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Drug Development & Delivery

July/August 2016 Vol 16 No 6 www.drug-dev.com

GLOBAL FORMULATION REPORT

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

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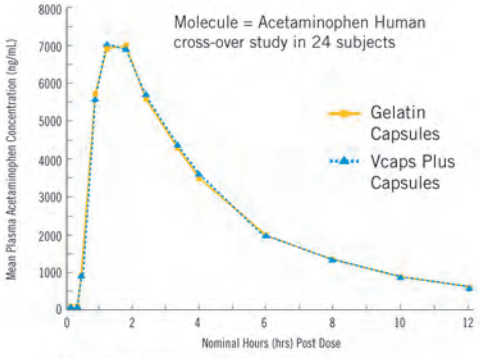

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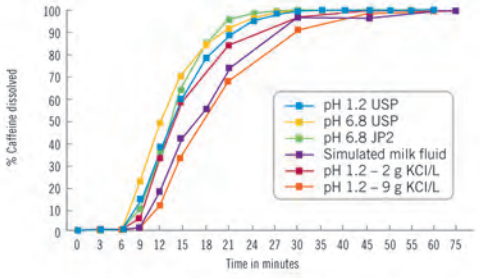

In-vitro dissolution of caffeine in Vcaps Plus capsules

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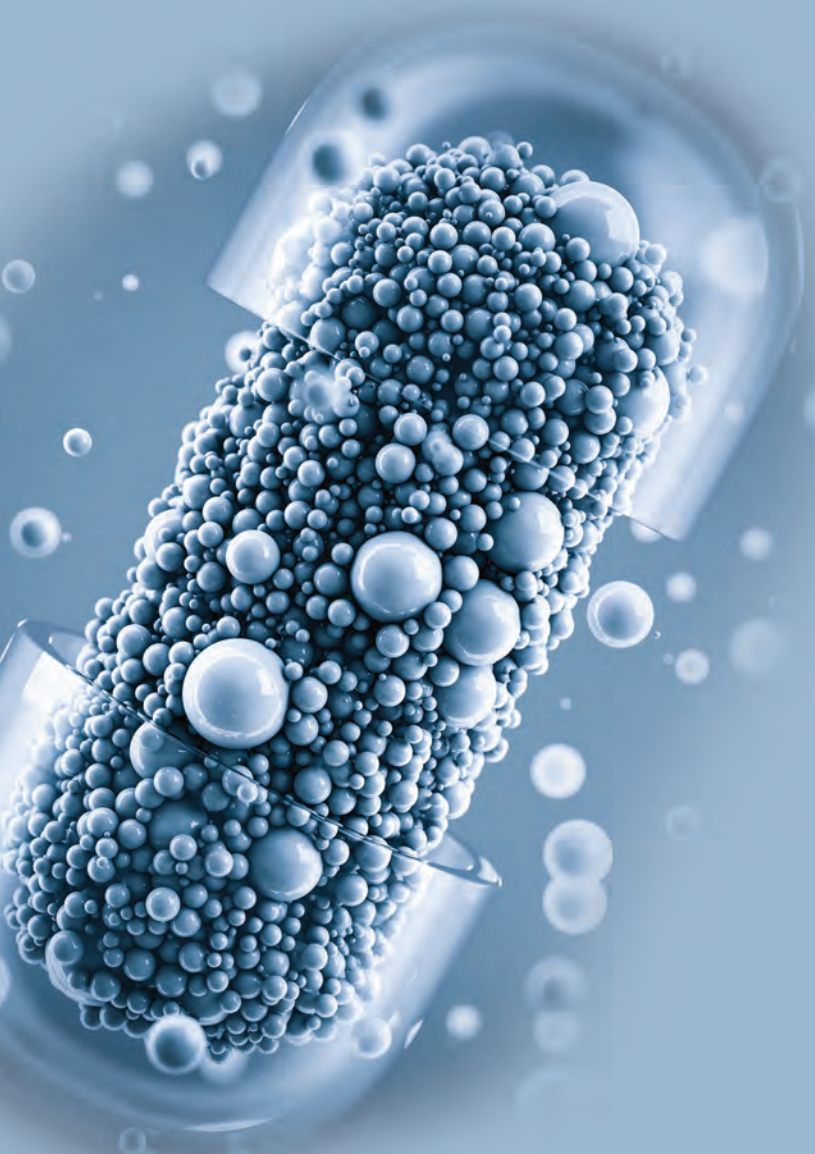

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It's one thing to know what products are on the market and in development. It's another to have detailed information about their form, formulation and use.

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Navigating PharmaCircle is as simple as using the single field Global Search interface or as detailed as a multi-parameter search using the Flexible Search interface with nested Boolean operators. The Panoramic Search engine permits multiparameter searches with a graphical output that can be easily distilled to provide the results you are looking for. The Detailed Search provides similarly detailed searches with tabular output. Drug label comparison tools and full-text document search capabilities help to further streamline research.

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Thermo Fisher Scientific & NIBRT Announce Scientific Collaboration

Thermo Fisher Scientific and the National Institute for Bioprocessing Research and Training (NIBRT) recently announced a scientific collaboration focused on the development of analytical solutions for the characterization of complex biopharmaceuticals.

Biopharmaceuticals represent protein molecules produced by genetically engineered living cells using large-scale industrial bioprocessing. The complexity of these molecules requires advanced analytical characterization strategies to ensure that biopharmaceuticals are produced to the highest possible quality level.

This collaboration will see NIBRT develop workflows on the Thermo Scientific biomolecule column range with its associated consumable portfolio in conjunction with sophisticated Thermo Scientific liquid chromatography systems and advanced Thermo Scientific Orbitrap high resolution mass spectrometers.

"This collaboration is important because it enables our team to access Thermo Fisher's world-leading columns and analytical instrumentation to develop total analytical solutions and streamline the characterization of complex biopharmaceuticals," said Dr. Jonathan Bones, principal investigator, NIBRT's Characterization and Compatibility Laboratory. "The availability of total analytical solutions to scientists across the world is empowering and motivates us at NIBRT to continually perform excellent impactful research."

"Analytical characterization of biopharmaceuticals remains a challenge for scientists and requires cutting-edge chromatography solutions and mass spectrometry detection," added Jakob Gudbrand, President of Chromatography and Analytical Technologies at Thermo Fisher. "NIBRT is an independent centre of excellence with collaborations across the major biopharmaceutical companies in the industry. This allows them to provide valuable insights to improve the technology, simplify analysis, generate informative characterization data, and understand these complex molecules - ultimately enabling scientists to move from sample to knowledge quickly and efficiently."

NIBRT's workflows and methods will be uploaded to the Thermo Scientific AppsLab library, a unique cloud-based applications compendium that enables scientists across the globe to access and download these total analytical solutions directly to their instruments enabling them to simplify their analysis, generate highly informative characterization data faster and understand their complex molecules better.

"We are delighted to be working with Thermo Fisher," said Dominic Carolan, CEO, NIBRT. "World class collaborations such as this are testament to Ireland's emergence as a global centre of excellence in all aspects of biopharmaceutical manufacturing."

The National Institute for Bioprocessing Research and Training (NIBRT) is a global centre of excellence for training and research in biopharmaceutical manufacturing. NIBRT is located in a world class facility in Dublin, Ireland. This facility is purpose built to closely replicate a modern bioprocessing plant with state-of the art equipment and enables NIBRT to offer the highest quality training and research solutions.

Thermo Fisher Scientific Inc. is the world leader in serving science, with revenues of $17 billion and more than 50,000 employees in 50 countries. Its mission is to enable its customers to make the world healthier, cleaner, and safer.

Adaptimmune Announces Commercial Development & Supply Agreement

Adaptimmune Therapeutics plc recently announced it has entered into a commercial development and supply agreement with Thermo Fisher Scientific. The new 10-year agreement augments Adaptimmune's exclusive license and supply relationship with Thermo Fisher for the Dynabeads CD3/CD28 Cell Therapy System (CTS) for use in the manufacture of Adaptimmune's SPEAR T-cell therapies.

Dynabeads CD3/CD28 CTS is designed to isolate, activate, and expand human T-cells. This technology provides coordinated and simultaneous activation and co-stimulation signals to T-cells, a process that is reported to produce T-cells with enhanced proliferation and with characteristics that enable prolonged persistence in vivo. Adaptimmune has an exclusive license for the IP associated with the use of Dynabeads CD3/CD28 to expand and activate all TCR-transduced T-cells in cancer, infectious, and autoimmune diseases.

"We are delighted to expand our collaboration with Thermo Fisher and secure continuity of supply of Dynabeads through commercialization," said Gwen Binder-Scholl, Adaptimmune's Chief Technology Officer. "Dynabeads CD3/CD28 have unique properties we believe optimize the manufacture of our SPEAR T-cell therapies, including the generation of younger and healthier T-cells leading to prolonged persistence of therapeutic cells in the blood. We look forward to continuing to work closely with Thermo Fisher as we progress toward the commercialization of our T-cell therapeutics."

"Thermo Fisher's market-leading cell therapy workflow solutions are enabling its customers to address the unique commercialization challenges of this market. We are pleased to expand our partnership with Adaptimmune, a leader in the T-cell immunotherapy space," added Oystein Aamellem, Director of Cellular Medicine for Thermo Fisher. "This agreement demonstrates our sustained commitment to advancing the development of our Dynabead CD3/CD28 technology to support the treatment of solid tumors, as well as other conditions that threaten human health."

Adaptimmune's SPEAR T-cell therapies are novel cancer immunotherapies that have been engineered through their T cell receptors (TCRs) to target and destroy cancer cells by strengthening a patient's natural T-cell response. T-cells are a type of white blood cell that play a central role in a person's immune response. Adaptimmune's goal is to harness the power of the T-cell and, through its multiple therapeutic candidates, significantly impact cancer treatment and clinical outcomes of patients with solid and hematologic cancers.

The manufacturing process consists of isolating T-cells from the blood of cancer patients; transferring affinity enhanced TCRs, which have been modified to recognize cancer cells, into the cells; activating and expanding the T-cells using Dynabeads CD3/CD28; and, introducing the affinity enhanced cells back into the patient to enable the patient's immune system to respond and attack cancer.

Caladrius Subsidiary, PCT, to Manufacture Phase III Cell Therapy Product for Kiadis Pharma

Caladrius Biosciences, Inc. recently announced that PCT has expanded its relationship with Kiadis Pharma by entering into an agreement for the manufacturing of cell therapy product for US and Canada clinical trial sites for a Phase III trial of Kiadis' lead product, ATIR101, for the treatment of blood cancers.

To date, PCT has provided engineering and process development services for Kiadis, which included optimizing its manufacturing process to incorporate functionally closed processing. Work is currently underway at PCT's Allendale, NJ, facility to expand its clean room capacity by 60% and to develop and implement cell therapy specific pharmaceutical grade quality systems.

"We are pleased to select PCT as our contract manufacturing organization in the US," said Manfred Rüdiger, PhD, Chief Executive Officer of Kiadis. "The manufacture and supply of study medication for our Phase III clinical trial with ATIR101 in the US and Canada is a critical component to the successful and smooth running of our clinical study and having a partner who is well established and highly experienced, like PCT, is very important. PCT has been an excellent advisor and provider of process development to Kiadis in the past, and we look forward to leveraging those efforts as we begin to broaden the activities of Kiadis in the US."

"We are pleased to expand our relationship with Kiadis to help bring new cell therapies to patients in need. Our Kiadis partnership is an excellent example of PCT's growth strategy in motion – initiation of process and manufacturing development partnerships that subsequently expand to clinical manufacturing projects. Our strategy is for our partnerships to culminate, upon regulatory approval of client products, with commercial-scale manufacturing and advancement toward the cell therapy factory of the future," said Robert A. Preti, PhD, President of PCT, and Senior Vice President, Manufacturing and Technical Operations and Chief Technology Officer of Caladrius Biosciences. "A growing number of cell therapy developers are partnering with PCT to take advantage of our quality, scalable, innovative, reliable, and cost-efficient manufacturing platforms and services to advance commercialization of cellular therapies."

In April 2016, the company reported positive Phase II results with its lead product ATIR101 in patients with blood cancer. The data showed that ATIR101 significantly reduced Transplant Related Mortality and significantly improved Overall Survival. In addition, ATIR101 did not elicit grade III-IV GVHD in any patient. ATIR101 has been granted Orphan Drug Designations both in the US and Europe. The company's second product candidate, ATIR201, addresses inherited blood disorders with an initial focus on thalassemia, a disease which results in destruction of red blood cells in patients. ATIR201 is expected to enter Phase I/II clinical development in the second half of 2016.

ERT Develops Industry's First Integration of Continuous Glucose Monitoring Data & eCOA

ERT, a leading provider of high-quality patient data collection solutions for use in clinical drug development, recently announced a data license agreement with Dexcom to integrate glucose information captured via continuous glucose monitoring (CGM) and traditional self-monitoring of blood glucose (SMBG) with symptomatic/quality of life data collected via its electronic Clinical Outcome Assessment (eCOA) system.

The wireless, integrated solution is actively used to collect endpoint data in worldwide clinical trials, generating larger data sets to analyze glycemic control with new therapies.

ERT designed and built a novel solution that integrates continuous glucose data to meet the increasing needs of clinical researchers. By integrating data collected on ERT's eCOA system with CGM data collected on Dexcom G4 CGM devices, clinical researchers gain expansive data sets to quantify what patients are experiencing as they manage their diabetes and diabetes-related symptoms. And, by leveraging ERT's trial oversight solution, Insights Cloud, clinical researchers gain access to holistic views and proactive monitoring of data quality and compliance, resulting in greater visibility into trial progress.

Glucometers have been integrated with ERT's eCOA system for several years, but now researchers can integrate retrospective CGM data with eCOA to collect even more endpoint data in their diabetes trials. The use of CGM as an adjunctive approach to traditional SMBG is poised for dramatic expansion within clinical research.

"Using CGM in clinical trials offers numerous advantages to clinical trial sponsors who truly seek to understand the full impact of diabetes on patients' quality of life," said Ron Sullivan, Executive Vice President, eCOA at ERT. "We are pleased to deliver the industry's first integrated eCOA/CGM solution and look forward to continuing our relationship with Dexcom as we explore other opportunities to enhance treatment satisfaction for the millions of patients worldwide who are living with and managing diabetes."

ERT is a leading provider of high-quality patient data collection solutions for use in clinical drug development. ERT delivers a combination of technology, services, and clinical consulting that increase the accuracy and reliability of patient data and improve the efficiency of the clinical development process. ERT delivers widely deployed solutions in centralized Cardiac Safety, Respiratory, and electronic Clinical Outcome Assessments (eCOA) – which includes patient-, clinician-, observer- and performance-reported outcomes – and cloud-based analytics and performance metrics. By efficiently integrating these solutions through a system built upon a scientific and regulatory foundation, ERT collects, analyzes and delivers safety and efficacy data critical to the approval, labeling and reimbursement of pharmaceutical products. For more information, visit www.ert.com.

Pluristem Reports Data Showing PLX-PAD Cells Effective in Treating Duchenne Muscular Dystrophy

Pluristem Therapeutics Inc. recently reported positive data from preclinical studies of its PLX-PAD cells in the treatment of Duchenne muscular dystrophy. The studies were conducted in conjunction with ADI, the Association Duchenne Israel, whose members are parents of children with Duchenne. They are committed to helping to find a cure for Duchenne muscular dystrophy through research, clinical trials, and advocacy.

Duchenne muscular dystrophy is the most common neuromuscular disorder and affects roughly one in 3,500 boys. The disease causes progressive muscle weakness, and leads to severe disability and death. There is currently no cure.

Following Pluristem's announcement of positive results from a Phase II clinical trial of PLX-PAD as a treatment for muscle injury, the Association Duchenne Israel approached Pluristem with a request to study PLX-PAD cells in Duchenne muscular dystrophy. Pluristem donated PLX-PAD cells for the preclinical studies, and the association supported the research in cooperation with Science in Action Ltd.

The studies demonstrated that, in a mouse model of muscular dystrophy, PLX-PAD cells reduced creatine phosphokinase (CPK), a marker of muscle degeneration or injury, by approximately 50% as compared to placebo. CPK levels were measured via a blood sample taken 5 days after each intramuscular PLX-PAD injection made at day 15 and day 29 of the study. Histological analyses of quadriceps and diaphragm muscles show PLX-PAD reduced levels of inflammation and necrosis, a type of cell death, and induced regeneration of muscle tissue.

"These preclinical data suggest that PLX-PAD cells could possibly be a breakthrough therapy to help treat symptoms of Duchenne muscular dystrophy. We are thankful for Pluristem's donation of PLX-PAD and are eager to continue studying the cells since new therapeutic approaches are needed to manage this disease, save children's lives, and give them hope and a chance for the future," said Hila Krupsky, CEO of ADI, the Association Duchenne Israel.

"Because PLX-PAD cells have already displayed efficacy in muscle regeneration in a Phase II muscle injury study, we believe our cell therapy may potentially be beneficial in Duchenne muscular dystrophy in human clinical trials," added Pluristem Chairman and CEO Zami Aberman. "We admire the commitment of the Association Duchenne Israel to find a cure for Duchenne muscular dystrophy, and we will work closely with them in an effort to develop a treatment for the children around the world who suffer from this disease."

Pluristem Therapeutics Inc. is a leading developer of placenta-based cell therapy products. The Company has reported robust clinical trial data in multiple indications for its patented PLX (PLacental eXpanded) cells. The cells release a cocktail of therapeutic proteins in response to inflammation, ischemia, hematological disorders, and radiation damage. PLX cell products are grown using the Company's proprietary three-dimensional expansion technology.

Allegro Ophthalmics Announces Positive Topline Results From Phase II Trial

Allegro Ophthalmics, LLC, recently announced that the Phase II clinical trial of Luminate (ALG-1001) in patients with vitreomacular traction (VMT) or vitreomacular adhesion (VMA) met its primary endpoint. In the Phase II, prospective, randomized, double-masked, placebo-controlled trial evaluating the safety and efficacy of intravitreal injections of Luminate in 106 study subjects, 65 percent of eyes treated with the 3.2 mg dose of Luminate achieved release of VMT or VMA by Day 90 (end of study), compared to 9.7 percent of those in the placebo control group (p=0.0129).

The study, which included three Luminate groups (2.0 mg, 2.5 mg, or 3.2 mg) and a balanced salt solution (BSS) placebo group, also found that Luminate was well-tolerated with no drug toxicity or intraocular inflammation noted with repeated intravitreal injections. These safety results are consistent with previously conducted Luminate studies on human subjects where there were no rod or cone photoreceptor dysfunction on full-field electroretinogram testing, no afferent pupillary defects, and no evidence of retinal tears or detachments.

"These findings appear to be very promising," says Michael Tolentino, M.D., Associate Professor Ophthalmology at the University of Central Florida, Director of Research for the Center for Retina and Macular Disease, and Clinical Investigator of this Phase 2 VMT study. "It is a very positive outcome to have 65 percent of eyes treated with the 3.2 mg dose of Luminate achieve VMT/VMA release by Day 90. These statistically significant findings, as assessed by the Duke Reading Center, coupled with the fact that Luminate has been shown to be well-tolerated, makes me optimistic that Luminate will provide meaningful clinical benefit to patients with VMT or VMA."

"These positive results continue to affirm the safety and efficacy of Luminate," says Vicken Karageozian, M.D., Chief Technical Officer, Allegro Ophthalmics. "The vitreolytic properties confirmed in this study and the anti-angiogenic properties demonstrated in earlier DME and neovascular AMD studies continue to validate our clinical development approach of advancing Luminate across multiple vitreoretinal indications."

Luminate, a first-in-class integrin peptide therapy, treats vitreoretinal diseases by targeting integrin receptors involved in cell signaling and regulation and in the construction of new and aberrant blood vessels. By utilizing two mechanisms of action (vitreolysis and anti-angiogenesis), Luminate has been shown in clinical studies to date to effectively regress and inhibit new blood vessel formation, as well as reduce vascular leakage to maintain and restore vision. Currently in Phase II clinical trials for multiple indications, including diabetic macular edema (DME) and non-proliferative diabetic retinopathy (NPDR), Luminate is an investigational drug not approved by the FDA for commercial sale in the U.S. Allegro maintains commercial rights to Luminate in all territories outside of Japan, Korea and China.

CiMaas & PharmaCell BV Enter Collaborative Agreement

CiMaas BV, a company developing cellular immunotherapy for cancer, and PharmaCell BV, a leading Contract Manufacturing Organization for Cellular Therapies and Regenerative Medicine in Europe, have agreed to collaborate in the clinical development of CiMaas' products. Under the agreement, PharmaCell will provide consulting services on writing GMP-compliant documents for the purpose of translating the CiMaas cell therapy processes into GMP. Options have been taken on a full technology transfer trajectory to be started and executed at a later date. A continuation option on a Phase I and possibly a Phase II clinical trial is also part of the agreement.

Gerard Bos, Chief Executive Officer of CiMaas said: "We are delighted to collaborate with PharmaCell and receive support in building our documents and technology in a fully GMP compliant manner for the development of our ATMPs (Advanced Therapy Medicinal Products)." Wilfred Germeraad, Chief Scientific Officer added: "It is a wonderful opportunity to work together and it will immediately speed-up our work in translating the lab procedures into clinical products ready to be tested in patients with cancer."

Alexander Vos, Chief Executive Officer of PharmaCell BV, said: "The CiMaas team has shown to be successful in bringing their technology to the point of preparing the initiation of clinical studies. We are excited to support them to make their production process GMP-compliant and help clear the path to bring their innovative therapies to benefit patients."

CiMaas BV aims to develop cellular immunotherapy for specific groups of cancer patients. The company will focus on the development of two unique products: a cancer vaccine using the patient's own immune (dendritic) cells and the production of donor natural killer cells. These methods can help to treat many oncological diseases. CiMaas will initially focus on lung cancer and multiple myeloma (MM, a type of bone marrow cancer also known as Kahler's disease). Both will be clinically tested in patients from January 2017. CiMaas (Cellular Immunotherapy Maastricht) is a spin-off of Maastricht University/Maastricht University Medical Centre+ (UM/Maastricht UMC+).

PharmaCell is a leading European-based CMO exclusively focused in the area of cell therapy and regenerative medicine. PharmaCell has experience in supporting Phase I through Phase III clinical trials and early commercial manufacturing in cell therapy in terms of manufacturing, Quality Control, storage, in-outgoing logistics and product release through its in-house QPs. Its services also include process and assay-development to ensure GMP compliance, robustness and scalability of cell therapy manufacturing processes. PharmaCell offers a unique manufacturing platform in Europe to support the growth of the cell therapy and regenerative medicine industry by means of its facility in Maastricht for early stage clinical trials and its Geleen facility fully equipped for late clinical stage and commercial scale manufacturing. Both manufacturing sites are GMP-licensed and inspected by EMA for commercial production of ATMPs.

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Global Formulation Report

The Pharmaceutical Industry constantly moves forward, at times, one step, at others, it's two steps, and on occasion, it's three or more. But like walking up a down escalator, it seems there is little progress as rising expectations make it appear the Industry is standing still. That perhaps best describes 2015 from the perspective of Drug Delivery and Formulation.

