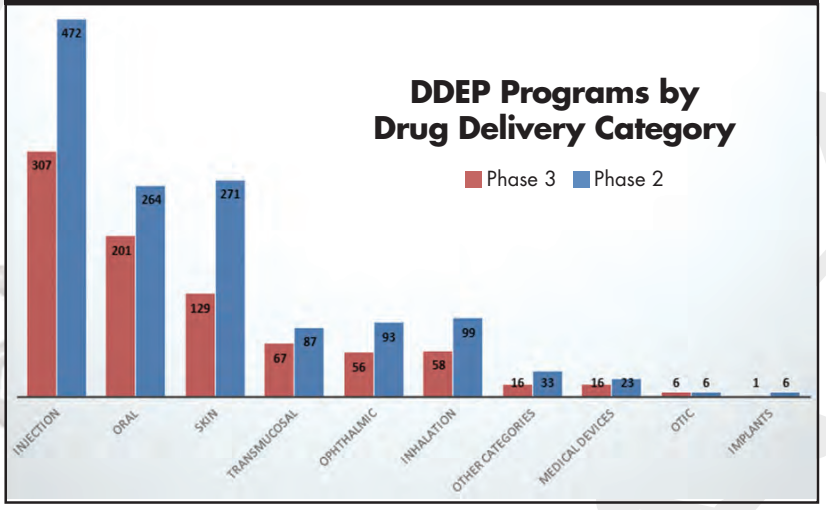
Data: PharmaCircle LLC

Figure 6. Phase 2 & 3 DDEP Products by Drug Delivery Category



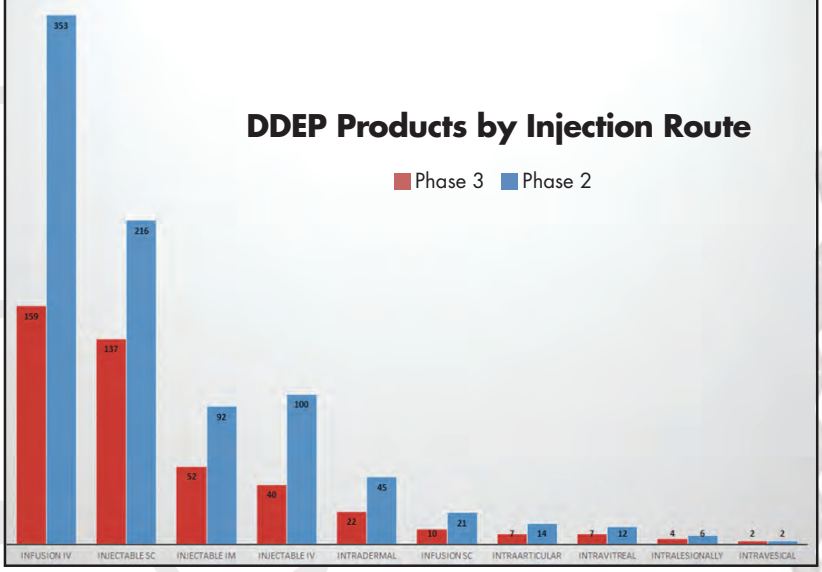
Data: PharmaCircle LLC

Figure 7. Phase 2 & 3 DDEP Programs by Drug Delivery Category



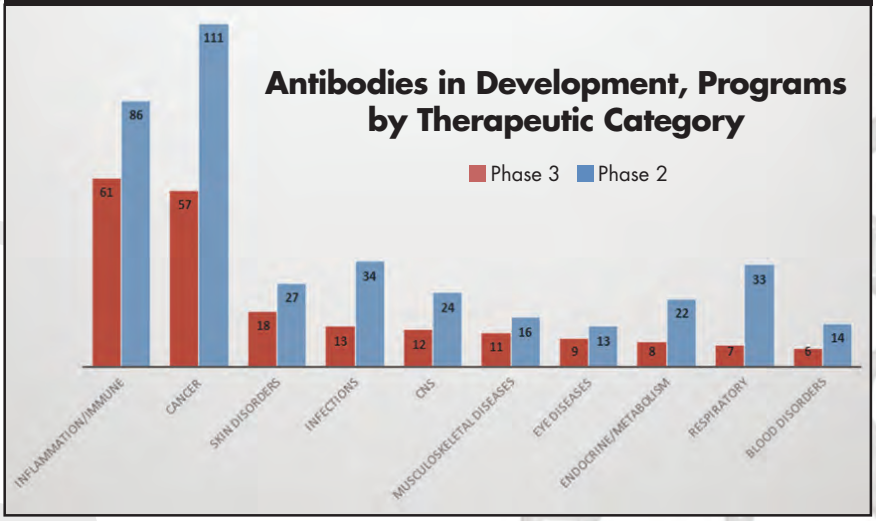
Data: PharmaCircle LLC

Figure 8. DDEP Products by Injection Route



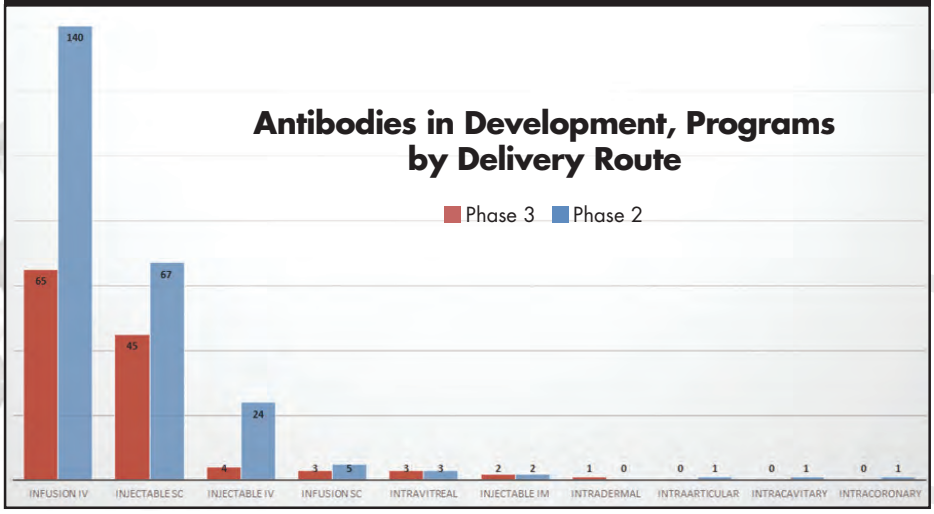
Data: PharmaCircle LLC

Figure 9. Antibodies in Development, Programs by Therapeutic Category



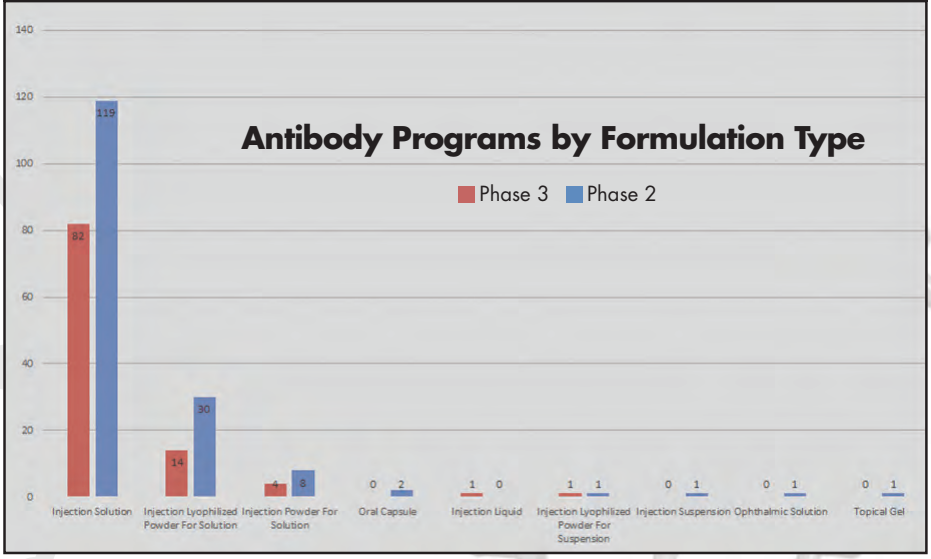
Data: PharmaCircle LLC

Figure 10. Antibodies in Development, Programs by Delivery Route



Data: PharmaCircle LLC

Figure 11. Antibody Programs by Formulation Type



Data: PharmaCircle LLC

10 Notable Fixed-Dose Combination Drug Approvals of 2014

There were two common themes for fixed-dose combination products approved in 2014: additive efficacy and enhanced convenience, with the expectation that both approaches would lead to better therapeutic outcomes. It's too easy to dismiss the benefits of enhanced compliance on improving therapeutic outcomes and reducing overall healthcare costs. Fewer daily doses to remember, or few "pills" to confuse patients, can reinforce taking medications as prescribed.

It's worth mentioning that there is no bright line defining what is the difference between a fixed-dose combination, drug-device, or formulation enhanced pharmaceutical product. Combining actives in a fixed-dose manner that is layered upon formulation enhancements, for example, sustained release, and then administered with a device is becoming increasingly common. Several of the products in this list could have just as easily been included in the Drug Delivery and Formulation or Drug-Device lists.

A very successful therapeutic approach for the past two decades has been the use of multiple antiviral agents to avoid the possibility of viral resistance. This multi-agent approach has proven its value in the treatment of HIV/AIDS, leading to sustained reductions in viral loads that in turn have allowed patients to live longer and healthier. 2014 saw the approval of another multidrug combination product for HIV/AIDS, Triumeq, a triple play of sorts, in this case, substituting a newer integrase inhibitor, dolutegravir, with a pair of well-validated nucleoside reverse transcriptase inhibitors. Protocols that once required taking several separate medications to treat HIV/AIDS, often on different dosing schedules, have been replaced with more convenient and better tolerated fixed-dose combination products, often a single oral dosage format.

The benefits of combination therapy for the treatment of Hepatitis C has been well understood with the clinical successes achieved by combining ribavirin and interferon alpha. With the development of oral antivirals for the treatment of Hepatitis C that are effective and well tolerated, attention has turned to combination oral agents with complementary antiviral activities. Gilead's Harvoni combines two agents in a single tablet and is dosed once daily with excellent outcomes in treating Hepatitis C. Abbvie's Viekira Pak, a four-agent fixed-dose combination product, takes the much less elegant approach of packaging four separate tablets, one for each antiviral. Three of the tablets are taken once daily, and the other twice daily. In theory, more effective with four separate agents addressing three separate antiviral mechanisms, the question is whether the formulation design and dosing schedule will compromise compliance and clinical outcomes. Expect a more elegant formulation in the near future. It shouldn't be that difficult to combine at least a couple of the agents into a single presentation and align dosing to a common once per day.

Contrave provides the unexpected, two agents in combination being effective for an indication not treated by either. A novel combination product, Contrave is approved for the management of obesity and combines bupropion, approved for the treatment of depression, and naltrexone, approved for the treatment of narcotic overdoses. Contrave fills a therapeutic void with an agent that does not seem to carry the cardiovascular risks associated with amphetamine-based anti-obesity products.

A more traditional approach is taken with Namzaric, a sustained-release single fixed-dose capsule that combines two agents approved for the treatment of Alzheimer's disease, donepezil and memantine. In practice, these two agents are commonly prescribed together, albeit as separate tablets and separate prescriptions. Namzaric promises to make compliance a little bit easier. Approval is a win for Adamas and a nice lifecycle play for their licensee Forest Labs (Actavis/Allergan), who are facing threats to their Namenda (memantine) franchise with the imminent approval of memantine immediate-release generic products.