Past years of technology development resulted in the approval of a variety of Drug Delivery Enabled/ Enhanced Products using well-validated oral, injectable, and inhalation technologies, but there was no true breakthrough. And then there was the disappointment of Afrezza and the promise of a practical non-injection delivery route for the systemic delivery of macromolecules. In retrospect, it seems that Exubera's failure almost a decade ago was not a simple issue of an unwieldy device, or poor execution. Afrezza's challenges confirmed there are still many challenges ahead for Drug Delivery & Formulation Professionals if they are to effectively deliver the next generation of molecules. There remains much opportunity for novel technologies to deliver macromolecules and poorly absorbed molecules orally. There is also the challenge of site-specific delivery to improve the tolerability of effective but toxic drugs. The rewards will be there for those that succeed in developing better products as evidenced by the spectacular financial success of Gilead's Harvoni. At the same time, 2015 made the point that me-too products, even those using unique technology platforms, but delivering unimpressive patient benefits, would fail to get physician, payer, and patient support.

Gene therapy showed itself to be an area of opportunity in 2015. Gene therapy is now at a similar stage as antibody therapies were three decades ago, promising but with significant technical challenges. Much needs to be done to make gene therapy a therapeutic reality, as there was for antibody therapy. The difference perhaps is that gene therapy will be even more dependent on delivery technologies to ensure the payload, a viral- or non-viral-based collection of DNA, is delivered in a manner so as to optimize efficacy and safety. With time, the demands of treatment will turn to convenience. The tools required to achieve optimal delivery of gene therapeutics will depend on both traditional drug delivery and formulation technologies as well as a full toolbox of genetic engineering capabilities. Future Drug Delivery & Formulation Professionals will need to have complete command of both classical and genetic-based delivery technologies to be successful.

This year's Global Formulation Report reviews the more interesting and formative events of 2015 related to drug delivery and formulation with the hope that it may stimulate a closer look at how these events might shape the future. It has been said that those who fail to learn from history are doomed to repeat it. The approach this year once again is to identify notable drug delivery and formulation events of 2015 with a series of articles that range from new product formulations to devices to combinations to transactions. Two new features this year include an update on the notable events of 2014 and Inflection Points 2015, where we identify five trends in the Pharma industry that have reached apparent tipping points.

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 2015 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.

For reference to last year's Global Formulation Report, please review the July/August 2015 issue at www.drug-dev.com.

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Ten Notable Drug Delivery & Formulation Approvals of 2015

As much as things change, they seem to stay the same, or at least they seem to follow the same well-worn paths and strategies. The difference in 2015 was that there were more approvals of CNS-targeted drug delivery and formulation-enhanced products, ranging from abuse-deterrent opioids, to schizophrenia medications, to a novel oral amphetamine. Fewer drug delivery modified biologics were approved in 2015 relative to the previous year, while three-dimensional printing of dosage forms (3DP) had its first product approval. Nanoparticles and liposomes were paired for the approval of an anticancer agent for a challenging indication, pancreatic cancer. There were also a number of formulation-enhanced drug device approvals in 2015 that are covered in the Ten Notable Drug-Device Approvals section in this report.

Interestingly enough, 2015 experienced the same number of first approvals for drug delivery and formulation-enhanced products, a total of 77, as were approved in 2014. The difference is that there weren't any approvals in 2015 that have the blockbuster potential of the 2014 approvals, for example Afrezza, Plegridy, and Movantik. The 2015 approvals for the most part were obvious formulation improvements using well-known technologies applied to previously approved actives. It's not clear if the 2015 approvals represent a slowdown in drug delivery and formulation product inventiveness, or simply an off year.

The question needs to be asked whether the opioid abuse-deterrent opportunity has basically collapsed in on itself. Each year sees new abuse- deterrent opioids entering the clinic, and 2015 was no exception. At the same time, abuse-deterrent opioids are advancing in the clinic, with some of them being approved, with or without explicit abuse-deterrent labeling. Unfortunately, few of these new abuse-deterrent products are capturing the sales necessary to provide a return on investment, and warrant additional investment in terms of technology and product development. The abuse-deterrent market seems to offer a classic example of a market in which low barriers to entry, and no new molecular entities, attracts multiple players with products that provide little differentiation beyond pricing. It will be interesting to see how this whole sector develops, but it is hard to be optimistic in the absence of a clear and definite patient benefit.

PEGylation and protein fusion programs continue to advance in the clinic, although it may be that 2014 turns out to be the high water mark for modified biologics approvals.

A number of products approved in 2015 are unlikely to approach anything close to blockbuster status but represent trends worth watching. Spritam, a 3DP orodispersible for the treatment of seizures, targets a relatively small market but may be useful for larger patient opportunities, although applications are not obvious. The technology's current unique selling proposition is the ability to prepare larger, on the order of a gram, doses of orodispersible products. It remains to be seen how many product opportunities this may mean, and whether 3DP is a more desirable dosing option than taking two lower dosage units using a more traditional technology approach. Cost in the end may determine the success of the 3DP technology unless additional high-value opportunities with significant clinical benefits can be identified.

Otiprio, an intraoperatively administered otic gel containing ciprofloxacin during tympanostomy, is the type of formulation-enhanced product opportunity that appears obvious once it has been revealed. Understanding the needs of patients and healthcare professionals can provide for a limitless number of product opportunities using drug delivery and formulation technologies. Typically used with pediatric patients, the gel formulation of Otiprio provides a slow release of ciprofloxacin after surgery, eliminating the need for follow-up treatment using drops. These small improvements to improve compliance, in this case, eliminating the needs to place ear drops in children, can make a big difference on clinical outcomes and preventing costly infections.

In the same sense of ensuring compliance, Tris' Dynavel XR, a sustained- release oral liquid formulation of amphetamine for the management of attention deficit disorder, not only provides an alternate presentation format, but can help ensure compliance with pediatric patients. It may also provide some abuse deterrence as it is harder to package and sell single-dose units of a liquid.

BioDelivery Sciences International (BDSI) received approval for another of its buccal delivery products, in this case Belbuca, for the treatment of chronic pain using buprenorphine, a partial agonist opioid. BDSI's Bunavail, using the same buccal technology, for the treatment of opioid addiction has fared poorly in the marketplace. It does raise the question as to whether buccal delivery, where the dosage form attaches itself to the inside of the cheek or the gum, really has any attractiveness from a patient perspective. None of the dozen or so buccal formulations approved to date have achieved significant market acceptance. The only buccal product that achieved significant commercial success was Actiq, a lozenge formulation of fentanyl, a premium priced product intended to be rubbed on the buccal mucosa, more a novelty lollipop than a true buccal delivery formulation.

The best way to understand 2015 from the perspective of drug delivery and formulation approvals is to look at individual approvals. We've selected 10 product approvals that are representative of the industry's output and direction and provided a little bit of relevant information and commentary. Not included are the drug-device approvals that include a drug delivery or formulation enhancement. These can be found separately in the Ten Notable Drug-Device Approvals of 2015 section of this report. A short section follows that provides an update on 2014's Notable Drug Delivery & Formulation Approvals. It's only one year, but in many cases, the eventual outcomes are already obvious for these products. ■

Adynovate

Active: rurioctocog alfa pegol
Molecular Weight[1]: ~300,000 Da
Indication: Hemophilia A
Delivery Route: Injection - Intravenous
Dosing Interval: Twice Weekly (prophylaxis)
Company: Baxalta

First Approval: 2015-11-13 (US)
Formulation Type: Injectable, PEG (20 kDa)
Technology Provider: Nektar
Presentation: Vial (Baxject II)
Review Status: Unknown
Development/Approval Time[2]: ~4.5 Years (US)

Claim to Fame: Patient friendly PEG-Protein products continue to roll out of company pipelines into clinical practice. In this case Adynovate provides patients with a twice weekly dosing option versus three to four times weekly for the unPEGylated protein. Adynovate uses a single 20 kDa branched PEG.

Belbuca

Active: buprenorphine HCl
Molecular Weight[1]: 504 Da
Indication: Chronic Pain
Delivery Route: Oral - Buccal
Dosing Interval: 12 to 24 Hours
Company/Partner: BioDelivery Sciences Intl./Endo

First Approval: 2015-10-23 (US)
Formulation Type: Transmucosal (BEMA)
Technology Provider: BioDelivery Sciences Intl.
Presentation: Film in Foil Sealed Pouch
Review Status: Standard (FDA)
Development/Approval Time[2]: 9.8 Years (US)

Claim to Fame: BDSI continues to gain approval for their buccal delivery products. Last year's buccal product approval, Bunavail, a buprenorphine/naloxone combination received limited acceptance. Hopes are high for Belbuca, but things might be foiled by business challenges facing Endo, BDSI's marketing partner, rather than any product or formulation related issue.

Dyanavel XR

Active: amphetamine
Molecular Weight[1]: 135 Da
Indication: ADHD
Delivery Route: Oral
Dosing Interval: 24 Hours
Company: Tris Pharma

First Approval: 2015-10-19 (US)
Formulation Type: Liquid Sustained Release (LiquiXR)
Technology Provider: Tris Pharma
Presentation: Liquid in Bottles
Review Status: Standard (FDA)
Development/Approval Time[2]: Unknown

Claim to Fame: Tris Pharma continues to expand their line of extended release liquid formulations of previously approved actives. These new formulations offer patients, especially children, alternatives to solid oral dosage forms. These liquid presentations may also provide some degree of compliance assurance and limit diversion.

Spritam

Active: levetiracetam
Molecular Weight[1]: 170 Da
Indication: Seizures
Delivery Route: Oral - Orodispersible
Dosing Interval: 12 Hours
Company: Aprecia Pharmaceuticals

First Approval: 2015-07-31 (US)
Formulation Type: Orodispersible (ZipDose)
Technology Provider: Aprecia Pharmaceuticals
Presentation: Oral Tablet
Review Status: Priority (FDA)
Development/Approval Time[2]: Unknown

Claim to Fame: Spritam represents the first 3DP (three-dimensional printing) dosage form approved by the US FDA. At this point the technology is being touted as being able to produce high dose (>1,000 mg) orodispersible presentations.

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

QUINSAIR

Active: levofloxacin hydrate
Molecular Weight[1]: 361 Da (monomer)
Indication: Pseudomonas Infections in Cystic Fibrosis Patients
Delivery Route: Inhalation - Nebulization
Dosing Interval: 12 Hours for 28 Days
Company: Raptor Pharmaceuticals

First Approval: 2015-03-26 (EU)
Formulation Type: Liquid for Nebulization
Technology Provider: Pari Pharma
Presentation: Ampoule, Zirela Nebulizer Handset
Review Status: Not Applicable
Development/Approval Time[2]: >8 Years (EU)

Claim to Fame: Rare diseases continue to be an attractive target for novel formulations that address a complication of the disease. Pari continues to be a first choice provider of high tech proprietary nebulizer technology for delivery actives to the lung. Their partnership with Raptor (who acquired Quinsair from Aptalis/Mpex) is complementary to their earlier partnership with PulmoFlow for Kitabis Pak, a tobramycin treatment for cystic fibrosis patients.

ONIVYDE

Active: irinotecan HCl
Molecular Weight[1]: 677 Da
Indication: Pancreatic Cancer
Delivery Route: Infusion
Dosing Interval: 2 Weeks
Company/Partner: Merrimack Pharmaceuticals/Baxalta

First Approval: 2015-10-22 (US)
Formulation Type: Nanoliposomal
Technology Provider: Merrimack (Hermes Biosciences)
Presentation: Injectable, Suspension
Review Status: Priority (FDA)
Development/Approval Time[2]: 8.8 Years (US)

Claim to Fame: This new formulation may realize the promise of both irinotecan and liposomes for what is a very challenging indication. Clinical results to date have been very encouraging and support the use of Onivyde as a category 1 second-line therapy for patients with metastatic adenocarcinoma of the pancreas.

INVEGA TRINZA

Active: paliperidone palmitate
Molecular Weight[1]: 665 Da
Indication: Schizophrenia
Delivery Route: Injectable - Intramuscular
Dosing Interval: 3 Months
Company: Janssen Pharmaceuticals

First Approval: 2015-05-18 (US)
Formulation Type: Injectable Depot (NanoCrystal)
Technology Provider: Alkermes
Presentation: Pre-Filled Syringe
Review Status: Priority (FDA)
Development/Approval Time[2]: ~5.5 Years (US)

Claim to Fame: Janssen has seemingly followed a standard playbook for lifecycle management with their medications for the management of schizophrenia. Invega Trinza is the logical follow-on three-month intramuscular formulation to the Invega ER Tablets (2006) and Invega Sustenna (2009) presentations. The NanoCrystal milling technology permits high drug loading.

OTIPRIO

Active: ciprofloxacin
Molecular Weight[1]: 331 Da
Indication: Otitis Media with Tympanostomy
Delivery Route: Otic - Intratympanic
Dosing Interval: One-time, Intraoperative
Company: Otonomy

First Approval: 2015-12-10 (US)
Formulation Type: Otic Gel
Technology Provider: Otonomy
Presentation: Vial, Otic Suspension
Review Status: Standard (FDA)
Development/Approval Time[2]: 5.2 Years (US)

Claim to Fame: An interesting compliance assuring formulation for the management of ear infections in the pediatric population. Using a thermosensitive polymer technology Otiprio is administered at the time of tympanostomy tube placement. A relatively small market, the product is in clinical development for additional otic indications.

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ARISTADA

Active: aripiprazole lauroxil
Molecular Weight[1]: 661 Da
Indication: Schizophrenia
Delivery Route: Injection - Intramuscular
Dosing Interval: 4 to 8 Weeks
Company: Alkermes

First Approval: 2015-10-05 (US)
Formulation Type: Prodrug, Lipid Conjugate
Technology Provider: Alkermes (LinkeRx)
Presentation: Prefilled Syringe
Review Status: Standard (FDA)
Development/Approval Time[2]: 5.2 Years (US)

Claim to Fame: Aristada uses a prodrug approach to providing extended circulating levels of the well-studied antipsychotic aripiprazole. The actual dosing is not particularly sophisticated or patient friendly involving the administration of up to 3.2 ml of a viscous solution through a 21-gauge needle.

ZOHYDRO ER

Active: hydrocodone bitartrate
Molecular Weight[1]: 299 Da
Indication: Chronic Pain
Delivery Route: Oral
Dosing Interval: 12 Hours
Company: Pernix Ireland Pain

First Approval: 2013-10-25 (US)
Formulation Type: Oral Barrier Film, Microparticles
Technology Provider: Alkermes (Elan SODAS)
Presentation: Capsule
Review Status: Standard (FDA)
Development/Approval Time[2]: 13.3 Years (US)

Claim to Fame: Originally approved in 2013, the Zohydro ER label was updated in 2015 to include the addition of inactive polyethylene oxide (PEO) microbeads. The PEO has no net impact on the dissolution rate or the pharmacokinetics, but causes the product to form a gel when contacted with water, making dose manipulation more difficult. Zohydro ER does not yet carry abuse deterrent labeling. (Note: the product IND was first filed by Elan in 2002, and later transferred to Zogenix in 2008. Development time might be considered 7.7 years, rather than 13.3 years from the initial IND.)

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

One Year Later

It has been more than a year since these products were approved and included in the list of 2014 Notable Drug Delivery & Formulation Approvals, and it's worth taking a look to see how they are doing. These short summaries can serve as a refresher and perhaps suggest some lessons.

Product: Movantik (naloxegol oxalate)

Update: Launched in both the US and EU, Movantik product has not been an immediate success, recording sales of $29 million in 2015, although analysts expect peak worldwide sales of $300 million. AstraZeneca has responded by taking on partners in the US and EU to provide more commercial resources.

Product: Bunavail (buprenorphine, naloxone)

Update: Sales have started slowly for Bunavail, with $5 million recorded in 2015, and peak sales estimated as reaching $60 million. The opioid dependence market has attracted multiple formulation-enhanced products and generics that have taken market share and put downward pressure on prices.

Product: Eloctate (efmoroctocog alpha)

Update: This biological for the treatment of Hemophilia A had a strong first year, recording $320 million in sales, with $460 million forecast for 2016. Eloctate will be included in Biogen's spin-out of the Hemophilia business.

Product: MabThera-PH20 (rituximab)

Update: Little information is available breaking out sales of the PH20 formulation. There is no obvious evidence that this enhanced formulation is being developed for the US market. MabThera/Rituxan may face generics as early as 2018.

Product: Plegridy (peginterferon beta-1a)

Update: Definitely a success, sales of Plegridy hit $339 million in 2015 and are forecast to reach $530 million in 2016. This has helped the Avonex brand sales as a whole, which are expected to reach $2.9 billion in 2016.

Product: Hysingla ER (hydrocodone bitartrate)

Update: Launched in early 2015 in the US, sales performance to date is a mystery as Purdue Pharma does not report sales. It's likely that sales are "soft" given the product's high price, the availability of hydrocodone/acetaminophen generics, limited formulary coverage, and government attention to the abuse of prescription opioids.

Product: Xartemis XR (oxycodone, acetaminophen)

Update: This product is a big disappointment, recording sales of less than $4 million in 2015. The market for opioids is at best flat, and likely declining with concern about abuse.

Product: Alprolix (eftrenonacog alpha)

Update: Alprolix recorded sales of $235 million in 2015, with a forecast of $330 million in 2016. Biogen is getting out of this therapeutic area with announced plans to spin out the Hemophilia franchise to existing shareholders.

Product: Copaxone (glatiramer)

Update: This lifecycle formulation of Copaxone has helped Teva retain sales in the face of generics and accounted for about 60% of total Copaxone sales in 2015.

Product: Iluvien (fluocinolone)

Update: Another commercial disappointment, worldwide sales totaled $22 million in 2015, falling short of analyst expectations.

Ten Notable Drug Delivery & Formulation-Related Transactions of 2015

From a high water mark of 419 in 2013, the number of Drug Delivery and Formulation-related transactions dropped about 20% in 2014, gaining a little in 2015 to reach a total of 342 transactions. This parallels the change in total BioPharma transactions, which also hit a high of 1,650 transactions in 2013, with a slide back toward 2012 levels in 2014 and 2015.

Drug Delivery & Formulation Transactions (2012-2015)				
	2015	**2014**	**2013**	**2012**
Amendment Deals	39	33	44	10
Company Acquisitions	22	18	30	14
Joint Ventures	2	2	4	0
Option Agreements	5	4	6	5
Pharma Services Deals	18	19	29	22
Product Acquisitions	13	22	18	17
Product Deals	148	146	158	143
Technology Acquisitions	4	2	4	1
Technology Deals	72	56	109	127
Termination Deals	17	23	12	16
All Drug Delivery & Formulation	**342**	**325**	**419**	**355**
All BioPharma (including DD&F)	**1482**	**1456**	**1650**	**1462**

Source: PharmaCircle Deals & Acquisitions Module

For the most part, there has been relatively little change in the types of deals being done in the Drug Delivery & Formulation sector. Product Deals and Acquisitions seem to be on par with earlier years, except for the spike in 2013. One area of difference is seen with Technology Deals, which are reduced considerably in both 2014 and 2015 relative to earlier years. This seems to be a real shift in the market. It could be that there are not enough "new and exciting" technologies being developed to warrant licensing, or it could be that an increasing number of technologies are coming off patent and are available to companies who are capable of implementing them in-house without external resources or licenses.

The most notable trend in 2015 was the emergence of a number of Drug Delivery & Formulation companies, mostly US based, that are bootstrapping themselves from the apparent purgatory of being a technology supplier to a company that has commercial operations. Generally done in preparation for approval of their own pipeline products, this has led to a run on "preowned" products, often drug delivery-enhanced versions of previously approved actives that failed to deliver large sales for their initial partners. These second-hand product deals generally have very limited upfront payments with potential value back-ended into milestones and royalties. This strategy provides technology companies with the hope of building a Specialty Pharma company that can be sold at a premium once the internal pipeline has received approval and the sales potential has been demonstrated. Drug Delivery companies have, for the most part, experienced disappointment with the traditional models of licensing out technology and products to Big pharma and Specialty Pharma companies. Too often, the licensees lose interest in a product if sales do not ramp up quickly enough. Interestingly, established Specialty Pharma companies are quite eager to swallow up these smaller commercial-stage Drug Delivery companies, at a healthy premium, once their product portfolios have demonstrated real-world commercial success.

The biggest single transaction event from a Drug Delivery & Formulation perspective was Sanofi's decision to return the rights for Afrezza to Mannkind. Officially announced early in January 2016, it was obvious much earlier that commercial returns for Sanofi were falling far short of expectations. The only question was how much patience Sanofi would show. It was obvious to to all that this was not going to be easy, based on the failed effort of Nektar and Pfizer a decade earlier. The poor performance of Afrezza will have a chilling effect on the development of

additional pulmonary-delivered macromolecules intended for systemic treatment. Safety issues, even if theoretical, generally trump improved convenience.

All-in-all, 2015 provided limited validation for Drug Delivery and Formulation products and technologies. Amendment and Termination Deals accounted for one-sixth of all transactions, and there were no significant product or technology deals, beyond Halozyme's Enhanze deals, that raised the profile or the value of the sector.

The Baxalta acquisition of Sigma-Tau's Oncaspar asset suggests that there is value to be found in older products with no obvious competition that address premium-priced niche products. First approved in 1994, Oncaspar product rights bounced around between Enzon, the product developer, and its licensees, Aventis/RPR and Medac, before being reacquired by Enzon in 2002. The product at that point reported sales of about $10 million. It was then acquired as part of a package deal by Sigma-Tau for $327 million in 2010 when Enzon divested its commercial product assets. Fast forward to 2015, and Sigma-Tau has managed to score a $900-million deal with Baxalta solely for Oncaspar and a later-stage cancer product targeted to pediatrics. An interesting transaction by any measure, it remains to be seen if the product acquisition will be as rewarding for Baxalta as it was for Sigma-Tau.

A number of 2015 transactions have been selected to provide a bit more insight into the mood of licensors and licensees. These are not the mega-dollar acquisitions seen in the larger BioPharma area, but rather the "nuts and bolts" type transactions that help finance the drug delivery and formulation sector, spur additional investment, and lead to breakthrough technologies and products. A look back at the Ten Notable Drug Delivery Transactions of 2014 provides an opportunity to review what has passed with a hope of understanding what is to come. ■

Product Licensing – Nucynta

Type: Product Licensing Agreement (US)
Product: Nucynta (tapentadol) Franchise
Indication: Chronic Pain
Delivery Route: Oral – Immediate Release, Sustained Release, Oral Liquid Solution

Licensor/Licensee: Janssen/Depomed
Agreement Announcement: 2015-01-15
Current Status: Marketed (US, EU, Other)
Deal Value: $1.05 billion

Deal Summary: Depomed gains full commercial rights to Janssen's Nucynta product portfolio in exchange for a little more than $1 billion. Depomed also assumes Janssen's responsibilities with regard to Grunenthal, the product originator and worldwide owner.

Comment: Depomed made the transition to a Specialty Pharma company a few years ago and will grow substantially with the acquisition of the Nucynta portfolio, from sales of about $115 million in 2014 to an estimated $800 million in 2020. The opioid market will see considerable "evolution" as the US Congress attempts to fight prescription drug abuse through legislation, while pharmaceutical companies continue to develop and introduce abuse-deterrent formulations. With no breakthrough chronic pain medications on the horizon, commercial success can be found by judiciously raising prices and investing heavily in product promotion.

Product Acquisition – Oncaspar

Type: Product Acquisition
Product: Oncaspar (pegaspargase), calaspargase pegol
Indication: Cancer, Acute Lymphoblastic Leukemia
Delivery Route: Injectable – Intravenous, Intramuscular
Seller/Acquirer: Sigma-Tau/Baxalta

Agreement Announcement: 2015-07-23
Current Status: Marketed (US, EU) – Oncaspar, calaspargase – Phase 3
Deal Value: $900 million

Deal Summary: Baxalta has acquired the Oncaspar franchise and a clinical- stage candidate from Sigma-Tau for approximately $900 million. Oncaspar is reported to currently have annual sales on the order of $100 million.

Comment: This is an unbelievable value appreciation for a product that is 30 years old, uses patent-expired first-generation PEGylation technology, and reported sales of $10 million just 15 years ago. It speaks to the pricing flexibility and profitability afforded products that address small, high-need markets. The addition of Oncaspar to Baxalta builds out their cancer portfolio with a marketed product, and fits with their portfolio of products targeted to the pediatric population, at this stage, mostly related to Hemophilia.

Product Deal Termination – ZP-PTH

Type: Product Licensing Agreement Cancellation
Product: ZP-PTH
Indication: Osteoporosis
Delivery Route: Transdermal
Licensor/Licensee: Zosano Pharma/Eli Lilly

Termination Announcement: 2015-09-28
Technology: Microneedle Patch (ZP Patch)
Current Status: Pre-Phase III
Original Deal Value: $440 Million Plus Royalties (Terminated)

Deal Summary: As part of the original deal signed in 2014, Eli Lilly invested $15 million in Zosano's initial public offering. Additional payments were to 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: This is a bit of a "head scratcher." A product development and licensing deal that is less than a year old is cancelled at the request of the licensee (Zosano), who then announces they will continue to develop the product. The reason would seem to be a lack of financial resources at Zosano to hold up their end of the deal, or a difference of opinions on the development strategy. But one has to wonder how well the product, and the relationship, was doing. It should have been possible to secure financing had there been positive development prospects. The original deal was a very traditional type of transaction, where Big Pharma essentially takes an option on a product candidate that offers an interesting business opportunity, or a competitive threat, if successfully developed. The termination of the deal unfortunately raises questions about the real-world potential of microneedles as an option for macromolecule delivery.

Technology Licensing – Oral Peptides

Type: Collaboration/Licensing Agreement (Worldwide)
Active: Three Undisclosed Targets
Indications: Diabetes, Obesity
Delivery Route: Oral
Licensor/Licensee: Emisphere/Novo Nordisk

Agreement Announcement: 2015-10-15
Technology: Oral Bioavailability Enhancement (Eligen)
Current Status: Undisclosed
Deal Value: Potentially $212 million plus Royalties

Deal Summary: Novo Nordisk receives exclusive rights to develop products in three molecule classes, and non-exclusive rights to a fourth class using Emisphere's Eligen technology. Emisphere receives $5 million upfront and a potential of $62.5 million in milestones for each of the exclusive class products, and $20 million in milestones for the non-exclusive class, plus royalties.

Comment: If at first you don't succeed, try, try, and try again. Emisphere has been developing and applying their Eligen technology to the development of oral macromolecule delivery for more than 25 years with little success. There may be reason to be optimistic with this vote of confidence from Novo Nordisk as the current Novo Nordisk product, NN9924, a GLP-1 peptide of >4,000 Dalton molecular weight was recently moved into Phase III testing. The oral delivery of macromolecules is a delivery challenge that would benefit from the validation associated with a first oral macromolecule approval.

Product Reacquisition – Onsolis

Type: Product Re-acquisition Agreement (US)
Product: Onsolis (fentanyl)
Indication: Cancer Pain
Delivery Route: Buccal - Film
Licensor/Licensee: BioDelivery Sciences International/Meda

Agreement Announcement: 2015-01-27
Technology: Buccal Film (BEMA)
Current Status: Approved (USA, EU, Other)
Deal Value: Undisclosed, Revenue Sharing

Deal Summary: BioDelivery Sciences (BDSI) re-acquired the rights from Meda to their buccal formulation of fentanyl for the treatment of breakthrough cancer pain eight years after the original agreement. Meda will share in the future commercial value of Onsolis, and retains European rights.

Comment: This tidies things up for BDSI in the US. Meda had moved away from the pain market in the US to focus on their respiratory portfolio. Since re-acquiring Onsolis rights in the US, BDSI has received approval for a new formulation of Onsolis. BDSI has entered into an agreement with Collegium to market Onsolis in the US. Terms are modest with a $2.5 million upfront and potential milestones of up to $21.5 million and an upper teen's royalty rate. For Collegium, Onsolis represents a good fit with their recently approved abuse-deterrent sustained-release formulation of oxycodone, Xtampza ER.

BDSI is taking an approach different than many drug delivery platform-based companies. Rather than evolve into an organization with sales and marketing capabilities, BDSI has now licensed out commercialization rights for all of their approved products, Onsolis, Belbuca, and Bunavail. Ultimate success will depend on the performance of not only the BDSI products, but also their commercial partners.

Company Acquisition / Spin Out – Adare Pharmaceuticals

Type: Company Acquisition & Spin Out
Company: Adare Pharmaceuticals
Business Sector: Specialty Pharma, Services Provider

Acquirer: TPG Capital
Agreement Announcement: 2015-04-02
Deal Value: Undisclosed

Deal Summary: TPG Capital acquired the assets of Aptalis Pharmaceutical Technologies from Actavis, and re-established it as a stand-alone company.

Comment: What a long strange road it has been for the people at Eurand. Originally spun out of American Home Products in 1999 and listed on NASDAQ in 2007, the company was acquired by TPG Capital in 2011 and folded into Axcan, being renamed Aptalis. Aptalis was then acquired by Forest in 2014, which was in turn acquired by Actavis later that year. Less than a year later, Aptalis Pharmaceutical Technologies has been spun out as Adare. The company seems to have survived pretty much intact with strong client-oriented development and manufacturing services as well as their own pipeline of clinical- stage products.

Technology Licensing - Enhanze

Type: Technology Licensing and Collaboration (Worldwide)
Technology: Injection Site Absorption Enhancer (Enhanze)
Actives: 9 Total (Undisclosed)
Indications: Undisclosed

Delivery Route: Injection – Subcutaneous
Licensor/Licensee: Halozyme/AbbVie
Agreement Announcement: 2015-06-03
Current Status: Marketed (EU, US)

Deal Summary: $23 million upfront, plus up to $130 million in milestones per target, plus tiered royalties.

Comment: The traditional drug delivery deal is still alive and well, at least for an increasingly well-validated technology like Halozyme's Enhanze. With an approved product using the Enhanze technology on the market (Roche's MabThera-PH20), the technology has proven that it is scalable and approvable. With the ever-expanding development pipeline of macromolecule therapeutics and the associated delivery challenges, technologies able to improve patient comfort, and manage larger dose subcutaneous injections, have a ready market. And it seems that the deal prices are going up as judged by Halozyme's follow-on deal in December 2015 for five collaboration targets with $25 million upfront and $160 million in milestones per target.

Product Licensing – Oxaydo

Type: Product Licensing Agreement (Worldwide)
Product: Oxaydo (oxycodone)
Indication: Pain
Delivery Route: Oral, Abuse-Deterrent
Licensor: Acura Pharmaceuticals

Licensee: Egalet
Agreement Announcement: 2015-01-08
Technology: Abuse-Deterrent (Acura Aversion)
Current Status: Marketed (US)

Deal Summary: $5 million upfront, plus up to $15 million in milestones and tiered royalties.

Comment: One of a pair of deals announced by Egalet to "bootstrap" commercial operations in the US. Oxaydo, originally approved by the FDA in 2011 and licensed to King Pharmaceuticals, fell by the wayside shortly after King was acquired by Pfizer. Another of the many abuse-deterrent opioids without abuse-deterrent label claims, Oxaydo has floundered in the marketplace. The commercial prospects for Oxaydo are limited, but it will help support Egalet commercial operations as it prepares for the approval of two later-stage abuse-deterrent analgesics, an extended-release morphine product, and an extended-release oxycodone product.

Product Licensing – Sprix

Type: Product Licensing Agreement (Worldwide)
Product: Sprix (ketorolac)
Indication: Pain
Delivery Route: Nasal
Licensor: Luitpold Pharmaceuticals

Licensee: Egalet
Agreement Announcement: 2015-01-08
Technology: Nasal Delivery (Aptar Classic Nasal Spray System)
Current Status: Marketed (US)

Deal Summary: $5 million upfront, plus up to $15 million in milestones and tiered royalties.

Comment: This is the second of Egalet's commercial product acquisitions announced January 2015. Originally approved in 2010, Sprix has had very limited commercial success, making it available for licensing. Along with Oxaydo, another rent-a-product asset, Sprix provides the Egalet sales and marketing group with the foundation of a pain franchise.

Product Deal Termination – Afrezza

Type: Product Deal Termination
Product: Afrezza
Indication: Diabetes
Delivery Route: Inhalation
Licensor/Licensee: Mannkind/Sanofi

Termination Announcement: 2016-01-05
Technology: Dry Powder (Technosphere), Device (Dreamboat)
Current Status: Marketed (US)
Original Deal Value: Up to $925 million in upfront and milestones, plus profit share

Deal Summary: The original deal signed August 2014 provided Sanofi with worldwide rights to Afrezza in exchange for $150 million upfront, milestones that could have reached $775 million, and a 65%/35% profit share with Mannkind. The cancellation basically hands the Afrezza rights back to Mannkind with no announcement of any financial terms.

Comment: Well that didn't last too long. Although formally cancelled the first week of 2016, the decision was made earlier in 2015. For Sanofi, the greatest cost of this failed partnership was not the lost upfront payments but the commercial resource costs and the lost opportunity to promote other portfolio products. It may have also influenced the recent personnel changes in the Sanofi Diabetes business sector. For Mannkind, it will be an uphill slog to find a new partner, or more likely take on the commercialization activities internally.

Product Joint Commercialization – Movantik

Type: Product Joint Commercialization Agreement (US)
Product: Movantik (naloxegol)
Indication: Opioid-Induced Constipation
Delivery Route: Oral
Licensor/Licensee: AstraZeneca/Daiichi Sankyo

Licensee: Daiichi Sankyo
Agreement Announcement: 2015-03-09
Technology: PEG-conjugate (Nektar Small Molecule Polymer Conjugate Technology)
Current Status: Marketed (US, EU, Other)

Deal Summary: $825 million, plus up to $625 million in milestones, less commission payments on sales.

Comment: It's not clear what triggered this agreement to share US commercialization responsibilities for Nektar's Movantik. AstraZeneca received a handsome upfront from Daiichi Sankyo, but forgoes the full commercial potential of Movantik. Sales results in 2015 with Movantik have arguably been disappointing, totaling just $29 million worldwide. Presumably, AstraZeneca wanted to hedge their near-term financial obligations with respect to product milestone payments. Since then, AstraZeneca has struck an additional agreement providing ProStrakan with sales and marketing rights to Movantik in a few smaller European markets.

One Year Later

So what has become of the Ten Notable Drug Delivery & Formulation-Related Transactions of 2014? A short summary of the more interesting outcomes provides an update on how these transactions have weathered the intervening time.

Licensor/Licensee: Trimel Pharmaceuticals/Endo
Product: Natesto (Nasal Testosterone, Approved)
Update: The deal died in 2015 with rights for Natesto returned to Trimel (renamed Acerus Pharma). US rights have since been licensed to Aytu BioScience.

Licensor/Licensee: Halozyme/Janssen Biotech
Technology: Enhanze Technology (Targets Undisclosed)
Update: The Halozyme website lists one product in Phase I testing (Oncology). Halozyme signed a couple of additional large-value Enhanze-related deals in 2015.

Licensor/Licensee: MannKind/Sanofi
Product: Afrezza (Inhaled Insulin, Approved)
Update: Collaboration cancelled, MannKind has announced their intention to assume marketing and sales responsibilities with a focus on specialists and pricing.

Licensor/Licensee: Zosano Pharma/Lilly
Technology: ZP-PTH (Parathyroid Hormone, Phase II)
Update: The collaboration has been terminated, Zosano intends to continue development on their own.

Licensor/Licensee: Zogenix/Endo
Product: Sumavel DosePro (Sumatriptan)
Update: The product is still being marketed by Endo. Sales appear to be modest and not material to Endo operations.

Licensor/Licensee: Evonik/BioDelivery Sciences International (BDSI)
Product: Buprenorphine Depot Injection (Preclinical)
Update: Nothing doing. The companies have provided no updates since the agreement was announced in October 2015. The BDSI website lists the collaboration product status as "Formulation Development."

Licensor/Licensee: Amunix/Biogen
Technology: EXTEN Prodrug Technology License (Factor VIII, Hemophilia)
Update: The collaboration currently has three separate hemophilia products in Discovery or Preclinical. Amunix has since signed an option exercise agreement with Lilly for Diabetes, and a product agreement with Naia.

Acquired/Acquirer: Activaero/Vectura Group
Asset: Activaero (Company)
Update: Seemingly a success, Activaero's assets have been integrated into Vectura with Activaero's lead product candidate, Favoril, currently listed in Phase III development. The Akita inhalation technology is noted as one of the company's technology platforms.

Acquired/Acquirer: Archimedes Pharma/ProStrakan
Asset: Company (Archimedes Pharma)
Update: Swallowed and digested. A $360-million acquisition, Archimedes was acquired largely for its "rag tag" collection of marketed products. Eighteen months later, it's hard to find any lingering evidence of Archimedes within ProStrakan (now Kyowa Kirin).

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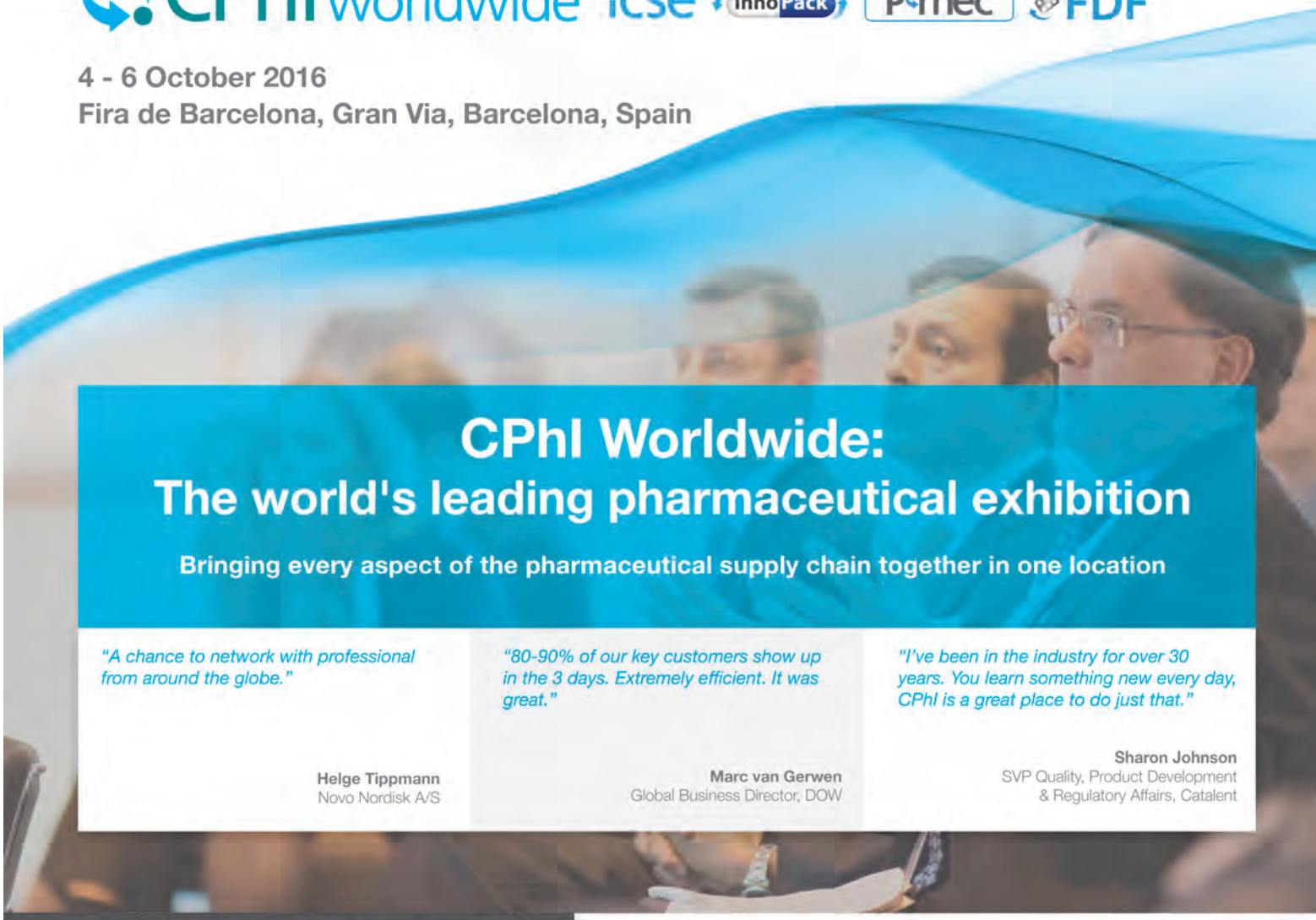

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Ten Notable Drug-Device Approvals of 2015

Objective-focused Drug Delivery & Formulation Professionals are ready to embrace whatever technology can help them achieve their goal of delivering a pharmaceutical product to best treat a defined medical condition. This means constantly refreshing a drug delivery and formulation toolbox with technologies that can modify the absorption, distribution, metabolism, and excretion performance parameters of a pharmaceutical.

For decades, the toolbox was limited and consisted largely of technologies or excipients that could retard or speed up the absorption of a pharmaceutical active. In the past three decades, however, there has been increasing interest and success in developing new toolbox resources that involve chemical modification of molecules, the manufacture of specifically sized drug particles, protein engineering, and the expanded use of ever-more sophisticated devices. While devices have been used for centuries, ranging from syringe-like devices for injection, to simple reeds to insufflate powders, it has been the past couple of decades where mechanics, married with electronics, have provided for important new drug delivery opportunities.

Again in 2015 drug-device approvals were well represented by products intended to improve patient convenience and compliance. In most cases, this meant making a less-than-comfortable delivery approach more comfortable. Once considered to be a major "no-no" for any product that hoped to gain broad patient uptake and commercial success, subcutaneous dosing has crossed over to the mainstream in terms of patient acceptance. Who would have imagined a decade ago that four of the top six selling pharmaceuticals in 2015 would require patients to inject themselves as often as several times a day? Dare we imagine injectable cancer therapies that are patient administered in the outpatient setting?

The success of these blockbuster products that depend on patient self-injection are largely the result of three converging factors: 1) The identification and optimization of truly effective pharmaceuticals, often macromolecules, for poorly treated indications; 2) The development of formulation technologies, often involving protein engineering, that permit dosing intervals to be spaced out for days or weeks; and 3) The development of consumer-friendly injection devices that take the sting and the fright out of self-injection.

It's one thing for an individual with type 1 diabetes to self-inject multiple times a day. It's something quite different for patients with chronic non-life-threatening conditions to self-inject for an indefinite period. Fortunately, for patients and companies, the injections are almost always subcutaneous, permitting the use of fine, short needles. It might be a quite different situation if the circumstances required regular intramuscular injections. By taking the sting out of injections, making the process simple, and formulating actives to smaller volumes, the use of outpatient injection is likely to expand, until of course there is a similarly effective oral treatment. Despite the outpatient success of injectables, one only needs to look at Pegasys and PEGIntron for an indication of how quickly products can be replaced when equally effective oral agents are introduced.

Beyond the approval of more, by now common, device optimized subcutaneous drug-device products for type 2 diabetes, 2015 saw a few interesting drug-device approvals that suggest good ideas don't need to be overly complex.

Adapt Pharma's Narcan Nasal Spray seems to be a simple but effective option for the management of opioid overdose in the outpatient setting. Likely to compete directly with Kaleo's Evzio, Narcan Nasal Spray provides for simple and intuitive administration: remove cap and spray up one nostril. That's it, not one squeeze in two nostrils or two squeezes in one nostril. One squeeze into one nostril. Narcan Nasal Spray, a very simple drug-device combination, will have a cost of goods advantage over Evzio that should provide for considerable market leverage.

Ionsys, the patient-controlled active transdermal delivery system for post-operative pain, is back on the market again. Off the market for several years, Ionsys was picked up from Johnson & Johnson by Incline Therapeutics, who were then acquired by The Medicines Company. Also approved in 2015 was Zalviso, a sufentanil sublingual tablet dispenser. Intended to be used to replace patient-controlled analgesia (PCA) in the inpatient setting, the device conjures up a vision of a high-tech Pez dispenser. The success of these products remains to be seen. Both products are intended for in-patient use. It seems their selling proposition is that they eliminate the need for an intravenous line, an infusion solution, and the associated pump, as are required with traditional PCA therapies. Neither device seems to eliminate the need for patient education and close monitoring, or improves safety. It will be interesting to see how these products perform in a very cost-constrained environment.

The 2015 FDA approval of Duodopa, an ambulatory pump system for the delivery of a levodopa/carbidopa formulation directly to the duodenum or jejunum, provides an important therapeutic treatment option for patients with Parkinson's disease. It isn't obvious that any current oral delivery technology can provide these two actives constantly and consistently to the small intestines over a 16-hour period. The opportunity apparently exists as suggested by the current sales of more than $200 million.

The Ellipta (GSK) and Respimat (Boehringer Ingelheim) dry powder inhalation platforms continued to roll out new respiratory products in 2015. Both platforms continue to capture market share in what is likely to be a highly genericized sector in just a few years.

The following Ten Notable Drug-device Products of 2015 provide a little more perspective on the drug-device approvals of 2015. Also included is a review of the progress made in 2015 by the Ten Notable Drug-Device Approvals of 2014. ■

Duodopa

Active: levodopa/carbidopa
Molecular Weight[1]: 197/226 Da
Indication: Parkinson's Disease
Delivery Route: Infusion - Intrajujeunal
Company: AbbVie

First Approval: 2004-03-10 (EU)
Formulation Type: Infusion Gel
Technology Provider: Smiths Medical (Infusion Pump)
Integral Device: CADD-Legacy 1400 Portable Infusion Pump

Claim to Fame: Approved in the US only in 2015, this drug-device combination involves the infusion of a gel formulation of levodopa and the decarboxylase inhibitor carbidopa into the jejunum via a percutaneous endoscopic gastrostomy with an outer transabdominal tube and an inner intestinal tube. Effective but clearly crying out for a better solution. This represents a significant medical need as evidenced by the more than $200 million in annual sales, prior to the US approval.