Combination products seem to be the new norm for products directed to Type 2 Diabetes. The common denominator in many of these products is metformin, a biguanide gluconeogenesis inhibitor. Metformin has seemingly become the "hydrochlothiazide" of diabetes treatment, incorporated into fixed-dose combination products with a wide variety of non-metformin actives. 2014 saw two fixed-dose combination metformin products approved, BMS' Xigduo XR and Mitsubishi Tanabe's Invokamet. Xigduo XR incorporates modified-release technology to permit once-daily dosing.

Purdue Pharma's Targiniq ER, an oxycodone/naloxone combination for the treatment of chronic pain, could just as easily been included in the list of Ten Notable Drug Delivery/Formulation-Enhanced products. In addition to being a simple agonist/antagonist combination product intended to deter opioid repurposing, Targiniq ER incorporates sustained-release technology to permit twice-daily dosing. Unlike Pfizer's Embeda morphine/naltrexone combination, Targiniq ER does not depend on the sequestering of an opioid antagonist. This may well help Targiniq ER avoid the stability problems that have seemed to plague Embeda. While Targiniq ER was approved in the US in 2014, it was first approved in 2009 in Europe.

Combination products combine the best thinking of clinical, regulatory, and formulation professionals. Take two or more actives, identify a pressing therapeutic need, add in drug delivery technologies to enhance convenience, and as appropriate a device, and you have a product that can help patients by providing better efficacy, safety, and/or convenience. The 10 products selected for this section provide a slice of what was accomplished in 2014 with hints of strategies we may see in future years. We've taken four of these products and provided a little more information and commentary to help describe the types of opportunities that are available when one does a little "formulation engineering."

Contrave

Active: bupropion hydrochloride, naltrexone hydrochloride
Molecular Weight[1]: 240 Da, 341 Da
Indication: Obesity
Delivery Route: Oral
Dosing Interval: 12 hours
Company/Partner: Orexigen/Takeda
First Approval: 2014-09-10 (USA)

Formulation Type: Tablet, Modified Release
Review Status: Standard (FDA)
USA Development/Approval Time[2]: ~7.3 years
Sales Potential: Undisclosed, < $500 million
Claim to Fame: An unusual combination pairing, an antidepressant and narcotic antagonist, for the treatment of obesity.

Comment: The development and clinical use of anti-obesity agents, typically amphetamine related, have been plagued with issues of abuse and more concerningly cardiovascular complications. The combination of bupropion and naltrexone, both considered to carry relatively little cardiovascular risk, offers a creative solution to a pressing health issue.

The efficacy of bupropion as an anti-obesity agent is perhaps not that surprising when one considers its structure. Bupropion is a cathinone derivative that differs from amphetamines by virtue of a ketone functionality at the benzyl carbon (beta carbon of the side chain). Cathinone, a Schedule I compound in the USA, is the active ingredient in the stimulant khat. Naltrexone also has some anti-obesity activity by virtue of its suppression of pro-opiomelanocortin inhibition, potentiating the actions of bupropion.

The anti-obesity market has seen new recent entrants in the past three years, all offering novel actives or combinations. To date none have been particularly successful and it remains to be seen how Contrave will do. At best Contrave might be looking at an upper limit of $500 million in annual sales.

Namzaric

Active: donepezil hydrochloride, memantine hydrochloride
Molecular Weight[1]: 379 Da, 179 Da
Indication: Dementia
Delivery Route: Oral
Dosing Interval: 24 hours
Company/Partner: Adamas/Forest (Actavis)
First Approval: 2014-12-23 (USA)
Formulation Type: Capsule, Extended Release Beads (memantine)

Review Status: Standard (FDA)
USA Development/Approval Time[2]: ~4.2 years
Sales Potential: Undisclosed, potentially >$500 million
Claim to Fame: A simple convenience targeted combination product, Namzaric is a lifecycle extension product for the Forest (Actavis) Alzheimer's portfolio.

Comment: With acetylcholinesterase inhibitors such as donepezil coprescribed with Forest's Namenda (memantine) in the majority of Alzheimer's patients it made obvious sense to combine the two agents in a single dosage form. This is a patient group for who increased convenience and simpler dosing has particular benefits.

For Forest (Actavis/Allergan) the product that was developed by Adamas Pharmaceuticals is an obvious lifecycle product. With their immediate release Namenda facing generics in 2015, and their Namenda XR formulation being taken up slowly, this extended release combination product may be just the answer.

There are no publicly available forecasts for annual sales but we expect annual sales to easily exceed $500 million, if conversion to Namenda XR and Namzaric can be successfully accomplished. Namenda IR sales alone top $1.5 billion.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Omidria

Active: phenylephrine hydrochloride, ketorolac tromethamine
Molecular Weight[1]: 167 Da, 255 Da
Indication: Cataract Surgery, Intraocular Lens Replacement
Delivery Route: Irrigation – intraoperative
Dosing Interval: Single dose, irrigation
Company: Omeros
First Approval: 2014-05-30 (USA)

Formulation Type: Solution for Reconstitution
Review Status: Standard (FDA)
USA Development/Approval Time[2]: ~6.4 years
Sales Potential: Not Disclosed, < $50 million
Claim to Fame: A practical intraoperative irrigation solution to prevent intraoperative miosis and reduce postoperative pain.

Comment: A good example of a simple convenience enhanced combination product that arises from understanding the needs of clinicians. Both actives, phenylephrine and ketorolac, are approved for intraoperative use but not for intracameral (within the eye) use. Omidria was studied for use as a component in the irrigation solution during cataract surgery and lens replacement. The approval package included nonclinical information on the intracameral use of the agents separately and in the approved Omidria combination. Ophthalmology has become a therapeutic area of interest to many companies given the needs of patients and clinicians and the relative absence of competition. Forecasts for Omidria are not available but peak sales are likely to well short of $50 million annually.

Harvoni

Active: sofosbuvir, ledipasvir
Molecular Weight[1]: 529 Da, 889 Da
Indication: Hepatitis C
Delivery Route: Oral
Dosing Interval: 24 hours
Company: Gilead
First Approval: 2014-10-10 (USA)
Formulation Type: Tablet

Review Status: Priority (FDA)
USA Development/Approval Time[2]: 2.4 years
Sales Potential: Billions and billions
Claim to Fame: The latest antiviral from Gilead, a combination product, is expected to advance the treatment of Hepatitis C and break all records for fastest product to reach each and every sales record.

Comment: A follow on to Gilead's 2013 blockbuster Sovaldi, Harvoni adds in ledipasvir to Sovaldi's sofosbuvir to create a one-two antiviral "punch". The development and approval time for Harvoni was remarkably short, apparently benefiting from the previous development and approval of Sovaldi. A logical follow on to Sovaldi, Harvoni will face some competition from AbbVie's multi-dose Hepatitis C medication Viekira Pak. But with once-a-day dosing versus Viekira Pak's once and twice-a-day dosing protocols, and both products showing excellent clinical outcomes, market share will likely come down to pricing and perceived value to the patient and the healthcare system.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Triumeq

Actives: abacavir sulfate/dolutegravir sodium/lamivudine

Molecular Weight[1]: 286/419/229 Da

Indication: HIV/AIDS

Delivery Route: Oral

Dosing Interval: 24 hours

Company/Partner: Viiv (GlaxoSmithKline)/Shionogi

First Approval: 2014-08-22 (USA)

Formulation Type: Oral, Tablet-Combination

Notable: Another fixed-dose antiviral combination product for the treatment of HIV/AIDS featuring three previously approved actives each available in single active dosage forms.

Akynzeo

Actives: netupitant/palonosetron hydrochloride

Molecular Weight[1]: 579/296 Da

Indication: Nausea & Vomiting, Post Chemotherapy

Delivery Route: Oral

Dosing Interval: Single dose, prior to chemotherapy

Company/Partner: Helsinn/Roche

First Approval: 2014-10-10 (USA)

Formulation Type: Oral, Capsule-Combination

Notable: Designed to provide immediate and extended anti-nausea benefits in a single fixed-dose oral combination product. Palonosetron provides immediate activity while netupitan, with a longer elimination half life, provides extended activity.

Xigduo XR

Actives: metformin hydrochloride/dapagliflozin propanediol

Molecular Weight[1]: 129/409 Da

Indication: Diabetes, Type 2

Dosing Interval: 24 hours

Delivery Route: Oral

Company/Partner: Bristol-Myers Squibb/AstraZeneca

First Approval: 2014-07-11 (Australia)

Formulation Type: Oral, Tablet-Combination, Modified Release

Notable: A member of the metformin combination club. Approved in a twice-daily formulation in the EU earlier in 2014 it was developed and approved first in Australia and then the USA as a once a day tablet.

Viekira Pak

Actives: dasabuvir/ombitasvir/paritaprevir/ritonavir

Molecular Weight[1]: 494/894/766/721 Da

Indication: Hepatitis C

Delivery Route: Oral

Dosing Interval: 12 hours/24 hours

Company/Partner: AbbVie

First Approval: 2014-12-19 (USA)

Formulation Type: Oral, Tablet-Combination Pack

Technology Provider: Internal

Notable: In the age of multi-agent viral therapies, Viekira represents the first 4 active combination product. While not elegant in terms of formulation design, four separate tablets, and differing dosing regimens, it has proven efficacy and offsets convenience issues with an aggressive pricing strategy.

Invokamet

Actives: metformin hydrochloride/canagliflozin

Molecular Weight[1]: 129/445 Da

Indication: Diabetes, Type 2

Delivery Route: Oral

Dosing Interval: 24 hours

Company/Partner: Mitsubishi Tanabe/Johnson & Johnson

First Approval: 2014-08-20 (USA)

Formulation Type: Oral, Tablet-Combination

Notable: Another member of the metformin fixed-dose combination club, but with Mitsubishi Tanabe's proprietary Sodium-Dependent Glucose Co-Transporter 2 Inhibitor, canagliflozin. It matches Xigduo XR as a once-daily formulation.

Targiniq ER

Active: oxycodone hydrochloride/naloxone hydrochloride

Molecular Weight[1]: 315/327 Da

Indication: Chronic Pain

Delivery Route: Oral

Dosing Interval: 12 hours

Company/Partner: Purdue Pharma

First Approval: 2009-01-23 (EU)

Formulation Type: Oral, Tablet-Combination, Abuse Resistant, Modified Release

Notble: Approved in the US only in 2014 this product uses an agonist/antagonist strategy for abuse deterrence and extends Purdue's significant abuse resistant opioid portfolio.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.

Ten Notable Drug-Device Approvals of 2014

The common theme for drug-device products in 2014 was improved patient convenience. This seems a very appropriate strategic response in a marketplace where multiple products treating the same condition are common, be they proprietary or generic. Distinguishing a product on the basis of the convenience and ease of use of the device is often a critical differentiator in a crowded market.

Improved convenience also leads to better therapeutic outcomes, in theory at least, reducing overall healthcare costs. Patients who take their medications on schedule and properly, be it injected or inhaled, are less likely to experience relapses or other complications. Simple devices that are easy to understand support proper use and regular dosing. This principle seemingly underlies the development of an increasing number of formulations offering reduced dosing frequencies, easy-to-use drug-device pairings, and even drug-drug combinations.

The biggest drug-device approval in 2014 surely was the FDA's approval of Mannkind's inhaled insulin, Afrezza. Intended to meet a major market need, a non-injectable option for insulin, while addressing the shortcomings of Nektar's Exubera, Afrezza seems well positioned to capture what opportunity there might be for managing type 2 diabetes via pulmonary administration. Partnered with Sanofi, the therapeutic and commercial success of Afrezza will be a strong indicator of the future for not only inhaled insulin but also other chronically dosed inhaled macromolecules.

Amgen's Neulasta Delivery System approval represents an interesting shift in the setting for the infusion of medications, at least on a single-dose basis. The Neulasta "kit" includes a small plastic infusion pump the size of a muffin-top that is applied to the patient's skin prior to discharge following a course of chemotherapy. The device is programmed to infuse Neulasta subcutaneously some 27 hours later. Rather than requiring the patient to return to the clinic or a doctor's office for the infusion, or requiring a home visit by a nurse, the patient walks out with the device already attached and simply removes it once the dose has been completed. And Amgen provides it at no additional cost. For the patient and healthcare system, this not-so-simple device represents a huge potential savings in cost.

2014 saw continuing efforts by companies to refresh and update their delivery devices, particularly injection and inhalation devices. GlaxoSmithKline continued to refresh its respiratory product portfolio in 2014, with the launch of Arnuity and Incruse Ellipta, using its Ellipta dry powder device. The Ellipta device offers a number of patient benefits over GlaxoSmithKline's tried and true Diskus dry powder device. The real question is whether the device will offer sufficient benefits to shore up the company's respiratory franchise from the influx of branded and generic dry powder inhalation products.

The inclusion of pens or prefilled syringes for the delivery of injectable medications has become an essential requirement for injectable products entering any chronic market, especially diabetes. 2014 saw incremental, rather than revolutionary, improvements in device design and patient-friendly features. Injection devices will need even more substantial improvements if Mannkind's Afrezza manages to gain significant patient and market acceptance.

There were two drug-device products approved in 2014 that are likely to find limited commercial success despite their rather novel approach to device integration. Trimel's Natesto intranasal gel device, designed to eliminate issues of inter-patient transfer of topically administered testosterone, faces market acceptance challenges with a 3x daily dosing schedule and a softening testosterone replacement market. It's questionable that it will succeed even with the support of Endo's increasingly substantial male health investments. Kaléo's Evzio seems that it will be a therapeutic if not commercial winner. The ability for law enforcement, EMS personnel, and family members to quickly and easily reverse narcotic overdoses in the field promises to save lives. Managed properly, and in conjunction with their Auvi-Q epinephrine delivery device and additional pipeline products, the company is likely to prosper.

Combining drugs with devices is all about improving patient convenience in hopes that it will improve compliance and patient acceptance. Limited advances in the development of oral formulations for the delivery of macromolecules will ensure there is continued investment in more effective and patient-friendlier drug-device combinations. If Afrezza can validate the efficacy, safety, convenience, and commercial viability of inhaled insulin, it is likely we will see many more inhaled proteins reach approval and the market.

The following Ten Notable Drug-Device Products of 2014 (four of them are highlighted in detail) provide a snapshot of what was approved last year and suggest future directions in drug-device development.

Afrezza

Active: insulin, human recombinant
Molecular Weight[1]: 5,808 Da
Indication: Diabetes, hyperglycemia
Delivery Route: Inhalation, Dry Powder
Company/Partner: Mannkind/Sanofi
First Approval: 2014-06-27 (USA)
Formulation Type: Dry Powder (Technosphere)
Technology Provider: Mannkind

Device: Dry Powder Inhaler (Dreamboat)
Review Status: Standard (FDA)
USA Development Time[2]: 13.5 years
Sales Potential: $1 billion +
Notable: After a long and expensive development program Afrezza will attempt to do what Exubera couldn't, gain market acceptance and profitability.

Comment: Both Mannkind and Sanofi have much riding on the success of Afrezza. Mannkind seeks vindication for their investment in Afrezza and Sanofi needs a driver for their diabetes portfolio. Afrezza is a remarkable combination of formulation and device design. The 'bong-like' device that was used with Exubera has been shrunk to the size of an asthma inhaler with Afrezza. The Afrezza Dreamboat device requires no cleaning and is simply replaced every couple of weeks. Launched in February 2015 industry experts are uncertain about how it will be accepted by patients and its eventual commercial success. Prescription figures suggest uptake will be slower than initially forecast which has caused analysts to drop their peak sales estimate from $2 billion to $1 billion.

While only a 6 kilodalton molecule the effective pulmonary delivery of insulin represents a huge step forward for the future of macromolecule delivery. It will be interesting to see what additional molecules Mannkind intends to incorporate into their Technosphere and Dreamboat technologies. Mannkind has shown it can be done, now the question is whether are patients and physicians are sufficiently interested in pulmonary rather than parenteral administration to accept the associated higher costs and additional safety monitoring requirements.

Natesto

Active: testosterone
Molecular Weight[1]: 288 Da
Indication: Hypoandrogenism
Delivery Route: Nasal
Company/Partner Company: Trimel/Endo
First Approval: 2014-05-28 (USA)
Formulation Type: Intranasal Gel
Technology Provider: Met P Pharma, Trimel

Device: Nasal Gel Pump
Review Status: Standard (FDA)
USA Development Time[2]: 9.8 years
Sales Potential: Not disclosed, <$50 million estimate
Notable: One of only a very few approved nasal delivery products intended for CNS delivery, Natesto employs a novel gel and device configuration.

Comment: A product that took almost ten years to develop from IND to approval, Natesto may have reached the market too late to realize it's full potential. Recent medical opinion and FDA restrictions on the prescribing of testosterone will negatively impact the market for testosterone replacement therapies much as women's hormone replacement therapy prescriptions and sales were impacted by negative clinical opinion more than a decade ago.

The novel gel and nasal device combination do point to additional opportunities for nasal delivered products. Seemingly intended to provide a delivery system that was effective and discreet while avoiding issues related to interpersonal transference of testosterone, the three-time daily dosing schedule does not compare well with topical gels that are administered daily or implants that last up to six months.

Sales estimates for Natesto are unavailable but it is unlikely the product will capture annual sales in excess of $50 million. Even with a twice-daily dosing regimen that is in development Natesto is unlikely to receive significant uptake, especially in a market with generic topical agents.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Evzio

Active: naloxone hydrochloride
Molecular Weight[1]: 327 Da
Indication: Opioid Overdose
Delivery Route: Injection – subcutaneous and intramuscular
Company/Partner: Kaléo
First Approval: 2014-04-03 (USA)
Formulation Type: Simple Saline Solution
Technology Provider: Kaléo

Device: Autoinjector (e-cue)
Review Status: Priority (FDA)
USA Development Time[2]: ~3.5 years
Sales Potential: Not Disclosed
Notable: Patient friendly delivery system that permits untrained individuals to quickly and easily treat opioid overdoses.

Comment: Evzio represents an important step forward in the management of opioid overdosing in the outpatient setting. Effectively a multimedia delivery device, Evzio provides printed and audio dosing instructions to allow untrained individuals to quickly and effectively administer the dose.

This simple device incorporates a prefilled syringe along with a gas cylinder that injects the naloxone over a five second period when pressed against the body, typically the thigh. More interesting is the "Intelligent Prompt System (IPS)" that provides audio step-by-step instructions in real time once the case wrapper is removed.

Evzio promises to offer families, as well as EMS and law enforcement officials, a user-friendly resource for rapidly treating individuals suspected of opioid overdosing. This follows the introduction of Auvi-Q/Allerject, an epinephrine autoinjector device by Kaléo (formerly Intelliject) in 2012 using the same device design. Even the premium price of the product represents a bargain if it can save a life.

Neulasta Delivery Kit

Active: empegfilgrastim
Molecular Weight[1]: 39,000 Da
Indication: Neutropenia
Delivery Route: Injection - subcutaneous
Company: Amgen
First Approval: 2014-12-23 (USA)
Formulation Type: PEGylation
Technology Provider: Amgen

Device: Autoinjector (On-body)
Review Status: Priority (FDA)
USA Development Time[2]: Unknown
Sales Potential: Not disclosed
Notable: A novel patient friendly technology-centric approach to increased patient convenience and better therapeutic outcomes.

Comment: The Neulasta Delivery Kit with the On-body Injector represents a reasonably high-tech approach to providing a prolonged single subcutaneous injection, mimicking an infusion pump, following chemotherapy. The difference is that the device is disposable and it is designed to deliver the dose a full 27 hours after the device is applied. The benefits appear to be twofold, the dose is administered over an extended period for improved tolerability, and compliance and convenience is improved. Rather than returning to the clinic for a post chemotherapy session infusion the patient can remain at home. The Neulasta system is applied by a healthcare professional following chemotherapy treatment and requires no further attention from the patient. The kit is provided at no extra cost.

The value of disposable on-demand or programmed delivery devices for acute conditions has not been validated. Alza and J&J's Ionsys on-demand fentanyl active delivery system for post-surgical inpatient use was a huge disappointment, essentially being withdrawn soon after approval and launch. The Neulasta Delivery Kit may well point to additional opportunities for higher tech single-use disposable injection devices.

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 submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.

Xultophy

Active: insulin degludec, liraglutide
Molecular Weight[1]: ~6,104 / 3,751 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: Novo Nordisk
First Approval: 2014-09-18 (EU)
Formulation Type: Aqueous
Technology Provider: Novo Nordisk
Integral Device: Prefilled Syringe (FlexTouch)
Notable: A combination product, Xultrophy incorporates the latest generation Novo Nordisk dose-adjustable prefilled insulin syringe system providing easier use and greater accuracy.

Kitabis Pak

Active: tobramycin
Molecular Weight[1]: 468 Da
Indication: Cystic Fibrosis
Delivery Route: Inhalation - nebulization
Company/Partner: PulmoFlow/Pari
First Approval: 2014-12-02 (USA)
Formulation Type: Aqueous
Technology Provider: Pari Pharma
Integral Device: Nebulizer (Pari LC)
Notable: Touted as the first defined drug-device combination approved for cystic fibrosis Kitabis Pak provides clarity for clinicians and patients with respect to optimal efficacy and safety with a defined formulation-device pairing.

Bydureon Dual

Active: exenatide
Molecular Weight[1]: 4,187 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: AstraZeneca/Amylin
First Approval: 2014-03-03 (USA)
Formulation Type: Biodegradable PLGA (Medisorb)
Technology Providers: Ypsomed, Alkermes
Integral Device: Dual-chamber Monodose (LyoTwist Trio)
Notable: Bydureon Dual provides incremental injectable delivery format/device convenience improvements that should translate into better compliance and therapeutic outcomes.

Tanzeum

Active: albiglutide
Molecular Weight[1]: 72,971 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: GlaxoSmithKline
First Approval: 2014-03-21 (EU)
Formulation Type: Fusion protein (Albufuse)
Technology Providers: Ypsomed, Novozymes
Integral Device: Dual-chamber Monodose (LyoTwist)
Notable: The first of Human Genome Science's albumin fusion proteins to reach approval, Tanzeum offers once-weekly dosing in conjunction with Ypsomed's patient friendly injection device.