Liletta

Active: levonorgestrel
Molecular Weight[1]: 312 Da
Indication: Contraception
Delivery Route: Intrauterine
Company/Partner: Medicines 360/Allergan

First Approval: 2012-08-16 (EU)
Formulation Type: Polydimethylsiloxane Membrane
Technology Provider: Allergan (formerly Uteron Pharma)
Integral Device: Hormone-Releasing Intrauterine Device

Claim to Fame: Approved in the US only in 2015, this is another of the many drug-device products previously approved in Europe. Developed by Medicines 360, Liletta is likely intended to provide a lower cost alternative to Bayer's well-received Mirena and Skyla intrauterine devices.

Repatha Pen

Active: evolucomab
Molecular Weight[1]: 141,800 Da
Indication: Hypercholesterolemia
Delivery Route: Injection - Subcutaneous
Company: Amgen

First Approval: 2015-07-17 (EU)
Formulation Type: Injection Solution
Technology Provider: Amgen via SHL Medical (SureClick Autoinjector)
Integral Device: SureClick Autoinjector

Claim to Fame: Repatha clearly represents a formulation challenge not amenable to a simple device solution. Dosed once-monthly, each dosing requires the use of three autoinjector pens, each delivering 1 ml containing 140 mg of active, all administered within 30 minutes. The challenge going forward will be to develop a higher concentration formulation with acceptable viscosity and stability, or integrating a patient- friendly subcutaneous infusion device.

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

Ionsys

Active: fentanyl HCl
Molecular Weight[1]: 336 Da
Indication: Post-Operative Pain
Delivery Route: Transdermal – Poration Iontophoresis
Company: The Medicines Company

First Approval: 2006-01-24 (USA)
Formulation Type: Hydrogel
Technology Provider: The Medicines Company (Originally Alza)
Integral Device: Sealed Unit with Battery and Integral Formulation (E-Trans)

Claim to Fame: After being withdrawn five years ago, Ionsys was reapproved by both the European and American regulatory bodies in 2015. Initial issues related to product integrity that underlay the product's earlier withdrawal have presumably been addressed, but the question remains as to the market's interest in a technology that is restricted to hospital use. Iontophoresis offers significant potential for the delivery of macromolecules, as well as small molecules that have a tight therapeutic index or are subject to potential abuse.

Praluent Pen

Active: alirocumab
Molecular Weight[1]: 146 kDa
Indication: Hypercholesterolemia
Delivery Route: Injection - Subcutaneous
Company/Partner: Regeneron/Sanofi

First Approval: 2015-07-24 (US)
Formulation Type: Liquid, Aqueous
Technology Provider: SHL Group (Disposable Autoinjector)
Integral Device: DAI Auto injector (SHL Group)

Claim to Fame: Much like Amgen's Repatha Pen, Praluent targets a similar indication with a comparable device. Unlike Repatha, dosing is limited to one injection every two weeks, without a once-per-month option. Dosage flexibility is provided with a 75-mg and 150-mg autoinjector pen options.

Toujeo SoloSTAR

Active: insulin glargine
Molecular Weight[1]: 6,063 Da
Indication: Diabetes, Types 1 & 2
Delivery Route: Injection - Subcutaneous
Company: Sanofi

First Approval: 2015-02-25 (US)
Formulation Type: Liquid, Aqueous
Technology Provider: Ypsomed
Integral Device: SoloSTAR Multidose Injection Pen

Claim to Fame: The apparent successor to Sanofi's Lantus SoloSTAR, both products use the same device but with Toujeo providing for better night-time hypoglycemia control with a lower volume injection. The Toujeo SoloSTAR is a lifecycle-enhancement product that brings additional patient benefits.

Zalviso

Active: sufentanil
Molecular Weight[1]: 387 Da
Indication: Post-Operative Pain
Delivery Route: Oral - Sublingual
Dosing Interval: >20 Minutes as Required

Company/Partner: AcelRx Pharmaceuticals/Grunenthal
First Approval: 2015-09-18 (EU)
Formulation Type: Sublingual (NanoTab)
Technology Provider: AcelRx Pharmaceuticals
Presentation: Handheld Tablet Dispenser (NanoTab Dispenser)

Claim to Fame: An interesting twist on patient-controlled analgesia (PCA). With the development of a dispenser that limits in-patient access to a fresh sublingual tablet of Zalviso no more often than every 20 minutes, Zalviso seems a bit like a Skinner Box treatment. Approved only in Europe, the product is undergoing a fresh Phase III trial to support a US registration.

Narcan Nasal Spray

Active: naloxone HCl
Molecular Weight[1]: 400 Da
Indication: Opioid Overdose
Delivery Route: Nasal
Dosing Interval: As Required

Company/Partner: Opiant Pharmaceuticals/Adapt Pharma
First Approval: 2015-11-18 (US)
Formulation Type: Liquid Spray, Aqueous
Technology Provider: Aptar Pharma
Presentation: Sealed Unit Dose (Aptar UDS)

Claim to Fame: The pharmaceutical industry's attention to the American opioid epidemic has resulted in another out-patient-friendly presentation for the treatment of opioid overdoses. The product's requirement of a single spray into one nostril may be more intuitive and less intimidating than the multimedia injection system incorporated into Kaleo's Evzio.

Vantobra

Active: tobramycin
Molecular Weight[1]: 468 Da
Indication: Pseudomonas Infections in Cystic Fibrosis Patients
Delivery Route: Inhalation - Nebulization
Company: Pari Pharma

First Approval: 2015-03-18 (EU)
Formulation Type: Liquid, Aqueous
Technology Provider: Pari Pharma
Integral Device: eFlow Rapid Nebulizer

Claim to Fame: Pari has been the technology supplier for multiple nebulized products for a variety of indications, including TOBI for the treatment of cystic fibrosis. Vantobra represents Pari's first approval as a product developer and uses a high-concentration formulation of tobramycin along with a new nebulizer that reduces administration times by almost two-thirds.

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

Stiolto Respimat

Active: olodaterol HCl/tiotropium bromide
Molecular Weight[1]: 386/472 Da
Indication: Chronic Obstructive Pulmonary Disease
Delivery Route: Inhalation - Nebulization
Company: Boehringer Ingelheim

First Approval: 2015-02-19 (EU)
Formulation Type: Liquid, Aqueous
Technology Provider: Boehringer Ingelheim
Integral Device: Respimat Soft Mist inhaler

Claim to Fame: Boehringer Ingelheim continues to roll out a full line of pulmonary targeted medications based on their proprietary Respimat device; Stiolto being number five by our count. A patient-friendly alternative to dry powder inhalers and metered dose inhalers, the Respimat platform powers a multibillion dollar respiratory franchise.

Boehringer Ingelheim

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

One Year Later

It has been more than a year later, and it's worth taking a look to see how the Ten Notable Drug-Device Approvals of 2014 have done. These short summaries will serve as a refresher and perhaps suggest some lessons.

Product: Afrezza

Update: The subject of much discussion, Afrezza has at the very least had a rocky introduction with the product returned to MannKind by Sanofi early in 2016. Unlike Exubera, there was little to complain about in terms of device design or convenience. Perhaps the inhaled insulin approach is ahead of its time, or perhaps it has too much "baggage" in terms of safety concerns.

Product: Natesto

Update: A nasal testosterone never seemed to be a great idea, and marketing partner Endo has since returned the product to Acerus (formerly Trimel), who have found a new partner for the product in Aytu Biosciences in the US. It's hard to be optimistic about this product's eventual commercial and clinical success.

Product: Evzio

Update: A novel injectable for the treatment of opioid overdose, Evzio has received good press coverage, but it's not clear that has translated into sales. The product will be under pressure with the 2015 approval of Narcan Nasal, offering a similar benefit but with a much lower cost base and more intuitive administration requirements.

Product: Bydureon Dual

Update: There is little specific information available for this product line extension, which provides patients with a prefilled once-a-week injection option for type 2 diabetes. Overall, the Bydureon brand grew to $580 million in sales in 2015, an increase of 32% year-over-year.

Product: Kitabis Pak

Update: There has been no public update on the status of Kitabis Pak since its 2014 approval. The company, Pulmoflow, provides no product information and states they are a licensing company.

Product: Tanzeum

Update: A long acting type 2 diabetes medication using an albumin-fusion strategy delivered with a dual-chamber syringe, Tanzeum has not taken off, reporting sales of about $60 million in 2015.

Product: Neulasta Delivery Kit

Update: Now called the Neulasta Onpro, this drug-device pairing seems to have been successful for Amgen and patients by helping ensure the final dose of Neulasta is administered after the patient has left the in-patient setting.

Product: Arnuity Ellipta

Update: Despite disappointing sales of about $5 million reported in 2015, GSK's Ellipta dry powder platform seems to be achieving lift-off with a variety of other actives, notably Breo Ellipta, in the face of generics targeting the older Diskus platform.

Product: Xultophy

Update: Approved in the EU in 2014, Xultophy filed for US approval in the third quarter of 2015, receiving unanimous positive vote from the Endocrinologic and Metabolic Drugs Advisory Committee of the US FDA in May.

Product: Trulicity

Update: This fusion protein for the treatment of type 2 diabetes made good headway in 2015, racking up sales of almost $250 million, with the prospect of reaching $1 billion in 2016.

Ten Notable Fixed-Dose Combination Drug Approvals of 2015

Compliance and efficacy, two sides of the same coin it seems. Compliance to a regimen that is not effective is no worse, or better, than a lack of compliance to a dosage scheme that is very effective. Getting real-world adherence to a dosage regimen proven effective in clinical trials can make the difference between good and poor clinical outcomes, and outcomes translate into physician perceptions and commercial success.

If the combination of two products is better than either of them individually, the challenge for the formulator is to make taking two or more agents as simple as taking either one of them. Enter the concept of the combination product, two or more actives that present themselves as a single agent.

No less important are the commercial implications of combination products. In many cases, combination products are variations on a novel therapeutic active, perhaps a potent antiviral blocker, or anti-diabetic agent, where benefit has been shown adding in a previously approved, generic, active. In most cases, the combination product is offered at the same price as the single agent proprietary active, or at most, a slight premium. Requiring the patient to fill two separate prescriptions, the branded active and a generic, could be sufficient disincentive for a patient to forego the medication because of the perceived cost. The alternative, lowering the cost of the branded pharmaceutical to make the cost more competitive, would reduce sales from patients who require only the branded product. The obvious answer is the combination product, where the cost of adding in a generic active is negligible to the manufacturer and can allow for a pricing premium, often making for a more attractive cost-benefit argument.

A real-world example of the challenges and the outcomes of "optimally" formulating a combination product can be seen with the 2014 approvals of Gilead's Harvoni and AbbVie's Viekira Pak for the treatment of Hepatitis C. Gilead's two-component combination product is dosed as a single tablet taken once a day. The AbbVie product, a four-component combination product, involves four separate tablets taken on two different dosing schedules. Both products are similarly effective, with perhaps a small benefit in terms of tolerability favoring Harvoni. At launch, AbbVie's Viekira Pak was sold at a discount to Harvoni, an important selling feature to gain formulary acceptance. Sales results for 2015 showed a marked difference in the performance of the two products. Harvoni racked up sales of $13.9 billion in its first year on the market, while Viekira Pak sales came in at $1.4 billion. While Harvoni certainly had the benefit of following Gilead's very successful single agent Sovaldi for Hepatitis C, an argument can be made that the Harvoni single tablet, once-a-day formulation was the major reason for the sales differences. Not only was there likely to be better patient and physician acceptance of the simpler dosing Harvoni regimen, it's possible that real-world outcomes were better with Harvoni because of better patient compliance. Convenience and compliance, partners in better outcomes clinically and commercially.

AbbVie seems to have learned its lesson, and in 2015, received approval for a new Hepatitis C combination product, combining three separate actives, taken once a day, as two tablets. The benefit of this once-a-day regimen is eroded a bit by the need to take two tablets, but perhaps a bigger concern is the recommendation that patients prescribed Technivie also take ribavirin. This adds another prescription, taken twice a day and requiring weight-adjusted dosing. Two steps forward and one step back? Formulation and compliance are elements of pharmaceutical product design that are too often not given sufficient consideration early enough in the development process.

Antiviral approaches to the treatment of Hepatitis C and HIV/AIDS involve hitting the viruses at several different points, requiring the development of multi-active products. 2015 saw the approval of a number of combination products for the treatment of HIV/AIDS which included: Evotaz and Genvoya (Gilead) and Dutrebis (Merck & Co.). After two decades, these companies have the drill down pat, introducing products that are not only multi-active, but offer single tablet, once-a-day dosing. In the case of Dutrebis, dosing is twice a day, which is likely to impact uptake unless efficacy, safety, and tolerability are superior to the once-a-day competitors.

2015 saw the approval of additional combination products targeted to the treatment of type 2 diabetes that involved a novel proprietary active co-formulated with metformin. Metformin seems to be the go-to add-on for most new diabetes treatments, demanding creative formulation solutions to allow for once-a-day dosing given its 4.7- to 8-hour half-life.

There were some not-so-obvious combination products approved in 2015 that seem to fit important patient and physician needs, for example, a cosmetic filling agent that includes a local anesthetic (Radiesse Plus), and a surgical sealant that delivers two clotting agents (Raplixa).

Combination products at their best can enhance the efficacy and safety of pharmaceutical treatments by helping ensure patient compliance. The 10 products identified as 10 Notable Fixed-Dose Combination Drug Approvals for 2015 that follow provide a sense of what was accomplished in the past year. Also included is a look back at the selections of 2014 and how they have progressed in the past year and a half. ■

Entresto

Actives: valsartan/sacubitril
Molecular Weight[1]: 436/412 Da
Indication: Heart Failure
Delivery Route: Oral
Dosing Interval: 24 Hours

Company: Novartis
First Approval: 2015-07-07 (US)
Formulation Type: Oral, Tablet-Combination
Review Status: Priority (FDA)
Development/Approval Time[2]: 5.8 Years

Claim to Fame: Offering a new therapeutic approach to the management of congestive heart failure, Entresto combines a novel angiotensin receptor neprilysin inhibitor with a well-regarded angiotensin receptor blocker. Initially touted as a blockbuster, it appears that growth will need to be slow and steady if it hopes to achieve its lofty expectations. Entresto ticks off the boxes in terms of patient needs but has found that it's hard for physicians to switch stabilized heart failure patients to a new therapeutic regimen, even if it offers improved outcomes.

Synjardy

Actives: empagliflozin/metformin HCl
Molecular Weight[1]: 451/129 Da
Indication: Diabetes, Type 2
Dosing Interval: 24 Hours
Delivery Route: Oral

Company/Partner: Boehringer Ingelheim/Eli Lilly
First Approval: 2015-05-27 (EU)
Formulation Type: Oral, Tablet-Combination
Review Status: Standard (FDA)
Development/Approval Time[2]: ~4 Years

Claim to Fame: The Eli Lilly/Boehringer Ingelheim partnership continues to roll out additional products for the treatment of type 2 diabetes. In this case, Empagliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor is paired with an old workhorse anti-diabetic, metformin, and wrapped up in a once-daily dosage form.

Glyxambi

Actives: empagliflozin/linagliptin
Molecular Weight[1]: 451/473 Da
Indication: Diabetes, Type 2
Delivery Route: Oral
Dosing Interval: 24 hours

Companies: Boehringer Ingelheim, Eli Lilly
First Approval: 2015-01-30 (US)
Formulation Type: Oral, Tablet-Combination
Review Status: Standard (FDA)
Development/Approval Time[2]: 3.6 Years

Claim to Fame: Like hypertension, the treatment of type 2 diabetes is increasingly focused on addressing more than one biological pathway. Glyxambi claims to be the first and only dual inhibitor combination therapy targeting the sodium glucose co-transporter-2 (SGLT2) and dipeptidyl peptidase-4 (DPP-4) pathways with a once-daily dosing regimen.

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

Tuzistra XR

Actives: codeine polistirex/chlorpheniramine polistirex
Molecular Weight[1]: 299/275 Da
Indication: Cough & Cold
Delivery Route: Oral
Dosing Interval: 12 Hours

Company/Partner: Tris Pharma/Vernalis
First Approval: 2015-04-30 (US)
Formulation Type: Oral, Liquid-Combination
Review Status: Standard (FDA)
Development/Approval Time[2]: 1.7 Years

Claim to Fame: "Sustained-release liquids are us" could be the slogan for Tris Pharma, a NJ-based drug delivery company that has done a remarkable job of continuing to formulate liquid-based products that meet real-world therapeutic needs. Tuzistra XR joins Dynavel XR as one of two Tris Pharma FDA- sustained-release oral liquid approvals in 2015.

Technivie

Actives: ritonavir/paritaprevir/ombitasvir
Molecular Weight[1]: 721/802/975 Da
Indication: Hepatitis C
Delivery Route: Oral
Dosing Interval: 24 Hours

Company: AbbVie
First Approval: 2014-12-19 (US)
Formulation Type: Oral, Tablet-Combination
Review Status: Priority (FDA)
Development/Approval Time[2]: Unknown

Claim to Fame: Second time's a charm? This is the same combination as the Viekira Pak, minus the dasabuvir component, but in a single-tablet formulation and once-daily dosing. Technivie is approved for a subset of Hepatitis C patients, Genotype 4, and is recommended to be used in combination with oral ribavirin, so it's still a two-dose combination of sorts, but much more convenient than the Viekira Pak multi tablet, multi-regimen presentation.

Radiesse Plus

Actives: durapatite/lidocaine
Molecular Weight[1]: 502/234 Da
Indication: Skin Wrinkles
Delivery Route: Injection - Subdermal
Dosing Interval: As Required

Company: Merz Aesthetics
First Approval: 2015-03-16 (US)
Formulation Type: Injectable, Pre-Filled Syringe
Review Status: Not Applicable (Device)
Development/Approval Time[2]: Unknown

Claim to Fame: This combination product, approved as a device, expands the Radiesse line, with a presentation that includes lidocaine to reduce post-injection pain. Nothing too fancy, but in the business of cosmetic surgery patient comfort ranks high in terms of desirable product features.

Orkambi

Actives: ivacaftor/lumacaftor
Molecular Weight[1]: 392/452 Da
Indication: Cystic Fibrosis
Delivery Route: Oral
Dosing Interval: 12 Hours

Company: Vertex Pharmaceuticals
First Approval: 2015-07-02 (US)
Formulation Type: Oral, Tablet
Review Status: Priority (FDA)
Development/Approval Time[2]: ~5 Years

Claim to Fame: A novel treatment for cystic fibrosis, these two actives provide complementary actions at the level of the CFTR protein that results in improved pulmonary function. Combining the two actives in a single tablet ensures both agents are taken in the approved fixed-dosage regimen.

VERTEX

Raplixa

Active: factor I/thrombin
Molecular Weight[1]: 340,000/36,000 Da
Indication: Surgical Sealants Fibrosis
Delivery Route: Topical
Dosing Interval: As Required

Company: The Medicines Company
First Approval: 2015-03-30 (EU)
Formulation Type: Powder, Vial with Spray Device
Review Status: Standard (FDA)
Development/Approval Time[2]: 4.9 Years

Claim to Fame: An alternative to traditional staples and stitches, the product can be "poured" onto the wound to stop bleeding, or applied with the RaplixaSpray device that makes it easier to treat difficult-to-reach, or large, bleeding areas.

THE MEDICINES COMPANY®

Genvoya

Active: tenofovir/elvitegravir/cobicistat/emtricitabine
Molecular Weight[1]: 287/448/776/247 Da
Indication: HIV/AIDS
Delivery Route: Oral
Dosing Interval: 24 Hours

Company: Gilead Sciences
First Approval: 2015-11-05 (US)
Formulation Type: Oral, Tablet
Review Status: Standard (FDA)
Development/Approval Time[2]: ~5 Years

Claim to Fame: : Another multi-active HIV/AIDS medication formulated as a single tablet for once-daily dosing. This approach not only helps to secure better compliance, it ensures the complete dosing regimen is taken as has been validated in clinical trials, no skipping this or that agent because it's too expensive or it's on a different dosing schedule. The four actives have elimination half-lives that range from 30 minutes to 13 hours. What's the secret to the successful formulation of a stable oral tablet that contains more than 500 mg of active and is dosed once daily? Genvoya provides validation that even multi-active products can be co-formulated into patient friendly dosage forms.

GILEAD

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

Dutrebis

Active: raltegravir/lamivudine
Molecular Weight[1]: 444/229 Da
Indication: HIV/AIDS
Delivery Route: Oral
Dosing Interval: 12 Hours

Company: Merck & Co.
First Approval: 2015-02-06 (US)
Formulation Type: Oral, Tablet
Review Status: Standard (FDA)
Development/Approval Time[2]: ~3 Years

Claim to Fame: From a formulation perspective, this single-dose combination provides enhanced bioavailability of the raltegravir component, permitting a 25% reduction in the dose relative to the previously approved single-agent product (Isentress). From a regulatory perspective, Dutrebis was approved in the US with no apparent expectation that the product would be sold domestically. It is currently listed at the FDA as Discontinued. This is becoming a more common strategy for products that are not sufficiently competitive for sale in the US, but are attractive products for sale in other markets where there is benefit in holding an FDA approval.

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

One Year Later

It has been more than a year later, and it's worth taking a look to see how the Notable Approvals of 2014 are doing. These short summaries will serve as a refresher and perhaps suggest some lessons.

Product: Contrave

Update: It was only a couple of years ago that there were expectations of billion- dollar products when the FDA approved a new generation of anti-obesity products. The expectations have been dashed. Contrave recorded sales of only $54 million in 2015, with a forecast of $85 million in 2016.

Product: Akynzeo

Update: Little commercial information is available for this product from Helsinn, a private company. Things seem to be going well based on the quality of marketing partners on board by the end of 2015 (Roche, Eisai, and Mundipharma) and approvals being received in additional territories.

Product: Namzaric

Update: Positioned as the obvious combination of two co-prescribed acetylcholinesterase inhibitors for Alzheimer's, Namzaric has struggled to capture market share with sales of $50 million in 2015, about 4% of the total Namenda franchise. It is expected to grow to about $500 million annually in the US by 2022.

Product: Targiniq ER

*Update:*Approved in the US and then promptly discontinued. It's not clear if the Targiniq ER had some sort of production-related issue as befell Allergan's morphine/naltrexone combination Embeda. More likely, the US registration was merely a strategy to support registration in other international markets, or perhaps the post-approval demands exceeded the expected financial returns in the US.

Product: Omidria

Update: A niche product of sorts, to manage intraoperative myosis and postoperative pain, Omidria has managed to gain momentum in terms of uptake and sales. Sales of $13 million in 2015 are expected to grow to $67 million in 2016.

Product: Viekira Pak

Update: Sales for Viekira, despite being outshone by the Gilead portfolio, posted up a very impressive $1.4 billion in worldwide sales in 2015, split 50/50 between the US and International markets.

Product: Harvoni

Update: There is little else that can be said about Harvoni. The product hit the right combination of efficacy, safety, and convenience, rocketing to sales of almost $14 billion in 2015.