Arnuity Ellipta

Active: fluticasone furoate
Molecular Weight[1]: 445 Da
Indication: Asthma
Delivery Route: Inhalation - dry powder
Company/Partner: GlaxoSmithKline
First Approval: 2014-08-20 (USA)
Formulation Type: Dry Powder
Technology Provider: GlaxoSmithKline
Integral Device: Dry Powder Inhaler (Ellipta)
Notable: The latest in a series of new and 'refreshed' dry powder inhalation products using GSK's next-generation Ellipta dry powder device that offers improved ease of use and dual active delivery without the need for co-formulation.

Trulicity

Active: dulaglutide
Molecular Weight[1]: 59,670 Da
Indication: Pain, chronic
Delivery Route: Injection - subcutaneous
Company/Partner: Eli Lilly
First Approval: 2014-09-18 (USA)
Formulation Type: Fusion Protein
Technology Provider: Eli Lilly
Integral Device: Prefilled Syringe, Pen
Notable: Another example of what has been an increasingly common strategy, Fc fused proteins in a patient friendly injection system intended to provide an extended duration of action while encouraging patient compliance.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.

Top 20 Product Sales in 2014

It's interesting to look at how drug delivery and formulation technologies are represented in the sales of pharmaceutical products worldwide. The analysis that follows largely relates to products that are enabled or enhanced by drug delivery and formulation technologies, including integral devices (DDEPs). In some sense, the assignment of products as DDEPs can seem arbitrary, but the rules are pretty simple. Oral pharmaceutical products that don't incorporate solubility-enhancing or dose-modifying technologies are not considered to be DDEPs. The same is true for topical and injectable products.

Any product that requires a separate, non-integral device, for example, an infusion pump, is not considered a DDEP. A product that includes an integral device, a multidose pen, for example, would be considered a DDEP. A topical agent that is administered by means of a transdermal patch is a DDEP, while a simple topical steroid is not, unless it incorporates some specific technology to modify or enhance absorption.

Sales in this section refer to manufacturer reported sales, and generally represent the ex-factory shipments and sales net of all discounts offered to purchasers and government agencies. These can vary from the figures reported from audits of prescriptions at the pharmacy and hospital levels that are extrapolated to full market sales estimates. Using manufacturer-reported figures also means that the products of certain private companies that do not publish their sales figures are excluded. The most notable with regard to DDEPs is the Purdue Pharma/Mundipharma/Napp Pharmaceuticals group and their sustained-release opioids.

Top 20 Pharmaceutical Products

The products in Table 1 are listed in order of published global sales. Most product categories will be obvious, but the DDEP category is worth explaining. In the case of DDEPs, there are three possible designations: Yes, No, and Partial. Partial refers to pharmaceutical products with one or more, but not all, marketed dosage forms incorporating a delivery technology or integrated device. Common examples of Partial DDEPs are products that are marketed in vials and prefilled syringes or pen-type devices. In the case of oral agents, the product line may include immediate-release and sustained-release dosage forms.

Table 1. Top 20 Pharmaceutical Products by Manufacturers Sales (2014)

Product	Company	2014	Rank	Molecule Type	Route	DDEP	Dosage Forms	First Approval
Humira	AbbVie	$12,543	1	Antibody	Injection	Partial	Syringe, Vial	2002/USA
Sovaldi	Gilead	$10,283	2	Small Molecule	Oral	No	Tablet	2013/USA
Remicade	Janssen/J&J	$9,916	3	Antibody	Injection	No	Vial	1998/USA
Enbrel	Amgen	$8,949	4	Protein	Injection	Partial	Syringe, Vial	1998/USA
Lantus	Sanofi	$8,435	5	Protein	Injection	Partial	Syringe, Vial	2000/USA
Abilify	Otsuka/ Bristol-Myers Squibb	$8,404	6	Small Molecule	Oral/ Injection	Partial	Tablet, ODT, Depot	2002/USA
Rituxan	Biogen/Roche	$7,553	7	Antibody	Injection	Partial	Vial	1997/USA
Advair (Diskus/HFA)	GlaxoSmithKline	$7,035	8	Small Molecule	Inhalation	Yes	DPI, MDI	1999/EU
Avastin	Genentech/Roche	$7,024	9	Antibody	Injection	No	Vial	2004/USA
Herceptin	Genentech/Roche	$6,868	10	Antibody	Injection	No	Vial	1998/USA
Crestor	AstraZeneca	$5,512	11	Small Molecule	Oral	No	Tablet	2002/EU
Lyrica	Pfizer	$5,167	12	Small Molecule	Oral	No	Capsule	2004/EU
Revlimid	Celgene	$4,980	13	Small Molecule	Oral	No	Capsule	2005/USA
Gleevec	Novartis	$4,746	14	Small Molecule	Oral	No	Tablet	2001/EU
Neulasta	Amgen	$4,599	15	Protein	Injection	Yes	Syringe, On-body Injector	2002/USA
Prevnar (7 & 13)	Pfizer (Wyeth)	$4,463	16	Vaccine	Injection	Yes	Syringe	2000/USA
Spiriva	Boehringer Ingelheim	$4,304	17	Small Molecule	Inhalation	Yes	DPI, MDI	2001/EU
Lucentis	Genentech/Roche	$4,303	18	Antibody	Injection	No	Vial	2006/USA
Copaxone	Teva	$4,237	19	Protein	Injection	Yes	Syringe	1996/USA
Januvia	Merck & Co.	$3,993	20	Small Molecule	Oral	No	Tablet	2006/Mexico

It's interesting to note how many biologics, antibodies, and proteins are in this Top 20 Sales list (11/20). This reflects in part their significant acceptance in clinical practice for conditions that had been poorly managed with small molecule therapeutics, but perhaps even more importantly, it reflects their premium pricing and extended market exclusivity. Any number of small molecule products approved in the same period also managed to reach the Top 20 list only to shed market share and sales once they lost market exclusivity. Among the nine small molecule products on the list, almost half will drop off this list in the next couple of years as their exclusivity expires and generic competitors enter the market.

In terms of delivery route, 12 of the 20 products are injectables, with 6 others primarily featuring oral presentations, and the remaining 2 administered by inhalation. This is a remarkable reversal of what was seen 1 and 2 decades ago when oral products targeted to chronic outpatient indications represented the majority of products on this list. Among the Top 20 products, 10 do and 10 don't incorporate formulation or device technologies. Of the 10 that do, and are considered DDEPs, fully half depend on formulation or integral device technologies, while the other half, designated as Partial, incorporate formulation technology or integral devices in a subset of their approved presentations.

Total sales for the Top 20 in 2014 amounted to USD $133.3 billion. Breaking out this total, DDEP-related products accounted for 53% of the total Top 20 sales; split 19% for full DDEP and 34% for Partial DDEP. If we look further to the full set of product sales actively monitored by PharmaCircle, which include only originator products in the major markets, the ratio shifts to a total 36% of sales accounted for by DDEPs.

Top Drug Delivery Enhanced/Enabled Pharmaceuticals (DDEPs)

Humira

Sales (Launch through 2014): $65 billion
Formulation(s): Injection Solution
Approved Indication(s): Rheumatoid Arthritis, Crohn's Disease, Psoriasis, Ulcerative Colitis
Delivery Route: Injection - Subcutaneous
Company: AbbVie
First Approval: 2002 (USA)
Presentation(s): Prefilled Syringe, Single-Dose Pen

Formulation Development: While the formulation for Humira has remained largely constant since launch, there have been changes in the drug/device configuration to better match outpatient needs. Launched in early 2003 with a vial presentation, a switch was made in mid-year 2004 to prefilled syringes, with a discontinuation of the vial presentation. This was followed in 2006 with a single- use disposable pen presentation. With twice-monthly maintenance dosing, the requirement for patient self-injection has not limited the uptake of Humira and its climb to the number one sales position.

Enbrel

Sales (Launch through 2014): $75 billion
Formulation(s): Injection Solution
Approved Indication(s): Rheumatoid Arthritis, Psoriasis, Ankylosing Spondylitis
Delivery Route: Injection - Subcutaneous
Company: Amgen
First Approval: 1998 (USA)
Presentation(s): Multidose Vials, Prefilled Syringe, Prefilled Autoinjector

Formulation Development: Launched by Immunex/Wyeth-Ayerst as a lyophilized powder for reconstitution, Enbrel has progressively added in multidose vials, prefilled syringes, and pen presentations. At the same time, dosing has been extended from twice weekly to once weekly at higher doses.

Lantus

Sales (Launch through 2014): $48 billion
Formulation(s): Injection Solution
Approved Indication(s): Diabetes - Type 1 & Type 2
Delivery Route: Injection - Subcutaneous
Company: Sanofi (USA)
First Approval: 2000
Presentation(s): Multidose Vial, Injection Pen (Disposable), Injection Pen (Reusable)

Formulation Development: With a requirement of daily dosing, attention with Lantus has been placed on making the injection process as convenient and as painless as possible. This has led to the introduction of room-temperature-stable (28 days) multidose disposable and reusable pen devices with increasingly fine needle gauges.

Abilify

Sales (Launch through 2014): $54 billion
Formulation(s): Oral Tablet, Oral Solution, Lyophilized Melt Tablet, Injection Solution, Lyophilized Powder for Suspension
Approved Indication(s): Schizophrenia, Bipolar Disease, Depression, Autistic Disorder
Delivery Route: Oral, Injection - Intramuscular
Company: Otsuka
First Approval: 2002 (USA)
Presentation(s): Tablet, Oral Solution, Injection Solution, Injection for Reconstitution (Depot)

Formulation Development: The formulation development of Abilify has paralleled the expansion of its label indications. Current formulations are intended to provide oral maintenance dosing with simple tablet formulations. Swallowing issues are addressed with melt tablet and oral solution presentations. Cyclodextrins are used as solubility enhancers with the injection solution presentation, while the product defaults to a lyophilized formulation requiring reconstitution for the depot presentation.

Prevnar (7 & 13)

Sales (Launch through 2014): $35 billion
Formulation(s): Injection Suspension with Adjuvant
Approved Indication(s): Pneumonia, Otitis Media
Delivery Route: Injection – Intramuscular
Company: Pfizer (Wyeth)
First Approval: 2000 (USA)
Presentation(s): Prefilled Syringe
Formulation Development: Introduced as a heptavalent vaccine in 2000, the vaccine was replaced with a broader coverage 13-valent presentation in Europe in 2009 and the USA in 2010. Intended as a prophylactic treatment, often in a public health setting, the use of prefilled syringes simplifies administration, although it is recommended to vigorously shake the syringe to re-suspend the adjuvant.

Advair/Seretide

Sales (Launch through 2014): $84 billion
Formulation(s): Inhalation Powder, Pressurized Inhalation Solution
Approved Indication(s): Asthma, COPD
Delivery Route: Inhalation
Company: GlaxoSmithKline
First Approval: 1999 (EU)
Presentation(s): Dry Powder Inhaler, Metered Dose Inhaler
Formulation Development: First approved in 1999 as a dry powder device combination product (salmeterol/fluticasone), it was followed a year later with a metered dose formulation. Advair quickly gained market acceptance and has been a multibillion-dollar product for more than a decade. With generics imminent, GSK seems intent on moving prescribers and patients to their new Ellipta drug/device products.

Neulasta

Sales (Launch through 2014): $38 billion
Formulation(s): PEGylated Protein, Injection Solution
Approved Indication(s): Neutropenia
Delivery Route: Injection – Subcutaneous
Company: Amgen
First Approval: 2002 (USA)
Presentation(s): Prefilled Syringe, On-Body Injector
Formulation Development: Neulasta is a PEG conjugated G-CSF first approved in 2002 as a prefilled syringe. A disposable autoinjector presentation approved in 2005 (USA) was subject to recalls in 2006 because of incomplete dose delivery and was withdrawn from the market. An "apply-now-deliver-later" device, the Neulasta On-Body Injector, was approved in 2014 and permits the healthcare professional to attach the device to the patient in a clinical setting and have a standard single dose of Neulasta administered subcutaneously by infusion about 24 hours later with no further patient or clinician involvement.

Rituxan/MabThera-PH20

Sales (Launch through 2014): $66 billion
Formulation(s): Injection Solution, Injection Site Absorption Enhancer
Approved Indication(s): Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid Arthritis, Granulomatosis
Delivery Route: Injection – Infusion, Injection – Subcutaneous (MabThera-PH20)
Companies: Biogen, Roche
First Approval: 1997 (USA)
Presentation(s): Vial
Formulation Development: 2014 saw the approval and introduction of a subcutaneous formulation of rituximab (MabThera-PH20) in the EU by Roche using Halozyme's Enhanze technology. This simplifies the usual dosing protocol that involves intravenous infusion over one to two hours.

Spiriva

Sales (Launch through 2014): $34 billion
Formulation(s): Inhalation Powder in Capsule, Inhalation Solution Pressurized
Approved Indication(s): Asthma, COPD
Delivery Route: Inhalation
Company: Boehringer Ingelheim
First Approval: 2001 (EU)
Presentation(s): Dry Powder Inhaler, Liquid Inhaler/Nebulizer
Formulation Development: First approvals were for the dry powder inhaler configuration that required a patient to insert a capsule into the device, administer the dose, then remove the spent capsule and occasionally clean the device. The Respimat presentation, first introduced in the EU in 2007, simplifies dosing and only requires weekly cleaning of the mouthpiece.

Copaxone

Sales (Launch through 2014): $31 billion
Formulation(s): Injection Solution
Approved Indication(s): Multiple Sclerosis, Relapsing, Remitting
Delivery Route: Injection – subcutaneous
Company: Teva
First Approval: 1996 (USA)
Presentation(s): Prefilled Syringe, Autoinjector
Formulation Development: Initially introduced as a lyophilized powder for injection, this injectable intended for outpatient use has evolved to include prefilled syringes and a higher dose formulation that permits extended dosing intervals (3 per week). A reusable autoinjector, the autoinject 2 (Owen Mumford), that fits the standard prefilled syringe is provided at no additional cost.

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The Future of the Pharma & Biotech Industries: Your Colleague's Perspectives

Drug Development & Delivery's Global Formulation Report in this issue has provided some notable facts, figures, and comments on what has been happening in the industry in a number of key sectors these past 18 months. As such, we thought it would be intriguing for our readers to hear what some of your colleagues believe will have a significant impact on the pharmaceutical and biotechnology industries throughout the next 5 to 10 years. We allowed the participants only a brief comment or two, and as expected, the responses were varied and thought-provoking.

"CDMOs of the future will have in-house drug substance and active pharmaceutical ingredient (API) manufacturing capability, drug product development, and commercial manufacturing capability of small molecule, large molecule, and biologics in a variety of dosage forms. APIs can be developed with improved properties for the drug product manufacturing, reducing the time required for formulating drugs in a suitable delivery system. There also will be a consolidation of the drug and device industry, which will prove beneficial when better devices to deliver dugs can be screened in the preclinical and early clinical phase of drug development. Understanding the site of efficacy in NCEs, the optimum site of absorption to better target delivery, and the use of better devices to deliver drugs will enhance success in drug delivery by reducing patient-to-patient variability and ensuring drugs are delivered to the target site to elicit clinical efficacy."

- Anil Kane, PhD, Executive Director, Global Head of Formulations, Pharmaceutical Development Services, Patheon

"As the economy has recovered, we seem to have come full circle and are now back to the point at which speed is the most critical factor in developing formulations. For a period of time, keeping costs down was the most important factor even if things took longer to get done. Now, formulators are being pressed to do more with less. In the early formulation development work, API is very precious and in a lot of cases, available amounts for formulation work are minimal. Companies that will be the most successful will be the ones that have the expertise to develop formulations with as little API as possible and will accomplish the formulation development work utilizing the principles of Quality-by-Design. In the next decade, it will be a necessity for formulations that are submitted in regulatory filings to be the product of a process that follows Quality-by-Design. It will no longer be a 'nice to have,' it will be a requirement."

- Paul Skultety, PhD, Vice President, Pharmaceutical Development Services, Xcelience

"One of the leading sources of drug candidate failures will be due to unsuitable GMP ingredients that are part of the final dosage formulations. With the high cost of development and delivery, the Pharmaceutical industry should rely more on their Excipient and API manufacturers to ensure the products being supplied are suitable for their intended end use to accomplish their desired development outcomes."

- Tom Donnelly, Director of Sales & Marketing, BioSpectra

"Fixed dose combinations (FDCs) will have a significant impact in multiple dosage forms throughout the next several years. The US Food and Drug Administration recently issued new guidance giving some additional exclusivity for filings with at least one new drug in the FDC product. A 'new' drug could mean either an NCE (New Chemical Entity) or a different dose of a previously approved drug, and such exclusivity offers market appeal for drug sponsors. At the same time, FDC products also appeal to patients because they provide a convenient and compliant means of dosing two drugs often taken together."

- Brad Gold, PhD, Vice President of Pharmaceutical Development, Metrics Contract Services

"We are living in the era of transformation. Formulations using 'nanoparticles' as a part of targeted drug delivery are expected to enter the market in the next 5 to 10 years. Nanoparticles can help in the controlled release of a drug, and may also deliver two different types of drugs at the same time, to give a stronger combination therapy, thereby increasing the efficacy of the drug."

- Dr. Siddharth Dutta, Frost & Sullivan Life Sciences & Healthcare Industry Manager

"Based on market trends, I believe there will need to be an increased focus on improving therapeutic outcomes and enhancing the overall patient experience, particularly in the area of injectable biologics that require self-administration. In addition to effective drug formulations, it will be critical to ensure that patients' needs are effectively understood and that we create delivery systems patients not only can use, but want to use, and are actively encouraged and motivated to continue to use. Successful delivery of biologics will depend on integrated systems that link the container and device, and incorporate an integrated approach to design for affinity, effective training and onboarding, and creative solutions (including gamification and connected health technologies) to improve adherence."

- Graham Reynolds, Vice President, Marketing & Communications, Pharmaceutical Delivery Systems, West

"The trend in the industry today is compatibility of both the active ingredients of a drug as well as its method of administration, ie, it must be 'patient friendly.' This is a direct reflection of a rapidly aging population and the rise in the home healthcare sector. In order to control costs and avoid cost-intensive therapies in a hospital or doctor's office setting, there is pressure to develop medicines that will enable more procedures in a private setting such as the home. Additionally, there is a rapid rise in therapies focused on conditions with small patient populations. These therapies, often 'Orphan Drugs,' are by US definition, drugs developed for treating conditions affecting fewer than 200,000 persons."

- Claudia Roth, Vice President, Innovation Management, Vetter Pharma International

"High-throughput solubility screening along with advanced thermodynamic modeling can help predict the solubility behavior of APIs. This creates an opportunity to perform dosage form selection in the early phases of drug development."

- Irena McGuffy, MS, PharmD, Director, Formulations Development, Catalent Pharma Solutions

"The advent of personalized healthcare, the desire to control healthcare costs, and the intelligence and curiosity of the patient population will collectively have the most dominant impact on the pharmaceutical and biotechnology industry in the coming years. This will result in the need for the industry to trend toward the design and development of smarter and more flexible medical products. The scaling of these products will require specialized platforms, including a synergistic overlay of more selective chemical matter, sophisticated diagnostics, specialized delivery devices, and targeted formulation platforms and dosage forms, which include novel functional excipient materials."

- David Vodak, Vice President, Bend Research, a division of Capsugel Dosage Form Solutions

"Today many of the top-selling drugs as well as the majority of drugs in development are biologics based. In parallel to this development, Drug Delivery (DD) and Formulation will continue to evolve throughout the next decade to better meet the needs of patients and clinicians for such drugs. This suggests we will see continuing improvements and refinements in patient-friendly injection device designs and configurations that could handle larger volume formats and as well as viscous drug formulations through subcutaneous injection. Many of these future drugs will be marketed with compliance tracking solutions and incorporate such patient-friendly technologies right from the beginning. Within the next decade, advancements will also include formulation and delivery device solutions for targeted delivery by both local as well as systemic administration."

- Tugrul Kararli, PhD, MBA, President & Founder, PharmaCircle

"I believe that the ability to conveniently administer drug subcutaneously with a programmable dose profile will fundamentally alter the trajectory of drug formulation, enabling companies to move from discovery into development faster, and increasing the probability of success in a clinical program."

- Michael Graffeo, Vice President, Business Development, Drug Delivery, Insulet Corporation

"Future innovation should be centered around improving patient outcomes by enhancing formulation and delivery technologies. For example, New Therapeutic Entities (NTEs) offer a huge upside, but for patients to see the benefits in access and cost efficiency, formulators need a clearer path to regulatory approval to spur innovation. By streamlining these guidelines, we can combine existing molecules with 'smart' delivery technologies and achieve the primary goal of patient compliance and improved health."

- Cindy R. Kent, MBA, VP & General Manager, 3M DDS

"Significant reduction in drug development timelines are predicted thanks to the emergence of in silico/computational models that analyze drug solubility, dispensability, and compatibility in one or more excipient systems; in vitro analytical models that predict bioavailability better; improved understanding of the transporter-mediated absorption; and elucidation of the biopharmaceutical role of excipients in drug delivery. Solid dispersion and continuous manufacturing technologies will be taking center stage, but the biggest, perhaps the most revolutionary change will result from shifting paradigms that demand rethinking of how drugs are selected and ultimately developed."

- Jasmine Musakhanian, Scientific & Marketing Director, Pharmaceutical Division, Gattefossé USA

"I believe we will see new excipients designed and engineered for specific delivery purposes as well as more "intelligent" device-mediated drug delivery technologies. Dow recently announced the launch of new HPMC polymers called Affinisol that were designed and engineered for hot melt extrusion applications, specifically for solid dispersions of poorly soluble drugs. Additionally, there are several companies developing devices that can provide real-time feedback to monitor a condition, control and regulate drug release, or respond to a biomarker."