Product: Invokamet

Update: Invokamet, another SGLT2 antidiabetic, recorded a very strong start, reporting combined sales with the single active version, Invokana, of more than $1.3 billion in 2015.

Product: Triumeq

Update: Triumeq reported strong sales in 2015, about $1.1 billion, and is capturing about one-third of new HIV prescriptions in the first quarter of 2016.

Product: Xigduo XR

Update: AstraZeneca claims in its 2015 Annual Report that its SGLT2 franchise products, including Xigduo XR and Farxiga, had captured more than 400,000 patients by the end of the year.

The Drug Delivery & Formulation Pipeline

So what does the global Drug Delivery and Formulation pipeline look like? How does it compare with the non-drug delivery enhanced/enabled pharmaceutical product pipeline? What is actually meant by the term pipeline? A few short definitions will make this section much easier to understand. It's surprisingly easy to mix up terms like Products and Programs, and be confused by how the numbers add up.

A Product is a pharmaceutical entity that is defined by its brand name and dosage form, but is independent of its stage of development or geography. For example Elecon Cream, Elecon Ointment, and Elecon Lotion are three separate Products. They may have the same actives in the same concentration but different formulations, with separate approvals and branding. Unless capitalized as Product, the term product is used to describe either a Program or Product in a general sense.

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 of which constitute separate Programs. This is why the number of Programs will always exceed the number of Products. This is particularly the case with a cancer pipeline development candidate that may be in Phase II development for a half a dozen different cancer indications.

For the most part, attention will be paid to Products. They best represent the basic number of entities being studied. At the same time, Programs can better give a sense of the breadth of the Pharmaceutical Industry's efforts. For example, a Product that has been Approved and is now Marketed for Depression, may also be in Phase III for Dementia. It's the same dosage form, perhaps an immediate-release tablet, and represents a significant therapeutic opportunity but does not qualify as a separate Product. In this case, the Product represents two separate Programs. Got it? It's not something you normally think about but makes a big difference in how Pipeline numbers are generated and presented. We'll clarify as appropriate in the accompanying text. Products may be considered to be like a bunch of grapes, with the individual grapes being the Programs.

Only publicly disclosed Products and Programs can be counted. This means there is generally a better count of early stage Products and Programs associated with smaller biopharmaceutical companies than Big Pharma. While these smaller companies are quite happy to disclose their pipelines, even as early as Research and Preclinical, larger companies prefer to limit early Program and Product disclosures, often with no obligation to do so. 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 at a post-Phase I stage of development.

The pipeline figures presented exclude Over the Counter (OTC) and Generic Product and Programs. Not only is it difficult to properly keep track of the many Generic Products in the major markets, in many cases there are so many so as to unreasonably dilute and skew the overall figures. For every approved innovator product, there may be a half dozen approved generics.

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, device, 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 end of May 2016.

Definitions

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.

Program - a Program is a Product approved or being developed for a defined indication.

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.

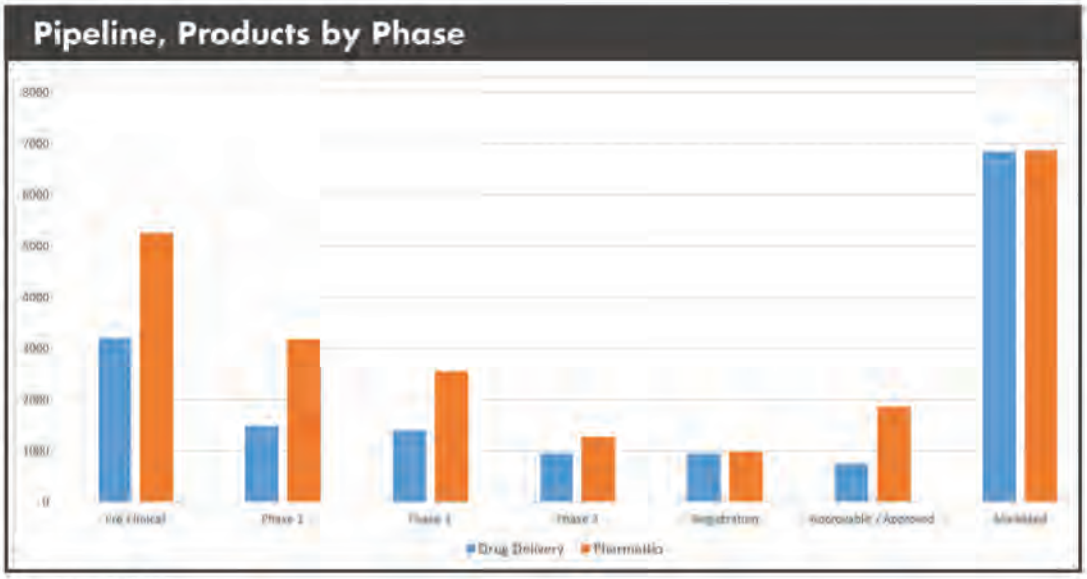
DDEP - Drug Delivery Enabled/Enhanced Product or Program, refers to any agent that requires the use of drug delivery or formulation technology.

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

Products 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.

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 Preclinical Stage, a difference that becomes smaller by the time we look at Phase III Products. This might suggest a trend towards less Drug Delivery & Formulation technology incorporation in the developing 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 and/or delayed-release 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 will be labeled as PharmaBio. At the same time, even an earlier stage product designed for the treatment of asthma by inhalation will be designated as a DDEP product even if the precise inhalation technology is undefined. This explains in part why the number of PharmBio 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.



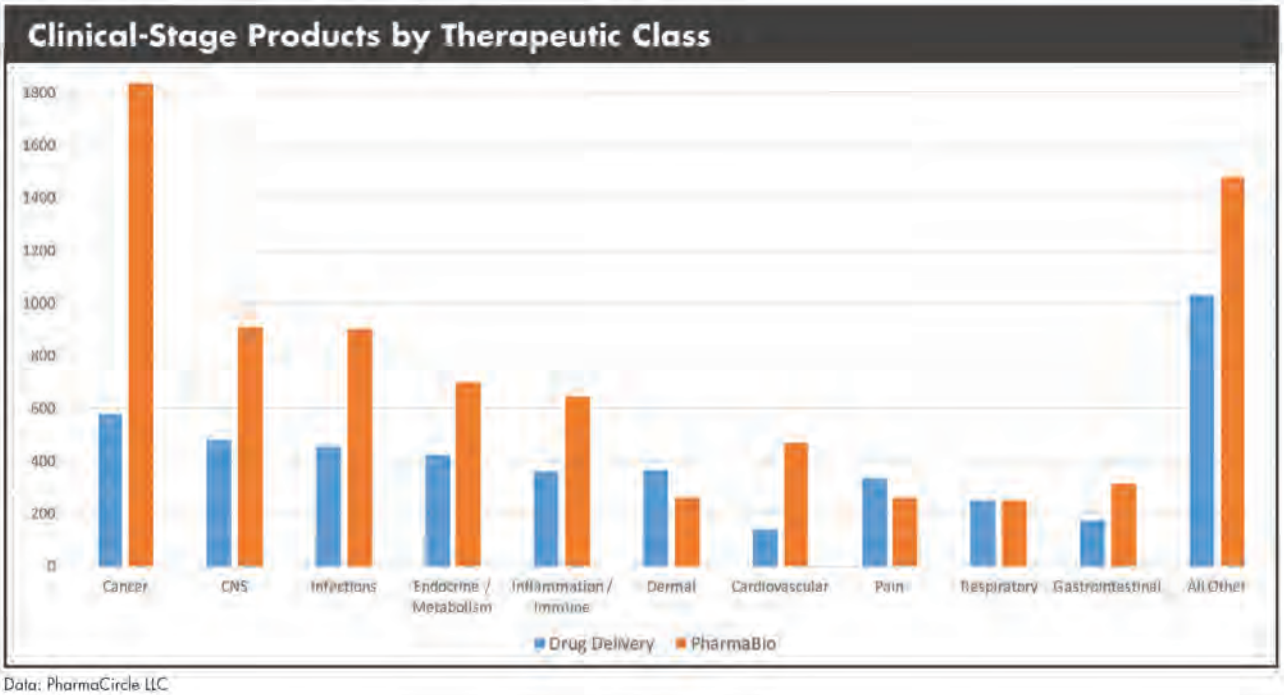
Data: PharmaCircle LLC

Another apparent oddity is the relatively equal number of Phase I and Phase II Products and Programs. Isn't there supposed to be at least some degree of attrition? This may again be an issue of disclosure with larger companies choosing to report Phase II but not Phase I Products and Programs.

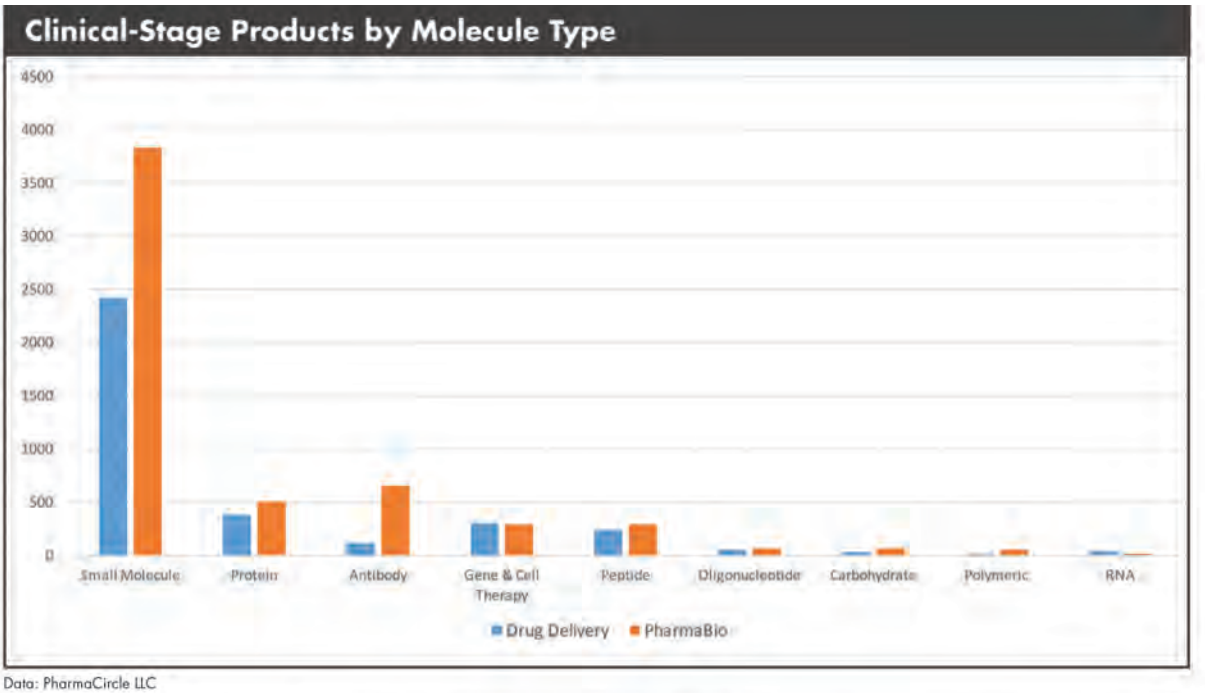
Despite these limitations, there are still some conclusions that can be made regarding the current state of Drug Delivery Enabled/Enhanced Products and Programs.

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 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.



Data: PharmaCircle LLC



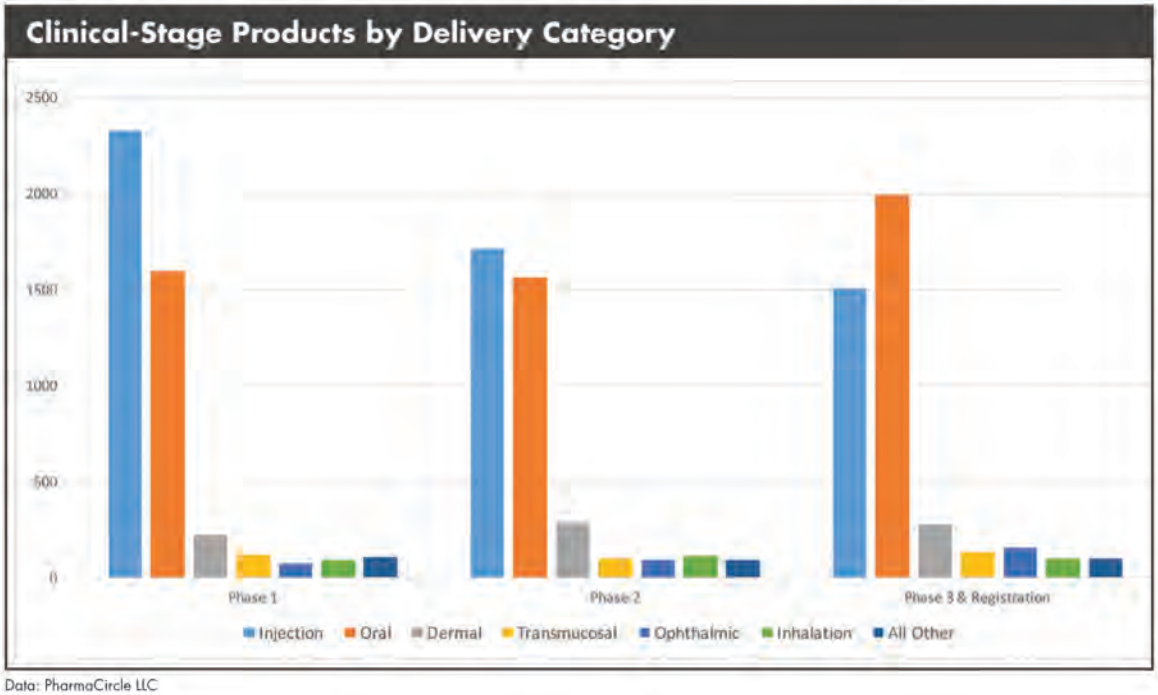
Data: PharmaCircle LLC

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.

Top Ten Therapeutic Classes in Clinical Development

It's interesting to compare DDEP and BioPharma Products as a function of their therapeutic focus. These numbers provide a general sense of where drug delivery and formulation technology is being applied in the development pipeline, and only cover products in clinical development (Phase I to III) or in registration and excludes Marketed and Preclinical products. It's worth prefacing the analysis with the recognition that in many cases, the use of a particular technology may not be announced or obvious for early stage products, tending to skew the results toward BioPharma Products.

Cancer ranks number one by far in terms of the emerging product pipeline, with DDEP products representing about one-quarter of the total. On a proportional basis, Pain and Respiratory represent the most common indications for the application of drug delivery and formulation technologies. The large number of Respiratory DDEP is not surprising given the importance of



Data: PharmaCircle LLC

pulmonary delivery as a major treatment strategy and the associated use of inhalation devices. In the case of Pain, the larger use of drug delivery and formulation technologies relates to the attention being given to sustained-release oral dosage forms, and more recently, abuse-deterrent technologies. The All Other therapeutic categories target Men and Women's Health, Genitourinary, Ophthalmic, Hematology, Musculoskeletal, and other less-common conditions.

Top Molecule Classes in Development

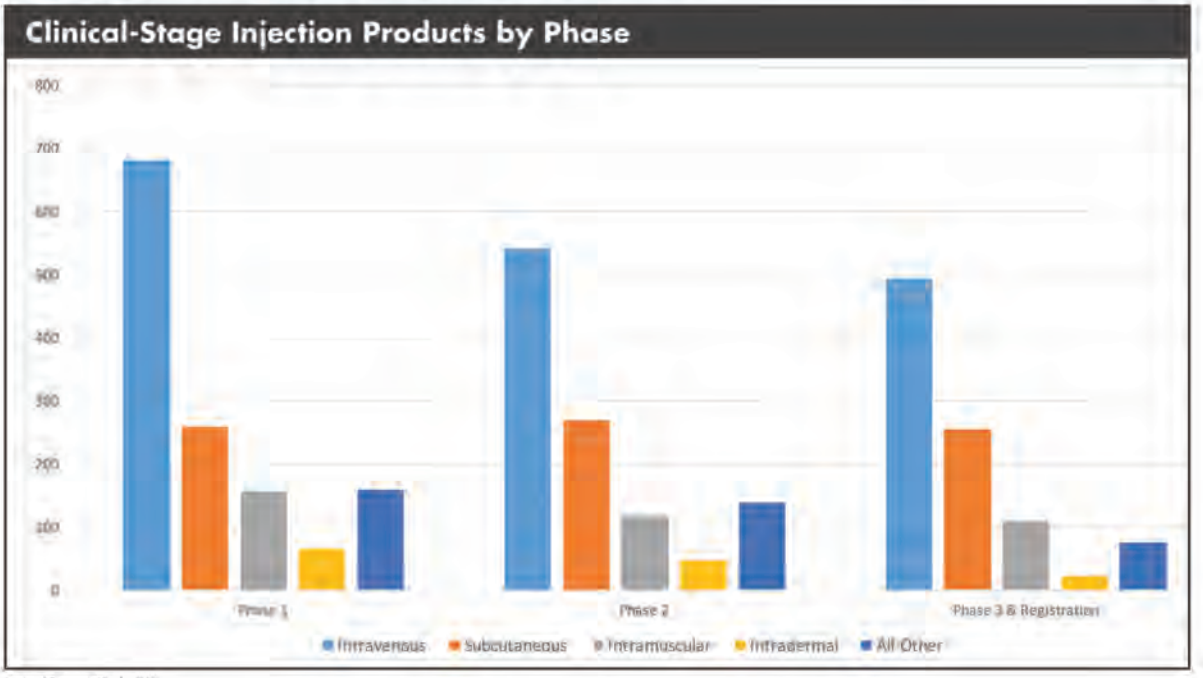
Looking once again at products in clinical development or in registration rather than approved, marketed, or preclinical products, and assessing the use of drug delivery and formulation technology as a function of molecule type confirms some more obvious assumptions. As expected, Small Molecule products constitute the largest number of clinical-stage candidates followed by Proteins and Antibodies. Interestingly, products that involve gene delivery or cell transfection come in at the No. 4 spot, ahead of Peptides. Proteins, Cell & Gene Therapy, and Peptides proportionately depend more heavily on the use of drug delivery and formulation technologies. Unsurprisingly, Antibody products, which are almost always administered by injection, have little reliance on drug delivery and formulation technologies, at least in the clinical development-stage setting. It is likely that many of these products may well make use of drug delivery technologies as they approach and reach the market, most notably devices to simplify and enable outpatient administration.

Top Delivery Categories by Phase

One way to understand where the Pharmaceutical Industry is headed with respect to the use of drug delivery and formulation technologies is to look at the clinical-stage product development pipeline. The data in Figure 4 once again presents the whole Pharma clinical-stage pipeline in terms of Products, rather than Programs. Drawing conclusions is not simple in this case. What we see is a steady increase in the proportion of Oral Products as we go from Phase I to Phase II to Phase III and Registration. Does this reflect a change in the Industry's interest in Injection as evidenced by the more recent Phase I Products, or does it recognize the fact that some products at a Phase I stage of development are only assessed as injectable formulations to gauge tolerability and assess pharmacokinetics? Or, are we once again facing the challenge of many products and programs being developed by Big Pharma only showing up in the public records at a Phase II or later stage of development? It is pretty clear though that Oral and Injection remain the top Delivery Categories for products in development with little indication that this will change anytime soon.

Injectible Delivery

Injection continues to be an increasingly attractive delivery route with the development of more sophisticated devices and technologies able to extend the dosing interval for weeks and months. As seen in the previous section, Injection is the preferred delivery route for early stage clinical development programs, especially for Phase I in which safety and basic pharmacodynamic information is being studied. With the increasing interest in biologics, that also means many macromolecule products have limited delivery route options beyond injection as they approach the market, raising the relative number of injection products. This may change in the future if the considerable challenge of delivering macromolecules orally though inhalation, orally, or transdermally can be met. Interestingly enough, the Intravenous route of administration remains the top injection route through Phase III, although relatively less than what was seen in Phase I. Subcutaneous dosing follows in second place, at about half the level of Intravenous and twice that of Intramuscular products. The All Other category includes a wide variety of injection routes, ranging from intraarticular to intraarterial to intracranial to intravitreal, in total, 37 additional routes. ■



Data: PharmaCircle LLC

Inflection Points 2015

The Pharmaceutical Industry continued to experience significant change in 2015. Stepping back and looking at these changes from a broader perspective suggests that some may have have accumulated to where they will have broad implications for the Industry going forward; what might be called inflection points. In this section, we identify five trends that have reached tipping points of sorts. Recognizing these changes and inflection points can suggest strategies to address the implied challenges and opportunities.

Opiod Abuse

Following 2 decades of increasing concern, it seemed the public and public officials not only took note but insisted on corrective actions. The groundswell of support for changes are likely to have positive and negative outcomes. Pushing too quickly on any matter can lead to poorly thought out actions, and in some cases, overshooting the intended target and objectives. Nonetheless, opioid abuse seemed to become the number one public health issue in America in 2015.

Concern with prescription opioid abuse and overuse is largely confined to the US, a result perhaps of the liberal prescribing of opioids, the absence of a comprehensive healthcare system, and legal and regulatory systems that are designed to move slowly. The result is that opioid overdose deaths have increased year over year for 15 years, accounting for nearly a half million deaths in that period.

Indicators that an inflection point was reached in 2015 was evidenced in numerous ways. These included the US Congress holding more hearings on the abuse of opioids, the increased number of abuse-deterrent opioids moving through the clinic and to approval, and a continuing drop in opioid prescriptions from the peak in 2012. 2015 also saw the approval of another outpatient-friendly treatment for opioid overdose, a nasal formulation of naloxone, in a seemingly interim attempt to stem the lethal consequences of opioid overdoses.

So what does this inflection point imply for the Pharmaceutical Industry? The most obvious implication is that prescriptions and sales of opioids will likely continue to drop for the foreseeable future, or at best hold to current levels. At the same time, more abuse-deterrent opioids will be reaching the market, putting pressure on companies, with the consequence of an escalation in sales and marketing investments to defend or build market share. In the end, it is most likely that managed care formulary providers will have the greatest influence on opioid product success, pushing prescribers to agents that provide the optimal balance of price and abuse-deterrent performance.

It will be interesting to see what the repercussions will be of limiting prescription opioid access. There will certainly be a drop in prescription opioid sales, but will this be accompanied by a drop in abuse- and opioid-related deaths? There are indications that the "street" is starting to see less prescription opioid availability, with black market fentanyl replacing the usual fallback choice of heroin. Much more potent than heroin, it's possible there may be an upcoming fentanyl epidemic that may mirror the experience of when cocaine was superseded by the more potent crack cocaine.

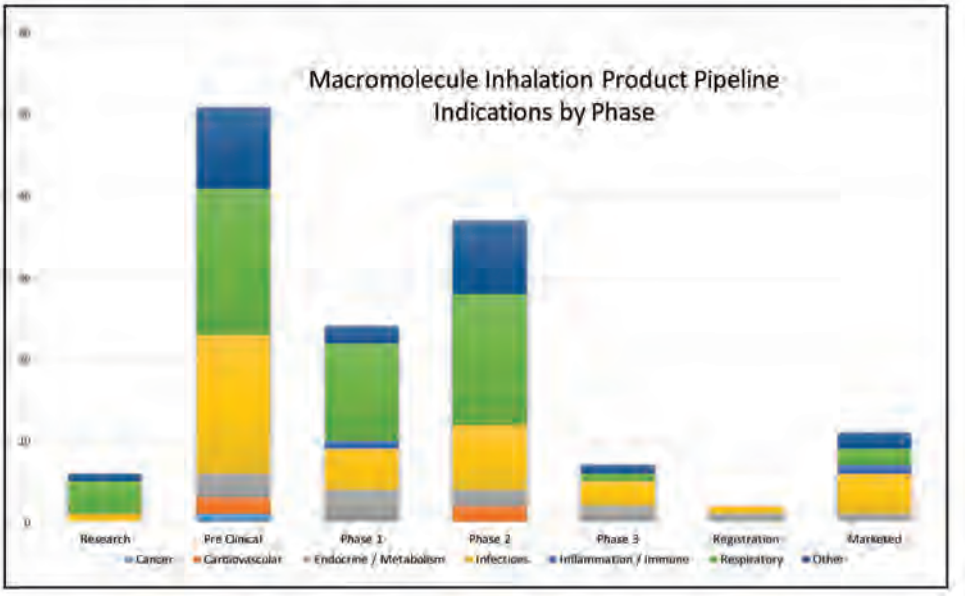
For every action there is a reaction. Things will certainly change, but will the epidemic be stemmed? The answer to the problem is the discovery and development of potent novel analgesics that have no abuse or addiction potential. This may be as elusive as the development of commercial-stage nuclear fusion energy.

Inhaled Systemic Pharmaceuticals

The disappointing commercial performance of Afrezza in 2015 was not only a disaster for Mannkind and their partner Sanofi, but it may also have delivered a fatal blow to the concept of systemic macromolecule delivery through the lung. If not a death-knell, it has probably set things back by as much as a decade. Afrezza's market flop also raises the question of whether the lung is an acceptable port of entry for any systemically acting medication. Despite strong evidence that systemic levels of therapeutics can be achieved when delivered by the lung, it may be that the implied convenience benefits are insufficient to address the safety concerns of patient and healthcare professionals.

The figure below provides a snapshot of the product pipeline for macromolecules being developed for administration by inhalation.

The numbers appear quite impressive and suggest there is significant interest in delivering macromolecule therapeutics by inhalation. Looking a little closer, one finds only one product among the eleven listed as Marketed that has a systemic



therapeutic effect – Afrezza. The remaining products are antibiotics and respiratory medications targeting local, non-systemic indications.

Looking a little further back into the pipeline reveals several products targeted to Endocrine/Metabolism indications. These are for the most part inhaled insulin products that have not yet been formally discontinued; in one case, the product has been listed as being in Phase III for 8 years and still seeking partners.

The delivery of macromolecules for systemic therapeutic effect hit a wall in 2015 for the second time. Is there an appetite for other companies to take on this challenge, with insulin or any other macromolecule? It's not a trivial challenge technically or financially, taking more than a decade and $1 billion for each of the two inhaled insulins to reach approval. Chances are the pipeline for inhaled macromolecules will be thinner in 2016 and 2017 that it was in 2015. Investment will follow the easier opportunities.

Pricing

There is nothing like a pharmaceutical company raising the price of a life-saving drug by 5000% to tip the public's opinion about pharma price increases from annoyance to outrage. Add in an arrogant publicity-seeking executive, and suddenly the playing field has been reset.

Despite reports noting that branded pharmaceutical price increases consistently exceeded the consumer price index over the past decade, the issue never caught the attention of the American Public or Congress. Inklings of a change were evident in 2011 when KV Pharmaceutical acquired the marketing rights to Makena (hydroxyprogesterone caproate), a well-known treatment for preterm labor first approved in 1956, and promptly raised the price from $15 per dose to $1,450 per dose, or $29,000 for a full course of therapy. This so angered patients, physicians, regulators, and politicians that it encouraged the FDA to announce they would not pursue pharmacies from filling prescriptions with compounded equivalents.

While Big Pharma and Specialty Pharma continued to raise prices well beyond cost of living for their patent-protected pharmaceuticals, little attention was focused on the practice. This changed in 2015, when Turing Pharmaceuticals acquired the rights to Daraprim (pyrimethamine), a treatment for toxoplasmosis, a product whose patents had expired in 1953, and raised single tablet prices from $13.50 to $750. The response was overwhelmingly negative, raising the attention of the US Congress.

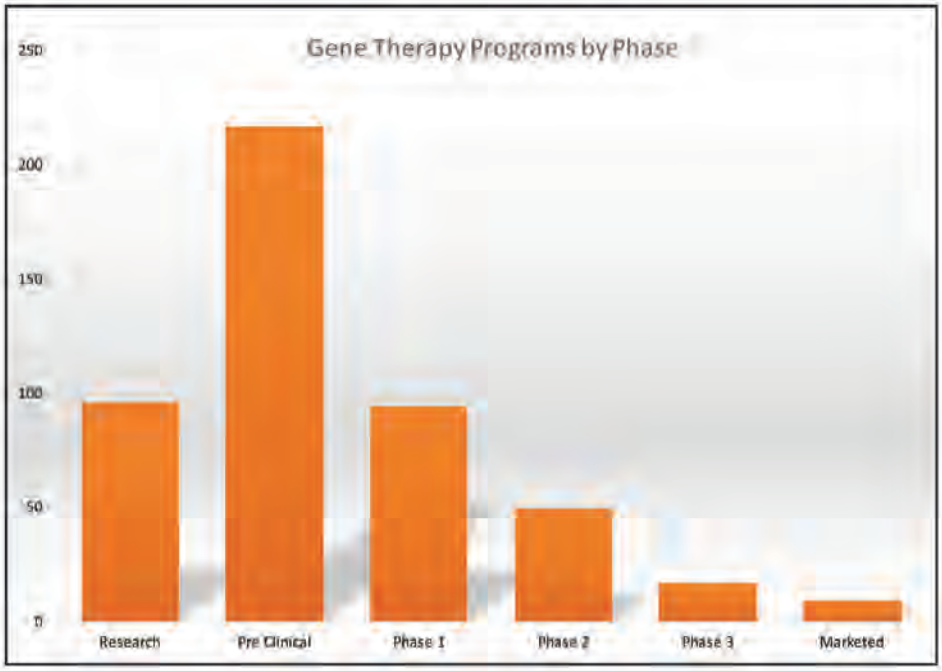
The net effect of the Daraprim pricing affair was to alert business analysts, the public, and federal agencies to the common strategy of companies raising prices in excess of inflation rates to boost income and increase profits. This led to an investigation of Valeant's pricing policies, as well as other companies, that sent their respective stock prices tumbling when it was revealed their profitability was largely dependent on unsustainable price increases.

It is unlikely that pricing will be an issue too distant from the public's, regulator's and the business community's consciousness going forward. This past year saw pricing used as a strategic element in AbbVie's attempt to compete in the Hepatitis C market in the face of an established market leader. And the UK's National Institute for Health and Care Excellence (NICE) continued to put pressure on companies to demonstrate cost effectiveness for new products on par with existing products if they hoped to gain listing on the UK's National Health System formulary.

The strategy of buying niche products and stoking revenue and earnings through large price increases will no longer be a winning approach to corporate development. Many companies that embraced this strategy over the past few years are now scrambling to figure out how to cover the debt they incurred, having assumed this aggressive pricing strategy would continue to yield ongoing outsized profits. The public and payers are not averse to paying premium prices for products that address challenging medical conditions in a cost-effective manner. The benefit just needs to match the price.

Gene Therapy

After nearly 2 decades, Gene and Cell Therapy products and companies were back in the news, in the clinic, and on the market in 2015. Once forecast to be approved in the early 2000s, the prospects for early Gene Therapy approval were dashed by the 1999 death of a patient being treated for Ornithine Transcarbamylase Deficiency with an adenoviral gene therapy at the University of Pennsylvania. Since then, there has been progress, with the first mainstream gene therapy, Chiesi's Glybera for Lipoprotein Lipase Deficiency, approved in Europe in 2012. Although the commercial response has been limited, largely due to its $1-million plus price tag, it achieved an important milestone in the development of Gene Therapy



that was reinforced by the 2015 approval of Amgen's Imlygic, talimogene laherparepvec, a genetically modified herpes simplex virus type 1 expressing granulocyte-macrophage colony-stimulating factor (GM-CSF), targeted to the treatment of melanoma.

The pipeline for Gene Therapy products is remarkably robust. The nine products listed as marketed is a bit misleading as the majority of these products are sold in markets not subject to the same regulatory scrutiny as in the US, EU, and Japan.

Gene and Cell companies also did very well in 2015, raising more than $1 billion to support their clinical development programs. It is likely that 2016 will see an acceleration in the development of these Gene and Cell Therapy products, but success will require these agents to compete with ever-improving protein and antibody products targeted to similar indications. The promise of Gene and Cell Therapy lies in their ability to provide a cure for serious genetic conditions by ongoing expression of a missing protein, replacing the need for regular treatment with protein therapeutics. But after a decade-long hiatus, the 2015 advances in Gene and Cell Therapy portend an exciting future for this novel approach to treatment and Drug Delivery.

Tax Inversions

The favored financial engineering tool of the 2010s for Big Pharma and Specialty Pharma companies hit a major bump in the road in 2015 with pushback from the US Congress and Administration. Tax inversions permitted a company to assume residency in another, lower tax jurisdiction, under certain conditions without a need to change ownership. This allowed the companies to significantly lower their effective tax rate on global profits, increasing overall profitability.

One of the earliest Pharma tax inversions was the merger of ICN and Biovail to create Valeant, and the assumption of a Canada domicile in 2010. This was followed in 2011 with Alkermes' merger with Elan Drug Technologies (Ireland), and in 2012 by Jazz Pharmaceuticals merger with Azur Pharma (Ireland). Things accelerated in terms of the total dollar value of the companies in 2013 when Perrigo and Actavis both assumed Irish incorporation status through mergers, with the Actavis inversion setting the financial foundation for its 2015 acquisition of Allergan. Endo and Horizon Pharma both took on Irish incorporation status in 2014, with Medtronic and Mylan following in 2015. And so the story continued, with some notable failures, AbbVie's overture to Shire, Pfizer's to AstraZeneca, and most recently the Pfizer – Allergan (formerly Actavis) merger.

Changes in US Treasury Department regulations in late 2015, and again in early 2016, has made it much less attractive for companies to undergo a tax inversion transaction solely for tax benefits. There are still financial benefits to be gained with inversion-type mergers, but they need to be bolstered by a strong strategic fit. That is in part the logic of Shire's restatement of their intent to follow through on their $32.5-billion acquisition of Baxalta to create the world's leading company for the treatment of rare diseases.

Going forward, companies will need to deliver profits the old fashioned way: better products. ■

Industry Perspectives

What Surprised You the Most This Past Year?: Your Colleague's Perspectives

Drug Development & Delivery's Global Formulation Report in this issue once again has provided our readers with highlighted (and notable) data on formulation and delivery, devices, fixed-dose combinations, transactions, and what's in the pipeline. We thought it would be interesting to ask some of your colleagues what they believe has surprised them most in the past year, and here is what they said!

"Advances in pharmacogenomics and biological therapies for 'personalized medicine' are in the process of revolutionizing the way we care for patients with cancer and many chronic diseases. Deciphering our human genomic make-up to administer tailor-made medicine for individual patients has unlimited exciting implications for the future. The recent availability of flexible and modular filing equipment has been a key enabling technology for the transition of personalized medicine from R&D to commercial reality. Novel primary packaging solutions will also play a key role in advancing personalized therapies for the future."

- Chris Weikart, PhD, Chief Scientist, SiO2

"Over the past year, we have seen a surge of growth in the Pharma & Biotech industries. Our clients have been putting more emphasis on flexible design within their manufacturing suites. It has interesting to watch the architectural implications that are inherent to flexible design as well as single-use and continuous manufacturing technologies. We have seen a reduction in the size of support spaces to manufacturing and opportunities to address material and personnel flows more efficiently within a facility."

- Christine A. Hofnagel, AIA, Senior Associate, JacobsWyper Architects

"We were surprised by the enormous growth in the biopharma sector. We believe that as the importance of innovative pharmaceutical drugs increases, so will the importance of convenient and modern packaging solutions in glass and plastic. Especially, we developed the MultiShell vials and the GX RTF ClearJect syringes in COP because it's the perfect material to meet the challenges and properties of the new biopharmaceuticals. Suitable syringes and the right vials allow packaging to keep pace with these innovative drugs."

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

"A big surprise this year was a noticeable shift in emphasis from autologous to allogeneic therapies. There is a growing understanding that standardized, commercial-grade biologic products in commercial quantities must be manufactured at a reasonable cost so that they can be widely used. While this has been a long-standing issue in the broader field of cell therapy, the change in emphasis is now evident in Japan's evolving approach to induced pluripotent stem cells, and in the growing efforts to manufacture allogeneic immunotherapies such as allogeneic CAR T-cell Immunotherapies."

- Karine Kleinhaus, MD, MPH, Divisional Vice President, North America, Pluristem Therapeutics

"The still relatively new gene-editing approach, CRISPR/Cas9, has proven to be a powerful tool and comparatively more attainable (easier to make, more cost-effective) research mechanism embraced by scientists across disciplines looking to modify gene structure. It has been impressive to see how rapidly this has moved toward human clinical trials. University of Pennsylvania researchers achieved NIH Recombinant DNA Advisory Committee support for their proposed clinical trial using CRISPR/Cas9 as the next iteration of modifying T cells to fight cancer. Their hope is to attain FDA allowance and approval by their institution to initiate it in 2016, which would make them first in the US. Editas announced late last year their aim to be in the clinic sometime in 2017 with their CRISPR-mediated approach to treat Leber Congenital Amaurosis, an inherited retinal disease impacting children. We look forward to potential advances as U Penn and Editas clinical trials undergo FDA review as we progress our program utilizing CRISPR/Cas9 to treat patients with Fanconi Anemia; an inherited blood disorder impacting young people."

- Michelle Berg, Vice President, Patient Advocacy, Abeona Therapeutics

"The past year has seen a definite shift to the development of higher volume products for subcutaneous delivery. Many small biotech and large pharmaceutical companies' product pipelines for biologicals are focused on delivering higher doses, less frequent administration, or a move to subcutaneous delivery in the home from intravenous delivery in a hospital setting. The ability to deliver higher volume subcutaneous therapies in a comfortable and convenient manner will become increasingly important to facilitate patient uptake and adherence to new therapies. Supporting the user with self-administration also holds great promise for reducing the burden of escalating healthcare costs."

- Michael Hooven, President & CEO, Enable Injections

"In the development of drug delivery systems for drugs and biologics, specifically combination products (CPs), it was most surprising to learn that despite the significant fanfare and reaction to the recent CP regulations issued by the FDA, there is a low perception within organizations that senior management is aware of the full extent and impact of device regulations on their internal drug/biologic development programs."

- Lilli Zakarija, MSME, MBA, Co-Founder & President, EdgeOne Medical Inc

"As continuous manufacturing reaches new heights, the industry is adopting rigorous and robust measures to minimize risks and avoid batch failures. The excipient manufacturers are strengthening their capabilities to supply the high functional quality ingredients to help minimizing those risks and saving time and cost of drug products. High functional excipients have been recognized for their utilities in multiple formulation technologies, conventional and non-conventional. As an example, the high functional excipient, such as copovidone (Kollidon® VA64), has been recognized as a gold standard in hot melt extrusion and in solid dispersion technologies, and on the other hand, it has been used as a dry binder in roller compaction and moisture-activated granulation and is also well suited to continuous manufacturing for increasing solubility of drugs and improving the tensile strength of the tablets."

- Shaukat Ali, PhD, Technical Support Manager, BASF

"Over the last year, the development process for NMEs has continued to become more challenging, with the usual issues of bioavailability and safety being supplemented with other key hurdles, including dose form uniformity, oral delivery of macromolecules, targeted and controlled-release delivery, customer and payer-friendly dose form development, scalability of the manufacturing process, and more. So just when we thought R&D complexity and productivity was tough, things got tougher. Thankfully, at the same time formulation technologies to enable solutions to these challenges have continued to advance, and drug development innovators have more options to get it right earlier, faster, and more efficiently if they plan early, think through their options, and partner with the right technology and formulation experts."

- Elliott Berger, Vice President, Global Marketing & Strategy (CMO), Catalent

"Enormous progress in personalized medicines has evolved over the past year. Yet, there is still a lot to do. In that respect, the integration of patient-customized formulation with drugs designed for individual patients will help achieve some of the progress still in front of us. For example, we continue to hear more and more from industry advocacy groups that there is a great opportunity for better pediatric formulations. What's surprising over the past year is the magnitude of the unmet needs for better formulated medicines for children. We've developed pediatric patient-centric products in the past using our taste-masking technology combined with patient-centric dosage forms, such as ODTs or taste-masked powders sprinkled on food, and we found these pediatric formulations are successful solutions to help parents and caregivers administer medications to children that are acceptable and encouraging compliance to treatments such as HIV, allergy, and pain management/fevers. We're continuing to solve these challenges to help more pediatric patients than ever before. Patients are at the heart of everything we do. Our partnerships with children's hospitals provides a direct resource to identify and help continue to satisfy unmet medical needs for us to help more children."

- Anthony Recupero, PhD, Senior Director Business Development, Adare Pharmaceuticals

"Several observations in the rapidly changing space of biopharmaceuticals. First, that after two decades of declines, the pharmaceutical industry is beginning to achieve greater rates of success with clinical trials from inception to market, indicating increasingly effective early stage screening and more patient-centric therapies. Second, I am impressed with the advances in human microbiome understanding and manipulation in treating disease. Third, I have been surprised that reproducibility initiatives have had issues in replicating clinical studies. And finally, that proving positive pharmacoeconomics does not necessarily justify high drug prices."

- Derek Hennecke, President of Xcelience, a division of Capsugel Dosage Form Solutions

"It's surprising that many pharma companies are not appreciating the power of modeling and simulation (M&S) software tools for formulation design and development. For example, we routinely conduct modeling/simulations to predict how our prototype should behave in order to match the desired target PK profile. It's a unique expertise of ours. Specifically, in the area of taste-masking bitter APIs, M&S can be very useful in determining the maximum amount of coating material that you can apply onto the drug containing particles so that it doesn't jeopardize bioequivalence or bioavailability expectations. We are asked increasingly to provide this solution, and we have the expertise behind it. Specifically, we have been using M&S for many years. M&S software is quite complicated. One of the experts involved in the development of the software made a comment to me that this software uses more differential equations than the program that sends humans onto the moon. To use M&S software efficiently, it requires great knowledge in math, coding, statistics, biopharmaceutics, and pharmacokinetics, etc. It takes years to develop the expertise to use it properly and efficiently. To understand the assumptions and limitations, to ask the right questions, to know if you have a good model, to know if the prediction is plausible…all of these take time and efforts, and we have M&S specialists who know how to make the best use of it."

- Jin-Wang Lai, Senior Director, Formulation & Analytical Labs, R&D, Adare Pharmaceuticals

"First, there was the impressive number of drug approvals in 2015. Great news of course! But it wasn't the sheer number that struck the attention, not so much as the nature, the efficiency, and speed by which these approved drugs had reached market. For instance, the majority (87%) of the 45 new drugs were receiving FDA approval on a first-try basis, without having to provide additional info to the FDA. In the not so distant past, only half the IND applications made it through the first round. In fact, the average time for drug approvals, counting from the moment FDA grants permission for human studies up to approval, was 7.5 years. With the FDA's expedited review processes, however, we saw that time reduced to an average of 5.2 years. Additionally, of the 11 drugs falling in the breakthrough category, 3 received expedited status, taking as little as 4.3 years! Is this the dawn of a new era where the industry and regulators finally get each other's pulse?"

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

Technology & Services Showcase

Excipients & Surfactants

ABITEC
AN ABF INGREDIENTS COMPANY

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THE POWER TO MAKE

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Global CRMO

AMRI®
Albany Molecular Research Inc.

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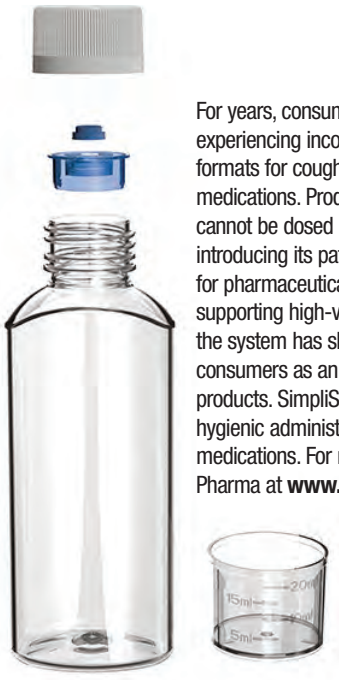
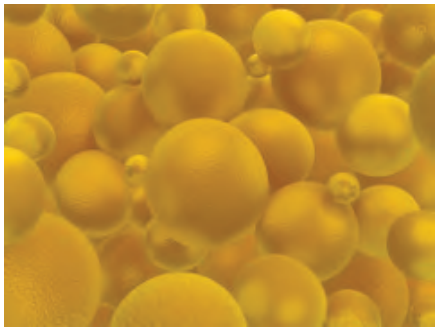
Technology & Services Showcase

Liquid Formulation Dispenser



For years, consumers and patients have been experiencing inconvenient and annoying packaging formats for cough and cold syrups and other liquid medications. Products are difficult to use; drugs cannot be dosed easily. **Aptar Pharma** is introducing its patented SimpliSqueeze™ technology for pharmaceutical applications. Successfully supporting high-volume consumer brands for years, the system has shown to be widely accepted by consumers as an added value feature for liquid products. SimpliSqueeze allows for precise and hygienic administration of all kinds of liquid medications. For more information, visit Aptar Pharma at **www.aptar.com/pharma.**

Nanoemulsion Formulations



Ascendia Pharmaceuticals offers services for contract formulation development of poorly soluble drugs. Our formulation approaches include nanoemulsions, amorphous solid dispersions, and nanoparticles. These technologies are suitable for oral or injectable delivery of drugs that are challenging to formulate. EmulSol is our technology for production of oil-in-water nanoemulsions, with droplet sizes in the range of 50-500 nanometers. Ascendia's process is novel in that it uses no organic co-solvents, and minimal surfactants. Our nanoemulsions use a high-shear homogenization process to create a suspension of the oil droplets in a water phase, with the drug solubilized within the interior of the oil droplets. Thus, when the nanoemulsion is delivered to the body, the drug is more readily bioavailable. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

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CAPSUGEL®

BEND RESEARCH™ encap drug delivery

Capsugel's Dosage Form Solutions business unit, with the addition of Bend Research and Encap Drug Delivery, solves customers' most pressing product development challenges, including bioavailability enhancement, modified release, abuse deterrence, biotherapeutic processing, and inhalation formulation. We utilize an integrated product development approach ensuring that our clients can rely on one partner from design to commercial-scale production of innovative drug product intermediates and finished dosage forms. Capsugel Dosage Form Solutions accelerates and improves product development through an array of technologies, including lipids and liquids, spray-dried dispersions, hot-melt extrusion, and through specialized manufacturing, including FDA/MHRA-accredited finished dosage sites that can handle highly potent, controlled substance, hormonal, and oncology compounds. High-quality science and engineering is core to our offering at each stage of the product development cycle and has enabled the successful advancement of hundreds of compounds. For more information, contact Capsugel Dosage Form Solutions at (541) 382-4100, dfsinquiry@capsugel.com, or visit **www.capsugel.com/dfs.**

Technology & Services
Showcase

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CRODA

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Technology & Services Showcase

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Technology & Services Showcase

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DELIVERY PLATFORM

Encochleated Drug Formulations: Enhancing Efficacy, Minimizing Toxicity

By: Roelof Rongen, MBA, MS

ABSTRACT

Drugs for serious fungal and microbial infections currently require intravenous administration at doses that are associated with significant toxicity. Orally administered, encochleated formulations of broad-spectrum fungicidal and anti-microbial medications may provide delivery of anti-infective drugs at therapeutic levels while minimizing drug-associated side effects. This mode of administration may also be applicable to other types of drugs that may be toxic at therapeutic doses.