- Michael Crowley, President, Theridian Technologies, LLC

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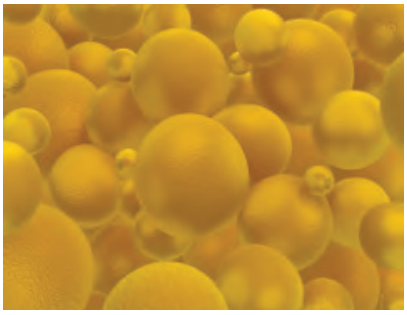

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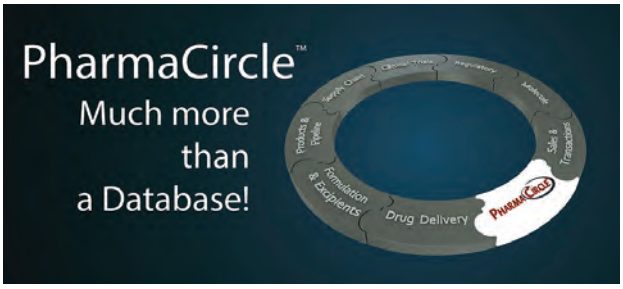

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Drug Development
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Nathan Caffo
President
Presage Biosciences

presage

Presage Biosciences: Comparing Multiple Drugs & Combinations Directly in a Patient's Tumor

Presage Biosciences is a Seattle-based oncology company pioneering the incorporation of human efficacy data much earlier in the drug development and clinical trial processes with its patented CIVO™ arrayed microinjection platform. The CIVO platform allows for simultaneous assessment of multiple drugs or drug combinations directly in a single solid tumor – while still in a patient's body – to assess efficacy, resistance, and drug synergies. Presage partners with oncology-focused pharmaceutical companies through strategic alliances to drive decisions about which drug candidates and drug combinations should be advanced to which patient populations. Presage is also actively pursuing drug programs through in-licensing and is using CIVO to develop a portfolio of promising oncology therapies to advance to the clinic. *Drug Development & Delivery* recently spoke with Nathan Caffo, President of Presage Biosciences, to discuss his company's technology with the potential to usher in a new era of cancer drug development and testing.

Q: How is Presage working to change the cancer drug development and clinical trial processes?

A: We believe the most important model for understanding cancer drug response is the human patient. So Presage has developed a radical new approach to assessing drug response that enables the use of human tumor response data much earlier in development than previously possible. The company's mission is to revolutionize the way drugs are selected, tested, and targeted with the goal of making better treatments and drug combinations available to patients.

Q: How can early human efficacy data impact the success of new drugs or drug combinations?

A: Being able to simultaneously evaluate multiple drugs and combinations directly in human patients and far earlier in development will be a game-changer for the pharma industry. Most cancer drugs that enter Phase I trials will never reach the market, and the tools used currently to translate programs from preclinical models to human patients have serious limitations. Using our CIVO technology, Presage can incorporate comparative drug efficacy data from human patients at several key points in the clinical trial process, ranging from pre-Phase I through assessment of novel combinations with approved drugs, all without exposing patients to the toxicity of systemic dosing.

Q: Can you discuss CIVO further and how it works?

A: Presage has developed a predictive in vivo assessment tool called CIVO that analyzes and compares multiple drugs and drug combinations in a single living tumor – while that tumor is still in the patient.

Our patented approach includes an arrayed microinjection technique and proprietary 3D analysis tools to help us understand the biology of tumor responses to drugs:

- The CIVO microinjection device inserts an array of multiple needles, each containing a different drug, dose, or combination into a tumor, delivering microdose cores of a drug directly into the tumor.
- Later, the tumor is resected for analysis. Quantitative analysis methodology enables Presage to assess drug interactions, tumor and stromal responses, and immune cell infiltrate provoked by different drugs – all across a range of drug concentrations.

Q: How is the Presage approach unique?

A: There is currently no other way to conduct multiple drug comparisons within a single living tumor. In fact, Presage was just granted its fifth US patent for CIVO. It can be used as an important complement to genomic-based approaches to identifying responder patient populations. Genomic approaches have certainly yielded results. However, as combinations of multiple targeted agents in oncology become increasingly used, clinicians and drug developers will run out of answers for which patient populations should be given which drugs. No longer will a common mutation in the target of a drug be enough to guide such decisions. Presage's CIVO enables a direct phenomic assessment that can elucidate the underlying biology of complex drug responses.

Q: What are the benefits of CIVO for companies developing drugs?

A: CIVO offers several specific benefits for companies developing drugs, including the following:

- Identification of novel drug combinations in biologically relevant in vivo models is possible at scale.
- Better decision-making about which drug combinations should be advanced to clinical trials in what patient populations, enabling evaluation of human data on a much more broad portfolio of assets with the same budgets.
- Assessment of immune response to oncology agents will be possible through microinjection in human patients prior to traditional Phase I studies.

Q: How is Presage currently using CIVO?

A: CIVO has been deployed with more than 100 approved and investigational drugs, and the predictive capability of the CIVO platform has been shown in multiple mouse models. Presage is evaluating the platform in a first-in-human study in collaboration with the Seattle Cancer Care Alliance (SCCA) and the Fred Hutchinson Cancer Research Center, with funding support from the National Cancer Institute (NCI). CIVO also is being employed in preclinical models, including canine cancer patients and human tumor xenografts in mice.

"Being able to simultaneously evaluate multiple drugs and combinations directly in human patients and far earlier in development will be a game-changer for the pharma industry. Most cancer drugs that enter Phase I trials will never reach the market, and the tools used currently to translate programs from preclinical models to human patients have serious limitations. Using our CIVO technology, Presage can incorporate comparative drug efficacy data from human patients throughout the clinical trial process, ranging from pre-Phase I through assessment of novel combinations with approved drugs."

Q: What kinds of results have you documented with CIVO?

A: We presented preclinical proof-of-concept data at the American Association for Cancer Research (AACR) meeting in 2014. The data showed that microinjection of several standard-of-care cancer drugs using the CIVO arrayed microinjection platform induced spatially defined, mechanism-specific tumor responses. In addition, CIVO analysis revealed that these outcomes correlated with responses to systemically delivered drugs and also identified pre-existing resistance to chemotherapy. This data shows that our CIVO technology sets the stage for a new type toxicity-sparing comparative drug efficacy study in humans.

Q: What is the history of Presage Biosciences?

A: Presage is based on technology invented in the lab of Dr. James Olson, a prominent pediatric oncologist at the Fred Hutchinson Cancer Research Center. As a doctor who treats children with brain tumors, he experienced first hand how poorly investigational drugs translated to the clinic. He was frustrated with the way drugs were traditionally assessed and invented the concept of arrayed microinjection to directly observe drug response in patients. We have evolved this technology into the current CIVO platform, which we are using to identifying effective drugs earlier in the development process based on clinically meaningful data.

Q: What are your partnership goals and objectives?

A: We already have two announced partnerships with innovative companies, Celgene and Millennium/Takeda Oncology, and we are in active discussions with several companies to employ CIVO in clinical studies to guide decisions about advancing drug combinations to particular patient populations. One area where I expect we can make a major impact is in the assessment of combinations with immunotherapy agents. I can't imagine how multiple drug combinations with immuno-oncology agents can be effectively evaluated without CIVO. How else can the involvement of a truly human immune system be modeled other than directly in a patient?

Q: What is your ultimate vision for the CIVO technology platform?

A: We would like to fundamentally improve how drugs and combinations are advanced to the clinic. Right now, only about 10% of oncology agents that enter a Phase I trial are ever approved by the FDA. We envision a day when that number, through better translational tools, rises to 50%. Drug developers and patients alike could benefit immensely. ◆

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TASTE-MASKING

Pharmaceutical Taste-Masking Technologies

By: Suniket Fulzele, PhD, and Sarah Rieschl

INTRODUCTION

Taste-masking techniques are applied to mask or overcome the bitter or unpleasant taste of active pharmaceutical ingredients/drugs to achieve patient acceptability and compliance. Oral administration of bitter or unpleasant tasting drugs is often the biggest barrier for patient groups, such as pediatrics and geriatrics.[1] A survey of American Association of Pediatricians reports unpleasant taste as the biggest barrier in the treatment of pediatric population.[2] Unless the active ingredient is tasteless or does not have any unpleasant taste, taste-masking plays a key role in the success of a final solid oral dosage form. The efficiency of taste-masking is often a key determinant for the success of specialized dosage forms like orally disintegrating tablets and films, and chewable tablets. The mechanisms of taste-masking techniques often rely on two major approaches: the first is to add sweeteners, flavors, and effervescent agents to mask the unpleasant taste, and the second is to avoid the contact of bitter/unpleasant drugs with taste buds. In the past few years, significant progress has been made in the area of taste-masking by applying novel strategies and techniques, such as hot-melt extrusion and microencapsulation. The following presents an overview and current status of the industrial approaches and platforms used for taste-masking in oral dosage forms.

TASTE-MASKING TECHNIQUES

Taste-masking techniques often go hand in hand with the formulation technology. In short, they need to be mutually compatible.[3] For example, coated particles obtained after fluid-bed coating should be able to withstand the tablet compression process used for the final dosage form (tablet) manufacturing.

FIGURE 1

A) Fluid-Bed Coater & B) Wurster Setup for Taste-Masking

The commonly used industrial techniques/methods of taste-masking include organoleptic methods, polymer coating, hot-melt extrusion, microencapsulation, complexation, and spray-drying.

Organoleptic Methods

This is the simplest and most convenient method of taste-masking. It involves adding a combination of sweeteners (sucralose, aspartame) and flavors (orange, mint) to mask the unpleasant taste of low to moderately bitter actives. In addition, effervescent agents (sodium bicarbonate, citric acid) can also be added to improve the mouth feel. Some formulations may include a bitterness blocking agent that masks the bitter taste or the perception of bitter on the tongue. Such bitter blockers may include adenosine monophosphate, lipoproteins, or phospholipids. These agents compete with the bitter active to bind to the G-protein coupled receptors on the tongue (receptor sites that detect bitter), thus suppressing the bitter taste.[4] It has also been found that sodium chloride can be added to a

formulation to mask bitterness as in the preparation of pioglitazone hydrochloride orally disintegrating tablets.[5]

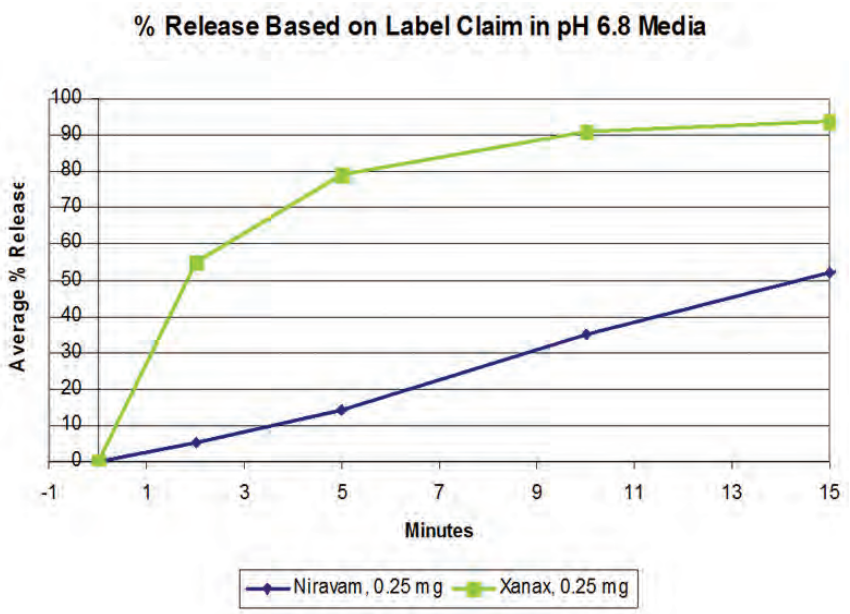
Polymer Coating

The simplest option is direct coating that provides a physical barrier over the drug particles with a composition that is insoluble in the mouth. Hydrophobic or hydrophilic polymers, lipids, and sweeteners can be used as coating materials, alone or in combination to produce a single or multi-layer coat. Methacrylic acid and methacrylic ester copolymers (Eudragit E-100, RL 30D, RS 30D, L30D-55, and NE 30D) have been effectively used for taste-masking with polymer coat levels varying from 10% to 40%, depending on the drug bitterness.[6] Fluid bed is often the technique of choice. Most recently, alternate approaches such as application of molten lipids [glyceryl palmitostearate (Precirol® ATO-5, Gattefosse, France) and glycerol behenate (Compritol® 888-ATO, Gattefosse, France)] on the surface of drug particles has been used as a solvent-free alternative.