INTRODUCTION

Fungal diseases present ongoing serious clinical challenges worldwide. These diseases include invasive candidiasis and aspergillosis, associated with 20% to 40% and 20% mortality rates, respectively. Opportunistic infections caused by cryptococcosis remain the most common cause of fungal disease- related deaths, occurring most frequently among HIV-infected individuals, those taking high doses of corticosteroid medications or undergoing chemotherapy, and in patients with immunodeficiencies, and some hematologic disorders.

Among HIV-infected individuals, about 1 million cases and 625,000 deaths from cryptococcosis occur annually due to the development of central nervous system disease. In the US, candida remains the fourth most common cause of healthcare-associated bloodstream infections, and according to the CDC, in some hospitals, it is the most common cause, with infections tending to occur among the sickest of patients. Some candida strains have become increasingly resistant to first-line and second-line anti-fungal treatment agents, with recent data demonstrating a marked shift among infections toward candida species with increased resistance to antifungal drugs, including azoles and echinocandins.[1]

While the drugs amphotericin B (AmB) and azole antifungals have provided effective therapy, the high incidence of infusion-related toxicity and nephrotoxicity with amphotericin B and the emergence of fluconazole-resistant strains of candida have prompted the search for therapeutic alternatives. Due to its toxicity, use of amphotericin B to treat a wide range of systemic fungal infections remains generally restricted to severe fungal infections in critically ill, or immunocompromised patients, but it remains the first-line therapy for invasive mucormycosis infections, cryptococcal meningitis, and certain aspergillus and candida infections.

The relatively new drugs echinocandins (anidulafungin, caspofungin, and micafungin) have been established in clinical guidelines and practice as primary treatment options for moderately to severely ill patients with invasive candidiasis. But while the echinocandins are among the best tolerated and safest class of available antifungals, acquired resistance to them has been increasingly reported, especially in C. glabrata.

Similar to other large lipopeptide antibiotics, echinocandins have limited oral bioavailability, requiring intravenous infusion.

A UNIQUE APPROACH: COCHLEATE LIPID-CRYSTAL NANOPARTICLE- TARGETED DRUG DELIVERY TECHNOLOGY

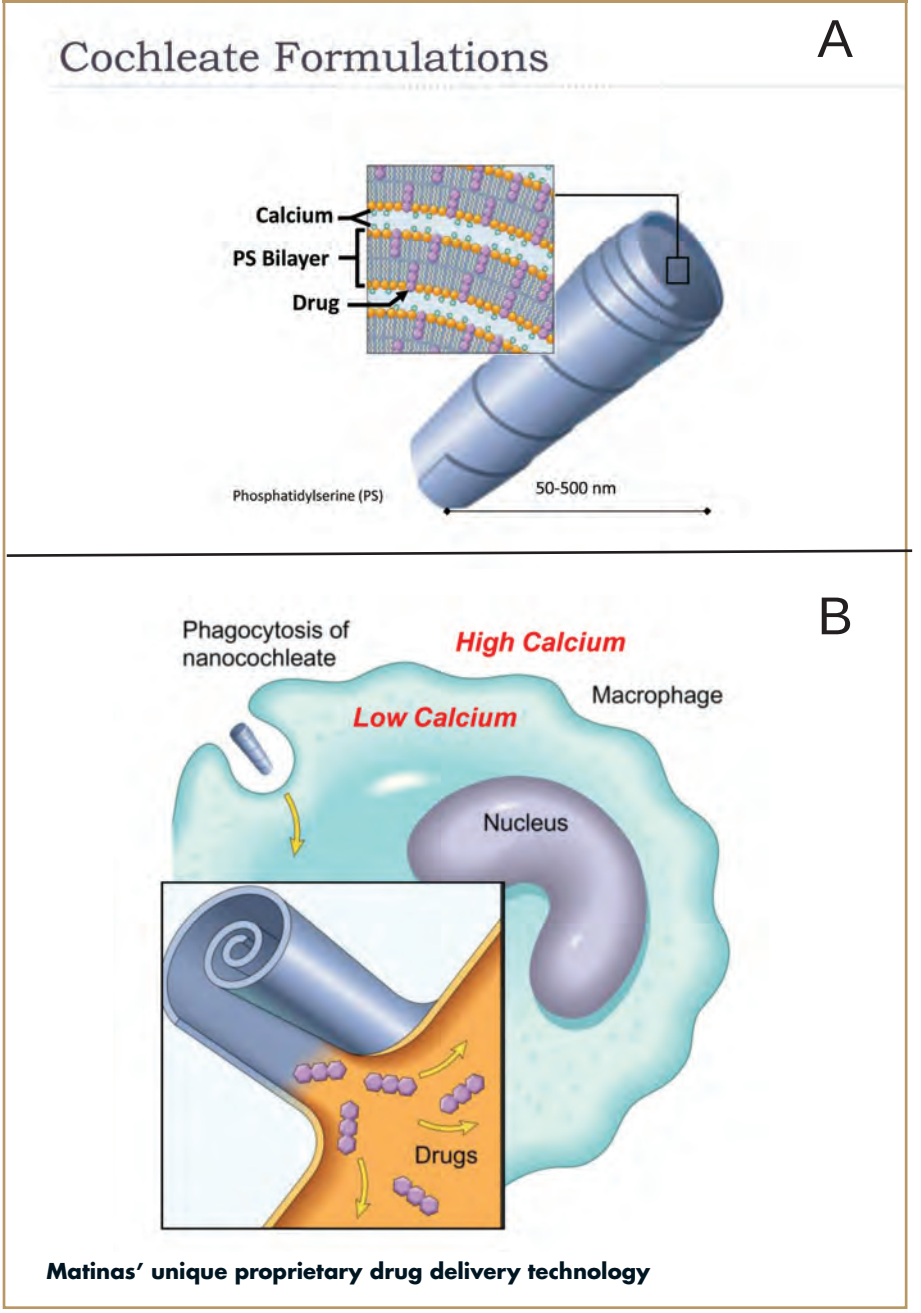
Unique approaches to treating these diseases that may provide effective anti-fungal treatment while minimizing severe toxicities include the development of such agents in unique formulations. Matinas BioPharma, a clinical-stage biopharmaceutical company focused on identifying and developing anti-fungal and anti-bacterial therapeutics for life-threatening infections, is currently testing its most advanced product, MAT2203, an orally administered, encochleated formulation of the broad-spectrum antifungal medication amphotericin B (AmB) for the treatment of serious and life-threatening fungal infections.

Developed by Raphael J. Mannino, PhD, Matinas' Chief Technology Officer, encochleation technology provides a unique means of formulation for drugs formerly deliverable only intravenously. Cochleates have a multilayer crystalline, spiral structure with no internal aqueous space that forms when a series of solid lipid sheets roll up and capture drug molecules in between the sheet, a process referred to as encochleation.[2,3]

Encochleation technology involves combining calcium and soy-derived phospholipids (PS), two naturally occurring materials, through a controlled crystallization process to envelop an Active Pharmacological Ingredient (API), such as AmB. The resulting lipid-crystal encochleated drug formulation of nano-sized particles, once administered, are engulfed by macrophages or other phagocytic cells. Lower calcium levels inside the macrophage compared to the high level of calcium outside the macrophage triggers the cochleate to open, thus releasing the drug inside the cell. Because the drug is sequestered in the solid cochleate particle or in the target cells, the rest of the body is protected from the toxicity of the desired medication.

In summary, the unique structure of the cochleate protects the compounds inside even though the outer layers of a cochleate may endure exposure to harsh environmental conditions or digestive tract enzymes. Cochleate technology allows for oral administration with targeted delivery to infection sites, as the cochleates are taken up by macrophages, which then travel to the site of infection and release the drug. Toxic drugs are sequestered until transported to the site of infection, thus decreasing their side effects, and potentially allowing efficacy at lower doses than achievable by other means of

FIGURES 1A&B



Matinas' unique proprietary drug delivery technology

administration.

Preclinical study results presented at the 2015 American Society for Microbiology's Interscience Conference of Antimicrobial Agents and Chemotherapy and International Society of Chemotherapy's International Congress of Chemotherapy and Infection (ICAAC/ICC 2015) showed encochleation technology's potential in delivering effective drugs at non-toxic levels to infected tissues. In the preclinical study, mice were infected with cells of Candida albicans. After infection, they were treated for 14 days with control, DAmB (Amphotericin B deoxycholate) 2 mg/kg intraperitoneal, or CAmB (MAT2203) 10 mg/kg oral.

MAT2203: ENCOCHLEATED FORMULATION MITIGATES SIDE EFFECTS & TOXICITY OF AMPHOTERICIN B

Study results showed that in Candida-infected mice, MAT2203 was taken up from the gastrointestinal (GI) tract resulting in significant concentrations of AmB in targeted tissues, but undetectable AmB levels in plasma. CAmB remained at 2x to 3x the minimal inhibitory concentration (MIC), whereas DAmB causes tissue levels to increase to 4x to 40x the MIC. The authors concluded that in Candida-infected mice, orally administered CAmB is taken up from the GI tract resulting in significant tissue concentrations above the MIC level. Contrary to DAmB, concentrations of AmB from CAmB accumulate rapidly in the tissues without escalating to extremely high levels during the second week of treatment, potentially mitigating side effects and toxicities.[4]

In a clinical Phase Ia single-dose, double-blind, dose-escalating, pharmacokinetic (PK) study of 48 healthy volunteers, oral CAmB demonstrated a positive safety and tolerability profile with no adverse events reported. These preclinical and clinical studies study provided support for multi-dose pharmacokinetic studies and Phase II efficacy studies for oral administration of CAmB.

Based on these results, Matinas Biopharma, in collaboration with the National Institutes of Health/National Institute of Allergy and Infectious Disease (NIH/NIAID), is currently enrolling patients in a Phase IIa open label clinical study of MAT2203. The study will assess the efficacy, safety, and pharmacokinetics of oral cochleate amphotericin B (CAMB) in the treatment of mucocutaneous candidiasis infections in patients who are refractory or intolerant to standard non intravenous therapies, with initial data anticipated in 2016.

Specifically, NIAID researchers, led by Principal Investigator Alexandra Freeman, MD, of NIAID's Laboratory of Clinical Infectious Diseases, will proceed with a Phase IIa, open-label, dose-titration study to assess the efficacy, safety, tolerability, and pharmacokinetics of MAT2203 in hereditary immuno-deficient patients with a recurrent or chronic mucocutaneous candidiasis infection (esophageal, oropharyngeal, vaginal) that is refractory to standard or tolerated non-intravenous therapies. These patients often develop candida infections that are resistant to treatment with standard anti-fungal regimens. This study is designed to enroll up to 16 patients, and will include 14-day dosing and evaluation periods. Depending on clinical response during each treatment period, investigators will have the ability to continue the effective dose for 28 total days or increase the dose of MAT2203 up to two times and extend treatment to a maximum of 54 days.[5]

MAT2501: ENCOCHLEATED FORMULATION OF AMIKACIN SHOWS ORAL BIOAVAILABILITY & TARGETED DELIVERY

Matinas is also developing a lipid-crystal nanoparticle formulation of amikacin, MAT2501, the company's lead antibacterial compound, an aminoglycoside antibiotic used to treat severe, hospital-acquired infections, including Gram-negative infections. Generally used as a last resort medication against multi-drug-resistant bacteria, the drug is administered either IV, intramuscularly, or through a nebulizer.

All aminoglycosides carry the potential risk of nephrotoxicity, with the risk being greatest in those with impaired renal function. A reduction in dosage is usually necessary if evidence of renal dysfunction occurs. Treatment with aminoglycosides can cause neurotoxicity in the form of hearing loss, numbness, skin tingling, muscle twitching, and convulsions; therefore, a need exists for an aminoglycoside formulation that would reduce the potential for this toxicity and allow for oral dosing.

On December 31, 2015, the company filed an Investigational New Drug (IND) application with the US FDA for, MAT2501. Company president and

"Matinas BioPharma's technology provides three unique benefits, including oral administration and bioavailability of medicines, which today are only able to be delivered intravenously, multi-organ protection from otherwise highly toxic compounds in a stable, solid particle, and delivery directly to sites of infection and/or inflammation, with the potential to achieve rapid tissue penetration, days ahead of therapeutic availability with injected drugs."

CEO noted that in "In preclinical studies, MAT2501 was shown to have oral bioavailability and provide targeted delivery of the powerful antibiotic, amikacin, directly to the site of infection in both disseminated non-tuberculous mycobacterium (NTM) infections as well as in NTM-lung diseases." Upon its review, the FDA gave the go-ahead to start the proposed Phase I study on January 29, 2016.

NTM has emerged as chronic infection posing a significant medical problem in a significant Orphan population (50,000-90,000 US patients). Approximately 40% of NTM patients become refractory to the standard 3-drug guideline regimen and needs alternative treatments.

MATINAS FAST-TRACK TO A SOLUTION FOR MULTI-DRUG-RESISTANT INFECTIONS

To date, the FDA has granted MAT2203 Qualified Infectious Diseases Product (QIDP) status with Fast-Track status for the treatment of invasive candidiasis and aspergillus, as well as QIDP for MAT2501, for the treatment of non-tuberculous mycobacterium (NTM) infections. Qualified Infectious Disease Product (QIDP) designation, provided under the Generating Antibiotic Incentives Now Act (GAIN Act), offers certain incentives for the development of new antibacterial or antifungal drugs, including eligibility for Fast-Track, priority review and, if MAT2203 and MAT2501 are ultimately approved by the FDA, eligibility for an additional 5 years of marketing exclusivity.

As MAT2203 and MAT2501 proceed along the clinical development pathway, Matinas continues to develop encochelated formulations for other drugs. Atovaquone, an alternative agent for prophylaxis and treatment of Pneumocystis pneumonia (PCP) and toxoplasmosis, is limited clinically by poor patient tolerability, saturable oral absorption, and nonlinear pharmacokinetics. PCP, an opportunistic fungal infection of the lung, is often lethal if not adequately treated. PCP typically affects patients who are immunocompromised, such as patients with HIV or who have undergone medical therapies involving chemotherapy, immune-suppressants, or a transplant.

In a preclinical study by Kumar et al conducted to determine the pharmacokinetics and efficacy of encochleated Atovaquone (CATQ) in immunocompromised mice infected with P. murina, CATQ performed significantly better than commercially available atovaquone, providing an atovaquone formulation promising for both treatment and prevention of PCP. Further studies of CATQ are underway.[6]

COCHLEATE TECHNOLOGY BRINGS THREE BENEFITS: ORAL ADMINISTRATION, REDUCED TOXICITY & TARGETED DELIVERY

Matinas BioPharma's technology provides three unique benefits, including oral administration and bioavailability of medicines, which today are only able to be delivered intravenously, multi-organ protection from otherwise highly toxic compounds in a stable, solid particle, and delivery directly to sites of infection and/or inflammation, with the potential to achieve rapid tissue penetration, days ahead of therapeutic availability with injected drugs.

While Matinas BioPharma is initially focusing on using the technology to improve the safety and oral bioavailability of toxic antimicrobial therapeutics, promising preclinical and Phase I data, combined with the broad applicability of this delivery platform, indicates potential success in reformulating many drugs to take advantage of the oral bioavailability, improved safety, and targeted delivery made possible using cochleates.

Work with encochleated with anti-virals (ability to attack reservoirs), anti-inflammatories (no GI-lesions in preclinical animal studies), and vaccines (significant improvement on traditional flu vaccines) is also underway.◆

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BIOGRAPHY

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Drug Development
EXECUTIVE

Jeffrey Bacha, MBA
Chairman & CEO
DelMar Pharmaceuticals

DelMar Pharmaceuticals: Polishing NCI Diamonds in the Rough With Modern Science

DelMar Pharmaceuticals, Inc. was founded to develop and commercialize new cancer therapies in indications where patients are failing or have become intollerant to modern targeted or biologic treatments. The company's lead drug in development, VAL-083, is currently undergoing clinical trials in the US as a potential treatment for refractory glioblastoma multiforme. VAL-083 has been extensively studied by the US National Cancer Institute and is currently approved for the treatment of chronic myelogenous leukemia and lung cancer in China. Published preclinical and clinical data suggest that VAL-083 may be active against a range of tumor types via a novel mechanism of action that could provide improved treatment options for patients. Jeffrey Bacha, Chairman & CEO of DelMar Pharmaceuticals, recently spoke with *Drug Development & Delivery* about the company's unique approach to developing VAL-083, the challenges in working within cancer indications associated with low survival, and the importance of strategic collaborations with universities and organizations to further develop its technology.

Q: Can you please provide some background on DelMar Pharmaceuticals for our readers?

A: DelMar was founded by myself and Dennis M. Brown, PhD, in 2010 around a drug candidate identified from prior work conducted by the US National Cancer Institute. VAL-083 had been studied in more than 40 published clinical trials sponsored by NCI. These studies demonstrated promising clinical activity against a number of tumors; however, like several other promising drug candidates of the era, VAL-083 was never commercialized. DelMar's strategy is to leverage that promising historical data with a robust, modern understanding of the drug's mechanism of action to identify opportunities to solve unmet clinical needs in the treatment of cancer today.

Q: How does DelMar's VAL-083 work and why is it so unique?

A: VAL-083 is a type of chemotherapy known as an alkylating agent. Alkylating agents bind to a tumor cell's DNA to interrupt cellular processes and kill the tumor. They are among the oldest types of cancer therapy still in use today. What we have demonstrated through our research in collaboration with institutions, such as MD Anderson Cancer Center and the BC Cancer Agency, is that the way VAL-083 binds to the tumor's DNA is different than other alkylating agents. This suggests – and our data supports – that VAL-083's activity is not subject to the same resistance mechanisms that hinder other treatments. Therefore, we have an opportunity to treat chemo-resistant cancers, and to consider combination therapies with other agents, including other chemotherapies and immunotherapy. Additionally, VAL-083 crosses the blood brain barrier. Most chemotherapies cannot. This provides an opportunity to treat brain tumors, which has been our primary area of clinical focus to date.

Q: How critical is historical data for a developing line of cancer therapies?

A: It is not critical, but it is certainly helpful in accelerating development as well as reducing cost, risk, and time to market.

Q: What are the top clinical indications for VAL-083?

A: Our focus is driven by our modern understanding of VAL-083's unique mechanism juxtaposed against historical clinical data from prior NCI-sponsored clinical trials. The first place this strategy has taken us is glioblastoma multiforme (GBM), which is the most common and aggressive form of brain cancer. Therapeutic options for GBM patients are limited, and patients who fail front-line therapy have a very poor prognosis.
The current standard-of-care in the treatment of GBM is surgery followed by chemotherapy combined with radiation. The challenge is that two-thirds of the patients diagnosed have tumors resistant to the chemotherapies available [mainly a drug called temozolomide (Temodar)]. Fortunately, researchers have developed an understanding of why patients fail Temodar – it is due to the activity of a DNA repair enzyme called MGMT. We have shown that VAL-083 is active independent of MGMT-mediated resistance mechanisms. That fact, combined with historical clinical data demonstrating activity of VAL-083 in the treatment of GBM give us confidence that we have an opportunity to treat patients whose tumors have failed or exhibit features making them unlikely to respond to Temodar. We have recently completed a Phase I/II clinical trial in refractory GBM.
Additional indications of interest – driven by our research into VAL-083's mechanism of action and historical clinical data – include non-small cell lung cancer, ovarian cancer, and childhood brain tumors. The FDA has granted VAL-083 an orphan drug designation for glioma, ovarian, and a type of childhood brain cancer known as medulloblastoma.

"VAL-083 is a type of chemotherapy known as an alkylating agent. Alkylating agents bind to a tumor cell's DNA to interrupt cellular processes and kill the tumor. They are among the oldest types of cancer therapy still in use today. What we have demonstrated through our research in collaboration with institutions, such as MD Anderson Cancer Center and the BC Cancer Agency, is that the way VAL-083 binds to the tumor's DNA is different than other alkylating agents."

Q: What are the challenges in working within cancer indications commonly associated with low survival expectations?

A: The biggest challenge is that the patients may be so sick that even if your drug works, it may be too late to help them in a meaningful way. To date, our data supports the potential to increase survival in refractory GBM patients who currently have a median survival of 2 to 5 months. We're excited to be able to offer a potential new therapy for these patients, but now that we have confirmed a dosing regimen for advanced clinical trials in refractory GBM, we will also begin exploring opportunities for newly diagnosed patients with a high expression of MGMT (the enzyme responsible for Temodar resistance). Being able to offer an effective therapy to these patients – before they are at the end stage – is where we hope to make the biggest impact in the treatment of GBM.

Q: How has DelMar established collaboration with MD Anderson and the University of British Columbia's Vancouver Prostate Center?

A: DelMar operates largely as a virtual company. Establishing research relationships with leading academic medical centers, such as MD Anderson, the University of British Columbia, the Mayo Clinic, and UCSF, have enabled us to access leading minds in our field and world-class infrastructure while maintaining our expenditures at a manageable level. In some cases, we have long-standing relationships with the researchers, in others, we have approached key investigators based on mutual interest or expertise described in their published research.

Q: What are the next steps for DelMar?

A: We presented top-line data from our refractory GBM trial at the American Association for Cancer Research (AACR) annual meeting and recently held an End of Phase II meeting with the FDA to discuss advancing VAL-083 into a pivotal Phase III clinical trial. We were very pleased with the FDA's feedback, and we look forward to advancing to Phase III as soon as practical. We also plan to expand our clinical focus into newly diagnosed GBM and lung cancer during 2016.
From a corporate perspective, we have taken steps to "up-list" our shares from the OTCQX to a senior US stock exchange – NASDAQ or NYSE – which we believe will position us to access the capital necessary to support late-stage clinical trials, continue to build our business, and unlock liquidity and value for our shareholders. ◆

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Combination Corner

Keys to a Robust Combination Product Design Verification & Validation

By: Lilli Zakarija, MSME, MBA

"How many samples do I need for testing?" This is the one of the most frequently asked questions as a device enters into the verification and validation phase of a device development program. Usually my response is one or all of the following:

- What does your Verification and Validation (V&V) Plan say about sample size, test method, and acceptance criteria?
- Have you conducted your risk assessment, and have the risk rankings been taken into account in establishing the acceptance criteria?
- Have you finalized your product requirements document (PRD)?

The responses to these questions shed light on whether or not the device development team has invested the appropriate amount of time to define critical design control activities that collectively would help identify the necessary samples required for testing. If these activities haven't been completed, which is sometimes the case, the team simply isn't ready to initiate design verification testing.

When discussing V&V testing, it is also important to keep in mind the difference between verification and validation. Verification means confirming the product has been designed correctly (robustness, reliability of performance against defined requirement/specifications, and integrity of product during worst-case conditions, such as temperature, drop, etc). Validation, on the other hand, seeks to confirm that the right product has been designed for the intended target market (is the final product what the end-user needs, and will it achieve the desired therapeutic benefit?).

COMMON PITFALLS IN V&V TESTING

The recent FDA regulations on Combination Products (CP) indicate that if the secondary constituent of the CP is a device, the device component development must be documented per, among other requirements, Design Controls. The Design Control process is typically defined as a multi-stage development approach from concept to commercialization. For the purposes of this article, the five phases are:

1. Concept
2. Planning
3. Design & Development
4. V&V
5. Manufacturing Transfer & Commercialization.

In order to achieve a successful V&V (the fourth stage), certain activities within each of the prior phases needs to be thoroughly completed. It is within the context of this phased approach that two common mis-steps, which can hinder execution of a successful V&V, are further discussed.

TABLE 1

Criteria	Topical Application	Subcutaneous Injection
Frequency of Hazard: Particulate in Delivered Product	High[1]	High[1]
Seriousness of Harm	Low	High
Resulting Risk to Patient	Acceptable	Unacceptable
Performance Metric	Attribute Data	Attribute Data
Acceptance Criteria[2]	90% confidence, 85% reliability	95% confidence, 95% reliability
Sample Size (per ANSI/ASQ Z1.4)	**14**	**58**

Note 1 – In this example, the occurrence of the failure is given a "High" rating because the device design is new (custom needle, custom stopper, etc), and at present, there is no historical data available to support a rating other than High.

Note 2 – The acceptance criteria selected in this example is for illustrative purposes only. Each development team must establish the desired acceptance criteria parameters for its own product.

1. Incomplete Requirements Within a PRD

In the planning phase of the project, the cross-functional team of drug + device team members will collectively develop the combination product requirements document (PRD). When the document is being drafted in the early phases of device and drug development, it is expected that there will be some requirements that are still unknowns that can only be established as either the device and/or drug is further developed. From a business and product development perspective, the team will need to determine whether it makes sense to delay device development efforts until those requirements can be defined or clarified.

Take as an example a new drug that will be delivered via a custom designed delivery device. The device will function as a container for the drug and diluent, upon activation mixes the two components, and then dispenses the final product topically onto the skin surface. The team collectively understands the type of device it wants to develop for its target customer base, yet the drug team at this stage of development is unable to confirm if the dose volume will be 3 mL or 6 mL. In the early planning stages, the PRD can be drafted to include a target range of volume, but the minimum dose volume requirement may need to be identified as a TBD. It is not uncommon for a development team to issue the PRD with a TBD, and during the Design Review, acknowledge that the TBD is present and needs to updated when additional information is available relative to the drug.

While the TBD was acknowledged in the planning phase, if the development team does not establish and commit to a timeframe by which the TBD must be resolved, the unresolved TBD will resurface as an issue when V&V protocols are being drafted or when testing is already completed and data analysis cannot be completed because the requirements have not been defined. While it seems like an unlikely scenario, these types of issues typically occur when teams fall victim to scope creep, tight timelines, critical team member turnover, or other factors.

It should also be noted that the TBD can even prevent the device team from proceeding to V&V because technically the Design Freeze (a critical product development milestone in the Design and Development stage) cannot happen without resolution of the open TBD requirement. Following on the example presented above, the drug volume is necessary to define corresponding device components for mixing, overall device size, or other design characteristics that are influenced by the necessity to accommodate the appropriate volume, but keep the device as small as possible.

2. Outputs of Risk Analysis are NOT Incorporated Into Test Acceptance Criteria

Conducting a risk assessment of the combination product is an activity that is initiated in the planning stages of the development process, and the assessment is continuously updated throughout the subsequent phases of the project as

"When discussing V&V testing, it is also important to keep in mind the difference between verification and validation. Verification means confirming the product has been designed correctly (robustness, reliability of performance against defined requirement/specifications, and integrity of product during worst-case conditions, such as temperature, drop, etc). Validation, on the other hand, seeks to confirm that the right product has been designed for the intended target market (is the final product what the end-user needs, and will it achieve the desired therapeutic benefit?)."

other development activities are conducted. It should be noted that the risk assessment is not a "one-and-done" document, rather it is a living document that continues to be updated throughout development and beyond product launch (commercialization).

During the assessment process, risks are identified, and mitigating factors are proposed to decrease identified risks to an acceptable level. The mitigating factors identify modifications/additions to the product requirements document or design specifications. In order to reduce the probability of occurrence, each risk mitigation must be evaluated to verify or validate that the risk has indeed been mitigated. The evidence of this evaluation is typically sourced from V&V test data. When developing the V&V plan, the test method and acceptance criteria must be identified for each requirement prior to conducting the V&V testing. If the risk assessment identifies that a specific device design feature carries a high risk of harm to the patient, the development team should consider this when establishing the acceptance criteria for the requirement. Typically, the greater the risk to the patient, the higher the parameters for the acceptance criteria as the team will want to have high confidence that the occurrence of that potential failure mode is minimal.

Let's consider the example presented above in which we have a drug product that is delivered topically and another variation in which the product is delivered via subcutaneous injection. As part of the reconstitution and mixing process, the device design incorporates a custom needle that, upon user activation, pierces a rubber stopper and then transfers diluent from one chamber to another. The product requirement indicates that the reconstituted product shall have no particulate or coring present in the product delivered to the patient, and the test method for the requirement is identified as USP <381>, Fragmentation. Table 1 compares how the risk profile for each product application impacts the acceptance criteria, and ultimately the necessary sample size, for this specific requirement, while using the same device design.

The different applications (topical vs subcutaneous) directly influence the resulting risk present to the patient if particles are present in the final reconstituted product, and this is further translated into an acceptance criteria (or risk profile) that is tolerable to the development team for this specific requirement. It is not uncommon for companies to advocate that their products will be of highest quality standards. Yet when they are requested to provide a large number of samples for testing to align with these quality standards, they actively try to reduce sample size to the lowest possible value. In some instances, this may be appropriate, however, as demonstrated by the example above, if the resulting risk to patient is high, reducing the sample size is usually not the best approach.

In order to conduct a successful V&V on the intended combination product, the key is to understand that the V&V testing is not an isolated activity and task. Several of the activities identified in the Design Control process are key inputs toward establishing proper acceptance criteria and ultimately appropriate sample size for each requirement contained within the PRD.

The following is a checklist of items and/or reminders to keep in mind for combination product teams when preparing for V&V testing and that will also ensure compliance to Design Control.

If TBD's Need to be Incorporated Into the PRD

- Assign responsibility to project team member and define time point when TBD should be resolved.

Document Responsibility & Timing in Design Review Meeting Minutes

- Resolve all design-related TBDs before Design Freeze milestone is completed.
- Ensure that TBDs are resolved before any formal V&V testing is initiated.

Leverage Risk Analysis Into V&V Activity

- Conduct a preliminary risk assessment of the device before testing is conducted on the device.
- Utilize outputs of risk assessment process as an input to defining acceptance criteria.
- Within V&V plan, establish acceptance criteria for each appropriate requirement prior to formal initiation of V&V testing.
- Update the risk assessment after testing is conducted on the device. ◆

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BIOGRAPHY

Lilli Zakarija is Co-Founder and President of EdgeOne Medical Inc, an ISO 13485- certified medical device testing firm and consultancy focused on supporting combination products through the device development (design control) process. Prior to founding EdgeOne Medical, she developed and led the global device engineering function for Baxter's BioScience division (now Baxalta) in support of all its combination (biologic and device) products and single-use, disposable medical devices. Ms. Zakarija earned both her BS in Biomedical Engineering, and Masters in Engineering Management from Northwestern University, and her Executive MBA from Kellogg School of Management.

PHARMACOLOGY MODELS

Early Phase Pharmacodynamic Models for Respiratory Drug Candidates

By: Robert Lins, MD, PhD

INTRODUCTION

In the past few years, the prevalence of respiratory diseases has grown significantly, and now about half a billion people around the world are thought to be affected. Furthermore, the mortality rate has doubled in the past 40 years, in stark contrast to other conditions, such as cardiovascular disease, cancer, and infections.[1]

The most common respiratory diseases are asthma and chronic obstructive pulmonary disease (COPD). Their increased prevalence can be attributed to an increase in exposure to common risk factors, and the ageing population.

Inhaled therapies predominate in treatment, and two different therapeutic agents are often given in combination. Advances in treatment are, for the most part, the result of better insights into the mechanisms that cause disease, particularly the role of inflammation. These insights have also resulted in the potential for phenotyping and endotyping to inform treatment. The phenotype represents those clinical features that are determined by a combination of the genotype and the environment, while the endotype represents the subtypes defined by distinct physiological mechanisms.

The pharmacodynamic techniques and surrogate outcome parameters that are used in developing new treatments for respiratory disease, however, lack sensitivity for testing new drugs. Several primary outcome measurements are commonly used in clinical trials in the respiratory field. These include dynamic lung volume after 1 second of forced expiration (FEV1), clinical exacerbations, and a variety of more subjective scales that measure impaired health and perceived wellbeing, such as the St George respiratory questionnaire (SGRQ), which is used in the study of COPD. These metrics all lack the required levels of sensitivity, and there is a poor correlation between the measurements and overall survival.[2]

There is a clear need for more effective and meaningful techniques across the board. These could help by reducing the number of patients who need to be included in trials, and the resulting increased efficiency of early development should lead to a lower attrition rate in confirmatory studies. Several new alternatives are already being used in clinical practice, but have yet to make the leap into drug development.

BODY PLETHYSMOGRAPHY

Spirometry is the standard method for measuring most relative lung volumes; however, it is incapable of providing information about absolute volumes of air in the lung. Thus, a different approach is required to measure residual volume, functional residual capacity, and total lung capacity. The technique of body plethysmography, also referred to as "body box," is increasingly used in clinical practice because it is better controlled and enables a greater number of more sensitive dynamic lung volumes to be made than with FEV1 or vital capacity. It is also capable of measuring other parameters, such as residual volume, oscillometry, diffusion

capacity for carbon monoxide, and airway resistance. Further advantages lie in using the box for testing reversibility of bronchoconstriction after administration of a bronchodilator, and its ability to offer more repeatable bronchial challenge tests. If used in clinical studies, it has the potential to give more sensitive measurements.

CHALLENGE METHODS

In clinical development, respiratory challenge tests allow proof-of-concept studies to be carried out in healthy volunteers, and also in patients who are only mildly to moderately ill. A number of different challenge tests are possible, including bronchoprovocation testing.

This test has been used for many years, and relies on the inhalation of increasing concentrations of a histamine solution and the responsiveness of the airway being measured, and can be used for the diagnosis and quantification of bronchial hyperreactivity. The test is commonly used in clinical practice for the diagnosis of asthma, and can replace or supplement reversibility testing, a protocol that is notorious for the number of false negatives it generates in well-controlled mild-to-moderate asthma. The test can also be used in COPD, specifically asthma-COPD overlap syndrome (ACOS). If it is used in clinical trials, it can increase recruitment potential, and thus decrease the screen failure rate. The test is also used in some reimbursement criteria.

The measurement used in these studies is PC20, ie, the concentration of challenge agent that produces a 20% reduction in FEV1. However, there are

FIGURE 1

Body Plethysmography, the So-Called "Body Box"

drawbacks. Histamine causes a number of adverse reactions, including headache, tachycardia, and bronchoconstriction, which makes it difficult to use successfully. There are alternatives with fewer drawbacks, which are used less frequently. These include metacholine, which exerts its action via the direct stimulation of bronchial smooth muscle cells, and adenosine, which has an indirect effect as it causes mast cell degranulation, which releases proinflammatory mediators. All three agents – histamine, methacholine, and adenosine – can be used for early proof-of-concept trials for either bronchoprotection or bronchodilation studies, largely in asthma.

For allergen testing, conditions have to be even more rigorously controlled to ensure exposure to external seasonal allergens is negated. Recently, the use of a mobile chamber was presented that could challenge up to nine patients within an optimal testing environment.[3]

Challenge tests can also be undertaken using inhaled lipopolysaccharide (LPS). This endotoxin is a toll-like receptor 4 (TLR4) agonist that activates cytokine production. It invokes an acute inflammatory response in the lung, which is one of the important mechanisms in play in asthma and COPD, and thus, can be used in the study of antiinflammatory drugs in these diseases. The endotoxin is administered via inhalation using an ultrasonic nebulizer, with a dose of up to 50 µg/ml of isotonic saline, or as an intravenous infusion of 4 ng/kg over a 2-minute period for other indications such as sepsis. Its effects are measured in induced sputum via the number of granulocytes, or the levels of various cytokines, such as TNF-alpha, IL-1beta, IL-6, IL-8, and IL-10.

As an example, in a Phase I single and multiple ascending dose proof-of-concept study in asthma, an LPS challenge was carried out on two cohorts, one consisting of healthy male subjects, and the other asthmatic

patients. The 50-µg/ml dose of endotoxin was inhaled over a 2-minute period via five deep breaths of the nebulized solution. Sputum induction was carried out at pre-set time points after the challenge using increasing concentrations of hypertonic saline, up to 5%.

The viral challenge model, meanwhile, can give high-quality proof-of-concept safety and efficacy data, notably in upper respiratory tract infections, and has been used by pharma companies in early phase development for some years now. It establishes clear correlates of protection for vaccines and antivirals, can be used to inform go/no go decisions, and facilitates the up-or-down selection of study arms. It is now being used increasingly in asthma trials, based on the insight that asthma is an inflammatory disease in which viral diseases can cause exacerbations. These trials require a dedicated isolation suite, ideally located within a clinical pharmacology unit run by an experienced team.

The problems are illustrated by a Phase I randomized, double-blind, placebo-controlled trial that was carried out, first in 12 healthy normal volunteers, and then, in the second part of the trial, in 60 asthmatic subjects, on a monoclonal antibody targeting human TLR-3 for the prevention of asthma exacerbations. Subjects were given intravenous doses of the antibody ahead of inoculation with human rhinovirus type 16. The primary endpoint was safety and tolerability in part 1 of the trial and, in the second part, efficacy, as measured by pulmonary function testing and patient-reported outcomes. A range of secondary endpoints included pharmacokinetics, pharmacodynamics assessed via additional pulmonary function tests, the cold symptom assessment score, and fractional excretion of nitric oxide (a parameter for inflammation), biomarkers in nasal lavage, immunogenicity, and pharmacogenomics.

While the first part of the trial was successfully executed in 4 months, there were major hurdles, such as gaining regulatory approval to test a drug with a new mechanism of action combined with the viral challenge. There was, however, a major recruitment challenge, as 160 healthy consenting volunteers had to be tested to enroll just 12 individuals. This was mainly a result of a higher-than-expected positive antibody status. In the second part, the antibody status, when combined with further challenging inclusion and exclusion criteria, led to a 100% failure rate for recruitment after the assessment of 80 asthmatic patients. Thus, the second part of the trial could not be completed, highlighting the challenges associated with patient recruitment for certain viral challenge studies.

MEASURING LUNG DISPOSITION OF INHALED DRUGS

Sputum induction can be used to assess the concentration of inhaled drugs and outcome biomarkers in the lower airways.[4] These biomarkers are inflammatory cytokines, and the induction technique is relatively simple: increasing concentrations of saline are inhaled. The simplicity and non-invasive nature of the technique have led to its widespread use in drug development. However, its reproducibility has been questioned for some time, and the preparation of sputum samples for bioanalysis is elaborate, time-consuming, and highly demanding, even for trained technicians. Few methodological studies have examined the influence of technical factors on the repeatability of sputum induction and collection, and thus there is no "gold standard" procedure.

However, good results are possible, as exemplified by one study carried out by SGS. A success rate of 29% was achieved in a patient group of 175, compared with just 10% in the literature, in non-smoking healthy volunteers, and 74% of 35 asthma patients, compared with 70% in the literature.[5] A high success rate was also achieved in healthy volunteers who smoke, albeit with too few subjects to allow firm conclusions to be made. With care, the technique can be operated reliably.

A second methodology, local bronchial pharmacokinetics, can be used to determine the time-concentration profile of drugs and cytokines in bronchoalveolar lavage fluid (BALF) when predicting therapeutic efficacy. It also allows simultaneous assessment of the local and systemic pharmacokinetics of single and repeated doses of inhaled drugs. To execute this invasive technique, a pulmonologist with experience in bronchoscopy is required, as the scope has to be wedged in different positions in the bronchial tree in order to infuse saline distant from the bronchoscope and collect BALF samples.

As an example, a Phase I, single-center, open-label trial was carried out in male healthy volunteers in the SGS Phase I clinical unit, with the aim of evaluating the local and systemic

pharmacokinetics of a nanobody targeting respiratory syncytial virus. The drug was administered to 41 healthy male volunteers as an oral inhalation of single or multiple doses, or as an intravenous infusion of a single dose. The aim was to determine local and systemic pharmacokinetics, as assessed by BALF and blood measurements, after single and repeated administration, as well as urinary pharmacokinetics, safety, and immunogenicity. In all, 44 healthy volunteers were included after 74 screen failures; three dropped out. The BALF procedure caused four moderate adverse events, three of which were fever and the fourth dyspnoea, and all recovered completely after a short time. The study was completed successfully, and delivered the robust data required for the PK/PD modelling of the study drug.

An alternative technique, functional respiratory imaging, relies on 3D segmented computer models of human organs. These are generated by combining different imaging techniques, including high-resolution computed tomography, MRI, and ultrasound, some of which include advanced computational tools developed in the aerospace industry, computational fluid dynamics, and finite element analysis.

This technique is currently able to support early phase clinical trials in asthma, COPD, idiopathic pulmonary fibrosis, cystic fibrosis, and sleep disorders. After constructing the models, airway resistance in different types of airways is measured, along with changes in lobar hyperinflation and lobar perfusion, with the further potential to measure local drug disposition. As it is non-invasive, it also has the potential to be used in later phase trials. When combined with positron emission tomography and inhaled radiolabelled drugs, there is further potential for the determination of pharmacodynamics.

SUMMARY

It is clear that classical primary respiratory endpoints are far from successful in exploratory and confirmatory studies. The new techniques that are being developed thus far have most potential in early phase, exploratory, clinical trials, but there may be the opportunity to apply at least some of them in the later stages of development. Only by the creative use of novel techniques to assist in the running of clinical trials will the major unmet medical needs be addressed in a timely and effective way. ◆

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BIOGRAPHY

Dr. Robert Lins is Project Director, Respiratory Diseases at SGS Clinical Research. He is an MD and certified specialist in Internal Medicine, Nephrology, and Hypertension. He earned his PhD in Medical Sciences from the University of Antwerp, and is also a Fellow of the Belgian College of Pharmaceutical Physicians. Dr. Lins began his career over 35 years ago, working in Animal Clinical Pharmacology at the Heymans Institute in Gent, Belgium, and has since been continuously active in the field of Human Clinical Pharmacology. He first studied renal patients and later founded the SGS Clinical Pharmacology Unit in Antwerp, Belgium, where many innovative human pharmacology models were developed for the study of cardiovascular, metabolic, CNS, infectious, and most recently respiratory drugs. These include bronchial challenge methods, a local bronchial PK model, and sputum induction. Dr. Lins has published many articles about clinical pharmacology in these different areas of research.

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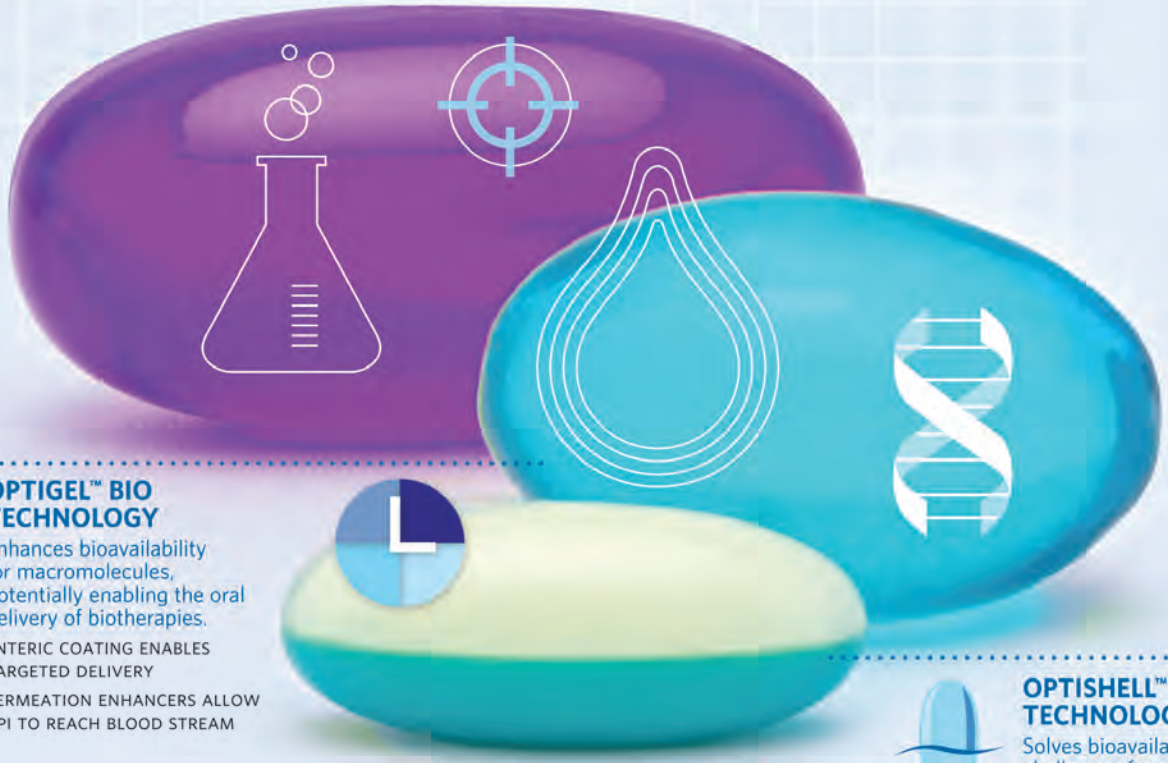

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