The second alternative involves deposition of successive layers of an active compound onto inert starter seeds, such as sugar spheres or celpheres. The bitter drug is dissolved or dispersed in an aqueous or non-aqueous solvent along with a binder to allow the adherence of the drug particles to the inert substrate. Some commonly used binders include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), povidone, Eudragit E-100, and carboxymethyl cellulose. The drug-layered beads are then subsequently coated with a taste-masking polymer that retards drug dissolution in the oral cavity. Various polymers used for taste-masking purposes are Eudragit E-100, ethylcellulose, HPMC, HPC, polyvinyl alcohol, and polyvinyl acetate.[7] The taste-masked coated beads can then be incorporated into the final dosage form, such as a capsule or a compressed tablet. CIMA LABS has extensive experience in this area in the form of their DuraSolv® and OraSolv® technologies.

A third approach involves granulating the drug and then coating the drug-loaded granules with a taste-masking polymer. Granulation decreases the surface area of the drug by increasing its particle size and thus minimizing the amount of taste-masking polymer required. Granulation-coat approach is preferred over layer-coat for high doses as the granulation process can afford high drug loading. Regardless of the approach, fluid-bed coating remains the industrial process of choice to apply polymer coat (Figure 1) for taste-masking.

FIGURE 2



Dissolution Profile of Immediate-Release Niravam & Xanax Tablets

One of the challenges of taste-masking is evaluating the success or efficiency of the taste-masking technology. In the author's experience, dissolution testing can be used as a surrogate test for taste by evaluating the drug release from the taste-masked beads at earlier time points. The FIP/AAPS (Federation International Pharmaceutique/American Association of Pharmaceutical Scientists) guideline recommends multi-point dissolution testing within early points of analysis (eg, ≤ 5 min) as a means to address the taste-masking properties of the formulation.[8] Data collected at these early time points may be used for in vitro evaluation of the taste-masking efficiency. Figure 2 shows the release comparison of Niravam tablets containing layer-coated taste-masked drug beads vs. the non-taste-masked Xanax tablets. A multi-point profile in neutral pH medium with early single point specification (NMT X% released at 5 or 10 min) is applied to determine the taste-masking efficiency.

FIGURE 3

Hot-Melt Extruder

Hot-Melt Extrusion

Hot-melt extrusion (HME) offers a relatively newer approach to taste-masking and provides advantages such as absence of organic solvents in the process, fewer processing steps, continuous operation, and scale-up capabilities.[9] For the purpose of taste-masking, the bitter active is mixed with other ingredients in a dry state. The mixture is filled in a hopper, conveyed, mixed, and melted by an extruder. The process subjects the materials to a heating process under intense mixing to obtain the taste-masked extrudates. The extrudate can then be milled or micronized to obtain taste-masked granules or particles, which are then incorporated into a suitable dosage form. Twin screw extruders (Figure 3) are one of the most popular extruders and provide advantages such as short transit time, convenient material feed, high shear kneading, and less over-heating.

Microencapsulation

Microencapsulation is a technology with a long history in the pharmaceutical industry, and taste-masking represents an expanded area of its application. In principle, microencapsulation provides the opportunity to encapsulate the bitter active and thus prevent its contact with taste buds. Microcaps® is one such well-recognized technology that applies coacervation/phase separation to produce different encapsulated polymeric membranes. The process primarily consists of formation of three immiscible phases, formation of the coat, and deposition of the coat. The formation of the three immiscible phases is accomplished by dispersing the core particles in a polymer solution. A phase separation is then induced by change in the temperature of polymer solution; change in the pH, addition of a salt, non-solvent, or by inducing a polymer-polymer interaction. This leads to deposition of the polymer coat on the core material under constant stirring. The core particles coated by the polymer are then separated from the liquid phase by thermal, crosslinking, or desolvation techniques leading to rigidization of the coat.[10] Microcaps are used in conjunction with Advatab® compressed ODT technology.

Complexation

Cyclodextrins have been extensively used for taste-masking bitter drugs by forming inclusion complexes with the drug molecule. Cyclodextrins are unique bucket-shaped cyclic oligosaccharides containing at least six D-(+)-glucopyranose units attached by alpha-(1,4)-glucosidic bonds with a molecular structure of hydrophobic cavity and hydrophilic exterior. The formation of inclusion complexes and its type depends on several factors like drug properties, processes involved, the equilibrium kinetics, formulation excipients, and the desired final dosage form and delivery system. Taste-masking is achieved by the interaction of cyclodextrins with proteins of the taste buds or by inhibiting the contact of bitter drug molecules with taste buds.

Ion exchange resins provide an alternative to cyclodextrins to achieve taste-masking by complexation.[11] Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. The preparation of the taste-masked complex involves suspending the resin in a solvent in which the drug is dissolved. The drug-resin complex formed is referred to as drug-resinate, which prevents direct contact of the drug with taste buds, thus providing taste-masking during administration. Upon ingestion, the resin exchanges the drug with the counter ion in the gastrointestinal tract, and the drug

is released to be absorbed. Commercially available ion exchange resins that may be used for taste-masking are based on methacrylic acid - divinyl benzene polymer and styrene - divinyl benzene polymer.

Spray-Drying

Spray-drying provides an alternate approach to taste-masking by applying a physical barrier coating. The bitter drug is either dissolved or dispersed along with the polymer in a suitable solvent followed by spray-drying. The process usually consists of three different steps: (1) atomization of feed into a spray, (2) spray-air contact (mixing and flow) followed by drying, and (3) separation of dried product from the air. The process provides the option of using aqueous and non-aqueous solvents. The dried product often includes granules or beads containing taste-masked encapsulated drug. The amount of polymer coat can sometimes retard the drug release, and therefore requires careful polymer selection and process design to afford taste-masking. Also, the formulation and processing can affect whether or not the polymer is "coated" on the surface or dispersed. The quality of taste-masking depends on providing a coat, not a dispersion. Some of the advantages of spray-drying include (a) less processing time being a single step process, (b) scale-up capability, and (c) wide variety in the choice of solvent and polymer.

SUMMARY

In summary, a variety of taste-masking technologies are available and used in the pharmaceutical industry today with new platforms being researched and developed constantly. The type of technology used depends largely on the physical and chemical properties of the drug substance and the desired final dosage form. Advances in taste-masking technologies throughout the past few years have enabled the pharmaceutical industry to provide commercial products with improved patient acceptability and compliance, especially with pediatric and geriatric populations; along with enhanced convenience for patients on the go. More companies are turning to taste-masking expertise to complement their product portfolios for oral dosage forms.◆

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BIOGRAPHIES

Dr. Suniket Fulzele is a experienced drug delivery and formulation development scientist. He currently works as Group Leader, Formulation Development at CIMA Labs, Brooklyn Park, MN. His expertise and interest include innovations in oral solid dosage forms and drug delivery technologies that enable pharmaceutical development of challenging molecules from prototype design to commercialization as well as technology transfer between sites. Dr. Fulzele earned his PhD in Pharmaceutics and has more than 8 years of pharmaceutical industry experience and 3 years of post-doctoral research experience. He has published more than 40 peer-reviewed research articles, 60 abstracts and posters, 1 book chapter, 3 excipient monographs, 2 patents, and 2 podium presentations at scientific meetings.

Sarah Rieschl is a Research Scientist at CIMA Labs in the Formulation Development group in Brooklyn Park, MN. She has been working in the pharmaceutical industry for more than 15 years and has extensive experience with product development and scale-up activities of oral solid dosage forms. She has published or contributed to 7 abstracts at national meetings and 1 research article. She earned her BS in Chemistry from Concordia College in Moorhead, MN.

BIOANALYTICS TECHNOLOGY

New Bioanalytical Technology Holds Promise for Alzheimer's Research

By: Stephen Turner

INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that is the leading cause of dementia in the elderly (60% of dementia cases), affecting 13% to 20% of people over the age of 65. In the US, 5 million people over age 65 are estimated to have Alzheimer's (65% are women), and 500,000 will die each year, making it the sixth leading cause of death. Estimates show that by 2050, 16 million people over age 65 will develop Alzheimer's unless medical research can develop better tools to diagnose and treat the disease.

In AD, the synaptic connections between neurons degenerate, and when neurons lose their connections, they cannot function properly and eventually die. As neuronal death spreads through the brain, the brain itself starts shrinking in a process called brain atrophy.

Unfortunately, only a few medications have been approved to help control cognitive loss in AD; however, they do not stop or reverse the underlying disease process. In fact, most new AD candidate drugs are failures. Only one agent has been approved since 2004 (memantine), and the failure rate since 2002 (excluding agents currently in Phase III) is 99.6%.[1]

The major challenge is that we do not know the etiology of AD – the molecular cascade of changes that underlie AD development. Recent research suggests that neurons die as a result of toxic metabolites that are unable to be removed properly from the brain through the blood vessels.

THE RISE OF MOLECULAR INFORMATION

New technology is urgently needed to comprehensively and rapidly identify the molecules produced by normal and AD-affected brain cells, which may also be present in related biofluids, such as serum and cerebrospinal fluid (CSF). At Protea, this is called Molecular Information - identifying the proteins, metabolites, and lipids that are produced by all living cells. In this way, researchers can profile the molecular networks and the molecular changes that occur, which can distinguish normal brain cell functions from AD biological processes. This new knowledge at the molecular level could then in turn lead to the development of a new generation of AD therapeutics.

Detection of early stages of AD is difficult, thus there is an urgent need to find new biomarkers to predict, diagnose, and monitor AD. Biomarkers are molecular markers that can be used to assess changes within cells that indicate the onset of disease. While AD biomarker discovery is now a major area of academic research, to date, there are no validated biomarkers for AD.

Alzheimer's disease slowly develops from its preclinical/presymptomatic early phase into a fully expressed clinical syndrome. AD biomarkers are needed that reflect core molecular elements of AD to enable early diagnosis and then monitor disease progression.

Genomic-based clinical medicine has expanded exponentially since the completion of the Human Genome Project, and scientists have identified several genes that can

increase the risk of disease onset. However, the presence of disease-linked genetic abnormalities does not necessarily mean that a person will develop the disease. Investigators worldwide are working to find additional AD-associated genes, and genetic profiling will likely be an important risk assessment tool for future use. For example, many AD drug clinical trials now include genetic testing for APOE4, an AD-associated risk gene.

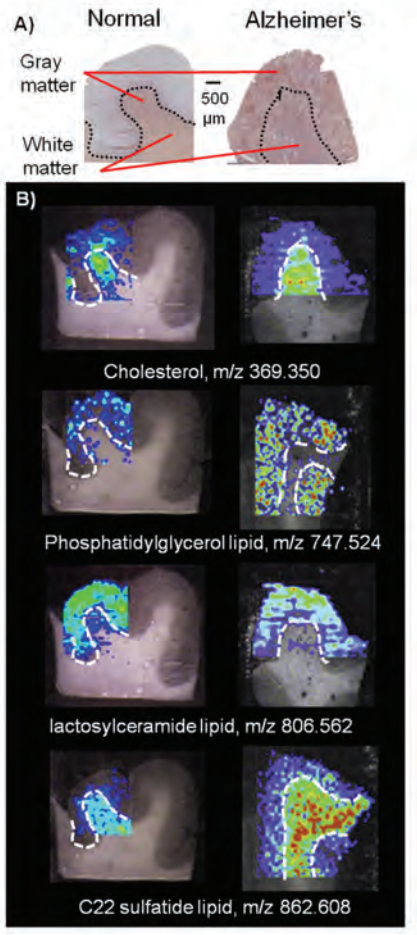
LIMITATION OF MASS SPECTROMETRY

Mass spectrometry, the gold standard for molecular identifications, is now being used to identify candidate AD biomarkers in CSF and blood. Mass spectrometers are advanced, laboratory-based instruments that are used to identify specific molecules present in biological samples. One goal is to identify and quantify proteins specific to different stages of AD. However, Mass spectrometry currently requires extensive sample preparation prior to analysis, including extractions and chromatographic separations that are time-consuming, costly, and require specialized laboratory skills. Thus, Mass spectrometry, while extremely powerful, is today relatively impractical for routine clinical testing and use in point-of-care environments, such as the OR and physicians' offices.

Protea has addressed this limitation of Mass Spectrometry by developing a new bioanalytics technology, known as LAESI (Laser Ablation Electrospray Ionization) that enables the rapid and direct analysis and visual depiction of molecules in tissue without the need for sample preparation. The technology works with mass spectrometers to enable large molecular datasets to be generated on biological samples, with results available in minutes. Fully automated, LAESI® has 2D and 3D molecular visualization and bioinformatics capabilities to display large datasets. It is not unusual to identify over 500 molecules in a single LAESI analysis. The molecular databases produced by LAESI aid the "molecular eyesight" of researchers, improving their prospects to find new biomarkers or molecular data that will provide new insight into AD's onset and progression.

At the June 2014 June meeting of the American Society of Mass Spectrometry (ASMS), a team of scientists from Protea and Waters Corp. (NYSE:WAT) presented the first application of LAESI technology to the molecular analysis of Alzheimer's brain cells. LAESI was coupled to a mass spec platform known as TWIMS (Traveling Wave Ion Mobility Spectrometry), which allowed additional molecular information to be collected to help identify molecules present in AD-affected brain tissue. Imaging human brain tissue sections by LAESI-TWIMS identified 165 lipids and metabolites mapping to normal or Alzheimer's brain tissue. Data analytics revealed that the molecules mapped in Alzheimer's brain samples pointed to a significant inflammatory response with lipid modifications compromising the brain tissue, corresponding to some of the latest publications on AD. This data illustrates the capabilities of applying LAESI technology to gain a deeper understanding of significant clinical conditions, particularly in areas where little progress has been made.[2]

FIGURE 1



LAESI technology maps unique lipid patterns in Alzheimer's brain tissue. A) Gross patterns of degeneration in normal brain tissue versus Alzheimer's brain tissue using Congo Red staining. Dark red patches are plaque development. B) Examples of lipid pattern alterations in AD found by LAESI-TWIMS. Patterns are shown as heat maps with red being the most intense expression and blue being least intense expression. Spatial metabolomics of Alzheimer's-diseased brains using laser electrospray ionization mass spectrometry (LAESI-MS). ASMS June 2014.

"New technology is urgently needed to comprehensively and rapidly identify the molecules produced by normal and AD-affected brain cells, which may also be present in related biofluids, such as serum and CSF. At Protea, this is called Molecular Information - identifying the proteins, metabolites, and lipids that are produced by all living cells. In this way, researchers can profile the molecular networks and the molecular changes that occur, which can distinguish normal brain cell functions from AD biological processes."

FORMING THE FOUNDATION FOR THE FUTURE OF AD RESEARCH

Protea is also collaborating with Roxana Carare, MD, PhD, at the University of Southampton, UK, a leading AD research laboratory. Dr. Carare is studying the accumulation of amyloid-β (Aβ) and toxic metabolites in the walls of the blood vessels of the brain that are contributing to dementia. It is increasingly recognized that the failure of elimination of amyloid-β (Aβ) with increasing age is a major factor driving this pathway, exacerbated in individuals with the recognized risk factor for dementia, the Apolipoprotein E4 genotype (APOE4). The dramatic failure of the many clinical trials in AD since 2000 has been attributed to complications related to the accumulation of waste products in the walls of blood vessels.

Our collaboration with the University of Southampton will apply LAESI molecular imaging technology to attempt to elucidate the aforementioned mechanisms and pathways, along with the combined effects of age, maternal and individual diet, and blood pressure on disease progression, forming a foundation upon which future AD research can be based. Together with the opportunities to monitor progressive changes in vascular function, this new molecular knowledge is expected to enable enhanced risk assessment and diagnosis, evaluation of therapeutic and lifestyle intervention efficacy, and identification of new therapeutic targets.

LAESI technology will be applied to mouse and human brain tissues in order to clarify the molecular changes that occur in the brain parenchyma and in the perivascular clearance pathways to identify new therapeutic targets for the treatment of dementias.

FIGURE 2

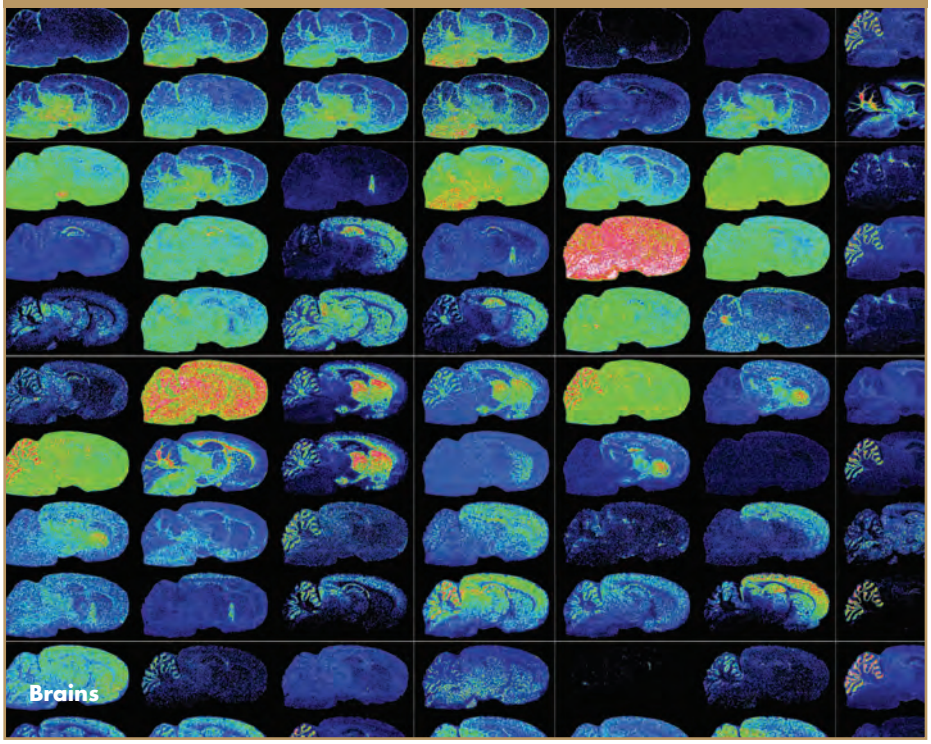


FIGURE 3

Developed by Protea Biosciences, the LAESI DP-1000 instrument provides rapid, comprehensive molecular analysis of cells and other biological samples without the need for sample preparation.

SUMMARY

The maintenance of cognitive health has a huge impact on the overall health and activity of humans as we age, with substantial social and economic impacts far beyond the individual. With the advent of LAESI technology, a next-generation capability is now available to rapidly and comprehensively provide molecular profiles of normal and AD-affected brain cells and tissues, to elucidate the molecular changes that comprise affected neurons in AD and other forms of dementia, offering the possibility of new, AD stage-specific biomarkers and points of therapeutic intervention for developing new treatments for Alzheimer's disease. ◆

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Contributors to the Article: Roxana Carare, MD, PhD, Faculty of Medicine, University of Southampton, UK; Peggi M. Angel, PhD, Senior Scientist, LAESI Mass Spectrometry Imaging, Protea Biosciences Group, Inc., Morgantown, WV.

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BIOGRAPHY

Stephen Turner is Chief Executive Officer and Chairman of the Board at Protea Biosciences Group, Inc., positions he has held since founding the company in July 2001. From 1999 to 2001, he served as President and CEO of Quorum Sciences, Inc. From 1984 to 1997, he was President and CEO of Oncor, Inc. He founded Bethesda Research Laboratories, Inc. in 1975 and served as its Chairman and CEO from 1975 to 1983, at which time, BRL became the molecular biology division of Life Technologies, Inc. Prior to commencing his career in biotechnology, Mr. Turner held the position of Director of Marketing for the Clinical Microbiology Division of Becton, Dickinson & Co. He earned his BA from Stanford University in 1967. In 1994, he was awarded the Ernst & Young Entrepreneur of the Year Award in Life Sciences for the Washington, DC, Region.

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External Delivery

Successful Business Failures

By: John A. Bermingham

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

Taking responsible risks and making mistakes that lead to failure is a part of business life. Almost everyone experiences failure in business at some point, but not everyone reacts the same way. Most people react to a business failure as though it is the end of the world. Those responsible for taking the risk that resulted in the failure are often chastised by management, may lose responsibility, and might even lose their job.

Today, however, management may look at risk-taking that results in a business failure as an event that may eventually lead the company to success. By risk, I am talking about responsible risk. This is risk where you have an idea, developed a detailed business case, consulted with others who are experts in the area, met with management to secure their buy-in, and if necessary, ensured the infrastructure can quickly be in place to support the idea should it be successful. Responsible risk is not taking a flyer on an idea and hoping for the best.

The obvious potential outcome from a business failure are job losses; brand damage; customer and vendor losses; a Chapter 7, Chapter 13, or a Chapter 11 bankruptcy; an auction, a liquidation, or a 363 pre-pack sale. What's not so obvious are the benefits that can be derived from a business failure.

One of things I learned early on at Sony was that taking responsible risk and then experiencing a failure was not going to cost you your job or career. Akio Morita, the Co-founder of Sony Corporation, always taught us that one of the paths to success was to take responsible risk. If that risk ended up as a failure, then our obligation was to determine why there was a failure and to learn from it.

Another positive outcome that can happen from a business failure is the recognition of, as the saying goes, a new door always opens when one has closed. That new door is a unique opportunity for success, so rather than focusing on a failure, why not focus on the potential for success? I once read that success does not breed success. It breeds failure. It is failure that breeds success.

Charles Dyson, the inventor of the Dyson vacuum had 1,526 prototype failures after building 1,527 prototypes. His failures drove him on to eventual success when he built the 1,527th prototype.

Another major positive benefit that can be gained from a business failure is strength and courage. It takes strength and courage to experience failure after failure and to continue on learning from your mistakes and not giving up. So I believe a business failure should not automatically be considered by management as a negative situation, especially when there is reasonable belief that these failures may be stepping stones on the pathway to success.

I believe Jim Belosic, the CEO of ShortStack, sums it all up for many of today's leaders in his statement that, "Most people see the word failure and think unrecoverable. Instead, I see failures as mini test results. I tried something, it didn't work, so let's gather up what we learned and try again." ◆

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